National Institute for Health and Care Excellence

NICE COVID-19 rapid guideline: managing COVID-19

[L] Evidence review for baricitinib

NICE guideline NG191

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Guideline version (Final)

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Objective

This evidence review aims to evaluate the evidence on the efficacy and safety of baricitinib for people hospitalised with COVID-19.

Review question

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review question for this evidence review is:

What is the efficacy and safety of baricitinib for adults, young people and children hospitalised with COVID-19?

Methodology

The evidence review was developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

Included studies

The searches for the effectiveness evidence were run on the 7th March 2022. The following databases were searched: Cochrane Central Register of Controlled Trials (Wiley); Embase (Ovid); MEDLINE (including epubs and in-process segments) (Ovid); Europe PMC (preprints only); NIH Covid-19 portfolio database (preprints only) and the World Health Organization Covid-19 database. Full search strategies for each database are provided in appendix B.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist. The search identified 195 references. These references were screened using their titles and abstracts and 8 full text references were obtained and assessed for relevance against the criteria in the PICO.

4 studies were excluded. Details of excluded studies are in appendix E.

4 studies are included in this evidence review. A summary of the included studies is shown in Table 1.

Table 1: Summary of included studies

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Ely 2022 Recruitment period: 23 December 2020 to 10 April 2021 Argentina, Brazil, Mexico, United States	RCT	Severe-critical COVID-19 Receiving invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO)	The study enrolled 101 patients who were 18 years of age or older and were hospitalised with confirmed SARS-CoV-2 infection. The mean age of participants was 58.6 years (SD 13.8), 54.5% (n=55) of participants were male. Most participants (93%) had symptoms onset within 7 days prior to enrolment and 87% of participants received systemic corticosteroids at baseline. All participants had at least one pre-existing comorbidity (diabetes, hypertension, chronic respiratory disease). Baseline characteristics were balanced between both treatment arms. Key exclusion criteria include: pregnant women, participants who received the following treatments prior to enrolment (tocilizumab, sarilumab, convalescent plasma, neutralising monoclonal antibodies for COVID-19, corticosteroids at doses >20mg per day administered for >14 days in the month prior to study enrolment)	Baricitinib + standard care; 4mg once daily for 14 days or until hospital discharge. Administered orally or via nasogastric tube	Placebo + standard care Standard care includes corticosteroids and remdesivir	All-cause mortality Worsening clinical status Ventilator free days Viral clearance Quality of life Adverse events

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Horby 2022 Recruitment period: 2 February 2021 to 29 December 2021 United Kingdom	RCT	Severe-critical COVID-19	8156 participants were randomised in this trial. The mean age of study participants was 58.1 years, a majority of participants were male (66%) and almost half of participants had at least one underlying co-morbidity (47%). 95% of participants were already in receipt of corticosteroids and 23% received tocilizumab. Almost 66% were receiving simple oxygen and 25% were in receipt of non-invasive ventilation. Baseline characteristics were balanced across treatment arms. Key exclusion criteria included pregnant or breast-feeding women, patients on dialysis or hemofiltration and patients with an active tuberculosis infection.	Baricitinib + standard care; 4mg once daily for 10 days or 2mg in children <9 years old or people with renal impairment or people receiving probenecid Administered orally or via nasogastric tube	Standard care alone Standard care includes corticosteroids, tocilizumab	Mortality Ventilation (non-invasive, invasive, extracorporeal membrane oxygenation) Median time to discharge and discharge status Safety
Kalil 2021 28 May 2020 to 1 July 2020 Denmark, Japan, Mexico, Singapore, South Korea, Spain, United Kingdom, United States	RCT	Moderate – severe COVID-19	1033 patients were enrolled in the trial, who were 18 years and older and were hospitalised with symptomatic COVID-19. The mean age of patients was 55.4 years and 64.1% were male. A majority of participants had at least one pre-existing co-morbidity (84.4%). Baseline characteristics were balanced between treatment arms. Key exclusion criteria include: pregnant women,	Baricitinib + standard care; 2mg tablets twice daily for up to 14 days or until hospital discharge. Administered orally	Placebo + standard care Standard care includes corticosteroids and remdesivir	All-cause mortality Worsening clinical status Ventilator free days Viral clearance Quality of life Adverse events

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
			immunocompromised patients, patients with a chronic medical condition and any patients who received a live vaccine or monoclonal antibodies within 4 weeks from trial enrolment			
Marconi 2021 June 2020 to January 2021 Argentina, Brazil, Germany, India, Italy, Japan, Mexico, Puerto Rico, Russia, South Korea, Spain, United Kingdom, United States	RCT	Moderate - severe COVID-19	1525 patients aged 18 years and over, with symptomatic COVID-19 were randomised for treatment. The mean age of participants was 57.6 years (SD 14.1). The majority of participants were male (63.1%). A majority of participants, 83.3% had symptoms for at least 7 days before trial enrolment. Most of the participants were also receiving systemic corticosteroid treatment (79.3%) and 99.7% of participants had at least one pre-existing co-morbidity. Baseline characteristics were balanced across both treatment arms. Key exclusion criteria include pregnant women, people who were receiving IMV or ECMO at baseline and any patients who received a live vaccine or monoclonal antibodies within 4 weeks from trial enrolment	Baricitinib + standard care; 4mg once daily for 14 days or until hospital discharge. Administered orally	Placebo + standard care Standard care includes corticosteroids and remdesivir	All-cause mortality Worsening clinical status Ventilator free days Viral clearance Quality of life Adverse events

See appendix F for full evidence tables.

Results

Review question: What is the efficacy and safety of baricitinib for adults, young people and children hospitalised with COVID-19?

Key results

Compared to standard care alone or standard care plus placebo, the combination of baricitinib and standard care reduces the risk of death for people in hospital with COVID-19.

What is the evidence informing this conclusion?

Evidence comes from 4 randomised controlled trials that compared the use of baricitinib alongside standard care with standard care alone in 10,816 patients hospitalised with COVID-19 (Ely 2022; Horby 2022; Kalil 2021; Marconi 2021). Most data are from the RECOVERY trial (Horby 2022) which included 8156 patients hospitalised with moderate to severe COVID-19.

Standard care within the trials varied but all the trials included a majority of patients receiving corticosteroids. Three trials included remdesivir as part of standard care (Ely 2022; Kalil 2021; Marconi 2021). One trial included a minority of patients receiving tocilizumab in addition to standard care (Horby 2022).

Due to variability in standard care, subgroup analyses were carried out to measure the effects of co-administered interventions on mortality, hospitalisation and recovery.

Publication status

One study was available as a pre-print (Horby 2022 (RECOVERY) posted to medRXiv on 3 March 2022 and has therefore not been peer reviewed.

Three studies are peer reviewed manuscripts (Ely 2022; Kalil 2021 and Marconi (COV-BARRIER) 2021).

Study characteristics

The mean age in the studies ranged between 56 and 58 years and the proportion of men ranged between 55% and 66%. The severity of COVID-19 across the studies was moderate to critical and one study included patients who were in critical stage with COVID-19 (Ely 2022) and receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). In all studies, the majority of participants had at least one comorbidity at randomisation. All the studies were single blind trials.

The largest study was the RECOVERY trial (Horby 2022), which included 8156 participants and contributed 75% of the number of participants included in this evidence review. This trial was based in the United Kingdom and 95% of participants received corticosteroids upon admission. Participants were randomised to receive 4mg baricitinib once daily for up to 10 days. 23% of patients in this trial also received tocilizumab in combination with baricitinib and 10% of patients were also randomised to other study drugs such as colchicine and aspirin. This trial included children aged 2 and older and patients with renal impairment and reduced dosing for these participants. This study also reported on the proportion of people who had received at least one dose of a COVID-19 vaccine (n= 3420/8156; 42%) .

The other 3 studies (Ely 2022; Kalil 2021; Marconi 2021) were based in centres around the world and were conducted earlier in the pandemic before the Omicron variant became prevalent and did not report vaccination status. As such the populations may not be directly relevant or comparable to the UK, where the Omicron variant is dominant (as of May 2022), and many people have been vaccinated. These studies also excluded people who received immunomodulatory agents such as tocilizumab and sarilumab. The studies randomised participants to receive baricitinib 4mg daily for up to 14 days, as per the United States Food and Drug Authority recommendations (FDA, 2021), and included corticosteroids and remdesivir in standard care regimens.

What are the main results?

Mortality and progression to invasive mechanical ventilation were significantly reduced in people who received baricitinib plus standard care compared to standard care alone or standard care plus placebo.

There was no subgroup effect of co-administered interventions (corticosteroids, remdesivir, tocilizumab) for the outcome of mortality.

There was a statistically significant increase in the number of patients who were discharged alive and the number of ventilator free days in people who received baricitinib plus standard care compared with standard care alone or standard care plus placebo.

No statistically significant differences were seen in the median time to recovery, days receiving ventilation or in the cessation of invasive mechanical ventilation.

Moderate quality evidence suggests that there is a lower incidence of serious adverse events in people who received baricitinib plus standard care compared with standard care alone.

See appendix H for full GRADE profiles and see appendix G for forest plots (note that forest plots were produced for outcomes where raw data was reported. In the absence of raw data, forest plots were not produced).

Our confidence in the results

Studies are heterogenous with both clinical and methodological diversity. However, sufficient information was provided by trial authors to assess the validity of the methods used and as such the risk of bias for most outcomes was assessed as low. For outcomes from the Ely 2022, Kalil 2021 and Marconi 2021 studies, there were some concerns surrounding the directness of the outcomes due to variation in standard of care treatment regimens across trial centres as well as a lack of reporting on vaccination status and prevalent COVID-19 variant. As such, some outcomes from Ely 2022, Kalil 2021 and Marconi 2021 were downgraded for indirectness. Where the RECOVERY (Horby 2022) trial contributed to an outcome alongside the other three studies, the outcome was not downgraded for indirectness as RECOVERY was the greatest contributing trial for the outcome. Outcomes were downgraded for imprecision where confidence intervals included the line of no effect and downgraded again if fewer than 300 people contributed to the outcome.

Evidence to decision

Benefits and harms

The panel considered evidence from 4 randomised controlled trials on the efficacy and safety of baricitinib plus standard care compared to standard care alone (Ely 2022, Horby 2022, Kalil 2021, Marconi 2021).

All the trials compared the effects of treatment with baricitinib on people with COVID-19 who required supplemental oxygen at randomisation. Most people were already in receipt of co-interventions such as corticosteroids and remdesivir but only 1 trial included people receiving tocilizumab (23% of the trial population in Horby 2022). Most people had a pre-existing co-morbidity at the time of study enrolment.

The evidence showed that baricitinib plus standard care significantly reduced mortality, duration of hospitalisation and disease severity. The panel recognised that the trials did not report any significant safety concerns with baricitinib. However, the BNF highlights that clinical trial data report an increased risk of venous thromboembolism and increased risk of diverticulitis in people treated with baricitinib, which the panel acknowledged. To identify serious adverse reactions to baricitinib, there is a Yellow Card reporting system for the Medicines and Healthcare products Regulatory Agency in place.

The panel emphasised the importance of directing baricitinib treatment appropriately to people who need supplementary oxygen specifically for COVID-19, in line with the evidence. This is because there may be people in hospital needing oxygen supplementation for other conditions, but who also have less severe COVID-19 where baricitinib is not needed. The recommendation therefore included the eligibility criterion of needing supplementary oxygen for COVID-19 to make this distinction.

This distinction is also made in the RECOVERY trial eligibility criteria, which stipulate confirmed SARS-CoV-2 infection and the presence of viral pneumonia syndrome, which would need supplemental oxygen. Although the RECOVERY trial criteria have evolved over time, this new wording is reflected in the NHS England clinical commissioning policy, and the panel's agreed criteria remain consistent with this.

The panel discussed the effects of combining other interventions with baricitinib such as corticosteroids, tocilizumab and remdesivir. At present, corticosteroids are administered to most people hospitalised with COVID-19 in the United Kingdom. From the studies, the evidence of effectiveness for baricitinib appears to be consistent regardless of treatment with systemic corticosteroids, remdesivir or an IL-6 receptor blocker such as tocilizumab. However, in the case of combination therapy of baricitinib with tocilizumab the panel agreed it could not be concluded from the evidence whether there was any added value or added harm in co-administration. As such, the panel agreed that clinicians should consider the clinical and contextual factors when deciding whether to use baricitinib or an interleukin-6 inhibitor, or both. These include availability, people's preference, severity of illness and deterioration, local policies and route of administration.

Baricitinib is contraindicated in pregnant and breastfeeding women. Women of childbearing potential should use effective contraception during treatment and after treatment, for at least 1 week. However, there is uncertainty regarding the benefit to harm ratio for women and their babies. The panel highlighted that the decision regarding the use of baricitinib should be made between the pregnant woman and their healthcare professional while discussing whether the potential benefit justifies the potential risk to the mother and baby.

Certainty of the evidence

The evidence comes from 4 randomised trials (Ely 2022, Horby 2022, Kalil 2021, Marconi 2021). The evidence shows that the combination of baricitinib with standard care alone statistically significantly reduced mortality and duration of hospitalisation in people with moderate to severe COVID-19.

The certainty of the outcomes from these studies was high to moderate. There are some concerns about indirectness with Ely 2022, Kalil 2021 and Marconi 2021 as these trials did not report on vaccination status and the prevalent COVID-19 variant at the time of study. Furthermore, these trials were not based in the United Kingdom there was heterogeneity between standard treatment regimens in the study centres which would affect applicability in the UK context. Lastly, these 3 studies were also conducted before the predominance of the Omicron variant and as such this

evidence may not be directly applicable to the UK context. The panel discussed that these variations may contribute to the additive effect sizes and some subgroup analyses may not have reached significance due to this variation. However, the panel also noted that there is likely to be no difference in the effectiveness of treatment with baricitinib in Omicron and non-Omicron variants as baricitinib is a host-directed treatment rather than antiviral treatment.

The panel noted that the Horby 2022 (RECOVERY) trial was the largest trial contributing to the evidence base with 8156 participants. The trial is also based in the United Kingdom and reported on vaccination status and prevalent variant at the time of study recruitment. There were no concerns raised about outcomes that were reported in this study.

Values and preferences

The panel were not aware of any systematically collected data on peoples' preferences and values. The evidence shows significant benefits from baricitinib use on mortality and duration of hospitalisation, which is likely to influence people's preferences for this drug. The panel acknowledged that there may be potential harms from treatment with baricitinib, however, they agreed that individual factors may influence people's' preferences to receive treatment.

The panel noted that the effects of treatment with tocilizumab either prior to, or following, baricitinib administration remain uncertain. The panel concluded that, in people who are clinically deteriorating, there may be a need to administer further interventions and in these cases co-administration of tocilizumab may be preferred by patients or their families or carers.

The panel noted the uncertain benefits and harms of baricitinib for pregnant and breastfeeding women, which may influence their preference for having this drug.

Resources

Baricitinib is currently licensed for use in the United Kingdom for rheumatoid arthritis and atopic dermatitis.

The panel discussed that due to recent reforms to virtual wards and hospital at home schemes, the availability of baricitinib should be considered. However, the panel agreed that, regardless of these changes, appropriate treatment plans can be devised for people to ensure equal access to treatment.

Cost-effectiveness was not assessed as part of the evidence review.

Equity

Baricitinib is contraindicated in pregnant and breastfeeding women. The panel noted the inequity of access that this may present and the need for suitable alternatives such as an interleukin-6 inhibitor.

The panel noted that baricitinib is not licensed in children and young people under 18 years and the safety profile is unknown for this age group, with only limited data included in the Horby 2022 trial.

Acceptability

The panel agreed that, based on the evidence and their clinical judgement, baricitinib is an effective intervention to administer to people with COVID-19, especially in the context of their condition deteriorating. As baricitinib is administered orally once daily, people with COVID-19 should find this treatment acceptable. Clinicians should consider the individual circumstances of the person and any clinical or contextual factors which may affect treatment options, such as safety concerns, patient preference and operational considerations.

Feasibility

As of April 2022, baricitinib had not been granted marketing authorisation for use in the treatment of COVID-19.

The panel explored when baricitinib should be administered and agreed that it can be administered early in the treatment pathway for people in hospital with COVID-19 who meet the criteria set out in the recommendation.

Appendices

Appendix A: PICO table

Review question:

What is the effectiveness and safety of baricitinib for adults, young people and children hospitalised with COVID-19?

Criteria	Notes
Population	Hospitalised adults, young people and children with confirmed COVID-19.
Interventions	Baricitinib NB: the review will include baricitinib as monotherapy or in combination with other drugs
Comparators	Standard care alone, standard care plus placebo or placebo alone Note: Standard care comprises best supportive care and in certain circumstances the use of additional drugs (such as dexamethasone, remdesivir).
Outcomes	**Effectiveness outcomes** • Mortality • Invasive mechanical ventilation (IMV) or intensive care admission (requirement and duration) • Hospitalisation (requirement and duration) • Supplemental oxygen (requirement and duration) • High-flow oxygen, continuous positive airway pressure or non-invasive ventilation (requirement and duration) • Symptom resolution or clinical recovery (number and time until) • Clinical worsening / deterioration (number and time until)

	• Sustained recovery (development of long-term effects of COVID measured at least 4 weeks from onset of acute COVID-19) • Virological clearance (negative PCR) / viral load **Safety outcomes** • Adverse events • Discontinuation due to adverse events The definitions of mechanical ventilation, non-invasive ventilation and other forms of respiratory support such as high flow nasal oxygen (HFNO) therapy or continuous positive airway pressure or non-invasive bilevel ventilation may differ across the studies. In the context of UK practice the following definitions should be considered: **Advanced respiratory support:** Invasive mechanical ventilation, bilevel positive airway pressure (BiPAP) via translaryngeal tube or tracheostomy, continuous positive airway pressure (CPAP) via translaryngeal tube, or extracorporeal respiratory support) **Non-invasive ventilation:** includes HFNO, CPAP, CPAP via tracheostomy, and non-invasive bilevel ventilation. Note: oxygen via (low flow) nasal cannulae or face mask does not fall within the categories above.
Settings	All settings in which patients are under the care of a secondary care clinical team for the management of COVID-19
Subgroups	• Adults > 50 years • Children <12 years of age • Disease severity at baseline (mild/moderate/severe/critical)

	• Gender • Ethnic background • Pregnant women • Comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity) • Time from symptom onset (≤7 days vs. > 7 days) • Vaccination status • Seronegative vs. seropositive • PCR confirmed COVID vs. not confirmed • COVID-19 variants • Asymptomatic with positive test vs. symptomatic with positive test
Study types	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If no systematic reviews or RCT evidence is available progress to: • Non-randomised controlled trials • Systematic reviews of non-randomised controlled trials • Cohort studies • Before and after studies • Interrupted time series studies

	Preprints will be considered as part of the evidence review.
Countries	Any
Timepoints	From 2020 onwards
Other exclusions	• Non-English language papers, studies that are only available as abstracts, and narrative reviews • Animal studies • Editorials, letters, news items, case reports and commentaries, conference abstracts and posters theses and dissertations
Equality issues	Sex, age, ethnicity, religion or beliefs, people with a learning disability and disabled people, socioeconomic status, people who are pregnant or breastfeeding, people whose first language isn't English, people who are homeless, refugees, asylum seekers, migrant workers and people who are homeless.

Appendix B: Literature search strategy

Search design and peer review

This search was developed in compliance with Appendix L of NICE's manual on developing guidelines.
A NICE information specialist conducted the literature searches for the evidence review. The searches were run on the 7th March 2022. This search report is compliant with the requirements of PRISMA-S.
The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.
The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.
Europe PMC and the NIH Office of Portfolio Analysis COVID-19 database were used to identify preprints.
Trial identifiers were added to the database searches following an initial search for relevant identifiers in clinicaltrials.gov; ISRCTN; WHO ICTRP; clinicaltrialsregister.eu; EU clinical trials information system. The following search terms were used in these databases…

(SARS OR COVID OR COVID19 OR corona OR coronavirus) AND
(Baricitinib OR olumiant OR LY3009104 OR INCB028050)

In the EU clinical trials information system (CTIS) only the drug terms were used.
The RECOVERY trial was removed from list of trial identifiers. The term "RECOVERY" is too imprecise and the multi-intervention nature of the (platform) trial means that most results from the trial do not relate to baricitinib. The trial website was searched directly for additional results and any results from RECOVERY on baricitinib should also be picked up by main database PICO searches.
The trial identifier 17830 was omitted as being too non-specific.
BREATH was amended to (BREATH adj trial*) in the database strategy.
The identifier P30CA014089 was removed. This relates to a general grant given a US cancer centre and is cited in all their research, not just their baricitinib COVID-19 trial.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Searches were date limited to lead on from the searches conducted for a draft Cochrane review on *Janus kinase inhibitors for the treatment of COVID-19* (Kramer et al, currently unpublished).
The Cochrane group monitored newly published RCTs up to the 20th October 2021, using the Cochrane COVID-19 Study Register (CCSR). The CCSR is compiled using daily searches of Medline and weekly searches of Embase and medRxiv, among other sources.

Search filters

- Covid-19 filter

The development of NICE's main database search strategy for Covid-19 is covered in: Levay P and Finnegan A (2021) The NICE COVID-19 search strategy for Ovid MEDLINE and Embase: developing and maintaining a strategy to support rapid guidelines. MedRxiv preprint. https://doi.org/10.1101/2021.06.11.21258749

- Systematic reviews filters

The MEDLINE SR filter was "Health-evidence.ca Systematic review search filter" from Lee et al. (2012). The standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

The Embase SR filter was "Health-evidence.ca Systematic review search filter" from Lee et al. (2012). The standard NICE modifications were used: pubmed.tw added to line medline.tw.

Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

- RCT filters

The MEDLINE RCT filter was McMaster Therapy – Medline - "best balance of sensitivity and specificity" version. The standard NICE modifications were used: randomized.mp changed to randomi?ed.mp.
Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.
The Embase RCT filter was McMaster Therapy – Embase "best balance of sensitivity and specificity" version.
Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association*, 94(1), 41-47.

Main search – Databases

Database	Date searched	Database platform	Database segment or version	No. of results downloaded

MEDLINE	7th March 2022	Ovid	1946 to March 04, 2022	17
MEDLINE in-process	7th March 2022	Ovid	March 04, 2022	4
MEDLINE epubs	7th March 2022	Ovid	March 04, 2022	12
Embase	7th March 2022	Ovid	1996 to March 04, 2022	90
Cochrane - CENTRAL	7th March 2022	Wiley	Issue 2 of 12, February 2022	4
Europe PMC preprints	7th March 2022	N/A	-	19
NIH COVID-19 portfolio preprints	7th March 2022	N/A	-	43
WHO Covid-19 Database	7th March 2022	N/A	-	65

Search strategy history

Database name: Medline

1 baricitinib.tw. (434)
2 olumiant.tw. (7)
3 (LY3009104 or "LY3009104").tw. (4)
4 (INCB028050 or "INCB 028050" or "INCB 28050").tw. (5)
5 or/1-4 (436)
6 SARS-CoV-2/ or COVID-19/ (145576)
7 (corona* adj1 (virus* or viral*)).ti,ab. (1697)
8 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab. (46100)
9 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. (154358)
10 or/6-9 (161606)
11 5 and 10 (111)
12 randomized controlled trial.pt. (559906)
13 randomi?ed.mp. (899390)
14 placebo.mp. (213379)
15 or/12-14 (954423)
16 (MEDLINE or pubmed).tw. (218888)
17 systematic review.tw. (172989)
18 systematic review.pt. (183135)
19 meta-analysis.pt. (153974)
20 intervention$.ti. (149218)
21 or/16-20 (485948)
22 11 and 15 (25)

23 11 and 21 (10)
24 22 or 23 (30)
25 (NCT05082714 or ATTKPATRASCOVID19).af. (0)
26 (NCT04340232 or "20-0738").af. (0)
27 (NCT04421027 or "I4V-MC-KHAA" or "2020-001517-21" or "COV-BARRIER").af. (2)
28 (NCT04362943 or "PAS-BAR-2020-04" or "COVID-AGE").af. (9)
29 (NCT04401579 or "ACTT-2" or "2020-001052-18" or "DMID-NIH" or jRCT2031200035).af. (4)
30 (NCT04970719 or "BADAS-ERC/EC/21/00311").af. (0)
31 (NCT04640168 or "ACTT-4" or jRCT2031200252).af. (1)
32 (NCT05056558 or "2021/BR8/P3/01").af. (0)
33 (NCT04832880 or AMMURAVID or "2020-001854-23").af. (0)
34 (NCT04373044 or "0S-20-3" or "NCI-2020-02685").af. (0)
35 (NCT04693026 or "2020/2637").af. (0)
36 (NCT04321993 or "SAIL-004").af. (0)
37 (NCT04346147 or "24032020" or "2020-001321-31" or Covid19COVINIB or "COVID-19 HUF").af. (9)
38 (NCT04358614 or "HPrato-4").af. (0)
39 (NCT04390464 or "TACTIC-R" or "2020-001354-22" or "282213" or CCTU0303).af. (3)
40 (NCT05074420 or "I4V-MC-KHAB" or "2021-001338-21" or "COV-BARRIER").af. (2)
41 (NCT04393051 or "BARICIVID-19").af. (0)
42 (NCT04320277 or "HPrato-3" or "BARI-COVID").af. (1)
43 (NCT04890626 or PanCOVID).af. (0)
44 (NCT04399798 or "2020-001185-11" or (BREATH adj trial*)).af. (9)
45 (NCT04891133 or SolidAct or "2021-000541-41" or "DisCoVeRy for Solidarity").af. (2)
46 (NCT04366206 or "GHTRB-2020-01").af. (0)
47 (NCT04365764 or "CIC1421-20-06").af. (0)
48 (NCT04345289 or "2020-001367-88" or "25032020").af. (5)
49 or/24-48 (67)
50 limit 49 to yr="2020-Current" (57)
51 (50 and english.lg.) not (letter or historical article or comment or editorial or news or case reports).pt. not (Animals/ not humans/) (41)
52 24 or 51 (46)
53 limit 52 to ed=20211011-20220307 (17)

Database name: Medline epubs

1 baricitinib.tw. (75)
2 olumiant.tw. (1)
3 (LY3009104 or "LY 3009104").tw. (0)
4 (INCB028050 or "INCB 028050" or "INCB 28050").tw. (0)
5 or/1-4 (75)
6 SARS-CoV-2/ or COVID-19/ (0)
7 (corona* adj1 (virus* or viral*)).ti,ab. (285)

8 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab. (5481)
9 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. (22199)
10 or/6-9 (22222)
11 5 and 10 (19)
12 (NCT05082714 or ATTKPATRASCOVID19).af. (0)
13 (NCT04340232 or "20-0738").af. (0)
14 (NCT04421027 or "I4V-MC-KHAA" or "2020-001517-21" or "COV-BARRIER").af. (1)
15 (NCT04362943 or "PAS-BAR-2020-04" or "COVID-AGE").af. (0)
16 (NCT04401579 or "ACTT-2" or "2020-001052-18" or "DMID-NIH" or jRCT2031200035).af. (0)
17 (NCT04970719 or "BADAS-ERC/EC/21/00311").af. (0)
18 (NCT04640168 or "ACTT-4" or jRCT2031200252).af. (0)
19 (NCT05056558 or "2021/BR8/P3/01").af. (0)
20 (NCT04832880 or AMMURAVID or "2020-001854-23").af. (0)
21 (NCT04373044 or "0S-20-3" or "NCI-2020-02685").af. (0)
22 (NCT04693026 or "2020/2637").af. (0)
23 (NCT04321993 or "SAIL-004").af. (0)
24 (NCT04346147 or "24032020" or "2020-001321-31" or Covid19COVINIB or "COVID-19 HUF").af. (0)
25 (NCT04358614 or "HPrato-4").af. (0)
26 (NCT04390464 or "TACTIC-R" or "2020-001354-22" or "282213" or CCTU0303).af. (0)
27 (NCT05074420 or "I4V-MC-KHAB" or "2021-001338-21" or "COV-BARRIER").af. (1)
28 (NCT04393051 or "BARICIVID-19").af. (0)
29 (NCT04320277 or "HPrato-3" or "BARI-COVID").af. (0)
30 (NCT04890626 or PanCOVID).af. (0)
31 (NCT04399798 or "2020-001185-11" or (BREATH adj trial*)).af. (0)
32 (NCT04891133 or SolidAct or "2021-000541-41" or "DisCoVeRy for Solidarity").af. (0)
33 (NCT04366206 or "GHTRB-2020-01").af. (0)
34 (NCT04365764 or "CIC1421-20-06").af. (0)
35 (NCT04345289 or "2020-001367-88" or "25032020").af. (0)
36 or/11-35 (19)
37 limit 36 to yr="2020 -Current" (18)
38 37 and english.lg. (18)
39 limit 38 to dt=20211011-20220307 (12)

Database name: Medline in-process

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4 (INCB028050 or "INCB 028050" or "INCB 28050").tw. (0)
5 or/1-4 (16)
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7 (corona* adj1 (virus* or viral*)).ti,ab. (12)
8 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab. (525)
9 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. (1460)
10 or/6-9 (1464)
11 5 and 10 (4)
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13 (NCT04340232 or "20-0738").af. (0)
14 (NCT04421027 or "I4V-MC-KHAA" or "2020-001517-21" or "COV-BARRIER").af. (0)
15 (NCT04362943 or "PAS-BAR-2020-04" or "COVID-AGE").af. (0)
16 (NCT04401579 or "ACTT-2" or "2020-001052-18" or "DMID-NIH" or jRCT2031200035).af. (0)
17 (NCT04970719 or "BADAS-ERC/EC/21/00311").af. (0)
18 (NCT04640168 or "ACTT-4" or jRCT2031200252).af. (0)
19 (NCT05056558 or "2021/BR8/P3/01").af. (0)
20 (NCT04832880 or AMMURAVID or "2020-001854-23").af. (0)
21 (NCT04373044 or "0S-20-3" or "NCI-2020-02685").af. (0)
22 (NCT04693026 or "2020/2637").af. (0)
23 (NCT04321993 or "SAIL-004").af. (0)
24 (NCT04346147 or "24032020" or "2020-001321-31" or Covid19COVINIB or "COVID-19 HUF").af. (0)
25 (NCT04358614 or "HPrato-4").af. (0)
26 (NCT04390464 or "TACTIC-R" or "2020-001354-22" or "282213" or CCTU0303).af. (0)
27 (NCT05074420 or "I4V-MC-KHAB" or "2021-001338-21" or "COV-BARRIER").af. (0)
28 (NCT04393051 or "BARICIVID-19").af. (0)
29 (NCT04320277 or "HPrato-3" or "BARI-COVID").af. (0)
30 (NCT04890626 or PanCOVID).af. (0)
31 (NCT04399798 or "2020-001185-11" or (BREATH adj trial*)).af. (0)
32 (NCT04891133 or SolidAct or "2021-000541-41" or "DisCoVeRy for Solidarity").af. (0)
33 (NCT04366206 or "GHTRB-2020-01").af. (0)
34 (NCT04365764 or "CIC1421-20-06").af. (0)
35 (NCT04345289 or "2020-001367-88" or "25032020").af. (0)
36 or/11-35 (4)
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38 37 and english.lg. (4)
39 limit 38 to dt=20211011-20220307 (4)

Database name: Embase

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2 baricitinib.tw. (1403)
3 olumiant.tw. (69)
4 (LY3009104 or "LY3009104").tw. (21)
5 (INCB028050 or "INCB 028050" or "INCB 28050").tw. (92)
6 or/1-5 (2829)
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8 (corona* adj1 (virus* or viral*)).ti,ab. (3350)
9 (CoV not (Coefficien* or co-efficien* or covalent* or covington or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk" or CoVR or CoVS)).ti,ab. (72292)
10 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. (248792)
11 or/7-10 (267210)
12 6 and 11 (864)
13 random:.tw. (1631541)
14 placebo:.mp. (414492)
15 double-blind:.tw. (183685)
16 or/13-15 (1833099)
17 (MEDLINE or pubmed).tw. (332507)
18 exp systematic review/ or systematic review.tw. (402105)
19 meta-analysis/ (235298)
20 intervention$.ti. (219348)
21 or/17-20 (792402)
22 12 and 16 (120)
23 12 and 21 (107)
24 22 or 23 (192)
25 (NCT05082714 or ATTKPATRASCOVID19).af. (2)
26 (NCT04340232 or "20-0738").af. (35)
27 (NCT04421027 or "I4V-MC-KHAA" or "2020-001517-21" or "COV-BARRIER").af. (30)
28 (NCT04362943 or "PAS-BAR-2020-04" or "COVID-AGE").af. (22)
29 (NCT04401579 or "ACTT-2" or "2020-001052-18" or "DMID-NIH" or jRCT2031200035).af. (41)
30 (NCT04970719 or "BADAS-ERC/EC/21/00311").af. (3)
31 (NCT04640168 or "ACTT-4" or jRCT2031200252).af. (10)
32 (NCT05056558 or "2021/BR8/P3/01").af. (1)
33 (NCT04832880 or AMMURAVID or "2020-001854-23").af. (2)
34 (NCT04373044 or "0S-20-3" or "NCI-2020-02685").af. (23)
35 (NCT04693026 or "2020/2637").af. (4)
36 (NCT04321993 or "SAIL-004").af. (66)
37 (NCT04346147 or "24032020" or "2020-001321-31" or Covid19COVINIB or "COVID-19 HUF").af. (43)
38 (NCT04358614 or "HPrato-4").af. (29)

39 (NCT04390464 or "TACTIC-R" or "2020-001354-22" or "282213" or CCTU0303).af. (34)
40 (NCT05074420 or "I4V-MC-KHAB" or "2021-001338-21" or "COV-BARRIER").af. (6)
41 (NCT04393051 or "BARICIVID-19").af. (9)
42 (NCT04320277 or "HPrato-3" or "BARI-COVID").af. (59)
43 (NCT04890626 or PanCOVID).af. (2)
44 (NCT04399798 or "2020-001185-11" or (BREATH adj trial*)).af. (30)
45 (NCT04891133 or SolidAct or "2021-000541-41" or "DisCoVeRy for Solidarity").af. (2)
46 (NCT04366206 or "GHTRB-2020-01").af. (4)
47 (NCT04365764 or "CIC1421-20-06").af. (4)
48 (NCT04345289 or "2020-001367-88" or "25032020").af. (39)
49 or/24-48 (422)
50 limit 49 to yr="2020-Current" (400)
51 (50 and english.lg.) not (letter or editorial or conference).pt. not (nonhuman/ not human/) not "case report".sh. not medline*.db. (340)
52 limit 51 to dc=20211011-20220307 (90)

Database name: CENTRAL

ID Search
#1 MeSH descriptor: [SARS-CoV-2] this term only
#2 MeSH descriptor: [COVID-19] this term only
#3 (corona* near/1 (virus* or viral*)):ti,ab,kw
#4 (CoV NOT (Coefficien* or "co-efficient" or “co-efficiency” or “co-efficiencies” or covalent* or Covington* or covariant* or covarianc* or "cut-off value" or "cut-off values" or "cutoff value" or "cutoff values" or "cut-off volume" or "cut-off volumes" or "cutoff volume" or "cutoff volumes" or "combined optimisation value" or "combined optimisation values" or "combined optimization value" or "combined optimization values" or "central vessel trunk" or "central vessel trunks" or CoVR or CoVS)):ti,ab,kw
#5 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel" or Ncov* or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or SARSCoV2* or "SARS-CoV2" or "severe acute respiratory syndrome" or "severe acute respiratory syndromes" or covid19 or covid-19 or covid):ti,ab,kw
#6 {or #1-#5} with Cochrane Library publication date Between Oct 2021 and Mar 2022, in Cochrane Reviews
#7 {or #1-#5} with Cochrane Library publication date Between Oct 2021 and Mar 2022, in Trials
#8 #6 OR #7
#9 baricitinib:ti,ab,kw
#10 olumiant:ti,ab,kw
#11 (LY3009104 OR "LY 3009104"):ti,ab,kw
#12 (INCB028050 OR "INCB 028050" OR "INCB 28050"):ti,ab,kw
#13 {OR #9-#12}
#14 #8 AND #13
#15 (trialsearch OR clinicaltrials):so
#16 #14 NOT #15

Database name: Europe PMC

FIRST_IDATE:[20211011 TO 20220307] AND (Baricitinib OR olumiant OR LY3009104 OR “LY 3009104” OR INCB028050 OR “INCB 028050” OR “INCB 28050”) AND ((covid OR covid19 OR covid2019) OR (corona* AND (virus* OR viral*)) OR CoV OR omicron OR (coronavirus* OR 2019nCoV* OR 19nCoV* OR "2019 novel" OR Ncov* OR "n-cov" OR (SARS-CoV-2*) OR (SARSCoV-2*) OR SARSCoV2* OR (CoV2*) OR (severe acute respiratory syndrome*) OR (COVID*2))) AND (FIRST_PDATE:(2020 OR 2021 OR 2022 OR 2023 OR 2024 OR 2025 OR 2026 OR 2027 OR 2028 OR 2029 OR 2030)) AND (SRC:PPR)

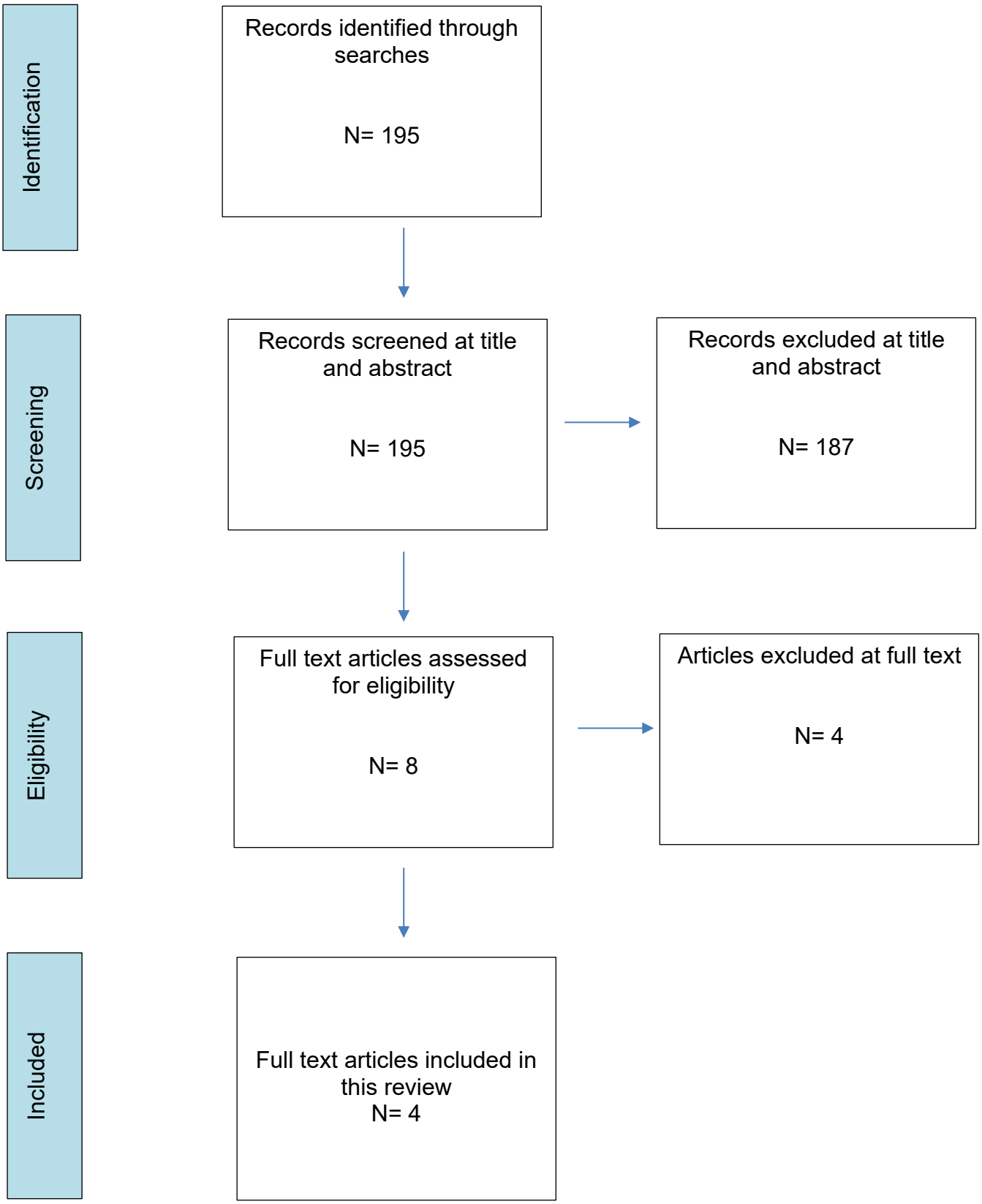
Database name: NIH COVID-19 portfolio preprints

Baricitinib OR olumiant OR LY3009104 OR “LY 3009104” OR INCB028050 OR “INCB 028050” OR “INCB 28050”
Limits: publication type = preprint; publication date = 2021-10-11 to 2022-03-07

Database name: WHO Covid-19 database

(Baricitinib OR olumiant OR LY3009104 OR (LY 3009104) OR INCB028050 OR (INCB 028050) OR (INCB 28050)) AND (da:(20211$ OR 2022$))

Appendix C: PRISMA diagram



Appendix D: Included studies

Ely, E.W., Ramanan, A.V., Kartman, C.E., de Bono, S., Liao, R., Piruzeli, M.L.B., Goldman, J.D., Saraiva, J.F.K., Chakladar, S., Marconi, V.C. and Alatorre-Alexander, J., 2022. Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial. *The Lancet Respiratory Medicine*.

Horby, P.W., Emberson, J.R., Mafham, M., Campbell, M., Peto, L., Pessoa-Amorim, G., Spata, E., Staplin, N., Lowe, C., Chadwick, D.R. and Brightling, C., 2022. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. *medRxiv*.

Kalil, A.C., Patterson, T.F., Mehta, A.K., Tomashek, K.M., Wolfe, C.R., Ghazaryan, V., Marconi, V.C., Ruiz-Palacios, G.M., Hsieh, L., Kline, S. and Tapson, V., 2021. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *New England Journal of Medicine*, *384*(9), pp.795-807.

Marconi, V.C., Ramanan, A.V., de Bono, S., Kartman, C.E., Krishnan, V., Liao, R., Piruzeli, M.L.B., Goldman, J.D., Alatorre-Alexander, J., de Cassia Pellegrini, R. and Estrada, V., 2021. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *The Lancet Respiratory Medicine*, *9*(12), pp.1407-1418.

Appendix E: Excluded studies at full text screening

Study	Reason for exclusion
Lin, Z., Niu, J., Xu, Y. et al. (2022) Clinical efficacy and adverse events of baricitinib treatment for coronavirus disease-2019 (COVID-19): A systematic review and meta-analysis. Journal of Medical Virology 94(4): 1523-1534	Systematic review with no additional RCTs beyond those included in this evidence review
Patoulias, Dimitrios, Doumas, Michael, Papadopoulos, Christodoulos et al. (2021) Janus kinase inhibitors and major COVID-19 outcomes: time to forget the two faces of Janus! A meta-analysis of randomized controlled trials. Clinical rheumatology 40(11): 4671-4674	Systematic review with no additional RCTs beyond those included in this evidence review
Sampath, A, Banerjee, A, Atal, S et al. (2021) Use of Baricitinib in Treatment of COVID-19: A Systematic Review.	Systematic review with no additional RCTs beyond those included in this evidence review
Zhang, X., Shang, L., Fan, G. et al. (2022) The Efficacy and Safety of Janus Kinase Inhibitors for Patients With COVID-19: A Living Systematic Review and Meta-Analysis. Frontiers in Medicine 8: 800492	Systematic review with no additional RCTs beyond those included in this evidence review

Appendix F: Evidence tables

Ely, 2022

Bibliographic Reference	Ely EW; Ramanan AV; Kartman CE; de Bono S; Liao R; Piruzeli MLB; Goldman JD; Saraiva JFK; Chakladar S; Marconi VC; ; Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial.; The Lancet. Respiratory medicine; 2022

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04421027
Study start date	23-Dec-2020
Study end date	10-Apr-2021
Aim of the study	To evaluate the efficacy and safety of baricitinib plus standard of care in critically ill hospitalised adults with COVID-19 who require invasive mechanical ventilation or extracorporeal membrane oxygenation
Country/geographical location	Argentina, Brazil, Mexico, United States
Study setting	Hospital
Population description	Patients were 18 years of age or older, who were hospitalised with confirmed SARS-CoV-2 infection. The mean age of participants was 58.6 years (SD 13.8), 54.5% (n=55) of participants were male. The majority of participants (93%) had symptom onset within 7 days prior to enrolment and 87% of participants received systemic corticosteroids at baseline. All participants had at least one pre-existing comorbidity (diabetes, hypertension, chronic respiratory disease). Baseline characteristics were balanced between both treatment arms.
Inclusion criteria	Hospitalised with coronavirus (SARS-CoV-2) infection, confirmed by polymerase chain reaction (PCR) test or other commercial or public health assay in any specimen, as documented by either of the following:

	• PCR positive in sample collected <72 hours prior to randomisation; OR • PCR positive in sample collected ≥72 hours prior to randomisation (but no more than 14 days prior to randomisation), • Documented inability to obtain a repeat sample (for example, due to lack of testing supplies, limited testing capacity, results taking >24 hours, etc.) and progressive disease suggestive of ongoing SARS-CoV-2 infection. • Requires invasive mechanical ventilation or ECMO at screening and randomisation. • Have indicators of risk of progression: at least 1 inflammatory marker>upper limit of normal (ULN) (C reactive protein [CRP], D dimer, lactate dehydrogenase [LDH], ferritin) with at least 1 instance of elevation >ULN within 2 days before study entry.
Exclusion criteria	• Are receiving cytotoxic or biologic treatments (such as tumour necrosis factor [TNF] inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], T-cell or B-cell targeted therapies (rituximab), interferon, or Janus kinase (JAK) inhibitors for any indication at study entry. Note: A washout period 4 weeks (or 5 half-lives, whichever is longer) is required prior to screening. • Have ever received convalescent plasma or intravenous immunoglobulin [IVIg]) for COVID-19. • Have received high dose corticosteroids at doses >20 mg per day (or prednisone equivalent) administered for ≥14 consecutive days in the month prior to study entry. • Strong inhibitors of OAT3 (such as probenecid) that cannot be discontinued at study entry. Have received neutralizing antibodies, such as bamlanivimab, casirivimab and imdevimab for COVID-19. • Have a diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only, no screening tests required). • Suspected serious, active bacterial, fungal, viral, or other infection (besides COVID19) that in the opinion of the investigator could constitute a risk when taking the investigational product. • Have received any live vaccine within 4 weeks before the screening or intend to receive a live vaccine during the study. Note: Use of non-live (inactivated) vaccinations is allowed for all participants. • Current diagnosis of active malignancy that, in the opinion of the investigator, could constitute a risk when taking the investigational product. • Have a history of venous thromboembolism (VTE) (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) within 12 weeks prior to randomization or have a history of recurrent (>1) VTE (DVT/PE). • Anticipated discharge from the hospital, or transfer to another hospital (or another unit), which is not a study site within 72 hours after study entry. • Have neutropenia (absolute neutrophil count <1000 cells/microliters). • Have lymphopenia (absolute lymphocyte count <200 cells/microliters).

	• Have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 times ULN. • Estimated glomerular filtration rate (eGFR) (Modification of Diet in Renal Disease [MDRD]) <30 millilitre/minute/1.73 meters squared. • Have a known hypersensitivity to baricitinib or any of its excipients. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study. Note: The participant should not be enrolled (started) in another clinical trial for the treatment of COVID-19 or SARS CoV-2 through Day 28. • Are pregnant or intend to become pregnant or breastfeed during the study. • Are using or will use extracorporeal blood purification (EBP) device to remove pro-inflammatory cytokines from the blood such as a cytokine absorption or filtering device, for example, CytoSorb®. • Are, in the opinion of the investigator, unlikely to survive for at least 48 hours after screening.
Intervention dosage (loading)	Baricitinib 4mg orally/via nasogastric tube delivery
Intervention dosage (maintenance)	Not reported
Intervention scheduled duration	14 days or until discharge from hospital; whichever occurred first
Intervention actual duration	Varied
Intervention route of administration	Orally or crushed for nasogastric tube delivery
Comparator (where applicable)	Placebo and standard protocol based on local practice
Methods for population selection/allocation	Participants were stratified according to the following baseline stratification factors: disease severity (hospitalised not requiring supplemental oxygen, requiring ongoing medical care [National Institute of Allergy and Infectious Disease Ordinal Scale; Table S1]; hospitalised requiring supplemental oxygen by prongs or mask [OS 5]; hospitalised requiring non-invasive ventilation or high-flow oxygen [OS 6]), age (<65 or ≥65 years), region (Europe, United States [US], or Rest of World), and use of dexamethasone and/or other systemic corticosteroids (yes/no) at baseline for COVID-19. An independent, external data monitoring committee oversaw the study and evaluated unblinded interim efficacy and safety analyses used for safety monitoring, evaluation of excess mortality or futility, and planned sample size re-estimation. An independent, blinded, clinical event committee adjudicated potential VTEs and deaths. Full details of

	the trial design, conduct, oversight, amendments, and analyses are provided in the protocol and statistical analysis plan available from the sponsor.
Methods of data analysis	Sample size re-estimation was to be conducted by the data monitoring committee (DMC) when approximately 1000-1100 participants had the opportunity to complete 28 days of the treatment period. The determination for final sample size increase was calculated based on formulas given in Mehta and Pocock (2010).2 This methodology requires the calculation of conditional power (CP) for statistical significance of the primary endpoint for the baricitinib versus placebo comparison. The CP could fall into 1 of the 3 zones: “Favourable”, “Promising,” or “Unfavourable.” “Favourable” corresponded to CP greater than 90%; “Promising” corresponded to CP between 30% and 90%; and “Unfavourable” corresponded to CP less than 30%. The sample size was not to be increased if the data landed in the “Favourable” or the “Unfavourable” zone. If the CP landed in the “Promising” zone, the sample size was to be increased to a maximum of 1700 participants or 90% CP. The sample size was not to be increased beyond 1700 participants, even if a greater sample size would be needed to achieve 90% CP. As there were 2 primary endpoints, the CP was calculated for each, based on 90% of alpha being allocated to Population 1. The decision to increase the sample size or not was to be based on the CP of the population with the largest CP. The DMC evaluated the CP for each primary on Jan 14, 2021. At that time 1073 participants had completed 28 days of treatment. The DMC recommended not to increase the study’s sample size. Efficacy data were analysed with the intent-to-treat population, defined as all randomised participants. For dichotomous and ordinal endpoints, logistic regression models, and proportional odds models were used, 9 respectively, with baseline stratification factors and treatment groups in the models. For continuous endpoints assessed at a single timepoint, analysis of variance models was used, with baseline stratification factors and treatment group in the models. For continuous measures over time, a restricted maximum-likelihood-based mixed-effects model of repeated measures was used, with treatment, baseline stratification factors, landmark days treatment-by-landmark-days-interaction as fixed categorical effects, and baseline score and baseline score-by landmark-days-interaction as fixed continuous effects. The log-rank test was used to evaluate treatment effect in time-to-event endpoints, with Kaplan-Meier curves and median survival estimated for each treatment group. The hazard ratio (HR) with 95% confidence intervals (CI) was calculated using a Cox proportional hazards model adjusted for baseline stratification factors. Pre-specified subgroup analyses for the primary and selected key secondary endpoints evaluated treatment effect across the following subgroups: baseline OS (OS 4, OS 5, OS 6, and OS 5 and OS 6 combined), baseline usage of remdesivir (yes/no), baseline usage of corticosteroids (yes/no), region, duration of symptoms prior to enrolment, age, sex, dexamethasone and/or other systemic corticosteroid used at baseline for primary condition, and comorbidities (where applicable). Efforts to use all available data and minimize missing data imputation were considered. For time-to-event endpoints with a positive outcome (recovery or improvement), the competing risk of death was handled by censoring at day 28 participants who died on or before day 28, which had the effect of ensuring that the time-to-event models would not assume those participants could recover/improve. The primary missing data imputation method for endpoints related to the ordinal

	scale was multiple imputations using a Markov model where each transition to a future state is dependent only on the previous state. The last observation carried forward was also used to impute ordinal scales and other secondary endpoints not involving ordinal scales. A graphical multiple-testing procedure for the primary and key secondary outcomes was prespecified to control for the Type I error rate at a two-sided alpha level of 0.05. Figure S2 includes the graph and results. The two primary analyses are at the top of the hierarchy. Population 1 was tested at 99% of the total alpha (0.05) and Population 2 at 1% of 0.05. The graph was set up so that if Population 2 succeeded at its alpha-level, it would pass its entire alpha to Population 1. If Population 1 had succeeded (whether or not Population 2 succeeded), it would have passed its entire alpha to the remaining key secondary outcomes successively, until one of them failed. As the Population 1 analysis failed, there was no alpha remaining to test the rest of the key secondary analyses.
Attrition/loss to follow-up	1 placebo participant lost to follow up and 1 withdrawal by subject
Source of funding	Eli Lilly and Company
Study limitations (Author)	The study had a small sample size (n=101) and the standard of care delivered to patients varied. The severity of COVID-19 disease also varied and as such, the immunomodulatory effects of treatment were not evaluated during the study period.
Study limitations (Reviewer)	The study had a small sample size and there was varying standard care dependent on local practice in the trial country. Variations in resource availability in different countries may also impact the concomitant treatments/standard care received by the patients and so this was not balanced between all arms.
Other details	This study is a pre-print and is an addendum study to Marconi 2021 COV-BARRIER study that focused on critically ill COVID-19 patients who were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation at enrolment. These participants were not included in the original population of the Marconi study and form a separate population group.

Study arms

Placebo + SoC (N = 50)

Baricitinib + SoC (N = 51)

Characteristics

Arm-level characteristics

Characteristic	Placebo + SoC (N = 50)	Baricitinib + SoC (N = 51)
Age Mean (SD)	58.8 (15.2)	58.4 (12.4)
Male No of events	n = 30 ; % = 60	n = 25 ; % = 49
Female No of events	n = 20 ; % = 40	n = 26 ; % = 51
Ethnicity - American Indian or Alaska Native No of events	n = 17 ; % = 34.7	n = 15 ; % = 30
Ethnicity - Asian No of events	n = 1 ; % = 2	n = 0 ; % = 0
Ethnicity - Black or African American No of events	n = 1 ; % = 2	n = 1 ; % = 2
Ethnicity - Multiple No of events	n = 0 ; % = 0	n = 2 ; % = 4
Ethnicity - White No of events	n = 30 ; % = 61.2	n = 32 ; % = 64

Characteristic	Placebo + SoC (N = 50)	Baricitinib + SoC (N = 51)
Ethnicity - Missing No of events	n = 1 ; % = NA	n = 1 ; % = NA
Obesity No of events	n = 29 ; % = 58	n = 28 ; % = 54.9
Diabetes (type I or type II) No of events	n = 16 ; % = 32	n = 20 ; % = 39.2
Chronic respiratory disease No of events	n = 2 ; % = 4	n = 1 ; % = 2
Hypertension No of events	n = 24 ; % = 48	n = 31 ; % = 60.8
Use of Remdesivir No of events	n = 2 ; % = 4	n = 0 ; % = 0
Use of Corticosteroid No of events	n = 44 ; % = 88	n = 43 ; % = 84.3
CRP (mg/L) Lower better Nominal	109.5	124.9
D-dimer (mg/L)	1.6	1.6

Characteristic	Placebo + SoC (N = 50)	Baricitinib + SoC (N = 51)
Lower better Nominal		
Lactate dehydrogenase (U/L) Lower better Nominal	543.6	499.5
Ferritin (pmol/L) Lower better Nominal	2836.9	2622

Outcomes

Baricitinib vs SoC/Placebo - Safety and efficacy outcomes

Outcome	Placebo + SoC, , N = 50	Baricitinib + SoC, , N = 52
All-cause mortality No of events	n = 29 ; % = 58	n = 20 ; % = 39.2
Ventilator free days Mean (SD)	5.5 (8.4)	8.1 (10.2)
Duration of hospitalisation Mean (SD)	26.1 (3.9)	23.7 (7.1)

Outcome	Placebo + SoC, , N = 50	Baricitinib + SoC, , N = 52
Number of participants who recovered No of events	n = 13 ; % = 26	n = 19 ; % = 37.3
Treatment emergent adverse event **Overall** No of events	n = 47 ; % = 94	n = 44 ; % = 88
Treatment emergent adverse event **Mild** No of events	n = 3 ; % = 6.1	n = 3 ; % = 6
Treatment emergent adverse event **Moderate** No of events	n = 11 ; % = 22.4	n = 17 ; % = 34
Treatment emergent adverse event **Severe** No of events	n = 33 ; % = 67.3	n = 24 ; % = 48
Death due to adverse event No of events	n = 3 ; % = 6.1	n = 5 ; % = 10
Serious adverse event No of events	n = 35 ; % = 71.4	n = 25 ; % = 50

All-cause mortality - day 28 subgroups

Outcome	Placebo + SoC, , N = 50	Baricitinib + SoC, , N = 51
Baseline corticosteroid use No of events	n = 26 ; % = 59.1	n = 16 ; % = 37.2
No baseline corticosteroid use No of events	n = 3 ; % = 6	n = 4 ; % = 8
Baseline remdesivir use No of events	n = 0 ; % = 0	n = 0 ; % = 0
No baseline remdesivir use No of events	n = 29 ; % = 60.4	n = 20 ; % = 39.2

Critical appraisal - Baricitinib RoB

All-cause mortality

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

All-cause mortality – baseline corticosteroid use

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

All-cause mortality – baseline no corticosteroid use

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

All-cause mortality – baseline remdesivir use

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

All-cause mortality – baseline no remdesivir use

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

Ventilator free days

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

Duration of hospitalisation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

Number of participants who recovered

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

Treatment emergent adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

Horby, 2022

Bibliographic Reference	RECOVERY Collaborative, Group; Horby, Peter W; Emberson, Jonathan R; Mafham, Marion; Campbell, Mark; Peto, Leon; Pessoa-Amorim, Guilherme; Spata, Enti; Staplin, Natalie; Lowe, Catherine; Chadwick, David R; Brightling, Christopher; Stewart, Richard; Collini, Paul; Ashish, Abdul; Green, Christopher A; Prudon, Benjamin; Felton, Tim; Kerry, Anthony; Baillie, J Kenneth; Buch, Maya H; Day, Jeremy N; Faust, Saul N; Jaki, Thomas; Jeffery, Katie; Juszczak, Edmund; Knight, Marian; Lim, Wei Shen; Montgomery, Alan; Mumford, Andrew; Rowan, Kathryn; Thwaites, Guy; Haynes, Richard; Landray, Martin J; Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis; medRxiv; 2022; 2022030222271623

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04381936
Study start date	02-Feb-2021
Study end date	29-Dec-2021
Aim of the study	To evaluate the effects of baricitinib in patients hospitalised with COVID-19
Country/geographical location	United Kingdom
Study setting	Hospital
Population description	8156 participants were randomised in this trial to receive baricitinib and standard care or standard care alone. The mean age of study participants was 58.1 years and 66% of participants were male. Almost half of participants had underlying comorbidity (47%), with 95% of participants already receiving corticosteroids, 23% receiving tocilizumab. Almost 66% were receiving simple oxygen and 25% were in receipt of non-invasive ventilation. Baseline characteristics were balanced across treatment arms.
Inclusion criteria	• Patients aged at least 2 years admitted to the hospital were eligible for the study if they had clinically suspected or laboratory-confirmed SARS-CoV-2 infection • No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial
Exclusion criteria	• Aged <2 years • eGFR <15 mL/min/1.73m2 or on dialysis or haemofiltration • Neutrophil count <0.5 x 109 116 /L • Had evidence of active TB infection • Were pregnant or breastfeeding
Intervention dosage (loading)	4mg baricitinib once daily 2mg baricitinib for patients with eGFR <60mL/min/1.73m2, or receiving probenecid, and for children aged <9 years

Intervention dosage (maintenance)	4mg baricitinib once daily 2mg baricitinib for patients with eGFR <60mL/min/1.73m2, or receiving probenecid, and for children aged <9 years
Intervention scheduled duration	Up to 10 days or until discharge if sooner
Intervention actual duration	Varied
Intervention route of administration	Orally or via nasogastric tube
Comparator (where applicable)	Usual standard of care (corticosteroids, remdesivir, tocilizumab, colchicine, aspirin, casirivimab and imdevimab)
Methods for population selection/allocation	Patients were assigned in a 1:1 ratio to either usual standard of care plus baricitinib or usual standard of care alone, using web-based simple (unstratified) randomisation with allocation concealed until after randomisation
Methods of data analysis	For all outcomes, intention-to-treat analyses compared patients randomised to baricitinib with patients randomised to usual care. In accordance with the prespecified statistical analysis plan for dealing with baseline imbalances in important prognostic factors, estimates of the effect of allocation to baricitinib on major outcomes were adjusted for age in three groups (<70 years, ≥70 to <80 years, and ≥80 years). Exploratory analyses were conducted without this adjustment and, separately, with further adjustment for other predefined subgroups of interest. For the primary outcome of 28-day mortality, the hazard ratio from an age-adjusted Cox model was used to estimate the mortality rate ratio. Kaplan-Meier survival curves were constructed to display cumulative mortality over the 28-day period. The same method to analyse time to hospital discharge and successful cessation of invasive mechanical ventilation, with patients who died in hospital on day 29 was used. Median time to discharge was derived from Kaplan-Meier estimates. For the pre-specified composite secondary outcome of progression to invasive mechanical ventilation or death within 28 days (among those not receiving invasive mechanical ventilation at randomisation), and the subsidiary clinical outcomes of receipt of ventilation and use of haemodialysis or haemofiltration, the precise dates were not available and so a log-binomial regression model was used to estimate the age-adjusted risk ratio. Estimates of rate and risk ratios (both denoted RR) are shown with 95% confidence intervals. Prespecified analyses of the primary outcome were done in subgroups defined by six characteristics at the time of randomisation (age, sex, ethnicity, days since symptom onset, level of respiratory support, and use of corticosteroids) with tests of heterogeneity or trend, as appropriate.

Attrition/loss to follow-up	30 participants withdrew consent in baricitinib arm 24 participants withdrew consent in standard care alone arm
Source of funding	UK Research and Innovation (Medical Research Council) and National Institute of Health Research
Study limitations (Author)	This randomised trial is open-label, and the use of tocilizumab during the follow-up period was slightly lower among those allocated to baricitinib compared with control (26% vs. 29%). Information on radiological, virological or physiological outcomes was not collected.
Study limitations (Reviewer)	The study was an open-label trial and as such, participants and carers were aware of the intervention. This is an ongoing trial, and safety outcomes for the trial were not fully reported.
Other details	Part of RECOVERY trial, approximately 10% of participants were also randomised to colchicine, aspirin and casirivimab and imdevimab.

Study arms

Baricitinib + Usual Care (N = 4148)

Usual Care (N = 4008)

Characteristics

Arm-level characteristics

Characteristic	Baricitinib + Usual Care (N = 4148)	Usual Care (N = 4008)
<70 years	n = 3142; % = 76	n = 3086 ; % = 77

Characteristic	Baricitinib + Usual Care (N = 4148)	Usual Care (N = 4008)
No of events		
70-79 No of events	n = 665 ; % = 16	n = 655 ; % = 16
80 or more No of events	n = 341 ; % = 8	n = 267 ; % = 7
Male No of events	n = 2740 ; % = 66	n = 2638 ; % = 66
Female No of events	n = 1408 ; % = 34	n = 1370 ; % = 34
Ethnicity - White No of events	n = 3192 ; % = 77	n = 3104 ; % = 77
Ethnicity - Black, Asian, and minority ethnic No of events	n = 457 ; % = 11	n = 455 ; % = 11
Ethnicity - Unknown No of events	n = 499 ; % = 12	n = 449 ; % = 11
Ventilation received - None No of events	n = 228 ; % = 5	n = 237 ; % = 6
Ventilation received - Simple oxygen No of events	n = 2770 ; % = 67	n = 2743 ; % = 68

Characteristic	Baricitinib + Usual Care (N = 4148)	Usual Care (N = 4008)
Ventilation received - Non-invasive ventilation No of events	n = 1016 ; % = 24	n = 911 ; % = 23
Ventilation received - Invasive mechanical ventilation No of events	n = 134 ; % = 3	n = 117 ; % = 3
Diabetes No of events	n = 961 ; % = 23	n = 941 ; % = 23
Heart disease No of events	n = 782; % = 19	n = 706; % = 18
Chronic lung disease No of events	n = 882; % = 21	n = 783; % = 20
HIV No of events	n = 13; % = 1	n = 9; % = 1
Severe liver disease No of events	n = 33; % = 1	n = 33; % = 1
Severe kidney impairment No of events	n = 101; % = 2	n = 79; % = 2
Any comorbidity No of events	n = 1957; % = 47	n = 1834; % = 46

Characteristic	Baricitinib + Usual Care (N = 4148)	Usual Care (N = 4008)
Use of corticosteroids No of events	n = 3962; % = 96	n = 3809; % = 95
Use of remdesivir No of events	n = 878; % = 21	n = 789; % = 20
Use of tocilizumab No of events	n = 951; % = 23	n = 921; % = 23
Plan to use tocilizumab within next 24 hours No of events	n = 391; % = 9	n = 365; % = 9
Colchicine No of events	n = 401; % = 10	n = 301; % = 10
Aspirin No of events	n = 462; % = 11	n = 453; % = 11
Casirivimab and imdevimab No of events	n = 440; % = 11	n = 449; % = 11
Received a COVID-19 vaccine No of events	n = 1755; % = 42	n = 1665; % = 42

Outcomes

Baricitinib + standard care vs standard care alone

Outcome	Baricitinib + Usual Care, N = 4148	Usual Care, N = 4008
Mortality 28 days No of events	n = 513; % = 12	n = 546; % = 14
Mortality - Baseline CRP <60mg/L No of events	n = 170; % = 12	n = 172; % = 13
Mortality - Baseline CRP >60<120mg/L No of events	n = 164; % = 13	n = 174; % = 14
Mortality - Baseline CRP >120mg/L No of events	n = 173; % = 12	n = 192; % = 14
Mortality - Use of tocilizumab No of events	n = 131; % = 14	n = 153; % = 17
Mortality - Use of tocilizumab within 24 hours No of events	n = 51; % = 13	n = 61; % = 17
Mortality - No use of tocilizumab No of events	n = 331; % = 12	n = 332; % = 12
Mortality - Use of remdesivir No of events	n = 84; % = 10	n = 100; % = 13

Outcome	Baricitinib + Usual Care, N = 4148	Usual Care, N = 4008
Mortality - No use of remdesivir No of events	n = 429; % = 13	n = 446; % = 14
Median time to being discharged alive (days) Median (IQR)	8 (5 to 17)	8 (5 to 20)
Discharged from hospital within 28 days No of events	n = 3337; % = 80	n = 3137; % = 78
Receipt of invasive mechanical ventilation or death No of events	n = 631; % = 16	n = 670; % = 17
Receipt of invasive mechanical ventilation or death - IMV No of events	n = 283; % = 7	n = 322; % = 8
Receipt of invasive mechanical ventilation or death - death No of events	n = 475; % = 12	n = 502; % = 13
Non-invasive ventilation No of events	n = 595; % = 20	n = 637; % = 21
Invasive mechanical ventilation No of events	n = 585; % = 20	n = 623; % = 21
Successful cessation of invasive mechanical ventilation No of events	n = 61/134; % = 46	n = 43/117; % = 37

Outcome	Baricitinib + Usual Care, N = 4148	Usual Care, N = 4008
Use of haemodialysis or haemofiltration No of events	n = 85; % = 2	n = 109; % = 3
Adverse events No of events	n = 323; % = 7.6	n = 345; % 8.7

Critical appraisal - Baricitinib RoB

Mortality

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Mortality – Baseline CRP <60mg/L

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Mortality – Baseline CRP >60<120mg/L

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Mortality – Baseline CRP>120mg/L

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Mortality – Use of tocilizumab

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Mortality – Use of tocilizumab within 24 hours

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Mortality – No use of tocilizumab

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Mortality – Use of remdesivir

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Mortality – No use of remdesivir

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Median time to being discharged alive

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Discharged from hospital within 28 days

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Receipt of invasive mechanical ventilation or death

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Receipt of invasive mechanical ventilation or death – invasive mechanical ventilation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Receipt of invasive mechanical ventilation or death - death

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Non-invasive ventilation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Invasive mechanical ventilation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Successful cessation of invasive mechanical ventilation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Use of haemodialysis or haemofiltration

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Kalil et al.

Bibliographic Reference	Kalil AC; Patterson TF; Mehta AK; Tomashek KM; Wolfe CR; Ghazaryan V; Marconi VC; Ruiz-Palacios GM; Hsieh L; Kline S; Tapson V; Iovine NM; Jain MK; Sweeney DA; El Sahly HM; Branche AR; Regalado Pineda J; Lye DC; Sandkovsky U; Luetkemeyer AF; Cohen SH; Finberg RW; Jackson PEH; Taiwo B; Paules CI; Arguinchona H; Erdmann N; Ahuja N; Frank M; Oh MD; Kim ES; Tan SY; Mularski RA; Nielsen H; Ponce PO; Taylor BS; Larson L; Rouphael NG; Saklawi Y; Cantos VD; Ko ER; Engemann JJ; Amin AN; Watanabe M; Billings J; Elie MC; Davey RT; Burgess TH; Ferreira J; Green M; Makowski M; Cardoso A; de Bono S; Bonnett T; Proschan M; Deye GA; Dempsey W; Nayak SU; Dodd LE; Beigel JH; ; Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19.; The New England journal of medicine; vol. 384 (no. 9)

Study details

Study design	Randomised controlled trial (RCT)

Trial registration (if reported)	NCT04401579
Study start date	28-May-2020
Study end date	01-Jul-2020
Aim of the study	To evaluate the effects of combination treatment with baricitinib and remdesivir in hospitalised patients
Country/geographical location	Denmark, Japan, Mexico, Singapore, South Korea, Spain, United Kingdom, United States
Study setting	Hospital
Population description	Patients were enrolled in the trial if they were in the hospital with symptomatic COVID-19. The mean age of patients was 55.4 years and 64.1% were male. Most participants had at least one pre-existing co-morbidity (84.4%).

Inclusion criteria	• Admitted to a hospital with symptoms suggestive of COVID-19.
	• Subject (or legally authorized representative) provides informed consent prior to initiation of any study procedures.
	• Subject (or legally authorized representative) understands and agrees to comply with planned study procedures.
	• Male or non-pregnant female adult > / = 18 years of age at time of enrolment.
	• Has laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction (PCR) or other commercial or public health assays in any specimen, as documented by either of the following:
	  o PCR positive in a sample collected < 72 hours prior to randomization; OR
	  o PCR positive in sample collected >/= 72 hours prior to randomisation, documented inability to obtain a repeat sample (e.g., due to lack of testing supplies, limited testing capacity, results taking >24 hours, etc.) AND progressive disease suggestive of ongoing SARS-CoV-2 infection
	• Illness of any duration, and at least one of the following:
	  o Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
	  o SpO2 < / = 94% on room air, OR
	  o Requiring supplemental oxygen, OR
	  o Requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO).
	• Women of childbearing potential must agree to either abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through Day 29. A
	• agrees to not participate in another clinical trial for the treatment of COVID-19 through Day 29.

Exclusion criteria	• Alanine Transaminase (ALT) or Aspartate Transaminase (AST) > 5 times the upper limit of normal. • Estimated glomerular filtration rate (eGFR) < 30 ml/min or patient is receiving haemodialysis or hemofiltration at time of screening. • Neutropenia (absolute neutrophil count <1000 cells/microliter) (<1.0 x 103/microliter or <1.0 GI/L). • Lymphopenia (absolute lymphocyte count <200 cells/microliter) (<0.20 x 103/microliter or <0.20 GI/L) • Pregnancy or breastfeeding. • Anticipated discharge from the hospital or transfer to another hospital that is not a study site within 72 hours. • Allergy to any study medication. • Received three or more doses of remdesivir, including the loading dose, outside of the study under the EUA (or similar mechanism) for COVID-19. • Received convalescent plasma or intravenous immunoglobulin [IVIg]) for COVID-19, the current illness for which they are being enrolled. • Received small molecule tyrosine kinase inhibitors (e.g., baricitinib, imatibib, genfinitib), in the 1 week prior to screening. • Received monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab]), or T-cells (e.g., abatacept) in the 4 weeks prior to screening. • Received monoclonal antibodies targeting B-cell (e.g., rituximab, and including any targeting multiple cell lines including B-cells) in the 3 months prior to screening. • Received other immunosuppressants in the 4 weeks prior to screening and in the judgement of the investigator, the risk of immunosuppression with baricitinib is larger than the risk of COVID-19. • Received >/= 20 mg/day of prednisone or equivalent for >/=14 consecutive days in the 4 weeks prior to screening. • Use of probenecid that cannot be discontinued at study enrolment. • Have a diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only, no screening required). • Suspected serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking the investigational product. • Have received any live vaccine (that is, live attenuated) within 4 weeks before screening, or intend to receive a live vaccine (or live attenuated) during the study. Note: Use of non-live (inactivated) vaccinations is allowed for all subjects. • Have a history of VTE (deep vein thrombosis [DVT] or pulmonary embolism [PE]) within 12 weeks prior to screening or have a history of recurrent (>1) VTE (DVT/PE).

	• Immunocompromised patients, patients with a chronic medical condition, or those taking a medication that cannot be discontinued at enrolment, who, in the judgment of PI, are at increased risk for serious infections or other safety concerns given the study products.
Intervention dosage (loading)	Baricitinib: 4mg daily dose (oral in 2mg tablets or through a nasogastric tube) Remdesivir: 200mg loading dose on day 1
Intervention dosage (maintenance)	Remdesivir: 100mg maintenance dose daily from day 2-10
Intervention scheduled duration	Baricitinib: 14 days or until hospital discharge (whichever was earlier) Remdesivir: 10 days or until hospital discharge (whichever was earlier)
Intervention actual duration	Varied
Intervention route of administration	Baricitinib: orally or via nasogastric tube Remdesivir: intravenous infusion
Comparator (where applicable)	Placebo and standard care
Methods for population selection/allocation	Randomisation was stratified by study site and disease severity at enrolment and was performed using a web-based Internet Data Entry System, Advantage eClinical SM. Severe disease was defined as participants in ordinal categories 7 and 6, and included those on ECMO, invasive or non-invasive mechanical ventilation, or high flow oxygen devices. Mild/moderate disease was defined as ordinal category 5 and 4, and included those on low flow oxygen devices (defined as 15L/min or less) and those not on supplemental oxygen
Methods of data analysis	The primary analysis was a log-rank test of time-to-recovery between remdesivir plus baricitinib and remdesivir plus placebo stratified by disease severity as defined above. The relevant treatment efficacy parameter is the “recovery rate ratio” (for the combination arm relative to control), which is akin to the hazard ratio in survival analysis but for the beneficial outcome of recovery. Two practical considerations result from considering time to a beneficial outcome. First, a recovery rate ratio greater than one indicates an improvement for the combination arm. Second, failure to recover and death are both censored at Day 29. Consequently, participants censored on the last observation day reflect two different states: death and failure to recover by Day 29. Hence, a breakdown of deaths by treatment arm is

	also important to understanding treatment efficacy. The key secondary analysis tested a difference in the ordinal score distribution between remdesivir plus baricitinib and remdesivir plus placebo at Day 15 using the “common odds ratio” from a proportional odds model, stratifying by baseline disease severity stratum. The study was designed to achieve 85% power for detecting a recovery rate ratio of 1.35 with a two-sided type-I error rate of 5%. Enrolment continued through April 19, 2020, to ensure at least 400 recoveries and to address subgroup analysis. Because the SAP did not include a provision for correcting for multiplicity when conducting tests for secondary outcomes, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes. More details can be found in the statistical analysis plan. Analyses were conducted using SAS version 9.4 and R version 3.5.1.
Attrition/loss to follow-up	In placebo arm, 40 were lost to follow up whereas in the treatment arm 41 were lost to follow up
Source of funding	National Institute of Allergy and Infectious Disease
Study limitations (Author)	The study was not powered to detect a difference in mortality between the two groups. The clinical status scoring systems had wider/different implications across trial centres and so as an outcome reporting of clinical status may vary between countries.
Study limitations (Reviewer)	Differences in standard care between trial centres may impact the study arms
Other details	Published, peer-reviewed manuscript

Study arms

Baricitinib + remdesivir (N = 515)

Remdesivir + placebo (N = 518)

Characteristics

Arm-level characteristics

Characteristic	Baricitinib + remdesivir (N = 515)	Remdesivir + placebo (N = 518)
Age Mean (SD)	55 (15.4)	55.8 (16)
Male No of events	n = 319; % = 63.1	n = 333; % = 64.3
Female No of events	n = 196; % = 38.1	n = 185; % = 35.7
Ethnicity - Asian No of events	n = 49; % = 9.5	n = 52; % = 10
Ethnicity - Black No of events	n = 77; % = 15	n = 79; % = 15.3
Ethnicity - White No of events	n = 251; % = 48.7	n = 245; % = 47.3
Ethnicity - Other or unknown No of events	n = 138; % = 26.8	n = 142; % = 27.4
Disease severity - Moderate No of events	n = 358; % = 69.5	n = 348; % = 67.2

Characteristic	Baricitinib + remdesivir (N = 515)	Remdesivir + placebo (N = 518)
Disease severity - Severe No of events	n = 157; % = 30.5	n = 170; % = 32.8
Co-existing conditions- None No of events	n = 64; % = 12.9	n = 91; % = 18.3
Co-existing conditions- One No of events	n = 148; % = 29.8	n = 122; % = 24.5
two or more No of events	n = 284; % = 57.3	n = 285; % = 57.2

Outcomes

Baricitinib vs Placebo/SoC - Efficacy and safety outcomes

Outcome	Baricitinib + remdesivir, N = 515	Remdesivir + placebo, N = 518
Number of recoveries No of events	n = 433; % = 84.1	n = 406; % = 78.4
Median time to recovery Mean (95% CI)	7 (6 to 8)	8 (7 to 9)
Mortality by day 28 No of events	n = 24; % = 4.7	n = 37; % = 7.1

Outcome	Baricitinib + remdesivir, N = 515	Remdesivir + placebo, N = 518
Median time to hospitalisation- With imputation for data for those who died Median (IQR)	8 (5 to 15)	8 (5 to 20)
Median time to hospitalisation- Among those who did not die Median (IQR)	8 (5 to 13)	8 (5 to 15)
Median days receiving oxygen - With imputation of data for those who died Median (IQR)	10 (4 to 27)	12 (4 to 28)
Median days receiving oxygen - Among those who did not die Median (IQR)	9 (4 to 24)	10 (4 to 28)
New use of oxygen during trial No of events	n = 16/70; % = 22.9	n = 29/72; % = 40.3
Median days of non-invasive ventilation or high flow oxygen - With imputation of data for those who died Median (IQR)	4 (3 to 9)	5 (2 to 12)
Median days of non-invasive ventilation or high flow oxygen - Among those who did not die Median (IQR)	4 (3 to 6)	4 (2 to 9)
New use of non-invasive ventilation or high-flow oxygen during trial No of events	n = 70/358; % = 19.6	n = 82/348; % = 23.6

Outcome	Baricitinib + remdesivir, N = 515	Remdesivir + placebo, N = 518
Median use of mechanical ventilation or ECMO - With imputation of data for those who died Median (IQR)	20 (9 to 28)	25 (11 to 28)
Median use of mechanical ventilation or ECMO - Among those who did not die Median (IQR)	13 (7 to 24)	16 (6 to 28)
New use of mechanical ventilation or ECMO during trial No of events	n = 46/461; % = 10	n = 70/461; % = 15.2
Serious adverse events No of events	n = 81; % = 16	n = 107; % = 21
Treatment emergent adverse events No of events	n = 207; % = 40.7	n = 238; % = 46.8

Critical appraisal - Baricitinib RoB

Number of recoveries

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable

Median time to recovery

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable

Mortality by day 28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable

Median duration of hospitalisation – with imputation of data for those who died

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable

Median duration of hospitalisation – among those who died

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable

Median days receiving oxygen – with imputation of those who died

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable

Median days receiving oxygen – among those who died

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable

New use of oxygen during trial

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable

Median days of non-invasive ventilation or high flow oxygen – with imputation of use for those who died

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable

Median days of non-invasive ventilation or high flow oxygen – among those who died

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable

New use of non-invasive ventilation or high flow oxygen during trial

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable

Median days of mechanical ventilation or ECMO – with imputation of use for those who died

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable

Median days of mechanical ventilation or ECMO – among those who died

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable

New use of mechanical ventilation or ECMO during trial

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable

Treatment emergent adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable

Serious adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable

Marconi, 2021

Bibliographic Reference	Marconi VC; Ramanan AV; de Bono S; Kartman CE; Krishnan V; Liao R; Piruzeli MLB; Goldman JD; Alatorre-Alexander J; de Cassia Pellegrini R; Estrada V; Som M; Cardoso A; Chakladar S; Crowe B; Reis P; Zhang X; Adams DH; Ely EW; ; Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial.; The Lancet. Respiratory medicine; 2021; vol. 9 (no. 12)

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04421027
Study start date	11-Jun-2020
Study end date	15-Jan-2021
Aim of the study	To evaluate the efficacy and safety of baricitinib in combination with standard care for the treatment of hospitalised adults with COVID-19
Country/geographical location	Argentina, Brazil, Germany, India, Italy, Japan, Mexico, Puerto Rico, Russia, South Korea, Spain, United Kingdom, United States
Population description	1525 patients aged 18 years and over, with symptomatic COVID-19 were randomised for treatment. The mean age of participants was 57.6 years (SD 14.1). Most participants were male 63.1%. A majority of participants, 83.3% had symptoms for at least 7 days before trial enrolment. Most of the participants were also receiving systemic corticosteroid treatment (79.3%) and 99.7% of participants had at least one pre-existing co-morbidity.
Inclusion criteria	Hospitalized with coronavirus (SARS-CoV-2) infection, confirmed by polymerase chain reaction (PCR) test or other commercial or public health assay in any specimen, as documented by either of the following: • PCR positive in a sample collected <72 hours prior to randomisation; OR • PCR positive in a sample collected ≥72 hours prior to randomisation (but no more than 14 days prior to randomisation), documented inability to obtain a repeat sample (for example, due to lack of testing supplies, limited testing capacity, results taking >24 hours, etc.) AND • progressive disease suggestive of ongoing SARS-CoV-2 infection. • Requires supplemental oxygen at the time of study entry and at randomisation.

	• Have indicators of risk of progression: at least 1 inflammatory marker >upper limit of normal (ULN) (C reactive protein (CRP) D dimer, lactate dehydrogenase [LDH], ferritin) with at least 1 instance of elevation >ULN within 2 days before study entry.
Exclusion criteria	• Are receiving cytotoxic or biologic treatments (such as tumour necrosis factor [TNF] inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], T-cell or B-cell targeted therapies (rituximab), interferon, or Janus kinase (JAK) inhibitors for any indication at study entry. Note: A washout period 4 weeks (or 5 half-lives, whichever is longer) is required prior to screening. • Have ever received convalescent plasma or intravenous immunoglobulin [IVIg]) for COVID-19. • Have received high dose corticosteroids at doses >20 mg per day (or prednisone equivalent) administered for ≥14 consecutive days in the month prior to study entry. • Strong inhibitors of OAT3 (such as probenecid) that cannot be discontinued at study entry. • Have received neutralizing antibodies, such as bamlanivimab, casirivimab and imdevimab for COVID-19. • Have diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only, no screening tests required). • Suspected serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking investigational product. • Have received any live vaccine within 4 weeks before screening or intend to receive a live vaccine during the study. Note: Use of non-live (inactivated) vaccinations is allowed for all participants. • Require invasive mechanical ventilation, including extracorporeal membrane oxygenation (ECMO) at study entry. • Current diagnosis of active malignancy that, in the opinion of the investigator, could constitute a risk when taking investigational product. • Have a history of venous thromboembolism (VTE) (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) within 12 weeks prior to randomisation or have a history of recurrent (>1) VTE (DVT/PE). • Anticipated discharge from the hospital, or transfer to another hospital (or another unit), which is not a study site within 72 hours after study entry. • Have neutropenia (absolute neutrophil count <1000 cells/microliters). Have lymphopenia (absolute lymphocyte count <200 cells/microliters). • Have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 times ULN. • Estimated glomerular filtration rate (eGFR) (Modification of Diet in Renal Disease [MDRD]) <30 millilitre/minute/1.73 meters squared. • Have a known hypersensitivity to baricitinib or any of its excipients. Are currently enrolled in any other clinical study involving an investigation product or any other type of medical research judged not to be scientifically or

	medically compatible with this study. Note: The participant should not be enrolled (started) in another clinical trial for the treatment of COVID-19 or SARS CoV-2 through Day 28. • Are pregnant or intend to become pregnant or breastfeed during the study. • Are using or will use extracorporeal blood purification (EBP) device to remove proinflammatory cytokines from the blood such as a cytokine absorption or filtering device, for example, CytoSorb® • Are, in the opinion of the investigator, unlikely to survive for at least 48 hours after screening.
Intervention dosage (loading)	Baricitinib: 4mg per day (2mg tablets)
Intervention dosage (maintenance)	Not reported
Intervention scheduled duration	For 14 days or until discharge from hospital, whichever occurred first
Intervention actual duration	Varied
Intervention route of administration	Oral or via nasogastric tube
Comparator (where applicable)	Placebo and standard care
Methods for population selection/allocation	Participants were enrolled by study investigators (or a designee). Randomisation was facilitated by a computer-generated random sequence using an interactive web response system and was permitted by a study investigator or designee to allocate participants 1:1 to the baricitinib group or the placebo group. Participants were stratified according to the following baseline factors: disease severity (NIAID-OS 4, 5, or 6), age (<65 or ≥65 years), region (Europe, USA, or the rest of the world), and use of corticosteroids for primary study condition (yes or no). Participants, study staff, and investigators were masked to the study assignment. An independent, external data monitoring committee oversaw the study and evaluated unblinded interim data for efficacy, futility, and safety. An independent, blinded, clinical event committee adjudicated potential venous thromboembolic events and deaths.
Methods of data analysis	Power calculations assumed that 75% of the total α was allocated to population 1, and that 60% of the participants were taking systemic corticosteroids at baseline. Two scenarios were considered. In the first, both population 1 and population 2 had a true treatment effect size of 7·5% (power 81%). In the second, population 1 had a true effect size of 4% and population 2 had an assumed effect size of 7·5% (power 54%). In the final (pre-unmasking) version of the

	statistical analysis plan, the total α was amended to be allocated 99% to population 1, recognising that population 2 was much smaller than previously anticipated and unlikely to succeed. To control the overall family-wise type I error rate at a two-sided α level of 0·05, a graphical testing procedure was used to test the primary and key secondary endpoint results in a hierarchical manner. For example, for the first key secondary analysis in the hierarchy (the proportion of participants with ≥1-point improvement on the NIAID-OS or live discharge from hospital at day 14) to be considered multiplicity-controlled significant, it was necessary to achieve statistical significance in the population 1 primary endpoint analysis. Each subsequent test relied on succeeding in the preceding test in the hierarchy (appendix 6 p 14). In this report we use the term "nominal p value" when referring to key secondary endpoints for which p values were direct from the prespecified statistical models and were unadjusted for multiplicity. Efficacy data were analysed in the intention-to-treat population, defined as all randomly allocated participants. Logistic regression was used for dichotomous endpoints, proportional odds models were used for ordinal endpoints, ANOVA was used for continuous endpoints, and mixed-effects models of repeated measures were used to assess continuous endpoints over time. Log-rank tests and hazard ratios (HRs) from Cox proportional hazard models were used for time-to-event analyses. These statistical models were adjusted for treatment and baseline stratification factors. Prespecified subgroup analyses for the primary and selected key secondary endpoints evaluated treatment effect across the following subgroups: baseline severity (NIAID-OS score 4, 5, or 6), baseline systemic corticosteroid use (yes or no), baseline remdesivir use (yes or no), geographical region (Europe, USA, or the rest of the world), sex, disease duration at baseline (<7 days or ≥7 days), and age at baseline (<65 years or ≥65 years). Safety analyses included all randomly allocated participants who received at least one dose of study drug and who were not lost to follow-up before the first post-baseline visit. Adverse events were inclusive of the 28-day treatment period. Statistical tests of treatment effects were done at a two-sided significance level of 0·05, unless otherwise stated (i.e., for the graphical multiple testing strategy). Statistical analyses were done with SAS (version 9.4 or higher) or R.
Attrition/loss to follow-up	20 lost to follow up in placebo group, 22 lost to follow up in treatment arm
Source of funding	Eli Lilly and Company
Study limitations (Author)	Heterogeneity of treatments across study regions and centres could affect outcomes for patients on standard care. The measurement of clinical status by ordinal scales to represent disease progression was a limitation as thresholds for disease progression vary.
Study limitations (Reviewer)	Due to the wide range of geographical regions participating in the trial, the levels and protocols for standard care may have had an impact on outcomes.
Other details	Peer-reviewed published manuscript and forms the phase 3 trial of COV-BARRIER.

Study arms

Baricitinib (N = 764)

Placebo (N = 761)

Characteristics

Arm-level characteristics

Characteristic	Baricitinib (N = 764)	Placebo (N = 761)
Age Mean (SD)	57.8 (14.3)	57.5 (13.8)
Male No of events	n = 490; % = 64	n = 473; % = 62
Female No of events	n = 274; % = 36	n = 288; % = 38
Hispanic or Latino No of events	n = 54; % = 33	n = 46; % = 29
Not Hispanic or Latino	n = 92; % = 57	n = 94; % = 59

Characteristic	Baricitinib (N = 764)	Placebo (N = 761)
No of events		
Not reported No of events	n = 16; % = 10	n = 18; % = 11
Obesity No of events	n = 250; % = 33	n = 253; % = 33
Diabetes (type 1 and type 2) No of events	n = 224; % = 29	n = 233; % = 31
Chronic respiratory disease No of events	n = 34; % = 4	n = 36; % = 5
Hypertension No of events	n = 365; % = 48	n = 366; % = 48
remdesivir No of events	n = 140; % = 18	n = 147; % = 19
Systemic corticosteroids No of events	n = 612; % = 80	n = 592; % = 78
Dexamethasone No of events	n = 566; % = 92	n = 533; % = 90

Outcomes

Baricitinib vs Placebo

Outcome	Baricitinib, , N = 764	Placebo, N = 761
Progression to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation- All randomised participants Nominal	27.8	30.5
Progression to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation- Participants who required oxygen supplementation and were not receiving systemic corticosteroids for COVID-19 at baseline Nominal	28.9	27.1
All-cause mortality No of events	n = 62; % = 8	n = 100; % = 13
Median time to recovery Median (IQR)	10 (9 to 11)	11 (10 to 12)
Duration of hospitalisation Mean (SD)	12.9 (0.4)	13.7 (0.4)
Number of ventilator free days Mean (SD)	24.5 (0.39)	23.7 (0.39)
Treatment emergent adverse event No of events	n = 334; % = 45	n = 334; % = 44

Outcome	Baricitinib, , N = 764	Placebo, N = 761
Death due to adverse event No of events	n = 12; % = 2	n = 31; % = 4
Serious adverse event No of events	n = 110; % = 15	n = 135; % = 18

Critical appraisal - Baricitinib RoB

Progression to high flow O2, NIV, IMV or death by day 28 – Population 1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

Progression to high flow O2, NIV, IMV or death by day 28 – Population 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

All-cause mortality

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

Median time to recovery

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

Duration of hospitalisation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

Number of ventilator free days

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

Treatment emergent adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

Serious adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

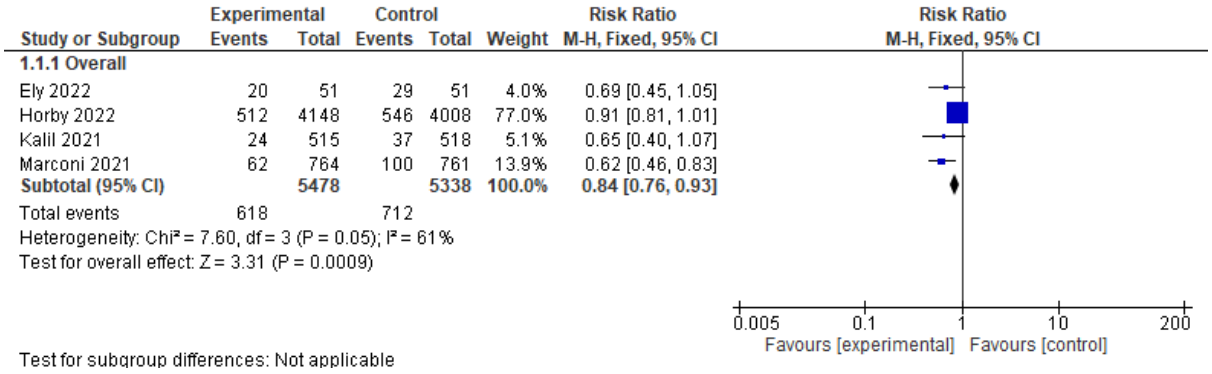
Death due to adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns

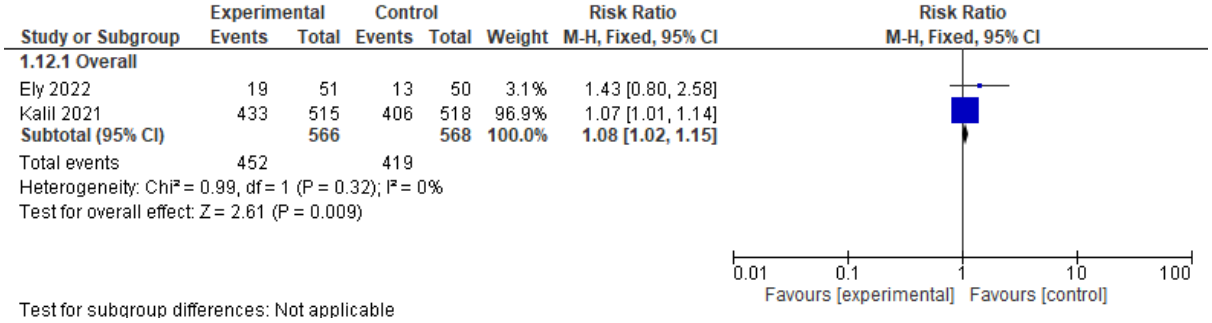
Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable

Appendix G: Forest Plots

All-cause mortality



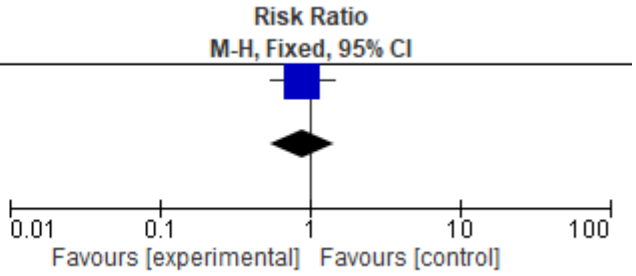
Number of patients who recovered



Progression to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation including ECMO or death by day 29

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marconi 2021	28	764	31	761	100.0%	0.90 [0.55, 1.48]
Total (95% CI)		**764**		**761**	**100.0%**	**0.90 [0.55, 1.48]**
Total events	28		31			

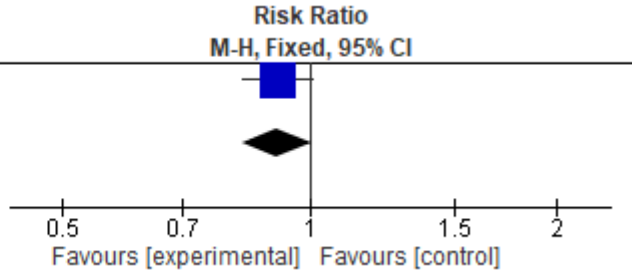
Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)



Progression to invasive mechanical ventilation or death

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Horby 2022	631	4014	670	3891	100.0%	0.91 [0.83, 1.01]
Total (95% CI)		**4014**		**3891**	**100.0%**	**0.91 [0.83, 1.01]**
Total events	631		670			

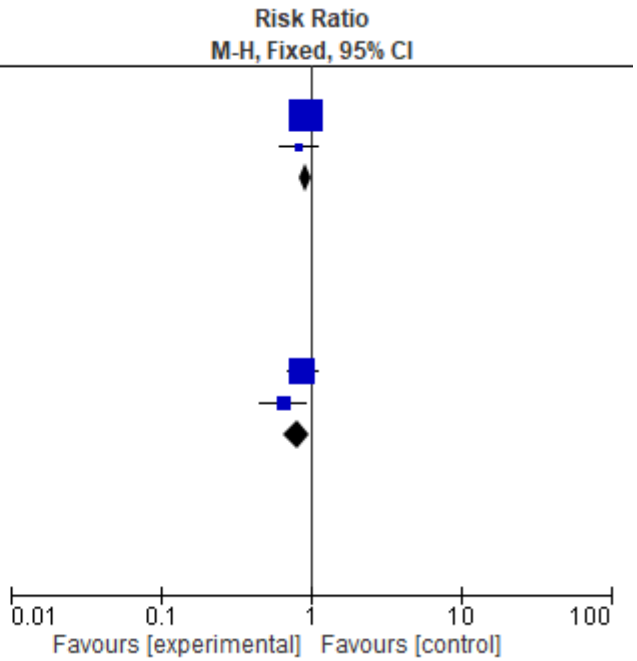
Heterogeneity: Not applicable
Test for overall effect: Z = 1.80 (P = 0.07)



Progression to ventilation

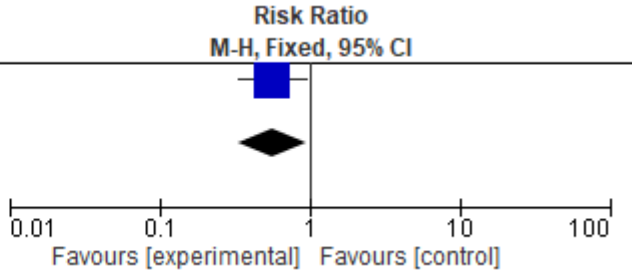
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.17.1 Non-invasive ventilation						
Horby 2022	585	2998	623	2980	88.3%	0.93 [0.84, 1.03]
Kalil 2021	70	358	82	348	11.7%	0.83 [0.63, 1.10]
Subtotal (95% CI)		**3356**		**3328**	**100.0%**	**0.92 [0.84, 1.01]**
Total events	655		705			
Heterogeneity: Chi² = 0.59, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 1.69 (P = 0.09)						
1.17.2 Invasive mechanical ventilation						
Horby 2022	131	2998	148	2980	68.0%	0.88 [0.70, 1.11]
Kalil 2021	46	461	70	461	32.0%	0.66 [0.46, 0.93]
Subtotal (95% CI)		**3459**		**3441**	**100.0%**	**0.81 [0.67, 0.98]**
Total events	177		218			
Heterogeneity: Chi² = 1.88, df = 1 (P = 0.17); I² = 47%						
Test for overall effect: Z = 2.18 (P = 0.03)						

Test for subgroup differences: Chi² = 1.43, df = 1 (P = 0.23), I² = 30.3%



Progression to use of oxygen

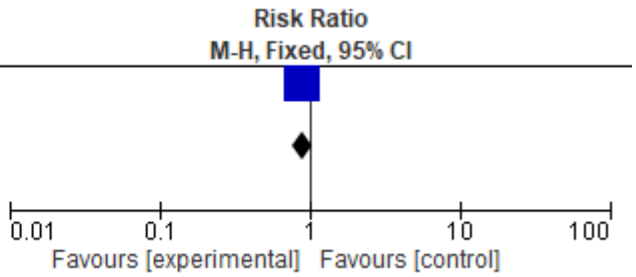
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kalil 2021	16	70	29	72	100.0%	0.57 [0.34, 0.95]
Total (95% CI)		**70**		**72**	**100.0%**	**0.57 [0.34, 0.95]**
Total events	16		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.16 (P = 0.03)						



Adverse events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Horby 2022	323	4148	345	4008	100.0%	0.90 [0.78, 1.05]
Total (95% CI)		**4148**		**4008**	**100.0%**	**0.90 [0.78, 1.05]**
Total events	323		345			

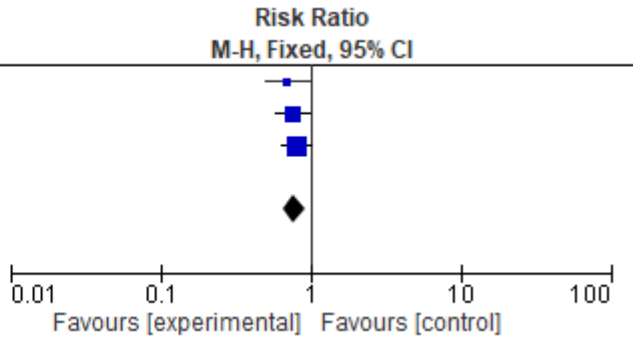
Heterogeneity: Not applicable
Test for overall effect: Z = 1.35 (P = 0.18)



Serious adverse event

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ely 2022	25	50	35	49	12.8%	0.70 [0.50, 0.97]
Kalil 2021	81	507	107	509	38.6%	0.76 [0.59, 0.99]
Marconi 2021	110	750	135	752	48.7%	0.82 [0.65, 1.03]
Total (95% CI)		**1307**		**1310**	**100.0%**	**0.78 [0.67, 0.91]**
Total events	216		277			

Heterogeneity: $Chi^2 = 0.61$, df = 2 (P = 0.74); $I^2 = 0\%$
Test for overall effect: Z = 3.10 (P = 0.002)

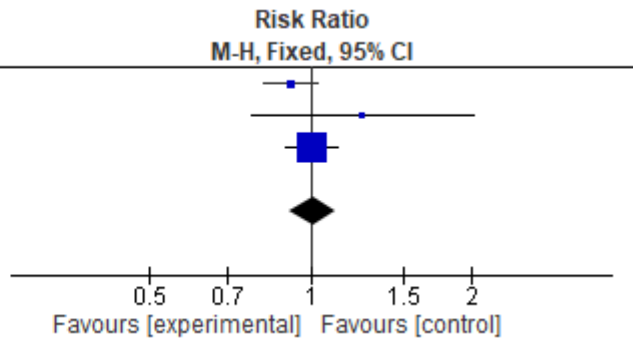


Treatment emergent adverse events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ely 2022	44	50	47	49	11.6%	0.92 [0.82, 1.03]
Kalil 2021	35	508	28	509	6.8%	1.25 [0.77, 2.03]
Marconi 2021	334	750	334	752	81.6%	1.00 [0.90, 1.12]
Total (95% CI)		**1308**		**1310**	**100.0%**	**1.01 [0.91, 1.12]**
Total events	413		409			

Heterogeneity: Chi² = 3.34, df = 2 (P = 0.19); I² = 40%

Test for overall effect: Z = 0.19 (P = 0.85)



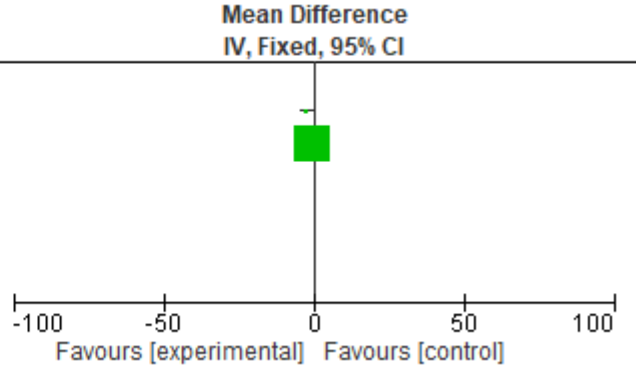
Duration of hospitalisation

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.9.1 Overall								
Ely 2022	23.7	7.1	51	26.1	3.9	50	0.0%	-2.40 [-4.63, -0.17]
Marconi 2021	12.9	0.4	764	13.7	0.4	761	100.0%	-0.80 [-0.84, -0.76]
Subtotal (95% CI)			**815**			**811**	**100.0%**	**-0.80 [-0.84, -0.76]**

Heterogeneity: Chi² = 1.98, df = 1 (P = 0.16); I² = 49%

Test for overall effect: Z = 39.08 (P < 0.00001)

Test for subgroup differences: Not applicable



Appendix H: GRADE profiles

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Standard Care	With baracitinib		Risk with Standard Care	Risk difference with baracitinib
All cause mortality - Overall											
10816 (4 RCTs)	not serious	serious[a]	not serious	not serious	none	Moderate	712/5338 (13.3%)	618/5478 (11.3%)	**RR 0.84** (0.76 to 0.93)	133 per 1,000	**21 fewer per 1,000** (from 32 fewer to 9 fewer)
Number of patients who recovered											
1134 (2 RCTs)	not serious	not serious	serious[b]	not serious	none	Moderate	419/568 (73.8%)	452/566 (79.9%)	**RR 1.08** (1.02 to 1.15)	738 per 1,000	**59 more per 1,000** (from 15 more to 111 more)
Progression to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation including ECMO or death by day 29											
1525 (1 RCT)	not serious	not serious	serious[b]	serious[c]	none	Low	31/761 (4.1%)	28/764 (3.7%)	**RR 0.90** (0.55 to 1.48)	41 per 1,000	**4 fewer per 1,000** (from 18 fewer to 20 more)
Progression to invasive mechanical ventilation or death											

Certainty assessment							Summary of findings				
7905 (1 RCT)	not serious	not serious	not serious	serious[c]	none	Moderate	670/3891 (17.2%)	631/4014 (15.7%)	**RR 0.91** (0.83 to 1.01)	172 per 1,000	**15 fewer per 1,000** (from 29 fewer to 2 more)

Progression to use of oxygen

142 (1 RCT)	not serious	not serious	serious[b]	not serious	none	Moderate	29/72 (40.3%)	16/70 (22.9%)	**RR 0.57** (0.34 to 0.95)	403 per 1,000	**173 fewer per 1,000** (from 266 fewer to 20 fewer)

Progression to non-invasive ventilation

6684 (2 RCTs)	not serious	not serious	not serious	serious[c]	none	Moderate	705/3328 (21.2%)	655/3356 (19.5%)	**RR 0.92** (0.84 to 1.01)	212 per 1,000	**17 fewer per 1,000** (from 34 fewer to 2 more)

Progression to invasive mechanical ventilation

6900 (1 RCT)	not serious	not serious	not serious	not serious	none	High	218/3441 (6.3%)	177/3459 (5.1%)	**RR 0.81** (0.67 to 0.98)	63 per 1,000	**12 fewer per 1,000** (from 21 fewer to 1 fewer)

Adverse events

8156 (1 RCT)	not serious	not serious	not serious	serious[c]	none	Moderate	345/4008 (8.6%)	323/4148 (7.8%)	**RR 0.90** (0.78 to 1.05)	86 per 1,000	**9 fewer per 1,000** (from 19 fewer to 4 more)

Serious adverse event

Certainty assessment							Summary of findings				
2617 (3 RCTs)	not serious	not serious	not serious	serious[b]	none	Moderate	277/1310 (21.1%)	216/1307 (16.5%)	**RR 0.78** (0.67 to 0.91)	211 per 1,000	**47 fewer per 1,000** (from 70 fewer to 19 fewer)

Treatment emergent adverse event

2618 (3 RCTs)	not serious	not serious	serious[b]	serious[c]	none	Low	409/1310 (31.2%)	413/1308 (31.6%)	**RR 1.01** (0.91 to 1.12)	312 per 1,000	**3 more per 1,000** (from 28 fewer to 37 more)

Duration of hospitalisation - Overall

1626 (2 RCTs)	not serious	not serious	serious[b]	not serious	none	Moderate	811	815	-		MD **0.8 lower** (0.84 lower to 0.76 lower)

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

Explanations

a. I squared >50%
b. Variation in standard care protocols between participating centres which could affect outcomes with treatment. Lack of reporting on vaccination status of participants
c. Confidence interval includes line of no effect