Effects of Janus kinase inhibitors in adults admitted to hospital due to COVID-19: a systematic review and individual participant data meta-analysis of randomised clinical trials

Alain Amstutz, Stefan Schandelmaier, Hannah Ewald, Benjamin Speich, Johannes M Schwenke, Christof M Schönenberger, Stephan Schobinger, Thomas Agoritsas, Kay M Tomashek, Seema Nayak, Mat Makowski, Alejandro Morales-Ortega, David Bernal-Bello, Giovanni Pomponio, Alessia Ferrarini, Monireh Ghazaeian, Frances Hall, Simon Bond, María Teresa García-Morales, María Jiménez-González, José R Arribas, Patricia O Guimarães, Caio A M Tavares, Otavio Berwanger, Yazdan Yazdanpanah, Victoria C Simensen, Karine Lacombe, Maya Hites, Florence Ader, Evelina Tacconelli, France Mentré, Drifa Belhadi, Clément R Massonnaud, Cédric Laouénan, Alpha Diallo, Aliou Baldé, Lambert Assoumou, Dominique Costagliola, Erica Ponzi, Corina S Rueegg, Inge C Olsen, Marius Trøseid, Matthias Briel

Summary

Background Evidence from randomised clinical trials (RCTs) of Janus kinase (JAK) inhibitors—compared with usual care or placebo—in adults treated in hospital for COVID-19 is conflicting. We aimed to evaluate the benefits and harms of JAK inhibitors compared with placebo or usual care and whether treatment effects differed between prespecified participant subgroups.

Methods For this systematic review and individual participant data meta-analysis (IPDMA), we searched Medline via Ovid, Embase via Elsevier, the Cochrane Central Register of Controlled Trials, the Cochrane COVID-19 Study Register, and the COVID-19 L·OVE Platform, including backward and forward citation searching (last search Nov 28, 2024), for RCTs (unpublished or published in any format and any language) that randomly assigned adults (aged ≥16 years) admitted to a hospital due to COVID-19 to receive either a JAK inhibitor (any type) or no JAK inhibitor (ie, received site-specific standard of care with or without placebo), and requested individual participant data (IPD) from the original trial teams. The primary outcome was all-cause mortality at day 28 after random assignment. We used two-stage meta-analyses adjusting for age and respiratory support, and pooled estimates using random-effects models. The assessment of individual-level effect modifiers was based solely on within-trial information and continuous modifiers were investigated as both linear and non-linear interactions. We used the Instrument for Assessing the Credibility of Effect Modification Analyses to appraise the subgroup analyses and the Grading of Recommendations Assessment, Development, and Evaluation approach to adjudicate the certainty of evidence. Grade 3 or 4 adverse events and serious adverse events by day 28, and adverse events of special interest within 28 days, were assessed among secondary outcomes. This study was registered with PROSPERO (CRD42023431817).

Findings We identified 16 eligible trials. IPD were obtained from 12 trials, corresponding to 12 902 adults admitted to hospital between May, 2020, and March, 2022. These trials represented 12 902 [96·1%] of 13 423 participants from all eligible trials worldwide. Seven trials evaluated baricitinib, three evaluated tofacitinib, and two evaluated ruxolitinib. Overall, 755 (11·7%) of 6465 participants in the JAK inhibitor group died by day 28 compared with 805 (13·2%) of 6108 participants in the no JAK inhibitor group (adjusted odds ratio [aOR] 0·67 [95% CI 0·55–0·82]; high-certainty evidence; 39 fewer per 1000 [95% CI 55 fewer to 21 fewer]). JAK inhibitors decreased the need for new mechanical ventilation or other respiratory support and allowed for faster discharge from hospital by about 1 day. We observed fewer grade 3 and 4 adverse events and serious adverse events in the JAK inhibitor group (14 fewer per 1000 [95% CI 24 fewer to 4 fewer]; moderate-certainty evidence). The rates of adverse events of special interest were similar across both groups. No credible subgroup effect on mortality at day 28 was found for ventilation status, type of JAK inhibitor, presence of comorbidities, timing of treatment initiation after symptom onset, C-reactive protein concentration, or concomitant use of dexamethasone or tocilizumab. We found a moderately credible effect modification by age, with younger participants showing larger relative treatment effects than older participants, but similar absolute treatment effects due to higher baseline risk for older participants.

Interpretation This IPDMA of RCTs in adults admitted to hospital due to COVID-19 found that JAK inhibitors reduced mortality across all levels of respiratory support, independent of dexamethasone or tocilizumab, and probably decreased serious and severe adverse events compared with no JAK inhibitors.

Funding This project has received funding from the EU's Horizon 2020 research and innovation programme under grant agreement number 101015736.

Lancet Respir Med 2025

Published Online May 13, 2025 https://doi.org/10.1016/S2213-2600(25)00055-4

See Online/Comment https://doi.org/10.1016/S2213-2600(25)00081-5

CLEAR Methods Center, Division of Clinical Epidemiology, Department of Clinical Research, University Hospital Basel and University of Basel, Basel, Switzerland (A Amstutz PhD, S Schandelmaier PhD, B Speich PhD, J M Schwenke MSc, C M Schönenberger MD, M Briel PhD); **Oslo Center for Biostatistics and Epidemiology** (A Amstutz, E Ponzi PhD, C S Rueegg PhD, I C Olsen PhD), **Department of Research Support for Clinical Trials** (E Ponzi, C S Rueegg, I C Olsen), **and Section for Clinical Immunology and Infectious Diseases** (Prof M Trøseid MD), **Oslo University Hospital, Oslo, Norway; Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK** (A Amstutz); **School of Public Health, University College Cork, Cork, Ireland** (S Schandelmaier); **MTA-PTE Lendület Momentum Evidence in Medicine Research Group, Medical School, University of Pécs, Pécs, Hungary** (S Schandelmaier); **University Medical Library Basel, University of Basel, Basel, Switzerland** (H Ewald PhD); **Patient representative, Bern, Switzerland** (S Schobinger MD); **Division of General Internal Medicine, University Hospital Geneva, University of Geneva, Geneva, Switzerland** (Prof T Agoritsas PhD); **MAGIC Evidence Ecosystem**

Foundation, Oslo, Norway (Prof T Agoritsas); **Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada** (Prof T Agoritsas, M Briel); **National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA** (K M Tomashek MD, S Nayak MD); **The EMMES Corporation, Rockville, MD, USA** (M Makowski PhD); **Hospital Universitario de Fuenlabrada, Madrid, Spain** (A Morales-Ortega PhD, D Bernal-Bello PhD); **Clinica Medica, Ospedali Riuniti di Ancona, Ancona, Italy** (G Pomponio MD); **Gastroenterologia ed Endoscopia Digestiva, Ospedali Riuniti Marche Nord, Fano, Italy** (A Ferrarini MD); **Pharmaceutical Research Center, Department of Clinical Pharmacy, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran** (M Ghazaeian PharmD); **Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK** (F Hall PhD, S Bond PhD); **La Paz University Hospital and Spanish Clinical Research Network, Madrid, Spain** (M T García-Morales MSc, M Jiménez-González MSc); **Infectious Diseases Unit, Internal Medicine Department, La Paz University Hospital, IdiPAZ, Madrid, Spain** (Prof J R Arribas MD); **Centro de Investigación Biomédica en Red de Enfermedades Infecciosas, Madrid, Spain** (Prof J R Arribas); **Hospital Israelita Albert Einstein, São Paulo, Brazil** (P O Guimarães PhD, C A M Tavares PhD); **Geriatric Cardiology Unit, Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil** (C A M Tavares); **The George Institute for Global Health, London, UK** (O Berwanger PhD); **Faculty of Medicine, Imperial College London, London, UK** (O Berwanger); **Université Paris Cité, Inserm, IAME, Paris, France** (Prof Y Yazdanpanah PhD, Prof F Mentré PhD, D Belhadi PhD, C R Massonnaud MD, Prof C Laouénan PhD); **Service**

Research in context

Evidence before this study

Clinical guidelines have interpreted the evidence from randomised clinical trials (RCTs) and aggregate data meta-analyses assessing the effects of Janus kinase (JAK) inhibitors in adults hospitalised for COVID-19 differently. Before this study, we systematically searched Medline and Embase (from inception to Aug 10, 2023) for meta-analyses using terms for JAK inhibitors, COVID-19, and randomised clinical trials based on existing filters, with no restrictions regarding language or geography. The most recent and largest meta-analyses of aggregate data at the time were published by WHO in January, 2023, and by Cochrane in 2022. These meta-analyses were based on four and six RCTs, respectively, and estimated an odds ratio of 0·83 (95% CI 0·74–0·93) and a risk ratio of 0·72 (95% CI 0·57–0·91) for mortality by day 28, respectively. The Cochrane review identified another nine registered RCTs that had surpassed their estimated completion dates, yet no data were available at the time. Both reviews emphasised the need for more high-quality evidence regarding the effects of JAK inhibitors across different disease severity subgroups, their short-term and long-term safety profile, and the effect of combining different immunomodulatory treatments.

Added value of this study

This updated systematic review included 12 RCTs and, to our knowledge, provides the first individual participant data meta-analysis (IPDMA) of the effects of JAK inhibitors in adults with COVID-19. When comparing JAK inhibitors with no JAK inhibitors, the results showed a significant survival benefit (ie, lower mortality rate by day 28 and day 60, and longer time to death), decreased need for new mechanical ventilation or other respiratory support, faster discharge from hospital by about 1 day, and evidence for fewer severe or serious adverse events with JAK inhibitors. Subgroup analyses found no credible effect modification by concomitant use of other immunomodulatory treatments (dexamethasone and tocilizumab), level of respiratory support, comorbidities, C-reactive protein (CRP) concentration, time of JAK inhibitor initiation after COVID-19 symptom onset, SARS-CoV-2 vaccination, and type of JAK inhibitor used. We found a moderately credible effect modification by age, with younger participants showing larger relative treatment effects than older participants, but similar absolute treatment effects due to higher baseline risk for older participants. The subgroup analysis could refute a hypothesis raised in a previous underpowered trial that participants vaccinated against SARS-CoV-2 who received a JAK inhibitor had more serious adverse events than unvaccinated participants.

Implications of all the available evidence

Our IPDMA presents the most comprehensive summary of all existing randomised evidence (including >96% of participants recruited globally on the topic) and subgroup analyses settling the issue of discordant guidelines. JAK inhibitors seem a safe and efficacious treatment option for adults hospitalised with COVID-19 when given in addition to usual care.

Introduction

During the COVID-19 pandemic, several potential therapies were investigated in large-scale randomised clinical trials (RCTs), including Janus kinase (JAK) inhibitors.[1] JAK inhibitors not only block JAK1 and JAK2 enzymes, which play a pivotal role in inflammatory processes, but also inhibit other protein kinases that are involved in SARS-CoV-2 cell entry.[2] Therefore, JAK inhibitors represented a promising treatment candidate for COVID-19, particularly for the inflammatory phase of the disease. Baricitinib, ruxolitinib, and tofacitinib were the most frequently evaluated JAK inhibitors in RCTs, yielding different results across individual trials.[3–14]

The most recent meta-analysis of aggregate data by WHO, published in January, 2023,[15] along with the 2022 Cochrane systematic review,[16] both examining JAK inhibitors for the treatment of COVID-19, are based on four to six RCTs.[4,7,8,12–14] Both meta-analyses emphasised the need for more high-quality evidence in several areas: the effects of JAK inhibitors across different disease severity subgroups, their short-term and long-term safety profile, and the effect of combining different immunomodulatory treatments against COVID-19. Moreover, the Cochrane systematic review identified at least another nine registered RCTs, not part of their review, that had passed their estimated completion dates and could provide additional evidence.

WHO's Clinical Management of COVID-19: Living Guideline recommended baricitinib for patients with severe or critical COVID-19, which could be combined with corticosteroids and IL-6 receptor blockers (ie, tocilizumab and sarilumab).[15] Clinical guidelines published by the US National Institutes of Health and the Infectious Diseases Society of America have interpreted the evidence differently.[17,18] Due to uncertainty in the available evidence and a potential harm (eg, major adverse cardiovascular events, cancer, and venous thromboembolism) of tofacitinib,[19] these clinical guidelines did not issue a class-wide recommendation for JAK inhibitors.[15,17,18] Similarly, there are different interpretations among regulators, with the US Food and Drug Administration (FDA) having approved baricitinib for the treatment of COVID-19 in patients who are admitted to hospital,[20] but the application having been withdrawn at the European Medicines Agency (EMA) due to insufficient evidence.[21]

An individual participant data meta-analysis (IPDMA) has advantages over aggregate data meta-analysis through standardisation of covariates, outcomes, and handling of missing data across trials, and consistently adjusting

for baseline differences across trials.[22] Additionally, an IPDMA can model individual-level interactions directly within studies, providing substantially greater power and avoiding ecological bias, when compared with a meta-regression of aggregate data across studies.[23–25]

To date, no IPDMA has been conducted to assess the treatment effect of JAK inhibitors to treat adults admitted to hospital due to COVID-19. We conducted a systematic review of all available RCTs on this topic to evaluate the benefits and harms of JAK inhibitors and potential subgroup differences using IPDMA methods.

Methods

Protocol registration, reporting, and methods guidance

This study was registered with PROSPERO (CRD42023431817). The results are reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (PRISMA-IPD) checklist, including its extensions for the search part of the study.[26–28] We closely followed guidance of the Cochrane Handbook for Systematic Reviews of Interventions[29] and the Individual Participant Data Meta-Analysis: A Handbook for Healthcare Research.[30] We set up a dedicated homepage to transparently share project progress and analysis code, and to regularly update on the data sharing process of all eligible trials.

Search strategy and selection criteria

In this systematic review and IPDMA, we included RCTs (unpublished or published in any format and any language) that randomly assigned adults (aged ≥16 years) admitted to a hospital due to COVID-19 to receive either a JAK inhibitor (any type) or no JAK inhibitor (ie, received site-specific standard of care with or without placebo).

We searched Medline via Ovid, Embase via Elsevier, and the Cochrane Central Register of Controlled Trials using terms for JAK inhibitors and COVID-19 based on existing filters.[16] For Medline and Embase, we added a Cochrane RCT filter.[31,32] Additionally, we searched the Cochrane COVID-19 Study Register and the COVID-19 L·OVE Platform and conducted systematic citation searching (backward and forward)[28] based on all included references after our updated search, using the CitationChaser software.[33] We last updated the search on Nov 28, 2024. All retrieved references were exported to EndNote 21 (version 21.2, Clarivate Analytics, Philadelphia, PA, USA) and database duplicates removed using the Deduklick algorithm[34] and Covidence. The detailed search strategy is available in the appendix (pp 3–10).

Each title and abstract were independently assessed for potential eligibility by two of three reviewers (AA, BS, or CSR). If either reviewer judged a study as potentially relevant based on the title or abstract, the full text was obtained and independently assessed by two further reviewers. Disagreements were resolved by discussion and, if necessary, by involving a third reviewer (MB).

Data collection

For potentially eligible RCTs, we requested the trial protocol to conduct a final eligibility check and the individual participant data (IPD). If the trial team did not respond after three attempts via email, we tried to contact the chief investigator by telephone. We checked the provided IPD against published results by reconstructing the original primary analysis. Where necessary, we discussed and resolved discrepancies directly with the corresponding study team.

Outcomes and effect modifiers

The primary outcome was mortality at 28 days after random assignment, combining data collected during treatment in hospital (in-hospital mortality) and after hospital discharge (out-of-hospital mortality). The secondary outcomes were: (1) mortality at day 60; (2) days to death within 60 days; (3) the need for new mechanical ventilation or death within 28 days; (4) clinical status at day 28 on an ordinal scale based on the WHO clinical progression scale;[35] (5) days until discharge or reaching discharge criteria up to day 28 (defined as reaching level 1 of the ordinal scale based on the WHO clinical progression scale); (6) viral clearance (participants with undetectable SARS-CoV-2 PCR) up to day 5; (7) viral clearance up to day 10; (8) viral clearance up to day 15; (9) quality of life at day 28; (10) number of participants with an adverse event (grade 3 and 4) or serious adverse event, except death, by day 28; (11) adverse events of special interest within 28 days, defined as thromboembolic events, secondary infections, reactivation of chronic infection (ie, tuberculosis, herpes simplex, cytomegalovirus, herpes zoster, and hepatitis B), serious cardiovascular and cardiac events, events related to signs of bone marrow suppression (ie, anaemia, lymphocytopenia, thrombocytopenia, and pancytopenia), malignancy, gastrointestinal perforation, and liver dysfunction or hepatotoxicity (grade 3 or 4). Detailed definitions of the outcomes are available in the appendix (pp 18–19).

We prespecified, as per study protocol (PROSPERO CRD42023431817), six potential effect modifiers for mortality at day 28. The study team, consisting of clinicians, statisticians, a patient representative, and a WHO treatment guideline representative, defined these modifiers based on the pathophysiology of acute COVID-19,[1] the mechanism of action of JAK inhibitors, and existing evidence from individual RCTs on the topic.[3–5,7,8,10,12–14] The study team considered the direction of effect modification on relative scales. First, we hypothesised that JAK inhibitors would have a larger relative effect on mortality in participants who received more extensive respiratory support (eg, high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation) compared with those who received no or only low-flow oxygen. Second, we considered that younger participants (analysed continuously, with age categorised as <70 years *vs*

de Maladies Infectieuses et Tropicales, Hôpital Bichat, AP-HP, Paris, France (Prof Y Yazdanpanah); **Department of Vaccines and Immunisation, Division of Infectious Disease Control, Norwegian Institute of Public Health, Oslo, Norway** (V C Simensen MD); **Sorbonne Université, Inserm, Institut Pierre-Louis d'Épidémiologie et de Santé Publique, Paris, France** (K Lacombe PhD, D Costagliola PhD); **AP-HP, Hôpital Saint-Antoine, Service de Maladies Infectieuses et Tropicales, Paris, France** (K Lacombe, A Baldé PhD, L Assoumou PhD); **Clinic of Infectious Diseases, Hôpital Universitaire de Bruxelles, Université Libre de Bruxelles, Brussels, Belgium** (Prof M Hites MD); **Département des Maladies Infectieuses et Tropicales, Hospices Civils de Lyon, Lyon, France** (Prof F Ader MD); **Centre International de Recherche en Infectiologie, Inserm 1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, École Normale Supérieure de Lyon, Université de Lyon, Lyon, France** (Prof F Ader); **Division of Infectious Diseases, Department of Diagnostics and Public Health, University of Verona, Verona, Italy** (E Tacconelli PhD); **Département d'Épidémiologie, Biostatistique et Recherche Clinique, Hôpital Bichat, AP-HP, Paris, France** (Prof F Mentré, D Belhadi, C R Massonnaud, C Laouénan); **Clinical Trial Safety and Public Health, ANRS Emerging Infectious Diseases, Paris, France** (A Diallo MD); **Clinical Research Safety Department, INSERM, Paris, France** (A Diallo); **Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland** (C S Rueegg); **Institute of Clinical Medicine, University of Oslo, Oslo, Norway** (Prof M Trøseid)

Correspondence to:
Dr Alain Amstutz, CLEAR Methods Center, Division of Clinical Epidemiology, Department of Clinical Research, University Hospital Basel, University of Basel, 4051 Basel, Switzerland
a.amstutz@usb.ch

For the **IPDMA handbook** see https://www.ipdma.co.uk/

For the **JAK inhibitor IPDMA homepage** see https://www.jakinhibitoripdma.org/

For the **Cochrane COVID-19 Study Register** see https://covid-19.cochrane.org/

For the **L·OVE Platform** see https://app.iloveevidence.com/topics

For the **CitationChaser software** see https://estech.shinyapps.io/citationchaser/

For **Covidence** see https://www.covidence.org/

See **Online** for appendix

For **model specifications** see https://github.com/alainamstutz/JAKi-IPDMA/tree/main

For the **R code** see https://github.com/alainamstutz/JAKi-IPDMA/tree/main

≥70 years only as a descriptive cutoff for the forest plot) would show a larger relative effect than older participants. Third, we hypothesised a larger relative effect in participants who started JAK inhibitor treatment later after the onset of COVID-19 symptoms (analysed continuously, with ≤5 days *vs* >5 days and ≤10 days *vs* >10 days used for descriptive purposes in the forest plot) than in those who started earlier. Fourth, we expected a larger relative effect in participants with higher concentrations of C-reactive protein (CRP) than in those with lower concentrations (analysed continuously, with ≥75 mg/L *vs* <75 mg/L used for descriptive purposes in the forest plot). Fifth, we predicted a relative effect modification based on comorbidity status, categorising participants as having no comorbidity, having one comorbidity (but not immunocompromised), having multiple comorbidities (but not immunocompromised), or being immunocompromised, without a hypothesis of the direction of effect modification. Sixth, we considered that concomitant COVID-19 medication (ie, no dexamethasone and no tocilizumab *vs* dexamethasone but no tocilizumab *vs* dexamethasone and tocilizumab *vs* no dexamethasone but tocilizumab) could modify the effect, without a hypothesis of the direction of effect modification. In addition, we prespecified a potential relative effect modification on adverse events by day 28—namely, to test whether there is a larger harm among participants previously vaccinated against SARS-CoV-2 than among those not previously vaccinated.[3] In post-hoc analyses, we conducted two more potential relative effect modifications on adverse events by day 28: across concomitant COVID-19 medications (as defined previously) and across participants at risk for serious adverse events from JAK inhibitors according to the EMA warning.[36] We were not able to explore prognostic effects of SARS-CoV-2 variants of concern because only one trial provided genomic data. Instead, we compared outcomes between trials that recruited in different time periods as a proxy, using a global chi-squared test. We did not adjust analyses of effect modification for multiplicity issues.

Missing data

If an outcome was missing for an entire trial, we excluded this trial from corresponding outcome analyses. If a subgroup covariate for an entire trial was missing (eg, vaccination status), we excluded this trial from corresponding effect modifier analyses. The primary analysis was a complete case analysis under a missing-completely-at-random assumption. However, we explored missingness patterns and conducted a sensitivity analysis using multilevel chained-equations techniques[37,38] under a missing-at-random assumption for the primary outcome (appendix p 11).

Data analysis

All participants were analysed as randomly assigned, adhering to the intention-to-treat principle. We applied an IPDMA two-stage approach.[30,39] In the first stage, we fitted appropriate regression models for each outcome (logistic binomial regression for binary, ordinal regression for ordinal, negative binomial regression for count, Cox regression for time to death, and Fine–Gray regression for time to discharge; detailed model specifications available on GitHub), obtaining a relative treatment effect estimate and its variance for each trial. We decided at the outset of the study to use odds ratios (ORs) as the main measure because we anticipated the pooling of studies from which we would not receive IPD, and because most RCTs report their effects in ORs. We adjusted all models for age (continuous) and respiratory support (categorical) at baseline. We applied Firth's penalisation correction in case of sparse data as per IPDMA recommendation.[30] In the second stage, we combined the estimates across trials in a random-effects model using the inverse-variance method, applied the maximum likelihood estimator for tau-squared, and used the Hartung–Knapp–Sidik–Jonkman approach to derive 95% CIs.[40] In addition, we calculated adjusted cumulative survival curves using pooled logistic regression including 95% CIs obtained from bootstrapping.[41]

To investigate potential effect modification while avoiding aggregation bias[25] (ie, based solely on within-trial information) we adhered to the two-stage approach. In each trial, we separately added the effect modifiers one after the other to the models as an interaction term with the treatment group, while keeping the adjustment variables in the models. We then synthesised the treatment–covariate interaction estimates and their variances in the second stage in a meta-analysis of interactions.[42] Continuous effect modifiers (ie, age, CRP concentration, and days since onset of COVID-19 symptoms) were added as linear treatment interaction terms. For purely descriptive purposes in the subgroup forest plot, we selected clinically meaningful cutoffs that were commonly applied in the individual trials. To explore possible nonlinear interactions, we used the multivariable fractional polynomial interaction approach (appendix p 12).[43,44] Exploratory and sensitivity analyses are outlined in the appendix (p 13).

We used R (version 4.2.3) for all analyses except for the multivariable fractional polynomials interaction analyses, which we did in Stata (version 18.0). p values of less than 0·05 were considered statistically significant. The R code is available on GitHub, where it was collaboratively developed, managed, and shared with IPD providers, including an audit trail of all analyses conducted.

Effect heterogeneity, risk of bias, and publication bias

We assessed heterogeneity of the treatment effect estimates using the I^2 statistic to calculate what proportion of the observed variance reflects variance in true effects rather than sampling error, and tau-squared to assess what the variance of the true effects is. Because I^2 is unsuitable to assess how much the effect size varies (except when it is 0) and tau-squared is hard to

interpret—particularly when the results are ratios, as in the case of this study—we added the prediction interval to evaluate and illustrate how much the true effects vary.[45] We evaluated the risk of bias in duplicate (AA, BS, and JMS) using the Cochrane Risk of Bias 2 tool.[46] Small-study effects that can suggest publication bias were explored using contour-enhanced funnel plots.[47]

Assessments of certainty of evidence and credibility of subgroup effects

We judged the certainty of evidence following the Grading of Recommendations Assessment, Development, and Evaluation approach.[48] The credibility of potential effect modification (defined as a $p_{interaction}$ value of less than 0·1) effects was assessed using the Instrument for Assessing the Credibility of Effect Modification Analyses (ICEMAN).[49] All assessments were conducted in duplicate, by two of three people (ie, AA, SScha, or MB), and discrepancies were discussed and resolved by consensus.

Ethics statement

All included trials obtained individual ethical approval. The Ethics Committee Northwest and Central Switzerland confirmed that no separate ethical approval was necessary for this IPDMA. We drafted and signed a data sharing agreement with each trial sharing IPD according to the legislation of the country of the respective trial sponsor. A description of patient and public involvement is included in the appendix (p 14).

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We identified a total of 2103 records searching the mentioned databases, and 2251 additional records with backward and forward citation searching (figure 1). After removing duplicates and ineligible records, we identified 19 RCTs from which we sought IPD (figure 1). Two RCTs were excluded because they had no full-text publication available and no investigator could be contacted to confirm eligibility. One RCT was excluded because the IPD received did not provide an event for any of our pre-specified outcomes, as per Cochrane handbook guidance.[50] From the remaining 16 eligible trials, which included a total of 13 423 participants, we received IPD for 12 RCTs. The characteristics of the four RCTs that only provided aggregate date are provided in the appendix (p 20).

The 12 trials included 12 902 participants from more than 20 countries admitted to hospital between May 4, 2020, and March 7, 2022 (table 1). Seven trials evaluated baricitinib,[3,4,7,8,9–12] three evaluated tofacitinib,[6,14,51] and two evaluated ruxolitinib.[5,52] Our IPDMA represents 12 902 (96·1%) of 13 423 randomly assigned participants with IPD on this clinical question. The four eligible RCTs without IPD (n=521) were included with aggregate data in a sensitivity analysis for the primary outcome (figure 1).

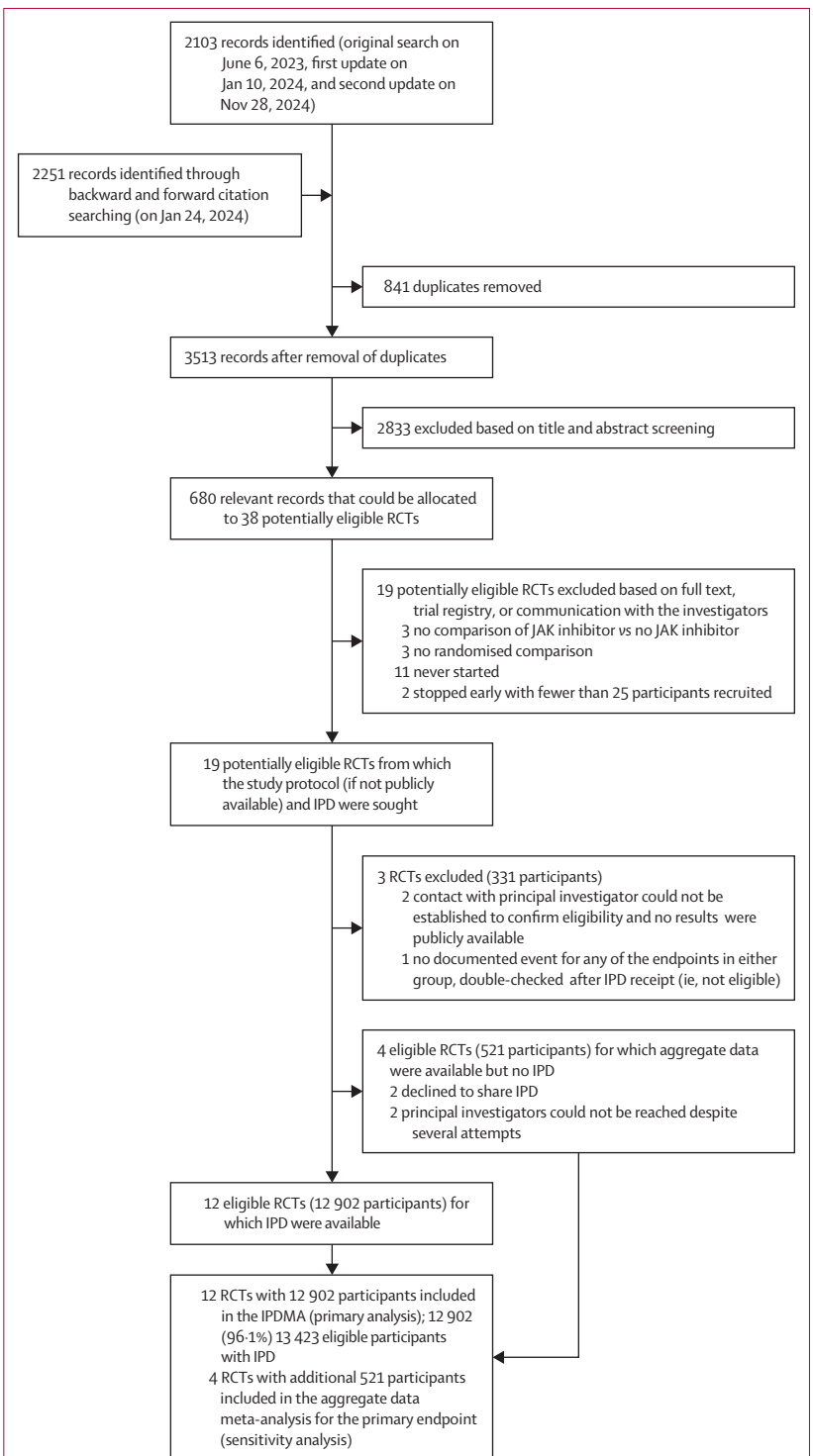


Figure 1: **Study selection**
IPD=individual participant data. IPDMA=individual participant data meta-analysis. JAK=Janus kinase. RCT=randomised clinical trial.

	Country	Sponsor	Funding	Number of randomly assigned participants	Number of women (%); number of men (%)	Median age (IQR), years	Recruitment period	Patient population	Interventions	Control	Follow-up time
ACTT-2[12]	Denmark, Japan, Mexico, Singapore, South Korea, Spain, UK, and USA	Public	Public; drugs and placebo provided by industry (Eli Lilly)	1033	381 (36·9%); 652 (63·1%)	56 (43–67)	May, 2020, to July, 2020	Adults admitted to hospital due to COVID-19 with any severity of disease	Baricitinib 4 mg once daily (orally or nasogastrically for 14 days or until discharge or death; 2 mg once daily if eGFR <60 mL/min) plus remdesivir intravenously (200 mg on day 1 and 100 mg from day 2 up to day 10 or discharge or death)	Placebo plus remdesivir intravenously (200 mg on day 1 and 100 mg from day 2 up to day 10 or discharge or death)	28 days
Bari-SolidAct[3]	Austria, Belgium, France, Germany, Ireland, Italy, Luxembourg, Norway, Portugal, and Spain	Public	Public; drugs and placebo provided by industry (Eli Lilly)	289*	218 (75·4%); 71 (24·6%)	60 (50–69)	June, 2021, to March, 2022	Adults admitted to hospital due to COVID-19 with severe disease	Baricitinib 4 mg once daily (orally or nasogastrically for 14 days or until discharge or death)	Placebo	90 days
COV-BARRIER[7,8]†	Argentina, Brazil, Germany, India, Italy, Japan, Mexico, Russia, South Korea, Spain, UK, and USA	Industry (Eli Lilly)	Industry (Eli Lilly)	1626†	608 (37·4%); 1018 (62·6%)	58 (48–68)	June, 2020, to Jan, 2021	Adults admitted to hospital due to COVID-19 with any severity of disease	Baricitinib 2 mg twice daily (orally or nasogastrically for 14 days or until discharge or death; 2 mg once daily if eGFR <60 mL/min)	Placebo	60 days
COVINIB[10]‡	Spain	Public	Public	110‡	34 (30·9%); 76 (69·1%)	55 (47–62)	Sept, 2020, to June, 2021	Adults admitted to hospital due to COVID-19 with any severity of disease	Baricitinib 4 mg once daily (orally for 7 days including self-administration)	Usual care	70 days
Ghazaeian and colleagues[51]§	Iran	Public	Industry (Zist Daru)	97§	50 (51·5%); 47 (48·5%)	51 (37–64)	Aug, 2021, to Nov, 2021	Adults admitted to hospital due to COVID-19 with any severity of disease	Tofacitinib 10 mg twice daily (orally for 14 days or until discharge or death)	Placebo	28 days
PANCOVID[9]¶	Spain	Public	Public; drugs provided by industry (Eli Lilly)	287¶	99 (34·5%); 188 (65·5%)	67 (62–74)	Oct, 2020, to Sept, 2021	Adults admitted to hospital due to COVID-19 with severe disease	Baricitinib 4 mg once daily (orally or nasogastrically for 10–14 days or until discharge or death; 2 mg once daily if age >75 years)	Usual care	60 days
RECOVERY[4]‖	UK	Public	Public	8130‖	2764 (34·0%); 5366 (66·0%)	58 (47–69)	Feb, 2021, to Dec, 2021	Adults admitted to hospital due to COVID-19 with any severity of disease	Baricitinib 4 mg once daily (orally for 10 days or until discharge or death; 2 mg once daily orally if eGFR <60 mL/min or receiving probenecid)	Usual care	28 days

(Table 1 continues on next page)

www.thelancet.com/respiratory Published online May 13, 2025 https://doi.org/10.1016/S2213-2600(25)00055-4

	Country	Sponsor	Funding	Number of randomly assigned participants	Number of women (%); number of men (%)	Median age (IQR), years	Recruitment period	Patient population	Interventions	Control	Follow-up time
(Continued from previous page)											
RUXCOVID[5]	Russia, USA, Brazil, Spain, Argentina, Peru, Türkiye, Mexico, UK, Colombia, France, and Germany	Industry (Novartis)	Industry (Novartis and Incyte)	432	197 (45·6%); 235 (54·4%)	57 (47–67)	May, 2020, to Sept, 2020	Adults admitted to hospital due to COVID-19 with mild or moderate disease	Ruxolitinib 5 mg twice daily (orally or nasogastrically for 14 days)	Placebo	28 days
RUXCOVID-DEVENT[52]**	USA and Russia	Industry (Incyte)	Industry (Incyte)	211**	74 (35·0%); 137 (65·0%)	NA††	May, 2020, to Dec, 2020	Adults admitted to hospital due to COVID-19 with severe disease	Ruxolitinib 5 mg twice daily (orally or nasogastrically for 14 days) or ruxolitinib 15 mg twice daily (orally or nasogastrically for 14 days)	Placebo	28 days
STOP-COVID[14]	Brazil	Public	Industry (Pfizer)	289	101 (34·9%); 188 (65·1%)	57 (45– 67)	Sept, 2020, to Dec, 2020	Adults admitted to hospital due to COVID-19 with mild or moderate disease	Tofacitinib 10 mg twice daily (orally or nasogastrically for 14 days or until discharge or death; 5 mg twice daily orally if eGFR <50 mL/min or receiving probenecid)	Placebo	28 days
TACTIC-R[11]‡‡	UK	Public	Public; drugs provided by industry (Eli Lilly)	282‡‡	76 (27·0%); 206 (73·0%)	60 (52–69)	May, 2020, to May, 2021	Adults admitted to hospital due to COVID-19 at moderate or high risk of severe COVID-19	Baricitinib 2 mg twice daily (orally or nasogastrically for 14 days or until discharge or death; 2 mg once daily if eGFR <60 mL/min or age ≥75 years)	Usual care	90 days
TOFACOV[6]	Italy	Public	Public; drugs provided by industry (Pfizer)	116	36 (31·0%); 80 (69·0%)	58 (51–66)	Sept, 2020, to Dec, 2021	Adults admitted to hospital due to COVID-19 with mild or moderate disease	Tofacitinib 10 mg twice daily (orally or nasogastrically for 14 days or until discharge or death)	Usual care	28 days

eGFR=estimated glomerular filtration rate. IPD=individual participant data. IPDMA=individual participant data meta-analysis. JAK=Janus kinase. RCT=randomised clinical trial. *Bari-SolidAct stopped prematurely and reported results from 284 randomly assigned participants due to external evidence; however, it continued recruitment among participants who were immunocompromised, allowing us to include five additional participants in this IPDMA. †The COV-BARRIER trial team published two manuscripts, one with the data of participants with severe COVID-19 disease and one with the data of participants with mild or moderate COVID-19 disease; however, it was the same trial, based on the same random assignment, and therefore we considered and analysed it as one trial. ‡The COVINIB trial included a third group treated with imatinib, but we did not include or receive the data for this group. §The trial from Ghazaeian and colleagues was stopped early and did not publish the data; we received the study protocol and IPD directly from the trial team. ¶The PANCOVID trial was an adaptive factorial design phase 3 trial with a tenofovir and lamivudine group, but we did not include or receive the data for this group. ||The RECOVERY trial included children, but we excluded participants younger than 16 years, as per our protocol. **The RUXCOVID-DEVENT trial was a three-group trial; the two intervention groups assessed different treatment dosages (ruxolitinib 5 mg twice daily *vs* 15 mg twice daily), yielding similar effects, so we grouped participants from both intervention groups together into one intervention group. ††The RUXCOVID-DEVENT trial provided age only as a binary variable (cutoff age 65 years). ‡‡The TACTIC-R trial included a third group treated with ravulizumab, but we did not include or receive the data for this group.

Table 1: **Characteristics of RCTs included in the IPDMA**

	Overall (n=12 902)	JAK inhibitor (n=6647)	No JAK inhibitor (n=6255)
Age, years*	58 (47–69)	58 (48–69)	58 (47–68)
Sex assigned at birth			
Female	4637 (35·9%)	2383 (35·9%)	2254 (36·0%)
Male	8265 (64·1%)	4264 (64·1%)	4001 (64·0%)
Vaccination†			
Any SARS-CoV-2 vaccine	3564 (32·7%)	1828 (32·4%)	1736 (33·1%)
No SARS-CoV-2 vaccine	7328 (67·3%)	3818 (67·6%)	3510 (66·9%)
Time from symptom onset to randomisation, days	10 (7–12)	10 (7–12)	10 (7–12)
Clinical status on WHO ordinal scale			
(2) Hospitalised without need for oxygen therapy (WHO score 4)	1152 (8·9%)	585 (8·8%)	567 (9·1%)
(3) Hospitalised with need for supplemental low-flow oxygen (WHO score 5)	8078 (62·6%)	4111 (61·9%)	3967 (63·5%)
(4) Hospitalised with need for high-flow oxygen or non-invasive ventilation (WHO score 6)	2959 (22·9%)	1534 (23·1%)	1425 (22·8%)
(5) Hospitalised with need for mechanical ventilation or ECMO (WHO score 7–9)	705 (5·5%)	414 (6·2%)	291 (4·7%)
Comorbidities			
No comorbidity	5428 (42·1%)	2750 (41·4%)	2678 (42·8%)
One comorbidity	3909 (30·3%)	2009 (30·2%)	1900 (30·4%)
Multiple comorbidities	3467 (26·9%)	1838 (27·7%)	1629 (26·0%)
Immunocompromised‡	98 (0·8%)	50 (0·8%)	48 (0·8%)
Dexamethasone and tocilizumab			
No dexamethasone and no tocilizumab	2101 (16·3%)	1069 (16·1%)	1032 (16·5%)
Dexamethasone but no tocilizumab	2870 (22·3%)	1503 (22·6%)	1367 (21·9%)
Dexamethasone and tocilizumab	7890 (61·2%)	4055 (61·0%)	3835 (61·4%)
Tocilizumab but no dexamethasone	34 (0·3%)	18 (0·3%)	16 (0·3%)
Remdesivir			
No Remdesivir	9407 (72·9%)	4827 (72·6%)	4580 (73·2%)
Remdesivir	3495 (27·1%)	1820 (27·4%)	1675 (26·8%)
CRP concentration, mg/L	86 (42–148)	85 (42–150)	86 (42–146)
Serological status§			
Undetectable anti-SARS-CoV-2 antibodies (anti-RBD and anti-nucleocapsid)	594 (33·9%)	285 (33·5%)	309 (34·4%)
Detectable anti-SARS-CoV-2 antibodies (anti-RBD or anti-nucleocapsid)	1157 (66·1%)	567 (66·5%)	590 (65·6%)
Virological status¶			
Detectable viral load	9594 (97·3%)	4839 (97·4%)	4755 (97·2%)
Undetectable viral load	265 (2·7%)	129 (2·6%)	136 (2·8%)

Data are median (IQR) or n (%). Some trials made use of country consent laws that allowed inclusion of participants aged 16 years and older and, hence, this was the age eligibility criterion we used. However, in our data, there were only three participants aged 16 years and four participants aged 17 years; therefore, we kept the term adult throughout the manuscript. CRP=C-reactive protein. ECMO=extracorporeal membrane oxygenation. IPD=individual participant data. JAK=Janus kinase. RBD=receptor-binding domain. *RUXCOVID did not contribute data to the baseline covariate of age in this table because IPD were provided through a virtual environment, with only summary estimates allowed as output; however, regarding the effect modifier analyses for age and time from symptom onset, RUXCOVID provided data because these result estimates were allowed as output. Similarly, RUXCOVID-DEVENT did not contribute data to this baseline covariate in this table because age was provided only as a binary variable (cutoff 65 years). †Data not available for COV-BARRIER, Ghazaeian and colleagues, and TACTIC-R. ‡Immunocompromised was defined in our study protocol (PROSPERO CRD42023431817) as the presence of at least one of the following medical conditions: active malignant neoplasm; lymphoid or myeloid neoplasms; haematopoietic stem-cell or solid-organ transplantation; HIV-positive with CD4-cell count below 350 cells or not on antiretroviral therapy; a primary immunodeficiency; rheumatoid arthritis; lupus; vasculitis; and inflammatory bowel disease or other autoimmune disorder for which a participant is being treated with systemic immunosuppressive medication. §Data only available for Bari-SolidAct and RECOVERY. ¶Data only available for ACTT-2, Bari-SolidAct, COV-BARRIER, RECOVERY, and TOFACOV.

Table 2: **Main baseline characteristics of participants from the 12 trials that provided IPD**

All 12 included RCTs were judged to be at low risk of bias for mortality at day 28 (appendix p 24) and for all secondary outcomes except the outcome of adverse events by day 28, for which five trials were classified as being of some concern of bias (appendix p 25). All RCTs systematically collected in-hospital and out-of-hospital mortality data at least until 28 days after randomisation.

In the IPD received, data on adjustment variables were missing for only eight participants overall. Data on the primary outcome were missing for 329 (2·5%) of 12 902 participants, and for less than 6·0% of participants in any individual trial. The proportion of missing data was similar across other outcomes, except for viral clearance, which had substantial missing data (appendix p 21). Seven trials[5,6,9,10,14,51,52] had to be excluded entirely from the viral clearance outcome analyses because they did not collect such data.

The 12 902 participants in our IPDMA had a median age of 58 years (IQR 47–69). 8265 (64·1%) participants were male and 4637 (35·9%) were female. 10 760 (83·4%) participants received dexamethasone at baseline, whereas only 3495 (27·1%) participants also received remdesivir (table 2). Patients were randomly assigned after a median symptom duration of 10 days (IQR 7–12). 3664 (28·4%) participants received non-invasive or mechanical ventilation at baseline, 3467 (26·9%) had multiple comorbidities, 98 (0·8%) were immunocompromised, and 3564 (32·7%) had received at least one SARS-CoV-2 vaccination. Baseline characteristics were similar between randomly assigned groups (table 2). Additional baseline characteristics are presented in the appendix (p 23).

Overall, 755 (11·7%) of 6465 participants in the JAK inhibitor group died by day 28 compared with 805 (13·2%) of 6108 participants in the no JAK inhibitor group (adjusted OR [aOR] 0·67 [95% CI 0·55–0·82]; p=0·0013; I^2=16%; 39 fewer per 1000 [95% CI 55 fewer to 21 fewer]; high-certainty evidence; tables 3, 4, figure 2A). All measures to assess heterogeneity of the treatment effect estimate indicated that the true effects of included trials did not vary considerably (figure 2A). The prediction interval ranges from 0·45 to 1·00, suggesting that a new trial would be likely to show benefit. At day 60, the mortality was 12·2% with JAK inhibitors (788 of 6454 participants) versus 13·6% (829 of 6090 participants) without JAK inhibitors (aOR 0·72 [0·61–0·86]; p=0·0019; I^2= 6%; prediction interval 0·54–0·96; table 3; appendix p 26). Participants in the JAK inhibitor group survived a median of 4 days longer than participants in the no JAK inhibitor group (adjusted hazard ratio [aHR] 0·73 [0·61–0·86]; p=0·0019; I^2=24%; prediction interval 0·51–1·03; table 3; appendix p 27, cumulative incidence curves in the appendix p 28).

The number of participants either requiring new mechanical ventilation or dying up to day 28 was lower in the JAK inhibitor group (1117 [17·2%] of 6505 participants) than in the no JAK inhibitor group (1163 [18·9%] of

6144 participants; aOR 0·80 [0·72–0·89]; p<0·0006; I^2=0%; prediction interval 0·71–0·90; 32 fewer per 1000 [95% CI 46 fewer to 18 fewer]; high-certainty evidence; tables 3, 4; appendix p 29). Participants receiving JAK inhibitors had better clinical status on an ordinal scale, namely less respiratory support at day 28 (aOR 0·79 [0·73–0·86]; p<0·0001; I^2=0%; prediction interval 0·71–0·88; table 3; appendix p 30), and could be discharged more quickly (aHR 1·11 [1·06–1·16]; p<0·0005; I^2=14%; prediction interval 1·06–1·15; absolute difference median 1 day less [95% CI 0–1 days less]; high-certainty evidence; tables 3, 4; appendix p 31) than those who did not receive JAK inhibitors. There was no conclusive evidence for a difference between groups in terms of viral clearance at days 5, 10, and 15 (table 3; appendix pp 32–34). Only one trial considered health-related quality of life and found no evidence for between-group differences.[3]

Within the first 28 days, there were fewer participants with at least one grade 3 or 4 adverse event or serious adverse events in the JAK inhibitor group than in the no JAK inhibitor group (1072 [16·1%] of 6647 participants *vs* 1047 [16·7%] of 6255; aOR 0·90 [0·83–0·97]; p=0·011; I^2=0%; prediction interval 0·80–1·01; 14 fewer per 1000 [95% CI 24 fewer to 4 fewer]; moderate-certainty evidence; tables 3, 4; appendix p 35). In the JAK inhibitor group, 382 (5·7%) of 6647 patients had a secondary infection and 283 (4·3%) of 6647 had thromboembolic event, whereas 330 (5·3%) of 6255 and 278 (4·4%) of 6255 patients in the no JAK inhibitor group had these events, respectively (appendix p 36). Of all 12 902 patients, 95 (0·7%) had a gastrointestinal perforation, 25 (0·2%) had reactivation of a chronic infection, 128 (1·0%) had liver dysfunction, and 502 (3·9%) had a cardiovascular or cardiac event, with similar rates across both groups (appendix p 36).

The meta-analysis for the primary outcome, including aggregate data from the additional four trials without IPD, supported the results from the primary analysis (appendix p 37). No small-study effect was detected (appendix p 38). Among the non-IPD trials, pacritinib and nezulcitinib were also evaluated. Across all trials (IPD and non-IPD), the between-trial comparison by type of JAK inhibitor provided no evidence for different effects across trials that assessed different types of JAK inhibitor (test for subgroup differences p=0·57; summary estimates across JAK inhibitor types were similar; appendix p 39). However, the evidence for ruxolitinib and tofacitnib was based on only three trials and the evidence for pacritinib and nezulcitinib from only one trial each. Similarly, effect estimates were similar across trials that recruited in different time periods. However, there was high uncertainty for the delta and omicron periods, because only two trials with 345 participants recruited during that period (appendix p 40).

Using a one-stage instead of a two-stage IPDMA approach yielded similar results across all outcomes (appendix pp 41–42). The five trials that were judged to be at some concern of risk of bias for the safety outcome (adverse events by day 28) showed similar results (appendix p 43). The sensitivity analysis assessing progression to mechanical ventilation among participants who were not ventilated at baseline and were still alive at day 28, as well as the sensitivity analysis for the safety outcome (adverse events by day 28), which analysed adverse events as a count outcome (ie, counting all adverse events that happened within

	JAK inhibitor (n=6647)	No JAK inhibitor (n=6255)	Intention-to-treat regression analysis point estimate (95% CI); p value; I^2
Primary			
All-cause mortality at day 28	755/6465 (11·7%)	805/6108 (13·2%)	aOR 0·67 (0·55–0·82); p=0·0013; I^2=16%
Secondary			
All-cause mortality at day 60	788/6454 (12·2%)	829/6090 (13·6%)	aOR 0·72 (0·61–0·86); p=0·0019; I^2=6%
Days until death within 60 days	12 (6–19)*	11 (6–17)*	aHR 0·73 (0·61–0·86); p=0·0019; I^2=24%
New mechanical ventilation or death at day 28	1117/6505 (17·2%)	1163/6144 (18·9%)	aOR 0·80 (0·72–0·89); p<0·0006; I^2=0
Clinical status on WHO ordinal scale at day 28†	..	..	aOR 0·79 (0·73–0·86); p<0·0001; I^2=0
(1) Outside of hospital alive or reached discharge criteria (WHO score 0–3)	5097/6483 (78·6%)	4768/6208 (76·8%)	..
(2) Hospitalised without need for oxygen therapy (WHO score 4)	75/6483 (1·2%)	81/6208 (1·3%)	..
(3) Hospitalised with need for supplemental low-flow oxygen (WHO score 5)	220/6483 (3·4%)	238/6208 (3·8%)	..
(4) Hospitalised with need for high-flow oxygen or non-invasive ventilation (WHO score 6)	173/6483 (2·7%)	170/6208 (2·7%)	..
(5) Hospitalised with need for mechanical ventilation or ECMO (WHO score 7–9)	163/6483 (2·5%)	146/6208 (2·4%)	..
(6) Dead (WHO score 10)	755/6483 (10·6%)	805/6208 (12·9%)	..
Days until discharge within 28 days	7 (4–10)‡	7 (4–11)‡	asHR 1·11 (1·06–1·16); p<0·0005; I^2=14%
Viral clearance at day 5§	317/4765 (6·7%)	322/4648 (6·9%)	aOR 0·95 (0·76–1·18); p=0·52, I^2=0
Viral clearance at day 10§	459/4928 (9·3%)	465/4788 (9·7%)	aOR 0·94 (0·86–1·03); p=0·13; I^2=0
Viral clearance at day 15§	559/4983 (11·2%)	564/4848 (11·6%)	aOR 0·96 (0·88–1·05); p=0·27; I^2=0
Participants with at least one grade 3 or 4 adverse event or serious adverse event (excluding death) within 28 days	1072/6647 (16·1%)	1047/6255 (16·7%)	aOR 0·90 (0·83–0·97); p=0·011; I^2=0

Data are n/N (%) or median (IQR), unless otherwise stated. Missing data by trial for each of the outcomes are detailed in the appendix (p 21). aHR=adjusted hazard ratio. aOR=adjusted odds ratio. asHR=adjusted subdistribution hazard ratio. ECMO=extracorporeal membrane oxygenation. GRADE=Grading of Recommendations Assessment, Development, and Evaluation. JAK=Janus kinase. *Descriptively among only those who reached the event (death); if converted into absolute differences, according to GRADE guidance,[53] this results in a median of 4 days more (95% CI 7–24 days) for the JAK inhibitor group; cumulative survival curves are available in the appendix (p 28). †No data available from RUXCOVID-DEVENT for this outcome. ‡Descriptively among only those who reached the event (discharge); if converted into absolute differences, according to GRADE guidance,[53] this results in a median of 1 day less (95% CI 0–1 days) for the JAK inhibitor group. §No data available from COVINIB, Ghazaeian and colleagues, PANCOVID, TOFACOV, RUXCOVID, RUXCOVID-DEVENT, and STOP-COVID for this outcome.

Table 3: **Primary and secondary outcomes for JAK inhibitor and no JAK inhibitor groups**

	Study results and measurements	Absolute effect estimates* for JAK inhibitor	Absolute effect estimates* for no JAK inhibitor	Absolute difference (95% CI), NNT	Certainty in effect estimates (quality of evidence)	Summary
All-cause mortality at day 28	aOR 0·67 (0·55–0·82); based on data from 12 902 participants from 12 trials	92 per 1000	132 per 1000	39 fewer per 1000 (95% CI 55 fewer to 21 fewer), NNT 26*; alternative ACR* of 1·81%, NNT 170	High	JAK inhibitors reduce 28-day mortality
New mechanical ventilation or death at day 28	aOR 0·80 (0·72–0·89); based on data from 12 902 participants from 12 trials	158 per 1000	189 per 1000	32 fewer per 1000 (95% CI 46 fewer to 18 fewer), NNT 32*	High	JAK inhibitors reduce progression to mechanical ventilation or death
Days until discharge or reaching discharge criteria up to day 28	asHR 1·11 (1·06–1·16); based on data from 12 902 participants from 12 trials	7 (median)	7 (median)	1 day less (95% CI 0–1 days less), NNT 42*	High	JAK inhibitors reduce time to hospital discharge
Grade 3 or 4 adverse event or serious adverse event within 28 days	aOR 0·90 (0·83–0·97); based on data from 12 902 participants from 12 trials	154 per 1000	167 per 1000	14 fewer per 1000 (95% CI 24 fewer to 4 fewer), NNH 71*	Moderate†	JAK inhibitors probably reduce severe and serious adverse events

ACR=assumed control risk. aHR=adjusted hazard ratio. aOR=adjusted odds ratio. asHR=adjusted subdistribution hazard ratio. GRADE=Grading of Recommendations Assessment, Development, and Evaluation. JAK=Janus kinase. NNH=number needed to harm. NNT=number needed to treat. *We used as ACR the weighted mean baseline risk across all trials (total number of events in control group divided by total observations in control group). For all-cause mortality, we provided an alternative ACR that reflects the COVID-19 in-hospital mortality rate (1·81%) based on estimates from the UK for the year 2023, obtained through OpenSAFELY.[54] We calculated the NNT or NNH from aORs and aHRs as well as the median time from randomisation to discharge from hospital according to GRADE guidelines.[53,55,56] †Outcome was rated down for risk of bias.

Table 4: **Summary of findings and certainty of evidence**

the first 28 days) rather than a binary outcome (ie, any adverse events by day 28), yielded similar point estimates but with higher uncertainty (appendix p 44). The remaining sensitivity analyses (multiple imputation of missing data for the primary outcome and days to sustained discharge) were consistent with the primary results (appendix p 44).

We observed probable effect modification by age, with younger participants showing larger relative benefits from JAK inhibitors than older participants (moderate credibility according to ICEMAN; figure 2B; appendix pp 15–17, 45–46). However, older participants still showed a survival benefit with JAK inhibitors, as indicated in the multivariable fractional polynomial interaction analysis (appendix p 47). On an absolute scale, participants aged 70 years or older (as an arbitrary descriptive cutoff) in the largest trial (RECOVERY trial) showed a 2% risk reduction, which was the same absolute effect as for participants younger than 70 years (appendix pp 45–46).

According to ICEMAN guidance, any effect modification with a $p_{interaction}$ value above 0·1 was not assessed regarding its credibility. There was no evidence for effect modification by ventilation status, comorbidity, or concomitant dexamethasone or tocilizumab use (figure 2B), nor for timepoint of treatment initiation after symptom onset or CRP concentrations (figure 2B; appendix pp 48–49).

Regarding the safety endpoint (adverse events by day 28), vaccination status did not modify the effect, nor did concomitant dexamethasone or tocilizumab use (appendix p 50). Patients at risk for serious adverse events from JAK inhibitors, according to the EMA warning, had similar estimates as those not at risk (appendix p 50).

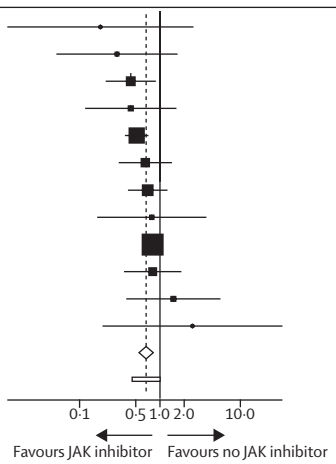
Discussion

This IPDMA of 12 RCTs, for which we obtained IPD for 12 902 adult (aged ≥16 years) patients with COVID-19 treated in hospitals worldwide, found a reduced risk for death with JAK inhibitors at 28 days (39 fewer deaths per 1000 or a number needed to treat of 26; high-certainty evidence; table 4). In addition, JAK inhibitors reduced mortality at 60 days, decreased the need for new mechanical ventilation or other respiratory support, and allowed for faster discharge from hospital by approximately 1 day. There was moderate-certainty evidence for fewer severe or serious adverse events in participants treated with JAK inhibitors than in those not given JAK inhibitors. We found a moderately credible effect modification by age, with younger participants showing larger relative treatment effects than older participants. We found no evidence for credible effect modification by concomitant use of other immunomodulatory treatments (dexamethasone or tocilizumab), level of respiratory support, comorbidities, CRP concentration, time of JAK inhibitor initiation after COVID-19 symptom onset, SARS-CoV-2 vaccination status, and type of JAK inhibitor used.

The findings of this IPDMA are in line with previous meta-analyses on the topic.[4,15,16] Our IPDMA expands the evidence by adding analyses of safety data and

A

	JAK inhibitor	Deaths JAK inhibitor	No JAK inhibitor	Deaths no JAK inhibitor	Weight (%)	Adjusted odds ratio	Adjusted odds ratio (95% CI)
COVINIB	53	0	54	2	0·6		0·18 (0·01–2·61)
PANCOVID	140	2	136	6	1·3		0·29 (0·05–1·66)
RUXCOVID–DEVENT	162	84	47	33	7·0		0·43 (0·21–0·89)
STOP–COVID	144	4	145	8	2·3		0·43 (0·12–1·60)
COV–BARRIER	758	82	765	129	21·4		0·51 (0·37–0·72)
Bari–SolidAct	137	15	140	21	6·3		0·66 (0·31–1·41)
ACTT–2	494	24	492	37	10·4		0·70 (0·40–1·24)
Ghazaeian and colleagues	46	3	51	4	1·7		0·79 (0·17–3·78)
RECOVERY	4061	513	3940	545	40·7		0·81 (0·70–0·93)
TACTIC–R	130	18	138	17	5·5		0·81 (0·36–1·85)
RUXCOVID	282	9	142	3	2·2		1·47 (0·38–5·66)
TOFACOV	58	1	58	0	0·6		2·54 (0·19–33·37)
Average treatment effect	**6465**	**755**	**6108**	**805**	**100**		**0·67 (0·55–0·82)**
Prediction interval							**0·45–1·00**
Heterogeneity: I^2=16%, τ^2=0·0214, p=0·28							



B

	JAK inhibitor	Deaths JAK inhibitor	No JAK inhibitor	Deaths no JAK inhibitor	Adjusted odds ratio	$p_{interaction}$	ICEMAN credibility assessment
No oxygen	571	20	553	25		0·22	Not assessed
Low-flow oxygen	4010	308	3888	329			
High-flow or non-invasive ventilation	1483	271	1382	327			
Mechanical ventilation or ECMO	401	156	281	124			
Age ≥70 years	1567	426	1395	398		0·027	Moderate credibility
Age <70 years	4898	329	4713	407			
No comorbidity	2685	160	2626	223		0·41	Not assessed
One comorbidity	1952	243	1858	247			
Multiple comorbidities	1780	342	1579	329			
Immunocompromised	48	10	45	6			
No dexamethasone, no tocilizumab	1024	76	983	89		0·80	Not assessed
Dexamethasone, but no tocilizumab	4119	497	3831	498			
Dexamethasone and tocilizumab	1304	174	1277	214			
Tocilizumab, but no dexamethasone	18	8	16	4			
Enrolment >10 days after symptom onset	2570	223	2448	288		0·89	Not assessed
Enrolment >5 days and ≤10 days after symptom onset	2795	296	2716	328			
Enrolment ≤5 days after symptom onset	949	152	906	156			
CRP ≥75 mg/L	3307	430	3162	454		0·54	Not assessed
CRP <75 mg/L	2734	297	2575	308			
Average treatment effect							

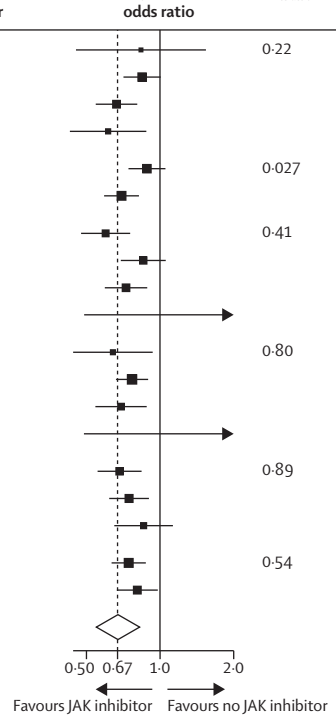


Figure 2: **Forest plot showing (A) all-cause mortality at day 28 and (B) subgroup analyses on all-cause mortality at day 28**
(A) The odds ratio is adjusted for age and clinical status at baseline, across all trials, in the first stage. In the second stage, the individual trial estimates are combined in a random-effects model. (B) ICEMAN assessments were conducted only in the case of statistical evidence of a $p_{interaction}$ value of less than 0·1.[49] The p values for the interaction were obtained using a two-stage IPDMA approach, which was based solely on within-trial interactions (deft approach).[25] First, to produce a treatment–covariate interaction estimate and its variance, a binomial regression was fitted in each trial separately, adjusted (where appropriate) for respiratory support and age, including the treatment and the treatment–covariate interaction. Second, the interaction estimates were combined across trials in a random-effects model, and the CI for the summary interaction was derived using the Hartung–Knapp–Sidik–Jonkman approach. For continuous covariates (age, symptom duration, and CRP concentration), a cutoff was chosen for descriptive purposes. However, these covariates were included as a continuous treatment–covariate interaction assuming linearity. Ordinal covariates (respiratory support, comorbidities, and comedication) were included similarly. Sizing of all squares are in proportion to the inverse variance of the estimates. aOR=adjusted odds ratio. CRP=C-reactive protein. ECMO=extracorporeal membrane oxygenation. ICEMAN=Instrument for Assessing the Credibility of Effect Modification Analyses. IPDMA=individual participant data meta-analysis. JAK=Janus kinase.

subgroup analyses, both of which were not possible in previous individual trials or aggregate data meta-analyses in such detail. For example, one of the trials that assessed baricitinib among participants with severe or critical COVID-19[3] suggested more serious adverse events in the subgroup of participants who were

vaccinated than in those who not vaccinated ($p_{interaction}$=0·057). However, the trial was stopped prematurely due to external evidence on the same clinical question (recruited only 284 [14·9%] of 1900 planned participants), the analysis was conducted post hoc, and subsequent exploratory analyses based on biomarkers did not provide an explanation for this potential harm.[57] Most importantly, our analysis, which was based on far more data, did not support this subgroup finding.

Another example is the observed relative treatment interaction by age. Although subgroup effects need to be viewed critically, the consistent direction of effect modification by age across the individual trials, the statistical evidence ($p_{interaction}$=0·027, assessed using a linear interaction), and the reassurance from the multifractional polynomial interaction analysis strengthened the credibility of this subgroup effect.

The most up-to-date WHO COVID-19 treatment guideline,[15] published in January, 2023, recommends using the JAK inhibitor baricitinib for patients with severe or critical COVID-19, but no other JAK inhibitor, whereas the US National Institutes of Health (NIH)[17] and the Infectious Diseases Society of America (IDSA)[18] COVID-19 treatment guidelines recommend baricitinib as first-line JAK inhibitor and tofacitinib as a possible alternative, but not ruxolitinib. We did not find evidence for different effects across the different types of JAK inhibitor (appendix p 39). However, this finding is based on a between-trial comparison only and should therefore be interpreted with caution.

Although the WHO COVID-19 treatment guideline suggests the option of triple immunomodulation (ie, JAK inhibitors, corticosteroids, and IL-6 receptor blockers), the NIH and IDSA COVID-19 treatment guidelines do not recommend this strategy due to insufficient evidence and potential greater risk of secondary infections. Among the participants who received the JAK inhibitor in addition to dexamethasone or tocilizumab, we did not observe an increase in short-term severe or serious adverse events, and found similar clinical benefit compared with participants who received less immunomodulatory therapy. Conversely, we observed fewer severe or serious adverse events in the JAK inhibitor group than in the no JAK inhibitor group, irrespective of additional immunomodulatory therapy. Existing evidence suggests that baricitinib could reduce secondary infections.[58] We were not able to confirm this specific association from our pooled data.

The FDA[59] and EMA[19] have issued warnings about increased risk of major adverse cardiovascular events, cancer, and venous thromboembolism associated with the use of JAK inhibitors among participants with chronic inflammatory conditions. During the follow-up window of 28 days with a maximum 14 days of JAK inhibitor treatment (as indicated for the treatment of COVID-19), we found no increase in grade 3 or 4 adverse events or serious adverse events, both overall (table 3), by at-risk subgroup (appendix p 50), and when stratified by adverse events of special interest (appendix p 36). Less than 6% of participants had a thromboembolic event or a secondary infection, cardiovascular and cardiac events were below 4%, and malignancies were negligible.

To our knowledge, this is the first IPDMA on the effects of JAK inhibitors to treat adults admitted to hospital due to COVID-19 that has summarised existing evidence of RCTs on the topic, including adverse events. Strengths are that our IPDMA included 96% of all eligible IPD worldwide; a published and registered study protocol with prespecified analyses; standardised outcome and covariate definitions and adjustment across all trials; a two-stage IPDMA model supported by a corresponding one-stage model that showed similar results; less than 0·5% missing data in adjustment variables; findings that were robust to sensitivity analyses; and hypothesis-driven, prespecified subgroup analyses, including a credibility assessment according to ICEMAN[49] and exploration of non-linear subgroup effects using multivariable fractional polynomials, and careful meta-analysis of interactions using deft plots.[25]

Our study has several limitations. First, only five (42%) of 12 trials contributed to the secondary outcome of viral clearance; these analyses were probably underpowered. Second, we could only reliably identify 98 (0·8%) of 12 902 participants with an immunocompromising condition as per our study protocol and hence could not provide reliable evidence for this subgroup. Third, both SARS-CoV-2 and the host evolved over time, changing the clinical phenotype of COVID-19. Only two trials recruited participants after December, 2021, when the omicron (B.1.1.529) SARS-CoV-2 variants of concerns and their sublineages became globally prevalent, resulting in uncertain effect estimates (appendix p 40). Moreover, only 3564 (32·7%) of 10892 participants in this study had received a SARS-CoV-2 vaccination. The absolute risk reductions with JAK inhibitors will be smaller in a better protected population and with predominantly less lethal variants of concerns such as omicron. As an example, assuming a control group mortality risk of 1·81% among patients admitted to hospital with COVID-19, based on 2023 in-hospital mortality data from the UK obtained through OpenSAFELY,[54] the number needed to treat to avoid one death increased from 26 to 170. Fourth, we acknowledge that our study population is not a homogeneous group in terms of SARS-CoV-2 variants, vaccination status, additional concomitant treatment (especially dexamethasone and tocilizumab), and clinical status at baseline. However, this heterogeneity is also present in most individual RCTs that recruited across

various clinical statuses and over an average half-year recruitment period.

This IPDMA summarises the body of evidence from RCTs for the use of JAK inhibitors among adults admitted to hospital due to COVID-19. Subgroup analyses suggested no increased harm among participants who were vaccinated compared with those who were unvaccinated and no evidence for differing effects among people with multiple comorbidities, receiving a combination of other immunomodulatory therapy, level of respiratory support, CRP concentration, and time of treatment initiation after symptom onset.

Contributors

AA, SScha, CSR, MT, ICO, and MB developed the concept and drafted the study protocol with input from SScho, TA, FM, AD, DB, CRM, CL, AB, LA, DC, and EP. HE developed the search strategy and conducted the systematic searches with input from AA. AA, CSR, CMS, and BS screened titles, abstracts and full texts, with input from MB. AA, BS, and JMS conducted the risk of bias assessments. AA and SScha conducted the Instrument for Assessing the Credibility of Effect Modification Analyses assessments. AA and MB conducted the Grading of Recommendations Assessment, Development, and Evaluation assessments. KMT, SN, MM, AMO, DBB, GP, AF, MG, FH, SB, MTGM, MJG, JRA, KL, MH, FA, ET, POG, CAMT, OB, and MT collected data. VCS and YY provided administrative and technical support and YY obtained the funding. AA managed the data and did the statistical analysis, supervised by SScha, CSR, ICO, and MB. All trial teams had access to their trial data and AA and MB verified all data. AA wrote the first draft of the manuscript, and all authors critically revised the manuscript for important intellectual content and had final responsibility for the decision to submit for publication.

Declaration of interests

BS and MB have received research grants form Moderna for COVID-19 vaccination research. BS has received honoraria for lectures and presentations from Moderna and Roche. FH and SB have received research grants from Eli Lilly and Alexion including the receipt of drugs to support TACTIC-R. FH has received honoraria for lectures and presentations from Boehringer Ingelheim and support for attending scientific meetings from Eli Lilly. JRA has received consulting fees from Abbvie, Merck, Pfizer, Sobi, Serono, Eli Lilly, and Roche; honoraria for lectures and presentations from Merck and Pfizer; and support for attending meetings from Merck and Eli Lilly. KL has received honoraria for lectures and presentations from Gilead, MSD, and Moderna; support for attending meetings from Gilead and MSD; is on an advisory board for XAV-19 (Xenothera, Nantes, France) vaccine development; and has stocks in SpikImm (anti-SARS-CoV2 monoclonal antibodies, by Truffle Capital in partnership with Institut Pasteur). MH has received honoraria for lectures and presentations from Pfizer, Gilead, Shionogi, MSD, and INSMED (all paid to the institution); support for attending meetings from Pfizer, Gilead, and PharmaMar; and is the President of the Belgian Society of Infectious Diseases and Clinical Microbiology. DC has received honoraria for lectures and presentations from Pfizer. MT is on an advisory board for Eli Lilly (pro bono) and is a member of the WHO Europe expert group on COVID-19 and mpox. OB has received research grants from AstraZeneca, Bayer, Pfizer, Servier, Novartis, and Amgen (all paid to the institution). TA is Chair of the MAGIC Evidence Ecosystem Foundation, a non-profit organisation that conducts research and guideline methodology and implementation, in particular providing methodological help to WHO for their living guideline on drugs for COVID-19, including the recommendations about JAK inhibitors. All other authors declare no competing interests.

Data sharing

Data from individual randomised clinical trials were provided by trial groups for the specific purpose of conducting this individual participant data meta-analysis. Any requests by other researchers for those data should be directed to the responsible party for individual trials.

Acknowledgments

This project has received funding from the EU's Horizon 2020 research and innovation programme under grant agreement number 101015736 (YY). AA was supported by a grant from the Swiss National Science Foundation (Postdoc.Mobility grant number P500PM_221961). CMS is funded by the Swiss National Science Foundation (MD-PhD grant number 323530_221860). We are grateful to all trial teams and participants who have participated in this study. This research includes data from the RECOVERY trial obtained through a request to the Infectious Diseases Data Observatory (IDDO), with help from Will Stevens. IDDO had no role in the production of this research. We acknowledge the US National Institute of Allergy and Infectious Disease Clinical Trials Data Repository (Accessclinicaldata@NIAID) with regards to the ACTT-2 trial data. This publication is based on research using data from the COV-BARRIER trial (funded by Eli Lilly) that has been made available through Vivli. Vivli has not contributed to or approved, and Vivli and Eli Lilly are not in any way responsible for, the contents of this publication. We acknowledge Incyte as a source for the RUXCOVID-DEVENT trial. Incyte is not in any way responsible for the contents of this publication. We acknowledge Novartis and ClinicalStudyDataRequest (CSDR) as sources of data for the RUXCOVID trial. CSDR has not contributed to or approved, and CSDR and Novartis are not in any way responsible for, the contents of this publication. We thank the Swiss Clinical Trials Organisation for their technical support and advice.

For **IDDO** see https://www.iddo.org/data-sharing/accessing-data

For **CSDR** see https://www.clinicalstudydatarequest.com/

For the **Swiss Clinical Trials Organisation** see www.scto.ch

References

1 Levy G, Guglielmelli P, Langmuir P, Constantinescu SN. JAK inhibitors and COVID-19. *J Immunother Cancer* 2022; **10:** e002838.
2 Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet* 2020; **395:** e30–31.
3 Trøseid MA, José R, Assoumou L, et al. Efficacy and safety of baricitinib in hospitalized adults with severe or critical COVID-19 (Bari-SolidAct): a randomised, double-blind, placebo-controlled phase 3 trial. *Crit Care* 2023; **27:** 9.
4 Abani O, Abbas A, Abbas F, et al, and the RECOVERY Collaborative Group. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. *Lancet* 2022; **400:** 359–68.
5 Han MKA, Antila M, Ficker JH, et al. Ruxolitinib in addition to standard of care for the treatment of patients admitted to hospital with COVID-19 (RUXCOVID): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Rheumatol* 2022; **4:** e351–61.
6 Ferrarini A, Vacca A, Solimando AG, et al. Early administration of tofacitinib in COVID-19 pneumonitis: an open randomised controlled trial. *Eur J Clin Invest* 2023; **53:** e13898.
7 Marconi VC, Ramanan AV, de Bono S, et al, and the COV-BARRIER Study Group. 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. *Lancet Respir Med* 2021; **9:** 1407–18.
8 Ely EW, Ramanan AV, Kartman CE, et al, and the COV-BARRIER Study Group. 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. *Lancet Respir Med* 2022; **10:** 327–36.
9 Montejano R, de la Calle-Prieto F, Velasco M, et al, and the PANCOVID Study Group. Tenofovir disoproxil fumarate/emtricitabine and baricitinib for patients at high risk of severe coronavirus disease 2019: the PANCOVID randomized clinical trial. *Clin Infect Dis* 2023; **76:** e116–25.
10 Morales-Ortega A, Farfán-Sedano AI, San Martín López JV, et al. Baricitinib or imatinib in hospitalized COVID-19 patients: results from COVINIB, an exploratory randomized clinical trial. *J Med Virol* 2023; **95:** e28495.
11 Hall FCC, Cheriyan J, Cope AP, et al, and the TACTIC-R Investigators Group. Efficacy and safety of baricitinib or ravulizumab in adult patients with severe COVID-19 (TACTIC-R): a randomised, parallel-arm, open-label, phase 4 trial. *Lancet Respir Med* 2023; **11:** 1064–74.
12 Kalil AC, Patterson TF, Mehta AK, et al, and the ACTT-2 Study Group Members. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med* 2021; **384:** 795–807.

For the **MAGIC Evidence Ecosystem Foundation** see https://magicevidence.org/

13 Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): a multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol* 2020; **146:** 137–46.e3.

14 Guimarães PO, Quirk D, Furtado RH, et al, and the STOP-COVID Trial Investigators. Tofacitinib in patients hospitalized with COVID-19 pneumonia. *N Engl J Med* 2021; **385:** 406–15.

15 WHO. Therapeutics and COVID-19: living guideline, 10 November 2023; https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2023.2 (accessed June 5, 2024).

16 Kramer A, Prinz C, Fichtner F, et al. Janus kinase inhibitors for the treatment of COVID-19. *Cochrane Database Syst Rev* 2022; **6:** CD015209.

17 US National Institutes of Health COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. 2024. https://www.covid19treatmentguidelines.nih.gov/ (accessed Aug 10, 2024).

18 Bhimraj A, Morgan RL, Nadig N, et al. IDSA Guidelines on the treatment and management of patients with COVID-19, part 1: treatment and management 2024. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ (accessed Aug 1, 2024).

19 The Lancet Gastroenterology & Hepatology. New restrictions on JAK inhibitors in the EU. *Lancet Gastroenterol Hepatol* 2023; **8:** 1.

20 US Food & Drug Adminstration. Coronavirus (COVID-19) update: FDA authorizes drug combination for treatment of COVID-19. 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-combination-treatment-covid-19 (accessed July 10, 2024).

21 European Medicines Agency. Olumiant—withdrawal of application for variation to marketing authorisation. 2022. https://www.ema.europa.eu/en/medicines/human/variation/olumiant (accessed July 10, 2024).

22 Simmonds MC, Higgins JPT, Stewart LA, Tierney JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clin Trials* 2005; **2:** 209–17.

23 Berlin JA, Santanna J, Schmid CH, Szczech LA, Feldman HI, and the Anti-Lymphocyte Antibody Induction Therapy Study Group. Individual patient- versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head. *Stat Med* 2002; **21:** 371–87.

24 Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010; **340:** c221.

25 Fisher DJ, Carpenter JR, Morris TP, Freeman SC, Tierney JF. Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach? *BMJ* 2017; **356:** j573.

26 Stewart LA, Clarke M, Rovers M, et al, and the PRISMA-IPD Development Group. Preferred reporting items for systematic review and meta-analysis of individual participant data: the PRISMA-IPD statement. *JAMA* 2015; **313:** 1657–65.

27 Rethlefsen ML, Kirtley S, Waffenschmidt S, et al, and the PRISMA-S Group. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. *Syst Rev* 2021; **10:** 39.

28 Hirt J, Nordhausen T, Fuerst T, Ewald H, Appenzeller-Herzog C, and the TARCiS study group. Guidance on terminology, application, and reporting of citation searching: the TARCiS statement. *BMJ* 2024; **385:** e078384.

29 Higgins JPT, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions version 6.4. 2023. https://training.cochrane.org/handbook (accessed June 6, 2024).

30 Riley RD, Tierney J, Stewart LA. Individual participant data meta-analysis: a handbook for healthcare research. Wiley, 2021.

31 Glanville J, Foxlee R, Wisniewski S, Noel-Storr A, Edwards M, Dooley G. Translating the Cochrane EMBASE RCT filter from the Ovid interface to Embase.com: a case study. *Health Info Libr J* 2019; **36:** 264–77.

32 Lefebvre C, Glanville J, Briscoe S, et al. Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. Cochrane handbook for systematic reviews of interventions version 6.3 (updated February 2022). Cochrane, 2022.

33 Haddaway NR, Grainger MJ, Gray CT. Citationchaser: a tool for transparent and efficient forward and backward citation chasing in systematic searching. *Res Synth Methods* 2022; **13:** 533–45.

34 Borissov N, Haas Q, Minder B, et al. Reducing systematic review burden using Deduklick: a novel, automated, reliable, and explainable deduplication algorithm to foster medical research. *Syst Rev* 2022; **11:** 172.

35 Marshall JC, Murthy S, Diaz J, et al, and the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis* 2020; **20:** e192–97.

36 European Medicines Agency. EMA recommends measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders. 2022. https://www.ema.europa.eu/en/news/ema-recommends-measures-minimise-risk-serious-side-effects-janus-kinase-inhibitors-chronic-inflammatory-disorders (accessed May 10, 2024).

37 White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011; **30:** 377–99.

38 Quartagno M, Carpenter J. jomo: a package for multilevel joint modelling multiple imputation. https://CRAN.R-project.org/package=jomo (accessed June 15, 2024).

39 Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Stat Med* 2017; **36:** 855–75.

40 IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol* 2014; **14:** 25.

41 Murray EJ, Caniglia EC, Petito LC. Causal survival analysis: a guide to estimating intention-to-treat and per-protocol effects from randomized clinical trials with non-adherence. *Res Methods Med Health Sci* 2021; **2:** 39–49.

42 Godolphin PJ, White IR, Tierney JF, Fisher DJ. Estimating interactions and subgroup-specific treatment effects in meta-analysis without aggregation bias: a within-trial framework. *Res Synth Methods* 2023; **14:** 68–78.

43 Royston P, Sauerbrei W. A new approach to modelling interactions between treatment and continuous covariates in clinical trials by using fractional polynomials. *Stat Med* 2004; **23:** 2509–25.

44 Sauerbrei W, Royston P. Investigating treatment-effect modification by a continuous covariate in IPD meta-analysis: an approach using fractional polynomials. *BMC Med Res Methodol* 2022; **22:** 98.

45 Borenstein M. Avoiding common mistakes in meta-analysis: understanding the distinct roles of *Q, I*-squared, tau-squared, and the prediction interval in reporting heterogeneity. *Res Synth Methods* 2024; **15:** 354–68.

46 Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366:** l4898.

47 Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 2008; **61:** 991–96.

48 Guyatt GH, Oxman AD, Vist GE, et al, and the GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336:** 924–26.

49 Schandelmaier S, Briel, M, Varadhan, R, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ* 2020; **192:** E901–06.

50 Deeks JJ, Higgins JPT, Altman DG, McKenzie JE, Veroniki AA, on behalf of the Cochrane Statistical Methods Group. Chapter 10: Analysing data and undertaking meta-analyses. https://training.cochrane.org/handbook/current/chapter-10 (accessed Aug 9, 2024).

51 Ghazaeian Monireh. IRCT | Efficacy and safety of tofacitinib on clinical improvement in hospitalized patients with COVID19: a randomized, double blind multi-centre clinical trial. https://irct.behdasht.gov.ir/trial/59357 (accessed Aug 8, 2024).

52 Rein L, Calero K, Shah R, et al. Randomized phase 3 trial of ruxolitinib for COVID-19-associated acute respiratory distress syndrome. *Crit Care Med* 2022; **50:** 1701–13.

53 Skoetz N, Goldkuhle M, van Dalen EC, et al, and the GRADE Working Group. GRADE guidelines 27: how to calculate absolute effects for time-to-event outcomes in summary of findings tables and Evidence Profiles. *J Clin Epidemiol* 2020; **118:** 124–31.

54 National Institute for Health and Care Excellence. Multiple technology appraisal: remdesivir and tixagevimab plus cilgavimab for treating COVID-19. COVID-19 statistics from OpenSAFELY-TPP database. 2024. https://www.nice.org.uk/guidance/ta971/evidence/final-draft-guidance-2-committee-papers-pdf-13423588240 (accessed Aug 20, 2024).

55 Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999; **319:** 1492–95.

56 Schünemann HJ, Vist GR, Higgins JPT, et al. Chapter 15: Interpreting results and drawing conclusions. https://training.cochrane.org/handbook/current/chapter-15 (accessed July 23, 2024).

57 Viermyr HK, Tonby K, Ponzi E, et al. Safety of baricitinib in vaccinated patients with severe and critical COVID-19 sub study of the randomised Bari-SolidAct trial. *EBioMedicine* 2025; **111:** 105511.

58 Sweeney DA, Tuyishimire B, Ahuja N, et al. Baricitinib treatment of coronavirus disease 2019 is associated with a reduction in secondary infections. *Open Forum Infect Dis* 2023; **10:** ofad205.

59 US Food & Drug Administration. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions. 2021. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death (accessed June 2, 2024).