Effectiveness and safety of janus kinase inhibitors in hospitalized patients with COVID-19: Systematic review and individual patient data meta-analysis of randomized trials

Authors to be discussed. All participating trial teams will be offered co-authorship in case of IPD sharing and reviewing of the study protocol & manuscript.

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Version 1.0; June 1st, 2023

Registration
https://www.crd.york.ac.uk/prospero/

1. Background and Rationale

Since the pandemic outbreak of the coronavirus disease 2019 (COVID-19), immense efforts have been undertaken to find effective treatments.[1–3] Severe COVID-19 is driven by overwhelming, dysregulated inflammation, representing an important target for therapy.[4,5] Janus kinase (JAK) 1/2 enzymes play a pivotal role in inflammatory processes as they mediate the intracellular signaling triggered by cytokine receptors. Thus, they present an important target for the treatment of COVID-19.[6] Instead of blocking only one cytokine at a time such as IL-6 receptor blockers (e.g. tocilizumab), JAK inhibitors may reduce cytokine action more effectively and broadly.[7]

Baricitinib, ruxolitinib, and tofacitinib are all generally considered to be non-specific JAK inhibitors, but some differences in the specificity and potency are described in the literature. Baricitinib has been defined as a JAK1/JAK2 inhibitor, ruxolitinib as JAK2 and tofacitinib as JAK3/JAK1 inhibitors.[8] Importantly, JAK inhibition (esp. JAK2) also interacts with red blood cell and platelet formation and therefore, ruxolitinib is used against a large group of myeloid cancers, called myeloproliferative neoplasms.[9–12] Other JAK inhibitors, such as baricitinib and tofacitinib, are used more commonly in various chronic inflammatory diseases.

COVID-19 RCTs investigating JAK inhibitors

Baricitinib (olumiant) is currently the drug most investigated against COVID-19. For several chronic autoimmune diseases, including rheumatoid arthritis, alopecia areata, and atopic dermatitis, the drug has demonstrated to be effective and, therefore, been approved by the European Medicines Agency (EMA). In addition, it shows a short half-life and few drug-drug interactions.[13] In patients hospitalized with COVID-19, baricitinib may be expected to be effective due to its anti-inflammatory properties but also by directly inhibiting SARS-CoV-2 from cellular entry.[14] A net anti-viral effect has, however, not been demonstrated in clinical trials yet, and concerns have been raised that baricitinib could in fact reduce the antiviral interferon response, as its transcription is also regulated by the JAK-pathway.[15,16]

For patients hospitalized with COVID-19, at least six randomized clinical trials (RCTs) have assessed baricitinib and showed conflicting results.[17–22]

The *ACTT2* trial reported a significant one-day reduction in median time to recovery with baricitinib in combination with remdesivir compared to remdesivir alone, especially among patients receiving high-flow oxygen or non-invasive ventilation.[17]

The *ACTT4* trial was a head-to-dead comparison between baricitinib and dexamethasone (in combination with remdesivir in both arms) and found no difference in mechanical ventilation-free survival by day 29.[18]

The manufacturer-sponsored, placebo-controlled *COV-BARRIER* trial, with approximately 80% of participants receiving dexamethasone, equally distributed across both groups, failed to show a difference in the primary endpoint (occurrence of disease progression to high-flow oxygen/non-invasive ventilation, invasive mechanical ventilation, or death by day 28), but showed a significant effect on 28-day mortality (8% in the baricitinib group vs 13% in the placebo group)[19], in particular in patients with severe disease[20].

The open-label platform trial *RECOVERY* randomised around 8000 hospitalised patients to baricitinib added to usual care or usual care alone. Usual care included dexamethasone as well as the IL-6 inhibitor tocilizumab (29% of patients).[21] An overall significant, but relatively small effect on mortality was shown. The main publication included an aggregate data meta-analysis, involving 12'000 patients from 9 RCTs that assessed baricitinib or another JAK inhibitor, showing an overall

relative reduction in mortality by about one-fifth (rate ration 0.80, 95% CI 0.71-0.89).[21] Other aggregate data meta-analyses on the same research question yielded a similar conclusion.[23–25]

The subgroup of RECOVERY patients treated with corticosteroids, IL-6 receptor blockers and baricitinib provided some evidence that baricitinib may have incremental survival benefit when administered in combination with other immunosuppressive therapy. The immunosuppressive effects of JAK inhibitors seem different to those of corticotherapy and pathophysiologically it makes sense that a combination would lead to an additive effect.[26,27]

Finally, the *Bari-SolidAct* trial, a multicentre, pan-European, double-blinded adaptive platform trial aimed at assessing the effect of baricitinib vs placebo, given in addition to SoC, in patients with severe or critical COVID-19.[22] The primary endpoint (mortality within 60 days) was not met, however, the trial was stopped due to slow recruitment and external evidence of benefit. In an exploratory subgroup analysis, a signal suggesting a potential treatment interaction by vaccination status was found, suggesting more harm in vaccinated than in unvaccinated participants, driven by respiratory complications and severe infections. Cautiously, the authors hypothesize that underlying factors such as comorbidities, age and other altered host immunity factors, rather than vaccination status, may explain these findings.[22]

While baricitinib was the most prominent JAK inhibitor investigated against COVID-19, other randomized trials evaluating ruxolitinib and tofacitinib showed negative or conflicting results.[28–32]

Variability among RCTs and knowledge gaps

Some variability related to study participants exists between the baricitinib RCTs. First, regarding patients' disease severity of the COVID-19 infection: Four trials[17–19,21] included COVID-19 patients irrespective of severity, while two[20,22] included only severe/critical COVID-19 patients. Second, regarding concomitant treatment: Usual care comparator, in particular the use of remdesivir, tocilizumab and dexamethasone among the study participants varied between trials. Third, vaccination status differed across trials with very few vaccinated participants in ACTT-2[17], and COV-BARRIER trials[19,20] and approx. 40% vaccinated participants in Bari-SolidAct[22] and RECOVERY[21]. The other RCTs assessing ruxolitinib and tofacitinib were small and varied in terms of patients' disease stage, standard of care (esp. with regards to dexamethasone), and doses used. A head-to-head comparison of different JAK inhibitors has never been performed.

The timing of JAK inhibitor administration has never been investigated systematically. In principle, JAK inhibitors should not be used too early in COVID-19 in order not to block interferon gamma pathway signaling needed to clear the virus. However, this may be in the same timeframe when pathological secretion of IL-6/IL-1 occurs, and a cytokine storm is starting. Therefore, JAK inhibitors may need to be combined with antiviral treatment and the timing needs to be carefully considered.[33]

Whether people, who already take immunosuppressive medications or have a immunosuppressive medical condition and use a JAK inhibitor due to COVID-19, are at an increased or reduced risk[34] for severe SARS-CoV-2 infection remains unclear, and evidence to guide treatment decision is lacking.

Harm and knowledge gaps

Given that JAK inhibition is essential for formation of red blood cells and platelets, anemia and thrombocytopenia can be induced by using JAK inhibitors (esp. JAK2 inhibitors). Moreover, by modulating the immune response via interferon gamma, reactivation of latent hepatitis B, herpes simplex, herpes zoster and tuberculosis is known, and the occurrence of lymphomas (esp.

aggressive B cell lymphomas[35]) has been observed. However, the short duration of treatment in COVID-19 patients likely prevents such serious side-effects. Other potential side-effects of JAK inhibitors that are being investigated include an increased thrombotic risk, serious heart and cardiovascular related events, and other types of cancer.[36] The US Food and Drug Administration (FDA) issued a warning about the side-effects of JAK inhibitors in September 2021[37] and the European Medicines Agency (EMA) in January 2023[38]. These warnings are based on a large-scale randomized clinical trial, that compared tofacitinib with anti-TNF agents in rheumatoid arthritis patients over 50 years of age with at least one cardiovascular risk factor[39]. Tofacitinib did not reach non-inferiority criteria and led to more major adverse cardiovascular events, cancer, and venous thromboembolism. Again, this may not be relevant for treatment with JAK inhibitors in COVID-19 due to the short treatment duration, however, more in-depth, and comprehensive safety data is needed.

The coadministration of JAK inhibitors along with IL-6 inhibitors (eg, tocilizumab) could produce additive immunosuppression with possible severe bacterial or fungal infections. However, the RECOVERY trial did not record more adverse effects for simultaneous use of baricitinib, tocilizumab, remdesivir and dexamethasone.[21]

WHO COVID-19 living guideline and aggregate data meta-analysis, including knowledge gaps

The WHO COVID-19 living guideline currently recommend baricitinib for patients with severe or critical COVID-19, in combination with corticosteroids and IL-6 receptor blockers (tocilizumab and sarilumab).[40] However, due to differences in the available evidence and a safety signal with tofacitinib[30], the WHO guidelines do not issue a class-wide recommendation, but instead issues a conditional recommendation against other JAK inhibitors such as ruxolitinib and tofacitinib.

Their living aggregate data meta-analysis is based on 4 RCTs with baricitinib[17,19–21], 1 with tofacitinib[30] and 1 with ruxolitinib[31]. Subgroup analyses were undertaken for JAK inhibitors as a class and revealed no evidence for effect modification by age (< 70 years vs older), critical versus severe COVID-19 (ventilation incl. non-invasive ventilation vs no ventilation), dexamethasone, remdesivir and anti-IL-6 use.

Besides the low-quality evidence for more adverse events leading to drug discontinuation in the tofacitinib trial, they did not find any other safety issue.

The WHO guidelines team further defines various research gaps regarding JAK inhibitors including the effect of combination therapy of baricitinib with corticosteroids and IL-6 receptor blockers on longer term outcomes, the effects of JAK inhibitors in settings where HIV infections, tuberculosis and certain fungal infections are endemic, the relative benefits of tofacitinib and ruxolitinib compared to baricitinib and the effect in children, pregnant and lactating women.

The current WHO living aggregate data meta-analysis did not include 4 additional published large-scale RCTs[22,29,41,42] on the topic and further relevant RCTs are registered and still ongoing (see next chapter). Also, the aggregate data meta-analysis did not assess subgroup analyses for vaccination status, multi-morbidity/immunosuppression, nor the effect by time since COVID-19 symptom onset.

Cochrane COVID-19 database review and aggregate data meta-analysis, including knowledge gaps

The Cochrane database review on JAK inhibitors for the treatment of COVID-19 concluded with moderate- to high-certainty evidence from 6 RCTs[17,19–21,28,30] that systemic JAK inhibitors are an effective treatment for COVID-19 in hospitalised patients, because they resulted in fewer deaths and a lower rate of clinical deterioration.[43] They found little or no difference in the rate of adverse events of any grade (including secondary infections), whilst JAK inhibitors probably decrease the

occurrence of serious adverse events. Subgroup analysis by severity of COVID-19 or type of agent failed to identify specific subgroups which benefit from systemic JAK inhibitors.

Moreover, the systematic review identified an additional 12-14 RCTs that are registered but had no full text available yet. These RCTs are evaluating primarily hospitalised patients and anticipate including 60 to 4000 participants. According to the trial registries, the estimated completion dates have passed for at least nine RCTs. The authors further conclude that there is an urgent need for high-quality evidence regarding the effects across different disease severity subgroups, the short- and long-term safety profile and the effect for combining different immunomodulatory treatments against COVID-19.

The planned individual patient data meta-analysis and the main objectives

Aggregate data meta-analyses often face challenges of poor and selective reporting in primary studies, publication bias and low power or even impossibility to assess how a participant-level covariates modify the treatment effect.[44–46] An individual patient data meta-analysis (IPDMA), instead, allows to standardize covariates and outcomes across trials, obtain study results that had not been provided by the trial publication, maximize power to assess heterogeneity of the treatment effect across subgroups, and consistently adjust for baseline differences across trials.[47] Also, an IPDMA can model individual-level interactions directly within studies, which has substantially greater power and avoids ecological bias compared with a meta-regression of aggregate data across studies.[48–50]

No IPDMA has been conducted to assess the effect of JAK inhibitors in COVID-19 patients.

We plan a systematic review and individual patient data meta-analysis of RCTs that evaluated JAK inhibitors in hospitalized COVID-19 patients due to the knowledge gaps outlined in the previous four paragraphs. Our **main objectives** are:

i)   To summarize the **overall benefit and harm** including **all available evidence, including** data from **registered but unpublished eligible RCTs**

ii)   To investigate where treatment effects **differ between pre-specified subgroups**, focusing on **severity of disease, COVID-19 vaccination status, comorbidity (incl. immunosuppression),** and **age**

iii)   To evaluate the **safety profile**, focusing on **cardiac, cardiovascular, and thromboembolic events,** and **secondary infections**

2. Methods

This systematic review and IPDMA will be conducted according to standards of the Cochrane Collaboration (https://training.cochrane.org/handbook) and follow guidance outlined in individual Participant Data Meta-Analysis: A Handbook for Healthcare Research (www.ipdma.co.uk).[51] Reporting will follow the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (PRISMA-IPD).[52]

Inclusion/Exclusion Criteria

Types of Studies

RCTs comparing JAK inhibitors with placebo or usual care in patients hospitalized for COVID-19 (no pseudo-randomized trials); unpublished (i.e., only registered) or published in any format and in any language. We consider eligible trials for which we are not able to obtain individual patient data in an additional aggregate data meta-analysis – and if possible, include them in the subgroup analyses.

1) Types of Participants
Hospitalized patients with a diagnosis of COVID-19 (as per trial definition, i.e., PCR-confirmed vs clinical diagnosis only). Adult patients 16 years or older.

2) Types of Interventions
The experimental intervention consists of the administration of JAK inhibitors at any dose for any period of time. The control intervention consists of no JAK inhibitors (i.e., placebo or usual care as defined by the local context). Studies that use treatment combinations with JAK inhibitors that do not allow for the investigation of effects specific to JAK inhibitors will not be included in this analysis.

3) Outcomes
We will consider RCTs that provide data on any of the outcomes specified for this IPDMA, see Chapter "Outcomes" below. The list of outcomes below was drafted based on the WHO core outcome set[53], the Core Outcome Measures in Effectiveness Trials (COMET) initiative for people with COVID-19[54], and discussions with COVID-19 trial teams, infectious diseases and rheumatology specialists and one patient representative from Switzerland.

Literature Search
We will search Medline/Ovid, Embase.com and the Cochrane Central Register of Controlled Trials using terms for JAK inhibitors (especially baricitinib (Olumiant), delgocitinib, filgotinib , fedratinib , oclacitinib (Apoquel), pacritinib, peficitinib, ruxolitinib (Jakavi), tofacitinib , tasocitinib (Xeljanz), upadacitinib (Rinvoq), nezulcitinib) and COVID-19 based on existing filters.[43,55] For Medline/Ovid and Embase.com, we will add a Cochrane RCT filter.[56,57] We will not impose any time or language restrictions. Additionally, we will search the Cochrane COVID-19 Study Register and the COVID-19 L·OVE Platform. See the detailed search strategy in *Appendix 1*.
We will conduct citation searching (backward/forward) based on the included references using the Citationchaser software (the Lens.org).[58]
We will update the searches once we have carried out a first analysis of gathered IPD.

Study Selection
Two review authors will independently assess potentially eligible titles and abstracts identified by our search. If either review author judges a particular study to be potentially eligible the full text will be obtained, and the two review authors will independently assess the eligibility of the full text article. Disagreements will be resolved by consensus, or, if necessary, by a third reviewer. The number of screened titles and abstracts, eligible for full text review, excluded and included in the analysis will be documented in a flow diagram detailing reasons for exclusion.

Request and collection of IPD
From potentially eligible RCTs, we will request protocols from investigators by email to perform a final eligibility check and to prepare data-sharing agreements. If no answer is received after three

attempts, we will contact the investigators via phone. Provided data will be checked against published results. Where necessary, we discuss and resolve discrepancies with the corresponding study team. To standardize outcomes across trials, we will follow the pre-specified definitions from our protocol.

Assessment of Risk of Bias

Two review authors will independently assess the risk of bias of the included trials using the Cochrane RoB tool 2.0.[59] Potential disagreements will be discussed and resolved through consensus. We will perform an sensitivity analysis based on risk of bias ratings (see below).

Datasets and Data Extraction

Two review authors will independently extract data on patient characteristics, randomization methods, interventions, and outcomes by using a standardized pre-piloted data extraction form in Covidence (www.covidence.org). We will inform the investigators of eligible trials about the project, its magnitude and nature and ask them to participate. If they agree, they will be able to comment on this protocol and be invited to co-author resulting publications (on the basis of the ICMJE criteria[60]). Collaborating investigators will be asked to provide trial protocols and anonymized individual patient data for all randomized patients in the included trials.

Specifically, we will ask for the following baseline data at randomization:
- **Age**
- **Sex**
- **Ethnicity**
- **Country** or region
- **Days with symptoms prior to randomization**
- **ICU care at randomization**
- **Severity of COVID-19** with respect to respiratory support (revised WHO clinical scale 2-5: 2- in hospital without need for oxygen therapy, 3- need for low-flow oxygen therapy, 4- need for high-flow oxygen therapy/non-invasive ventilation, 5- mechanical ventilation/ECMO)
- **Concomitant treatment**: Dexamethasone/systemic glucocorticoids; remdesivir; tocilizumab/other anti-IL-6 drugs; antibiotics; anticoagulants; interferons; any systemic immunosuppressive medication other than dexamethasone/JAK inhibitors/anti-IL-6; none of the above
- **Immunosuppression** as defined as the presence of at least one of the following medical conditions: active malignant neoplasm; lymphoid or myeloid neoplasms; hematopoietic 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; inflammatory bowel disease or other autoimmune disorder for which a patient is being treated with systemic immunosuppressive medication
- **Comorbidities, other than immunosuppression**: chronic lung disease (COPD, Asthma, etc.); chronic liver disease; cardiovascular/cardiac disease (coronary heart disease, stroke, peripheral arterial disease, aortic disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism; incl. other cardiac disorders); arterial hypertension; diabetes mellitus; obesity (BMI 40 kg/m2 and above); current smoker; none of the above
- **C-reactive protein**

- **SARS-CoV-2 vaccination status**
- **SARS-CoV-2 viremia at enrolment** (or binary: PCR-positive vs clinical diagnosis)
- **SARS-CoV-2 variant**
- **SARS-CoV-2 serology** (anti-RBD & anti-S)

Missing data

Missing data will be addressed with the corresponding study teams and, where possible, retrospectively collected. For the remaining missing data of important covariates (i.e., used for adjustment), we will use multiple imputations chained equation techniques.[61] If an outcome is missing for an entire trial, we exclude this trial from the corresponding analyses. If an important covariate (i.e., used for adjustment) is missing for an entire trial, we will not impute any data for this covariate in the trial dataset.

For the imputation of important covariates, we will create and analyze 100 multiply imputed datasets, separately by trial, using the default settings of the mice 3.0 package in R. The parameters of substantive interest will be estimated in each imputed trial dataset separately. According to the nature of the variable, linear regression, logistic regression, or ordinal regression will be used in the respective equations. Since we are using a two-stage approach (see Chapter "Analysis" below), we will pool the repeated estimates into the final estimate, by trial, using Rubin's rule.[61]

Outcomes

The **primary outcome is mortality at 28 days** after randomization, combining data collected during hospitalization (in-hospital mortality) and after hospital discharge (out-of-hospital mortality).

Secondary effectiveness outcomes include:
(i) mortality at and within 60 days
(ii) new mechanical ventilation among survivors within 28 days
(iii) clinical status at day 28 on an ordinal scale (1= outside of hospital alive/reached discharge criteria [WHO clinical progression scale 0-3]; 2= hospitalized without need for oxygen therapy [WHO scale 4]; 3= hospitalized with need for supplemental oxygen [WHO scale 5]; 4= hospitalized with need for high-flow oxygen or non-invasive ventilation [WHO scale 6]; 5= hospitalized with need for mechanical ventilation or extracorporeal membrane oxygenation (ECMO) [WHO scale 7-9]; 6= dead [WHO scale 10])
(iv) days until discharge or reaching discharge criteria up to day 28 (defined as reaching level 1 of the clinical status ordinal scale)
(v) viral clearance (proportion of patients with absence of virus replication by polymerase chain reaction) up to day 5, day 10, and day 15
(vi) quality of life at day 28

Secondary safety outcomes include:
(i) participants with an adverse event grade 3 or 4 (according to the Common Terminology Criteria for Adverse Events[62]), or a serious adverse event, excluding death, by day 28
(ii) adverse events of special interest within 28 days: a) thromboembolic events (venous thromboembolism, pulmonary embolism, arterial thrombosis), b) secondary infections (bacterial pneumonia including ventilator-associated pneumonia, meningitis and encephalitis, endocarditis and bacteremia, invasive fungal infection including pulmonary

aspergillosis), c) Reactivation of chronic infection including tuberculosis, herpes simplex, cytomegalovirus, herpes zoster and hepatitis B, d) serious cardiovascular and cardiac events (including stroke and myocardial infarction), e) events related to signs of bone marrow suppression (anemia, lymphocytopenia, thrombocytopenia, pancytopenia), f) malignancy, g) gastrointestinal perforation (incl. gastrointestinal bleeding/diverticulitis), h) liver dysfunction/hepatotoxicity (grade 3 and 4)

(iii) adverse events, any grade (according to the Common Terminology Criteria for Adverse Events[62]) and serious adverse event, excluding death, within 28 days, grouped by organ classes using MedDRA classification[63]

The number of days for all outcomes refers to number of days since randomization.
We provide further details about the definitions of outcomes in *Appendix 2* below.

3. Analysis

Primary analysis

All patients will be analyzed in the study group to which they were randomized (intention-to-treat principle). We do not expect rare outcomes (<1%) nor small trials (15-50 participants) based on already available published RCTs on the topic. Therefore, we plan to apply an IPDMA two-stage approach.[44,46,51] The first stage involves the separate analysis, by trial, to derive the treatment effect estimates and their variances. We will use binomial logistic regression for the binary outcomes, ordinal logistic regression for the ordinal outcomes and cox regression for time-to-event outcomes – applying restricted maximum likelihood estimation. We will adjust for baseline patient characteristics (age, respiratory support at baseline (ordinal scale 1-3 vs 4-5), dexamethasone use at baseline (y/n), remdesivir use at baseline (y/n), anti-IL-6 use at baseline (y/n)). In the second stage, the treatment effect estimates obtained in the first stage are then combined across all trials (or across each JAK inhibitor class trials), using a random-effects model to allow for between-trial heterogeneity in the true treatment effect.[46,51,64]

Subgroup analyses

To investigate potential effect modification, we will use a similar IPDMA two-stage approach as described above, by first obtaining within-study interaction estimates in each trial and then pooling these treatment-covariate interaction estimates and their variances across trial. Using a two-stage approach automatically avoids aggregation (or ecological) bias, meaning that the within-trial interaction estimates (between individual covariate value and individual response to treatment) are clearly separated from the between-trial interaction estimates.[46] This is sometimes referred to as the "deft" approach.[50] We will plot treatment effects in each participant subgroup for each trial alongside a forest plot of the within-trial interactions.

We will keep the same adjustment variables as in the primary analysis model. We will visually explore heterogeneity in interaction estimates across trials (using the forest plots). We will add the continuous effect modifiers as linear treatment interaction terms and use the multivariable fractional polynomials interaction (MFPI) approach to explore non-linear relationships.[65,66] For the MFPI analysis, a one-stage IPDMA approach is needed. Therefore, for these analyses on the primary endpoint, we will use hierarchical multilevel models with stratified intercepts for trial.

The credibility of sub-group effects, for which we find an interaction p-value smaller than 0.1, will be assessed, independently and in duplicate, using the Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN).[67]

Pre-specified subgroup analyses according to the following PICO:

Population	Hospitalized COVID-19 patients (any severity)			
Intervention	JAK inhibitor (any class)			
Comparator	Standard of care +/- placebo			
Outcome	<u>**Primary outcome: All-cause mortality at day 28**</u>			
Subgroup	Covariate	Hypothesis	**Evidence and Reference**	**Analysis**
	Ventilation requirement (proxy for disease severity)	Larger relative benefit from JAK inhibitors in patients with more severe disease/more ventilation requirements (anti-inflammatory properties of treatment relatively more important than anti-viral properties)	Same trend suggested in several trials[17,21,22,31] across all JAK inhibitor classes, esp. strong in ACTT trials. IPDMA on remdesivir found effect modification.[68] Pathophysiological explanation: Levy et al.[33]	4 groups: a) without oxygen, b) low-flow oxygen, c) high-flow oxygen/non-invasive, d) invasive ventilation/ECMO (WHO clinical scale 2 vs 3 vs 4 vs 5). Two-stage approach.
	Age	Larger relative benefit from JAK inhibitors in younger patients (more immunomodulation still possible)	Same trend suggested in several trials across all JAK inhibitor classes.	Linear interaction term (two-stage approach) and MFPI (one-stage approach)
	Comorbidity incl. immunosuppression	Direction of effect modification unknown, if any, but important to assess given that JAK is an immunomodulatory drug	Unknown	4 groups (if possible): a) no comorbidity (see Chapter "Datasets and Data Extraction" for the definition of comorbidities) b) one comorbidity c) multiple comorbidities d) immunosuppressed (if possible; see Chapter "Datasets and Data Extraction" for the definition of immunosuppression)
	Concomitant COVID-19 treatment (Dexamethasone, Remdesivir, Tocilizumab)	No relative interaction with JAK-inhibitor on primary outcome. However, influences absolute risk reduction.	No trial showed a relative interaction effect.	4 groups (if possible): a) patients without Dexamethasone nor Tocilizumab (effect of JAKi alone) b) patients with Dexamethasone and Tocilizumab (effect of JAKi + Dexamethasone + Tocilizumab) c) patients with Dexamethasone but no Tocilizumab (effect of JAKi + Dexamethasone) d) patients with Tocilizumab but no Dexamethasone (effect of JAKi + Tocilizumab) -> if this group exists in the trials.

Population	Hospitalized COVID-19 patients (any severity)			
Intervention	JAK inhibitor (any class)			
Comparator	Standard of care +/- placebo			
Outcome	**Secondary outcome: Any adverse event grade 3 or 4 or serious adverse event**			
Subgroup	**Covariate**	**Hypothesis**	**Evidence and Reference**	**Analysis**
	Prior vaccination for COVID-19	More harm in vaccinated patients	Safety signal from Bari-SolidAct[22]: In a subsequent post hoc analysis, there was a significant interaction between vaccination status and treatment allocation on the occurrence of serious adverse events in vaccinated participants treated with baricitinib. Vaccinated partici- pants were on average 11 years older, with more comorbidities.	2 groups: Patients with any dose of vaccination vs no dose. Two-stage approach

Exploratory and sensitivity analyses

1) *Univariable subgroup analyses, according to the following PICO:*

Population	Hospitalized COVID-19 patients (any severity)			
Intervention	JAK inhibitor (any class)			
Comparator	Standard of care +/- placebo			
Outcome	Primary outcome: All-cause mortality at day 28			
Subgroup	**Covariate**	**Hypothesis**	**Evidence and Reference**	**Analysis**
	Start of JAK inhibitor since symptom onset	Larger relative benefit from JAK inhibitors in patients with later treatment initiation (anti-inflammatory properties, i.e., against cytokine storm, relatively more important than anti-viral properties).	Pathopysiological explanation: Levy et al.[33] Most trials show a trend according to hypothesis; however, COV-BARRIER (Marconi et al.[19]) shows the contrary.	Linear interaction term (two-stage approach) and MFPI (one-stage approach)
	C-reactive protein	Larger relative benefit from JAK inhibitors in patients with higher C-reactive protein (= more inflammation)	Pathopysiological explanation: Levy et al.[33] No prior evidence. Ruxcovid showed no trend in any direction.	Linear interaction term (two-stage approach) and MFPI (one-stage approach)
	SARS-CoV-2 variant	No relative interaction regarding JAK-inhibitor on primary outcome. However, influences absolute baseline risk.		Depending on data received

2) *Multivariable subgroup analyses*

In order to investigate which patient group across subgroup dimensions (e.g., a vaccinated, immunosuppressed, ventilated, old patient vs a vaccinated, immunocompetent, non-ventilated, young patient) benefit the most or the least from JAK inhibitors, we will explore various

multivariable subgroup analysis methods[69], such as random forest clustering[70] or latent class analyses[71–74].

3) Between-trial subgroup comparisons
We will consider the following between-trial analyses:
- Comparison of RCTs with a low risk of bias or some concerns versus RCTs with a high risk of bias for outcomes at risk for bias. If the analysis suggests a credible and important difference, we will focus our interpretation on trials with low risk of bias.
- Comparison of trials using different classes of JAK inhibitors

4) Pooling with trials that do not share individual patient data
As a sensitivity analysis, we will add trials for which we only receive aggregate. We will pool them in the second stage of the two-stage approach for available outcomes and, if possible, in the subgroup analyses by pooling reported within-trial treatment-covariate interaction estimates.

5) Sensitivity analyses on secondary endpoint models and definitions
- Alternative definition/analysis for the secondary effectiveness endpoint 'new mechanical ventilation among survivors within 28 days': Number of patients who newly received mechanical ventilation or extracorporal membrane oxygenation or died within 28 days post randomization *vs* those known alive and without new mechanical ventilation. This means, the denominator will also include patients with mechanical ventilation at baseline since they can still reach the other endpoint (death) of this composite outcome.
- Alternative definitions/analyses for the secondary safety endpoint 'participants with an adverse event grade 3 or 4, or a serious adverse event, excluding death, by day 28':
  - We will calculate the incidence rate of these adverse events between the treatment groups with a Poisson regression analysis that accounts for all events and different follow-up duration for each participant.
  - We will conduct a time to first adverse event analysis, considering death as a competing risk.

GRADE
We will judge the certainty of evidence, independently and in duplicate, following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach of the most patient-relevant outcomes to report in a Summary of Findings table.[75] The GRADE system uses the following criteria for assigning grades of evidence:
- a) High: We are very confident that the true effect lies close to that of the estimate of the effect
- b) Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- c) Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- d) Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

We plan to stratify the primary effect estimate according to varied high/low absolute baseline risk (high/low background mortality).

Statistical software

We will use R version 4.1.0 or higher (R Foundation for Statistical Computing, Vienna, Austria[76]), and Stata, version 15.1 (College Station, Texas, USA[77]), especially for the MFPI analyses. We chose p < .05 as the level of statistical significance and no adjustments will be made for multiple comparisons.

4. Roles and Responsibilities

The Basel team will be responsible for drafting the initial protocol and incorporating comments from other investigators into the protocol, conducting the literature search and evaluating eligibility, contacting authors, obtaining data, and abstracting data as necessary, conducting the initial analyses, reporting the initial analyses to co-investigators and responding to their feedback in conducting subsequent analyses, and drafting the initial report and responding to feedback in modification of the report.

Investigators from eligible trials will be responsible for providing their protocol, study report, and complete data set with all necessary associated information, feedback on the analyses and the final paper.

5. Registration, data and code sharing

The systematic review and IPDMA and its study protocol will be registered and published on PROSPERO (https://www.crd.york.ac.uk/prospero/). The code will be published and shared on Github. The provided datasets will not be used outside of the scope of this IPDMA without discussion and agreement from the principal investigators of the original trials.

6. Patient and Public Involvement

Two patient representatives were already involved (active consultation on study protocol and publication) for a very similar IPDMA on a different COVID-19 medication. We build upon this input and will engage at least one more patient representative to review this study protocol, focusing on endpoint selection and definition. The same will apply for the corresponding results manuscript.

7. Conflicts of interest

None of the authors declares any financial conflicts of interest related to JAK inhibitors.

8. Funding

This IPDMA is funded by EU-RESPONSE (www.eu-response.eu)

9. Ethics

Ethical approval is not required for this type of study using data in the public domain.

10. Amendments

Should amendments to the existing protocol be necessary, they will be incorporated and uploaded to PROSPERO with the appropriate rationale, date and history of changes.

11. Results dissemination

All results will be published in a peer-reviewed biomedical journal.

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Appendix 1

Detailed Search Strategy

a) Search Narrative
- **Overall search structure and development:**

(COVID-19 search terms)	We used and adapted the CADTH COVID-19 Search String[55] for Ovid Medline. With the Polyglot Search Translator[78], we translated that string to match the syntax for Embase.com and CENTRAL. For Embase.com, we changed ADJX to NEAR/X+1[79].
AND (JAK inhibitors search terms)	We adapted and elaborated the Cochrane COVID-19 Study Register search string from the Cochrane living Database Review[43] to match the other databases we sought.
AND (RCT filter)	We used the following Cochrane RCT filters: Medline Ovid: **Highly Sensitive Search Strategy (2011 version)**[57] Embase.com: Highly Sensitive Search Strategy (30 April 2023 revision)[56]01/06/2023 23:11:00

- **Colour-coding** was used to facilitate reading and understanding the search string and has no other meaning.
- **No limits** were applied. Searches were done exactly as described.
- **Seed references** were used to check for further potentially relevant text words and MeSH terms (using the Yale MeSH Analyzer[80]) and to test the search:
  Medline (Ovid) search finds 11/12: (35123660 OR 33306283 OR 35617986 OR 36226977 OR 35368384 OR 32470486 OR 34133856 OR 35057599 OR 34480861 OR 35908569 OR 36627655OR 34210790).ui. (*Note: 34210790 not found because of the RCT filter*)
  Embase.com search finds 12/12: (35123660 OR 33306283 OR 35617986 OR 36226977 OR 35368384 OR 32470486 OR 34133856 OR 35057599 OR 34480861 OR 35908569 OR 36627655 OR 34210790):ui (*Note: 35368384 and 35908569 had to be searched with title*)

b) Database Searching

1) Medline via Ovid MEDLINE(R) ALL

(COVID-19/ or COVID-19 Drug Treatment/ or exp COVID-19 Testing/ or COVID-19 Vaccines/ or SARS-CoV-2/ or ((coronavirus/ or coronaviridae/ or betacoronavirus/ or coronavirus infections/) and (disease outbreaks/ or epidemics/ or pandemics/)) or (nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARS-COV2 or SARSCOV2 or SARS coronavirus 2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2).ti,ab,kf,nm,ot,ox,rx,px. or ((new or novel or "19" or "2019" or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).ti,ab,kf,ot. or (longCOVID* or postCOVID* or postcoronavirus* or postSARS*).ti,ab,kf,ot. or ((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kf,ot. or ((Wuhan or Hubei) adj5 pneumonia).ti,ab,kf,ot.)

AND (exp "Janus Kinase Inhibitors "/ or exp "Janus Kinases"/ OR (JAK? OR TYK2 OR (Janus ADJ2 kinase) OR Apoquel OR atinvicitinib OR Baricitinib OR brepocitinib OR Delgocitinib OR deucravacitinib OR deuruxolitinib OR Fedratinib OR Filgotinib OR fosifidancitinib OR gusacitinib OR ifidancitinib OR ilginatinib OR ilunocitinib OR itacitinib OR izencitinib OR Jakafi OR Jakavi OR

lorpucitinib OR mivavotinib OR momelotinib OR Nezulcitinib OR nimucitinib OR Oclacitinib OR Olumiant OR Pacritinib OR Peficitinib OR pumecitinib OR Rinvoq OR ropsacitinib OR rovadicitinib OR Ruxolitinib OR Tasocitinib OR Tofacitinib OR Upadacitinib OR Xeljanz OR zasocitinib OR "INCB 028050" OR INCB028050 OR "LY 3009104" OR LY3009104 OR "JTE 052" OR "JTE 052A" OR JTE052 OR JTE052A OR "LEO 124249" OR "LEO 124249A" OR LEO124249 OR LEO124249A OR "GLPG 0634" OR GLPG0634 OR "SAR 302503" OR SAR302503 OR "TG 101348" OR TG101348 OR "PF 03394197" OR "PF03394197" OR "SB 1518" OR SB1518 OR "ASP 015K" OR ASP015K OR "HSDB 8259" OR HSDB8259 OR "INC 424" OR INC424 OR "INCB 018424" OR INCB018424 OR "CP 690550" OR CP690550 OR "ABT 494" OR ABT494 OR "TD-0903" OR TD0903).ti,ab,kw,kf.)

AND (randomized controlled trial.pt. OR controlled clinical trial.pt. OR randomized.ab. OR placebo.ab. OR drug therapy.fs. OR randomly.ab. OR trial.ab. OR groups.ab.)

NOT (exp animals/ not humans/)

Note:
- ab: abstract
- exp: explode
- fs: floating subheading
- kf: Keyword Heading Word
- kw: keyword heading
- nm: Name of Substance Word
- ot: Original Title
- ox: Organism Supplementary Concept Word
- pt: Publication Type
- px: Protocol Supplementary Concept Word
- rx: Rare Disease Supplementary Concept
- ti: title

2) Embase.com (Elsevier)

('sars-related coronavirus'/de OR 'coronavirus disease 2019'/exp OR 'Severe acute respiratory syndrome coronavirus 2'/exp OR (('coronavirinae'/de OR 'Coronaviridae infection'/de OR 'betacoronavirus'/de OR 'coronavirus infection'/de) AND ('epidemic'/de OR 'pandemic'/de)) OR (nCoV* OR 2019nCoV OR 19nCoV OR COVID19* OR COVID OR SARS-COV-2 OR SARSCOV-2 OR SARS-COV2 OR SARSCOV2 OR 'SARS coronavirus 2' OR 'Severe Acute Respiratory Syndrome Coronavirus 2' OR 'Severe Acute Respiratory Syndrome Corona Virus 2'):ti,ab,kw,tt OR ((new OR novel OR 19 OR 2019 OR Wuhan OR Hubei OR China OR Chinese) NEAR/4 (coronavirus* OR 'corona virus*' OR betacoronavirus* OR CoV OR HCoV)):ti,ab,kw,tt OR (longCOVID* OR postCOVID* OR postcoronavirus* OR postSARS*):ti,ab,kw,tt OR ((coronavirus* OR 'corona virus*' OR betacoronavirus*) NEAR/4 (pandemic* OR epidemic* OR outbreak* OR crisis)):ti,ab,kw,tt OR ((Wuhan OR Hubei) NEAR/6 pneumonia):ti,ab,kw,tt)

AND ('Janus Kinase Inhibitors'/exp or 'Janus kinase'/de or 'Janus kinase 1'/de or 'Janus kinase 2'/de or 'Janus kinase 3'/de OR 'protein kinase TYK2'/de OR 'JAK-STAT signaling'/de or (JAK$ OR TYK2 OR (Janus NEAR/3 kinase) OR Apoquel OR atinvicitinib OR Baricitinib OR brepocitinib OR Delgocitinib OR deucravacitinib OR deuruxolitinib OR Fedratinib OR Filgotinib OR fosifidancitinib OR gusacitinib OR ifidancitinib OR ilginatinib OR ilunocitinib OR itacitinib OR izencitinib OR Jakafi OR Jakavi OR lorpucitinib OR mivavotinib OR momelotinib OR Nezulcitinib OR nimucitinib OR Oclacitinib OR Olumiant OR Pacritinib OR Peficitinib OR pumecitinib OR Rinvoq OR ropsacitinib

OR rovadicitinib OR Ruxolitinib OR Tasocitinib OR Tofacitinib OR Upadacitinib OR Xeljanz OR zasocitinib OR "INCB 028050" OR INCB028050 OR "LY 3009104" OR LY3009104 OR "JTE 052" OR "JTE 052A" OR JTE052 OR JTE052A OR "LEO 124249" OR "LEO 124249A" OR LEO124249 OR LEO124249A OR "GLPG 0634" OR GLPG0634 OR "SAR 302503" OR SAR302503 OR "TG 101348" OR TG101348 OR "PF 03394197" OR "PF03394197" OR "SB 1518" OR SB1518 OR "ASP 015K" OR ASP015K OR "HSDB 8259" OR HSDB8259 OR "INC 424" OR INC424 OR "INCB 018424" OR INCB018424 OR "CP 690550" OR CP690550 OR "ABT 494" OR ABT494 OR "TD-0903" OR TD0903):ti,ab,kw)

AND ('randomized controlled trial'/exp OR 'controlled clinical trial'/de OR random*:ti,ab,tt OR 'randomization'/de OR 'intermethod comparison'/de OR placebo:ti,ab,tt OR (compare:ti,tt OR compared:ti,tt OR comparison:ti,tt) OR ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)) OR (open NEXT/1 label):ti,ab,tt OR ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt OR 'double blind procedure'/de OR (parallel NEXT/1 group*):ti,ab,tt OR (crossover:ti,ab,tt OR 'cross over':ti,ab,tt) OR ((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt OR (assigned:ti,ab,tt OR allocated:ti,ab,tt) OR (controlled NEAR/8 (study OR design OR trial)):ti,ab,tt OR (volunteer:ti,ab,tt OR volunteers:ti,ab,tt) OR 'human experiment'/de OR trial:ti,tt) **NOT** ((((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database or databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt)) OR ('cross-sectional study'/de NOT ('randomized controlled trial'/exp OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt)) OR ('case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt)) OR ('systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt)) OR (nonrandom*:ti,ab,tt NOT random*:ti,ab,tt) OR 'random field*':ti,ab,tt OR ('random cluster' NEAR/4 sampl*):ti,ab,tt OR (review:ab AND review:it) NOT trial:ti,tt OR ('we searched':ab AND (review:ti,tt OR review:it)) OR 'update review':ab OR (databases NEAR/5 searched):ab OR ((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de) OR ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de)))

Note:
- ab: abstract
- de: do not explode
- exp: explode
- kw: keyword heading
- ti: title
- tt: Original non-English title

3) Cochrane Central Register of Controlled Trials (CENTRAL)

((nCoV* OR 2019nCoV OR 19nCoV OR COVID19* OR COVID OR SARS-COV-2 OR SARSCOV-2 OR SARS-COV2 OR SARSCOV2 OR "SARS coronavirus 2" OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "Severe Acute Respiratory Syndrome Corona Virus 2" OR ((new OR novel OR 19 OR 2019 OR Wuhan OR Hubei OR China OR Chinese) NEAR/3 (coronavirus* OR ("corona" NEXT virus*) OR betacoronavirus* OR CoV OR HCoV)) OR longCOVID* OR postCOVID* OR postcoronavirus* OR postSARS* OR ((coronavirus* OR ("corona" NEXT virus*) OR betacoronavirus*) NEAR/3 (pandemic* OR epidemic* OR outbreak* OR crisis)) OR ((Wuhan OR Hubei) NEAR/5 pneumonia)):ti,ab,kw)

AND ((JAK? OR TYK2 OR (Janus NEAR/2 kinase) OR Apoquel OR atinvicitinib OR Baricitinib OR brepocitinib OR Delgocitinib OR deucravacitinib OR deuruxolitinib OR Fedratinib OR Filgotinib OR fosifidancitinib OR gusacitinib OR ifidancitinib OR ilginatinib OR ilunocitinib OR itacitinib OR izencitinib OR Jakafi OR Jakavi OR lorpucitinib OR mivavotinib OR momelotinib OR Nezulcitinib OR nimucitinib OR Oclacitinib OR Olumiant OR Pacritinib OR Peficitinib OR pumecitinib OR Rinvoq OR ropsacitinib OR rovadicitinib OR Ruxolitinib OR Tasocitinib OR Tofacitinib OR Upadacitinib OR Xeljanz OR zasocitinib OR "INCB 028050" OR INCB028050 OR "LY 3009104" OR LY3009104 OR "JTE 052" OR "JTE 052A" OR JTE052 OR JTE052A OR "LEO 124249" OR "LEO 124249A" OR LEO124249 OR LEO124249A OR "GLPG 0634" OR GLPG0634 OR "SAR 302503" OR SAR302503 OR "TG 101348" OR TG101348 OR "PF 03394197" OR "PF03394197" OR "SB 1518" OR SB1518 OR "ASP 015K" OR ASP015K OR "HSDB 8259" OR HSDB8259 OR "INC 424" OR INC424 OR "INCB 018424" OR INCB018424 OR "CP 690550" OR CP690550 OR "ABT 494" OR ABT494 OR "TD-0903" OR TD0903):ti,ab)

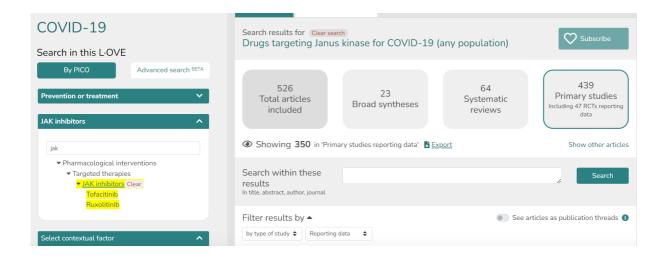4) Cochrane COVID-19 Study Register (https://covid-19.cochrane.org/)

Search string 1 added via search bar	Search string 2 added via search bar	Integrated filters activated	Hits
(Janus OR JAK? OR TYK2 OR Apoquel OR atinvicitinib OR Baricitinib OR brepocitinib OR Delgocitinib OR deucravacitinib OR deuruxolitinib OR Fedratinib OR Filgotinib OR fosifidancitinib OR gusacitinib OR ifidancitinib OR ilginatinib OR ilunocitinib OR itacitinib OR izencitinib OR Jakafi OR Jakavi OR lorpucitinib OR mivavotinib OR momelotinib OR Nezulcitinib OR nimucitinib OR Oclacitinib OR Olumiant OR Pacritinib OR Peficitinib OR pumecitinib OR Rinvoq OR ropsacitinib OR rovadicitinib OR Ruxolitinib OR Tasocitinib OR Tofacitinib OR Upadacitinib OR Xeljanz OR zasocitinib OR "INCB 028050" OR INCB028050 OR "LY 3009104" OR LY3009104 OR "JTE 052" OR "JTE 052A" OR JTE052 OR JTE052A OR "LEO 124249" OR "LEO 124249A" OR LEO124249 OR LEO124249A OR "GLPG 0634" OR GLPG0634 OR "SAR 302503" OR SAR302503 OR "TG 101348" OR TG101348 OR "PF 03394197" OR "PF03394197" OR "SB 1518" OR SB1518 OR "ASP 015K" OR ASP015K OR "HSDB 8259" OR HSDB8259 OR "INC 424" OR INC424 OR "INCB 018424" OR INCB018424 OR "CP 690550" OR CP690550 OR "ABT 494" OR ABT494 OR "TD-0903" OR TD0903)	(random* OR RCT OR placebo OR trial OR blind* OR "Intervention assignment" OR "Treatment and management" OR intervention)	-	TBD

Search development: Using the integrated filter "Randomised" on our JAK search string resulted in 84 hits (tested 01/06/2023). Using the integrated filters "Interventional", "Treatment And Management", and "Randomised" resulted in 76 hits (tested 01/06/2023). So instead of using those filters via the filter bar, we added a search string containing these filter terms and other terms related to RCTs to the JAK search string (171 hits when tested on 01/06/2023).

5) COVID-19 L·OVE Platform (https://iloveevidence.com)

We will use the search "By PICO" function and activate the filter categories "Type of question: Prevention or treatment" "and "Intervention: JAK inhibitors". Within the primary studies, we will select the filters "by type of study: RCT" and "by reported data – reporting data" as shown in the screenshot.

Appendix 2

Primary and secondary outcome definitions

Outcome	Definition
Primary endpoint: All-cause mortality at day 28	Number of patients who died within 28 days post randomization *vs* those known alive. We will include all available mortality information (in- and out-of-hospital data).
All-cause mortality at and within 60 days	We will include all available mortality information and conduct two analyses: a) "at day 60": We assumed that a) patients discharged to home were alive at day 60 and b) patients discharged to palliative care/hospice were dead. In trials that did not collect any data after day 28, we will assume that patients alive at day 28 were still alive at day 60. b) "within 60 days": as a time-to-event analysis until 60 days follow-up, censoring patients at the maximum follow-up time of the trial, at day 60 of follow-up, their date of loss of follow-up or study withdrawal, whichever occurred first.
New mechanical ventilation among survivors at day 28	Number of patients who newly received mechanical ventilation or extracorporal membrane oxygenation AND survived within 28 days post randomization *vs* those known alive and without new mechanical ventilation. Thus, this analysis reflects progression to ventilation among survivors and thus, we will restrict the denominator to those not on mechanical ventilation at baseline and still alive at day 28.
Clinical status at day 28	Number of patients at each level of the 6-point ordinal scale measuring respiratory support and COVID-19 disease severity (modified WHO clinical progression scale): 1: outside of hospital alive/reached discharge criteria (WHO score 0-3) 2: hospitalized without need for oxygen therapy (WHO score 4) 3: hospitalized with need for supplemental oxygen (WHO score 5) 4: hospitalized with need for high-flow oxygen or non-invasive ventilation (WHO score 6) 5: hospitalized with need for mechanical ventilation or extracorporal membrane oxygenation (WHO score 7-9) 6: dead (WHO score 10) If a patient died prior to day 28, then we assumed level 6. If a patient was discharged or reached discharge criteria (level 1) prior to day 28, then we assumed level 1. If there was daily data for the ordinal score available but with missing data for single days, then we carried last observed value forward unless for day 28, whereby we first considered data from the window (+/- 3 days).
Days until discharge/ reaching discharge criteria up to day 28	Days until hospital discharge or reaching discharge criteria, i.e., reaching clinical status 1 on the of 6-point ordinal scale. Patients who died prior to day 28 are assumed not having reached discharge, i.e. counted as 28 days. Otherwise, we used the censoring data, i.e., censored participants at day 28, at their date of loss of follow-up, or study withdrawal, whichever occurred first.
Viral clearance at day 5 Viral clearance at day 10 Viral clearance at day 15	Number of patients with undetectable SARS-CoV-2 PCR (as per definition in the source trial) from nasopharyngeal or oropharyngeal swabs at days 5, 10, and 15 *vs* those with detectable PCR. To qualify as having an undetectable PCR at day 5, the patient had to have a result in his/her last swab up to (and including day 5); i.e. if a patient had, for instance, an undetectable PCR on day 4 and no swab/PCR on day 5, the result from day 4 counted; if a patient had, for instance, an undetectable PCR on day 2, but a detectable PCR on day 5, the result from day 5 counted. The same approach was used for the day 10 (window 6-10 days) and at day 15 (window 11-16 days).
Quality of life at day 28	Quality of life measured on any validated scale at day 28. In addition, we will check for longer term quality of life data and pool data if comparable time points are available. If different scales are used, we will use standardized mean differences for pooling.
Adverse event grade 3 or 4 or serious adverse event within 28 days	Number of patients with an adverse event (AE), grade 3 or 4 or serious adverse event (according to the Common Terminology Criteria for Adverse Events[62]), excluding deaths, within 28 days post randomization *vs* those without any AE or serious AE.
Adverse events of special interest within 28 days	Adverse events of special interest, within 28 days post randomization: a) thromboembolic events (venous thromboembolism, pulmonary embolism, arterial thrombosis), b) secondary infections (bacterial pneumonia including ventilator-associated pneumonia, meningitis and encephalitis, endocarditis and bacteraemia, invasive fungal infection including pulmonary aspergillosis), c) Reactivation of chronic infection including tuberculosis, herpes simplex, cytomegalovirus, herpes zoster and hepatitis B, d) serious cardiovascular and cardiac events (including stroke and myocardial infarction), e) events related to signs of bone marrow suppression (anaemia, lymphocytopenia, thrombocytopenia, pancytopenia), f) malignancy, g)

	gastrointestinal perforation (incl. gastrointestinal bleeding/diverticulitis), h) liver dysfunction/hepatotoxicity (grade 3 and 4)
All adverse events within 28 days, grouped by organ classes	All adverse events, any grade (according to the Common Terminology Criteria for Adverse Events[62]), and serious adverse event, excluding death, grouped by organ classes (using MedDRA classification[63]), within 28 days post randomization.