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Ruxolitinib in addition to standard of care for the treatment of hospitalized patients with COVID-19 (RUXCOVID): results of a randomized, double-blind, placebo-controlled, phase 3 trial

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Summary (300/300 words)

Background

COVID-19 is associated with acute respiratory distress and cytokine release syndrome. Ruxolitinib (Janus kinase [JAK]1/JAK2 inhibitor) reduces inflammatory cytokine levels in disorders characterized by cytokine dysregulation, including graft-versus-host disease, myelofibrosis, and secondary hemophagocytic lymphohistiocytosis.

Methods

RUXCOVID was an international, randomized, double-blind, phase 3 trial of ruxolitinib plus standard of care (SOC) versus placebo plus SOC in patients with COVID-19. Patients (hospitalized but not on mechanical ventilation or in the intensive care unit [ICU]) were randomized 2:1 to ruxolitinib 5 mg twice daily or placebo for 14 days (14 additional days were allowed if no improvement). The primary endpoint was a composite of death, respiratory failure (invasive ventilation), or ICU care by day 29, analyzed by logistic regression including region, treatment, baseline clinical status, age, and sex. ClincialTrials.gov: NCT04362137.

Findings

Between May 4 and September 19, 2020, 432 patients were randomized to ruxolitinib (n=287) or placebo (n=145) plus SOC. The primary objective was not met: the composite endpoint occurred in 34/284 ruxolitinib-treated patients (12·0%) versus 17/144 placebo-treated patients (11·8%; odds ratio, 0·91; 95% CI, 0·48-1·73; p=0·769). Median time to recovery was 1 day faster (numerically) with ruxolitinib versus placebo (8 vs 9 days; hazard ratio, 1·10; 95% CI, 0·89-1·36). By day 29, rates of mortality, invasive ventilation, and ICU care with ruxolitinib versus placebo were 3·1% versus 2·1%, 7·7% versus 6·9%, and 10·6% versus 11·8%, respectively. A trend favoring ruxolitinib was observed in patients with body mass index >30 kg/m^2 and those with higher clinical severity scores; however, subgroup analyses were not adjusted for multiplicity. Common adverse events were headache (8·0%) and diarrhea (7·8%).

Interpretation

Ruxolitinib 5 mg twice daily showed no benefit in the overall study population. A larger sample is required to determine the clinical importance of trends for increased efficacy in patient subgroups.

Funding

Novartis and Incyte.

Research in context

Evidence before this study

Prior to the start of this study (May 2020), evidence regarding pharmacotherapy in severe COVID-19 was extremely limited. There were indications that severe disease and death may be related to hyperinflammation, with similarities to cytokine release syndrome. Studies suggested that agents that block inflammatory pathways, including the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, should be evaluated as treatment for severe COVID-19. Because ruxolitinib, a potent and selective inhibitor of JAK1 and JAK2, had previously shown efficacy in controlling inflammatory cytokine dysregulation in other disorders, such as graft-versus-host disease, myelofibrosis, and secondary hemophagocytic lymphohistiocytosis, it was considered a candidate for the treatment of severe COVID-19 disease.

Added value of this study

This study showed that, in an international population of patients hospitalized for COVID-19 who were not on invasive mechanical ventilation or in the intensive care unit, ruxolitinib 5 mg twice daily plus standard-of-care treatment did not significantly improve outcomes over placebo plus standard-of-care treatment.

Implications of all the available evidence

The recent, North American ACTT-2 study of baricitinib (a JAK1/JAK2 inhibitor) combined with remdesivir in COVID-19 found that addition of the JAK inhibitor to antiviral treatment reduced time to recovery, in particular in hospitalized patients requiring high-flow oxygen support. Two recent trials of tocilizumab in COVID-19 also found that patients with more severe disease were more likely to benefit from immunosuppressive therapy. RUXCOVID was compatible with these more recent studies: although the proportion of patients on high-flow oxygen was small (n=22/432; 5%), a trend toward greater efficacy of ruxolitinib versus placebo was noted in this subgroup. No benefit was observed in patients with no or low-flow oxygen requirements. Much is still being learned about COVID-19, and a need exists to identify patients who would benefit from specific treatments. In novel global health crises, robust a priori sample-size estimates are not always possible. Therefore, we suggest that adaptive designs, including futility analyses and sample-size reestimation, be built into future studies conducted under these conditions.

Introduction

COVID-19, a disease caused by SARS-CoV-2, was declared a global pandemic on March 11, 2020, by the World Health Organization (WHO).[1] As of February 10, 2021, 107 million cases of COVID-19 had been reported, with 2·35 million deaths worldwide.[2] While many people with COVID-19 develop mild or uncomplicated illness, most have some form of respiratory involvement.[3-5] Approximately 20% develop severe disease resulting in pneumonia, hospitalization, and oxygen support; 5% require admission to the intensive care unit (ICU) and invasive mechanical ventilation.[3-5]

On infection, the virus activates the innate and adaptive immune systems, resulting in the release of pro-inflammatory cytokines in an attempt to eliminate the virus.[6] As the disease progresses, the innate immune system response contributes to oxidative injury and alveolar membrane damage, resulting in hypoxia.[6] Hypoxemia is further exacerbated by pulmonary micro- and macrothromboses.[7,8]

Severe disease can be complicated by acute respiratory distress syndrome (the primary cause of death in 70% of COVID-19 fatalities), sepsis and septic shock, and/or multiorgan failure, which have all been linked to the host inflammatory response.[9-12] The marked increase in immune cells and pro-inflammatory chemokines and cytokines, including interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor (TNF), drives lung injury and the activation of additional pro-inflammatory pathways via the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, resulting in further lung inflammation, lung lesions, respiratory dysfunction and failure, and in some cases, death.[8,10]

Many patients with severe respiratory disease due to COVID-19 have features consistent with cytokine release syndrome (CRS),[13] also referred to as cytokine storm, which is related to increased activation of the JAK/STAT pathway.[11] Unlike the systemic CRS that can be caused by chimeric antigen receptor T-cell therapy, CRS-like cytokine storm in COVID-19 predominantly occurs within the lungs.[12] Predictive criteria for cytokine storm risk in COVID-19 were recently proposed, with potential to enable a tailored preventive approach by identifying patients at high risk.[14] In the early stages of the development of treatment strategies for severe COVID-19 disease, it was suggested that host-directed therapies, including JAK inhibition and other immunotherapies, might be of benefit to patients with cytokine storm.[15-17]

Ruxolitinib is a potent and selective inhibitor of JAK1 and JAK2, approved for the treatment of myelofibrosis, polycythemia vera, and steroid-refractory acute graft-versus-host disease (GVHD; US only).[18] Ruxolitinib reduces levels of inflammatory cytokines in disorders in which cytokine dysregulation plays a role, including GVHD[19] and hemophagocytic lymphohistiocytosis.[20-22]

The activity of ruxolitinib in CRS-related diseases warranted investigation of its use in severe COVID-19 disease in those patients with clear symptoms and a positive test for SARS-CoV-2 without progression to intubation or need for ICU care. Furthermore, independent investigator-initiated studies revealed potential clinical benefit from the addition of ruxolitinib to best available therapy.[23,24] Here we report the primary analysis of RUXCOVID (NCT04362137), a global phase 3 study evaluating ruxolitinib plus standard of care (SOC) versus placebo plus SOC in hospitalized patients with COVID-19 not requiring invasive ventilation. The primary endpoint was a composite of death, respiratory failure (requiring invasive mechanical ventilation), or ICU care, by day 29.

Methods

Study Design

RUXCOVID was a randomized, double-blind, placebo-controlled, multicenter, phase 3 study (**Appendix Figure S1**) evaluating the efficacy and safety of ruxolitinib plus SOC vs placebo plus SOC in patients with COVID-19.[25] The study was conducted in 61 centers across 12 countries (Russian Federation, United States, Brazil, Spain, Argentina, Peru, Turkey, Mexico, United Kingdom, Colombia, France, and Germany; **Appendix Table S1**). The study was approved by the institutional review board or central ethics committee at each participating institution and conducted in accordance with the Declaration of Helsinki.

Patients

Patients were required to be ≥12 years old and hospitalized for confirmed COVID-19 (by polymerase chain reaction test or another rapid test from the respiratory tract). Additionally, patients had to meet ≥1 of the following criteria: pulmonary infiltrates (chest x-ray or chest computed tomography scan); respiratory frequency ≥30/min; requiring supplementary oxygen; oxygen saturation ≤94% on room air; or arterial oxygen partial pressure (PaO_2)/fraction of inspired oxygen (FiO_2) <300 mm Hg (40 kPa). Patients were excluded due to any of the following conditions: uncontrolled infection besides COVID-19; currently intubated or intubated between screening and randomization; in ICU at time of randomization; on antirejection,

immunosuppressant, or immunomodulatory drugs (ie, tocilizumab, ruxolitinib, canakinumab, sarilumab, anakinra); unable to ingest tablets at randomization; pregnant or nursing. Full inclusion/exclusion criteria can be found in the **Appendix** and in the protocol (available online with the full text of this article). As in other studies early in the pandemic,[26,27] inclusion was based on clinical criteria rather than hyperinflammation/cytokine storm because, at the time of study initiation, there were no clear cytokine-level criteria associated with COVID-19 that could have reliably been used. Eligible participants were only included in the study after providing informed consent, as approved by each institutional review board/independent ethics committee.

Randomization and masking

Patients were randomly assigned (2:1) to receive oral ruxolitinib or oral matching-image placebo. Block randomization, with a block size of 3, was used to decrease the risk of imbalance. Randomization was stratified by geographic region (North America, Western Europe, Eastern Europe, Latin America, and other). Randomization was done by Interactive Response Technology (IRT). The investigator contacted the IRT system, which assigned a randomization number to each participant, linking them to their unique medication number. Medication numbers were automatically assigned to medication packs. Study treatments were identical in packaging, appearance, taste, and odor.

Participants, investigator staff, persons performing the assessments, and the clinical trial team remained blinded throughout the trial. Unblinding occurred in the case of participant emergencies and at the conclusion of the study

Procedures

Patients received oral ruxolitinib (Novartis Pharma AG, Stein, Switzerland) 5 mg twice daily (BID) or oral placebo, for a total of 14 days. An additional 14 days of study drug was allowed if, in the opinion of the investigator, the patient's clinical signs and symptoms were not improving or worsened, and the potential benefit outweighed the risk.

Ruxolitinib 5 mg twice daily is the approved starting dose in the US for treatment of steroid-refractory acute graft-versus-host disease with demonstrated anti-inflammatory effect.[28] It is also the starting dose recommended for patients with myelofibrosis with a platelet count of 50×10^9/L to $<100\times10^9$/L.[18] Therefore, ruxolitinib 5 mg twice daily was included in this study.

Study treatment was given in combination with SOC therapy according to the investigator's clinical judgment, with appropriate monitoring of potential drug-drug interactions. Permitted concomitant therapies included antivirals (including remdesivir), corticosteroids (including dexamethasone), heparin, anticoagulants, antiemetics, calcineurin inhibitors, azole fungal prophylaxis, broad-spectrum antibiotics, narcotics, and sedatives. Prohibited medications were other JAK inhibitors, aspirin (>150 mg/day), and fluconazole (>200 mg/day).

Dose reductions or interruptions were allowed in the case of drug toxicities (see **Appendix**). If the patient became intubated during the study, an aqueous suspension of the study medication could be delivered via nasogastric tube. Hospitalized patients were assessed daily through day 29 (end of study) for vital signs, oxygen saturation (SpO_2), fraction of inspired oxygen (FiO_2), consciousness, hematology (every other day), clinical chemistry (every other day), in-hospital outcomes, and biomarkers (day 7). Patients who were discharged during the study period were subsequently assessed daily through day 29, via telephone, for clinical status, ventilatory status, adverse events (AEs), and prior or concomitant nondrug therapies. On the date of discharge, patients on oxygen by nasal cannula (≤2 L/min) were assessed for SpO_2 on room air, based on investigator medical judgement. On days 15 and 29, discharged patients had all assessments performed in clinic.

Outcomes

The primary endpoint was a composite of death, respiratory failure (requiring invasive mechanical ventilation), or ICU care, by day 29.

Secondary efficacy endpoints included mortality rate by day 29, respiratory failure by day 29, ICU care by day 29 (post hoc), duration of hospitalization, changes in clinical status, and changes in the National Early Warning Score 2 (NEWS2; **Appendix Figure S2**). Changes in clinical status were measured using the COVID-19–specific 9-point (0-8) ordinal scale proposed by the WHO in February 2020 (**Appendix** and **Table S2**). Assessments included the proportion of patients with improved/deteriorated clinical status scores at day 29; time to ≥1-point improvement from baseline; and mean change in the score from baseline at day 15 and at day 29. Changes in NEWS2 included time to discharge or NEWS2 score ≤2 for 24 hours, whichever came first; and change from baseline in NEWS2 score.

Exploratory efficacy endpoints included time to recovery (a post hoc measure to allow comparison with the recent ACTT-2 study), independence from noninvasive ventilation, and oxygen therapy; duration of ICU stay, supplementary oxygen, and invasive mechanical ventilation; and ratio to baseline in levels of exploratory biomarkers, including C-reactive protein (CRP), ferritin, and D-dimer. Biomarker samples were analyzed in central (for post hoc measures of TNF-α, interferon [IFN]-γ, IL-10, IL-2RA, IL-6, IL-8) and local (ferritin, CRP, procalcitonin, IL-6 [if available], D-dimer) laboratories.

Treatment-emergent AEs were defined as those occurring, or increasing in severity, between the first dose of study medication and the last study visit and were assessed and graded according to the Common Terminology Criteria for Adverse Events (version 5·0). The safety population included all patients who received ≥1 dose of study medication.

Statistical analysis

The study was designed to have ≥80% power to detect an absolute difference of 15% between the treatment groups in the proportion of patients meeting the primary endpoint (based on multiple sample size calculations assuming the rate of the primary outcome in the control group to be in the range of 30%-80%)—the required sample size was 402 patients.

The primary endpoint was analyzed by a logistic regression model with treatment group, region, baseline WHO (0-8) clinical status (≤3, ≥4), age, and sex as covariates. The estimated odds ratio (OR, <1 favors ruxolitinib), p values, and 95% CIs were calculated. Retrieved dropout (RDO) data after study treatment discontinuation were collected. If RDO data were available up to Day 29, those were used for analysis. If no RDO data were collected after study treatment discontinuation, the RDO data were not complete to Day 29, or patients withdrew from the study prior to Day 29, then the patient was considered to meet the primary endpoint, unless they were in one of the following scenarios: (1) there was no occurrence of death, mechanical ventilation, or ICU care in all the available data and patients were discharged from the hospital or (2) the last available data (either on treatment or off treatment) were from day 15 or later and there was no occurrence of death, mechanical ventilation, or ICU care in all the available data.

A post hoc analysis of the primary endpoint examined subgroups defined by baseline demographic and disease state parameters. The subgroup analyses were explored using the same logistic regression model as described for the primary analysis with the additional term of

subgroup factor (if not already included in the model) and the interaction term of subgroup and treatment. No adjustment was made for multiplicity. Secondary and exploratory endpoints were similarly analyzed without adjustments for multiplicity. Time to discharge/recovery was analyzed using a proportional hazards model for competing risk analysis, which included treatment, region, age, sex, baseline WHO (0-8) clinical status, and the interaction term of baseline WHO (0-8) clinical status and treatment as covariates. Patients who were not discharged and did not die were censored at their last assessment date. Median (95% CI) times to discharge/recovery were estimated by the Kaplan-Meier method stratified by baseline clinical status, with dead patients being censored at the maximum follow-up time in the study. For both time to discharge and time to recovery, hazard ratio (HR) and 95% CIs were calculated. HR >1 favors ruxolitinib. This study was registered with ClincialTrials.gov (NCT04362137).

Role of the funding source

The study was sponsored and designed by Novartis and Incyte. Data were analyzed and interpreted by the sponsors in collaboration with all the authors; the sponsors were unaware of the treatment group assignments until database lock. The first draft of the manuscript was prepared by medical writers funded by Novartis and Incyte, with guidance from the authors. All authors reviewed and amended the manuscript, take responsibility for the accuracy and completeness of the data, and verify that the study as reported conforms to the protocol and statistical analysis plan. All authors agreed to the submission of the manuscript for publication.

Results

Between May 4, 2020, and September 19, 2020, 432 patients were randomized 2:1 to receive ruxolitinib (n=287) plus SOC or placebo (n=145) plus SOC (randomized analysis set; **Figure 1**). The greatest proportion of patients were from the Russian Federation (40%; 171/432), followed by the United States (11%; 48/432), Brazil (9%; 41/432), and Spain (9%; 39/432) (see **Appendix Table S1** for all study sites). Patients who developed respiratory failure and/or required ICU care at randomization (ruxolitinib, n=2; placebo, n=1) were excluded from the primary efficacy analyses. The safety set comprised 424 patients who received ≥1 dose of study drug (ruxolitinib, n=281; placebo, n=143).

Baseline demographics and disease characteristics were well balanced between the two treatment groups (**Table 1**). Mean patient age was 56·5 (SD, 13·3) years; 28·2% (122/432) were ≥65 years old and none were <18 years old (range, 20-90 years). Most patients were white

(81·3%; 351/432), and nearly half (46·5%; 201/432) had a body mass index (BMI) >30 kg/m^2. The median time between the onset of COVID-19 symptoms and randomization was 11 (IQR, 8-14) days. Most patients had mild disease (WHO [0-8] clinical status of 3 [hospitalized, no oxygen support], 32·6% [141/432]; WHO [0-8] clinical status of 4 [low-flow oxygen support], 62·0% [268/432]); only 5·1% [22/432] of patients had a WHO [0-8] clinical status of 5 (severe disease; noninvasive ventilation or high-flow oxygen support). Most patients had pneumonia (99·1%; 428/432). At baseline, 249/432 (57·6%) patients were receiving steroids and 28/432 (6·5%) were receiving remdesivir. Rates of concomitant therapy use at baseline by region (eg, antithrombotics, systemic corticosteroids, remdesivir) are shown in **Appendix Table S3**. Concomitant therapy used at any time during the study is shown in **Appendix Table S4**.

The study failed to meet the primary objective (**Table 2**): composite endpoint of death, respiratory failure requiring invasive mechanical ventilation, or ICU care by day 29 occurred in 34/284 patients (12·0%) in the ruxolitinib arm vs 17/144 patients (11·8%) in the placebo arm (OR, 0·91; 95% CI, 0·48-1·73; p=0·769; OR <1 favored ruxolitinib).

The subgroup analysis for the primary outcome (**Figure 2**) revealed that for most subgroups, the proportions of patients who met the primary endpoint were similar between ruxolitinib and placebo. The strongest interaction between subgroup and primary endpoint in ruxolitinib versus placebo was for BMI (>30 kg/m^2 vs ≤30 kg/m^2; unadjusted p=0.034). There was a trend in favor of ruxolitinib in patients with a BMI >30 kg/m^2 (OR, 0·41; 95% CI, 0·15-1·08); however, since the analysis was not adjusted for multiplicity, it should be interpreted with caution. Patients in North America had a better response with ruxolitinib versus placebo than patients in other regions (OR, 0·19; 95% CI, 0·04-1·01); however, this was driven by a high proportion of patients meeting the primary endpoint in the small placebo subgroup (5/16; 31·3%). When assessed by baseline WHO (0-8) clinical status (3, 4, and 5), findings suggested that patients with a higher clinical status score (ie, more-severe disease) had a better response to ruxolitinib (OR <1) than those with a lower baseline clinical status (status 3: OR, 1·16; 95% CI, 0·20-6·66; status 4: OR, 0·90: 95% CI, 0·43-1·90; status 5: OR, 0·28; 95% CI, 0·03-2·78). However, the sample size for patients with the most severe clinical status (score of 5) at baseline was small (n=20). Lower odds ratios were observed (which favored ruxolitinib over placebo) in patients who were aged <65 years (OR, 0·69; 95% CI, 0·31-1·53); used corticosteroids at baseline (OR, 0·77; 95% CI, 0·33-1·80); had no hypertension at baseline (OR, 0·64; 95% CI, 0·25-1·66); and had >10 days between onset of symptoms and randomization (OR, 0·65; 95% CI, 0·28-1·54). No subgroup

analysis was done by remdesivir use since the proportion of patients receiving remdesivir was small (6·5% [28/432] with baseline use, 11·6% [49/424] with use at any time). An additional post hoc analysis examined the effect of steroid treatment at any time during the study on the proportion of patients meeting the primary endpoint: among patients with any steroid use, 13·8% (28/203) in the ruxolitinib group and 13·0% (13/100) in the placebo group met the primary endpoint; among patients with no steroid use, 8·5% (7/82) in the ruxolitinib group and 9·1% (4/44) in the placebo group met the primary endpoint. Note that these steroid use subgroups were defined partly by post-randomization variables, and the subgroup memberships were influenced by treatments the patients received during the study. Thus, we cannot attribute any observed effect (or lack thereof) in this subgroup analysis to the investigational treatment since it could be due to differences in patient population.

The proportions of patients meeting the individual components of the primary endpoint were similar between the treatment groups (**Table 2**). Change in WHO (0-8) clinical status over time was similar across treatment arms (**Appendix Figure S3**) as were the median times to discharge and NEWS2 value of ≤2 maintained for 24 hours (**Table 2**). The median time to recovery was numerically shorter in the ruxolitinib arm vs placebo arm (8 days [95% CI, 8-9 days] vs 9 days [95% CI, 7-11 days]; HR, 1·10 [95% CI, 0·89-1·36]) (**Table 2**). The difference in median time to recovery between ruxolitinib and placebo arms was numerically larger in patients with higher baseline WHO (0-8) clinical status scores (WHO [0-8] clinical status 3: 9 vs 7 days; WHO [0-8] clinical status 4: 8 vs 10 days; WHO [0-8] clinical status 5: 11 vs 15 days; **Appendix Table S5**). Additional secondary endpoints are reported in **Appendix Table S6**.

The effect of treatment on inflammatory biomarkers (CRP, ferritin, D-dimer, procalcitonin, TNF-α, IFN-γ, IL-10, IL-2RA, IL-6, and IL-8) was also assessed (**Appendix Figure S4**). Over the 29 days of study, decreases were observed in the median levels of CRP (42·4 mg/L [IQR, 16·6-93·2 mg/L] to 3·1 mg/L [IQR, 1·3-7·2 mg/L] with ruxolitinib vs 45·0 mg/L [IQR, 16·7-81·6 mg/L] to 2·6 mg/L [IQR, 1·0-5·7 mg/L] with placebo), ferritin (628 µg/L [IQR, 301-1276 µg/L] to 254 µg/L [IQR, 113-513 µg/L] with ruxolitinib and 462 µg/L [IQR, 264·5-999·5 µg/L] to 200 µg/L [IQR, 91-464 µg/L] with placebo), and D-dimer (0·735 mg/L FEU [IQR, 0·400-1·335 mg/L FEU] to 0·540 mg/L FEU [IQR, 0·300-1·000 mg/L FEU] with ruxolitinib and 0·700 mg/L FEU [IQR, 0·440-1·260 mg/L FEU] to 0·520 mg/L FEU [IQR, 0·320-1·020 mg/L FEU] with placebo). Levels of IFN-γ, IL-10, IL-2RA (marker of T-cell activation), and IL-6 decreased (improved) over time

while IL-8, procalcitonin, and TNF-α levels did not. However, no appreciable difference in biomarker levels was observed between ruxolitinib and placebo arms.

Overall, 266/424 (62·7%) patients experienced an AE (**Appendix Table S7**). The most common treatment-emergent AEs in the ruxolitinib vs placebo arms were headache (8·2% [23/281] vs 7·7% [11/143]) and diarrhea (7·5% [21/281] vs 8·4% [12/143], respectively) (**Table 3**).·No meaningful differences in rates of AEs were observed between treatment arms: any AEs, 61·6% (173/281) with ruxolitinib vs 65·0% (93/143) with placebo; grade ≥3 AEs, 12·5% (35/281) vs 16·1% (23/143), respectively. Rates of infection and cytopenia, which were AEs of special interest, were similar between the ruxolitinib and placebo treatment arms: infection (excluding tuberculosis), 8·5% (24/281) vs 9·1% (13/143); leukopenia, 2·5% (7/281) vs 3·5% (5/143); anemia, 2·1% (6/281) vs 0·7% (1/143); thrombocytopenia, 1·1% (3/281) vs 1·4% (2/143), respectively.

There were 46/424 (10·8%) patients who experienced serious adverse events (SAEs; **Appendix Table S8**) with 45/424 patients (10·6%) experiencing an SAE with a grade ≥3. Of these patients, 31/281 (11·0%) were in the ruxolitinib arm and 15/143 (10·5%) were in the placebo arm, with 31/281 (11·0%) and 14/143 (9·8%) being grade ≥3, respectively. A total of 12 patients died during the study (9/281 patients [3·2%] in the ruxolitinib arm and 3/143 patients [2·1%] in the placebo arm); no deaths were considered related to treatment.

Discussion

RUXCOVID was a randomized, phase 3 study evaluating the safety and efficacy of ruxolitinib plus SOC compared with placebo plus SOC in patients with COVID-19. The study did not meet its primary objective, and ruxolitinib was not associated with clinically meaningful improvements versus placebo in the secondary or exploratory endpoints. Overall, clinical status and inflammatory biomarker levels improved over time and were similar in both treatment arms. Ruxolitinib was well tolerated, and rates of treatment-emergent AEs and SAEs were comparable between arms. A trend was seen for greater efficacy of ruxolitinib versus placebo with increased disease severity for the primary endpoint and for the exploratory endpoint of time to recovery. There was also a trend for greater efficacy with ruxolitinib in patients with high BMI.

The results from our study differ from those reported in the recently published ACTT-2 study of baricitinib (a JAK1/JAK2 inhibitor) plus remdesivir.[26] Several possible factors may account for

these differences. Ruxolitinib and baricitinib inhibit JAK1 and JAK2 with similar potency,[17] but potential differences in how downstream proteins such as STAT3 are impacted, especially in the presence of an antiviral drug, cannot be discounted. Levels of phosphorylated STAT3—which has an immunomodulatory role—were significantly greater in various immune cell types isolated from patients with COVID-19–related pneumonia and decreased following treatment with baricitinib in ACTT-2.[26] Although ruxolitinib can also inhibit STAT3 phosphorylation,[29] this was not specifically examined in the present study and could contribute to the observed differences. Study designs were different: the RUXCOVID study had a composite primary endpoint that included mortality, respiratory failure, and ICU care, whereas ACTT-2 had a primary endpoint of time to recovery. Differences in regions may also have affected outcomes. Most patients (>90%) in the ACTT-2 study were treated in North America as opposed to only 11% (48/432) in the present study (in which the small North American subgroup appeared to do better with ruxolitinib). The variability in clinical settings, SOCs, and outcome (such as variation in how patients are triaged to ICUs, with “ICU care” being a component of the composite endpoint) was probably higher in our study, and thus the sensitivity to detect a clinical effect of ruxolitinib may have been lower, even with the inclusion of region in the logistic regression model.

More patients had severe COVID disease (eg, more patients requiring high-flow oxygen or noninvasive mechanical ventilation) in ACTT-2 than in the RUXCOVID study. In the present study, median time to recovery for ruxolitinib compared with placebo was 11 vs 15 days (HR, 1·51 [95% CI, 0·44-5·19]) in patients with more severe disease (WHO [0-8] score 5; noninvasive ventilation or high-flow oxygen); median time to recovery was lower for patients treated with baricitinib + remdesivir in this subgroup of the ACTT-2 study (10 vs 18 days; rate ratio for recovery, 1·51 [95% CI, 1·10-2·08]). Median time to recovery was 8 days with ruxolitinib vs 9 days with placebo in the overall study (HR, 1·10; 95% CI, 0·89-1·36), similar to what was seen in the ACTT-2 study (7 vs 8 days; rate ratio for recovery, 1·16 [95% CI, 1·01-1·32]).

Findings from tocilizumab studies also suggested that patients with more severe disease are the most likely to benefit from treatment with immunomodulatory agents.[30,31] It is possible that patients with COVID-19 require treatment with an immunomodulatory agent in combination with antiviral medication. In ACTT-2, all patients received remdesivir in combination with baricitinib; however, in RUXCOVID, only 12% (49/424) of patients received remdesivir at any time during the study (**Appendix Table S4**). Additionally, baricitinib has been found to prevent viral entry through inhibition of numb-associated kinases (NAKs),[32] which suggests that the mechanism of

action in COVID-19 may be different from that of ruxolitinib, which does not substantially inhibit NAKs at tolerated doses.[17]

A further difference between the ACTT-2 study and RUXCOVID was the choice of dose level: the dose of ruxolitinib used in RUXCOVID (5 mg BID) was at the low end of the dosing range (5-25 mg BID), while that for baricitinib in ACTT-2 (4 mg daily) was at the high end of the dosing range (1-4 mg daily).[18,26] Ruxolitinib at a dose of 5 mg BID showed benefit in a phase 2 study of ruxolitinib in COVID-19[24] and demonstrated efficacy in GVHD.[28] A further motivation for using this dose for the present study was to minimize the risk of cytopenia and infection (ultimately, these AEs were not more prevalent in the ruxolitinib group in this study). Nevertheless, higher initial doses (≥10 mg BID) are routinely used in treating myelofibrosis and GVHD,[18] with a pronounced decrease in inflammatory cytokines observed.[29]

Although the design of our study was scientifically sound (a randomized, double-blind, placebo-controlled study), some limitations and weaknesses could not have been predicted at the time of the study design. The overall therapeutic landscape and SOC changed substantially during the study, and this change may have impacted the proportion of patients meeting the primary endpoint in the control arm. Remdesivir became the SOC in the United States, but not in all countries where our study took place. More recent studies, like ACTT-2, demonstrated the benefit of combination therapy in this setting. Therefore, although the large geographic diversity of our study was a potential strength, making more generalizable conclusions possible, it may be a limitation due to geographic variation in SOC.

Although no other studies have used ICU care as an outcome measure, the possibility of exceeding local ICU capacities was of urgent concern at the time of the study design. However, the timing and use of ICU care varied according to medical practice among centers, which may have impacted our results both by reducing the numbers of eligible patients on high-flow oxygen, who may or may not have been in ICU care, and by introducing variation in the determination of the primary endpoint. Given the inevitable uncertainty in designing studies in a global health crisis caused by a novel disease, futility analysis and/or sample-size reestimation could be considered, especially when no earlier-phase trials have been conducted and it is not clear whether a drug will demonstrate clinical benefit or what the treatment effect could be.

Additionally, at the inception of the study, it was not known which patient groups might benefit the most from treatment. In RUXCOVID, patients were not screened for cytokine storm, and it was assumed that this was the major mechanism of pulmonary hyperinflammation. Patients with COVID-associated hyperinflammation have since been defined as those with a CRP of >150 mg/L and/or a ferritin level of >1500 µg/L.[33] In RUXCOVID, fewer than one-quarter of the patients met this criterion (based on the IQRs of CRP and ferritin). Recent studies suggest that patients with more-severe disease, including those with signs of hyperinflammation, may be the ones that benefit most from treatment with immunomodulatory agents. The DEVENT study evaluated ruxolitinib 5 mg BID and 15 mg BID vs placebo in patients with COVID-19 who required mechanical ventilation.[25] The DEVENT study did not meet its primary endpoint: mortality through day 29 in the two treatment arms vs placebo was 55·2% vs 74·3% (OR, 0·42 [95% CI, 0·171-1·023]; *p*=0·028) in the 5-mg arm and 51·8% vs 69·6% (OR, 0·46 [95% CI, 0·201-1·028]; *p*=0·029) in the 15-mg arm.[34] These findings should be considered in the design of future studies. Moreover, there is a need to identify the subset of patients who would benefit the most from specific treatments, including treatment with immunomodulatory agents. Finally, because robust a priori sample-size estimates are unlikely to be possible in novel global health crises, we suggest that adaptive designs, including futility analyses and sample-size reestimation, be built into future studies conducted under these conditions.

Contributors

All authors contributed to the design of the study and/or collection, analysis, or interpretation of study data. All authors contributed to the drafting and revising of the manuscript and have approved the final version of the manuscript for publication. All authors are accountable for the content and integrity of the manuscript.

Declaration of interests

IG, AG, ALB, AR, JS-O, FT, RT, and SS have no competing interests. MKH has received research funding paid to her institution from Sanofi Genzyme, Nuvaira, and Sunovion and has received drug for a clinical trial from Novartis. MA has participated in clinical studies funded by AbbVie, AstraZeneca, EMS, Eurofarma, GSK, Humanigen, Janssen, Novartis, Sanofi Genzyme, Angion Biomedica Corporation, and Beigene; has received honoraria from Aché, AstraZeneca, Chiesi, Eurofarma, IPI ASAC Brasil, and Sanofi; has received meeting or travel support from AstraZeneca, GSK, Novartis, and Sanofi Genzyme; and has participated in data safety monitor boards and/or advisory boards for Sanofi Genzyme, Chiesi, AstraZeneca, Abbott, and Zambom.

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Data sharing

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com

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Tables

Table 1. Baseline patient demographics and disease characteristics

Demographic variable	**RUX** (n=287)	**Placebo** (n=145)	**Total** (N=432)
Age (years)			
Mean (SD) [range]	56·4 (13·7) [22-90]	56·9 (12·5) [20-84]	56·5 (13·3) [20-90]
Age category, n			
≥65 years	83 (28·9%)	39 (26·9%)	122 (28·2%)
Sex, n			
Male	162 (56·4%)	73 (50·3%)	235 (54·4%)
Race, n			
White	242 (84·3%)	109 (75·2%)	351 (81·3%)
American Indian or Alaska Native	26 (9·1%)	13 (9·0%)	39 (9·0%)
Black or African American	6 (2·1%)	9 (6·2%)	15 (3·5%)
Asian	5 (1·7%)	5 (3·4%)	10 (2·3%)
Multiple	3 (1·0%)	2 (1·4%)	5 (1·2%)
Unknown	5 (1·7%)	7 (4·8%)	12 (2·8%)
Ethnicity, n			
Hispanic or Latino	93 (32·4%)	39 (26·9%)	132 (30·6%)
Not Hispanic or Latino	184 (64·1%)	93 (64·1%)	277 (64·1%)
Not reported	1 (0·3%)	6 (4·1%)	7 (1·6%)
Unknown	8 (2·8%)	7 (4·8%)	15 (3·5%)
Weight (kg)			
n	283	145	428
Mean (SD)	85·2 (18·8)	87·2 (18·7)	85·9 (18·8)
BMI (kg/m^2)			
n	282	144	426
Mean (SD)	29·9 (5·6)	31·0 (6·5)	30·3 (5·9)
BMI >30 kg/m^2, n	129 (44·9%)	72 (49·7%)	201 (46·5%)
Country, n			
Russian Federation	114 (39·7%)	57 (39·3%)	171 (39·6%)
United States	32 (11·1%)	16 (11·0%)	48 (11·1%)

Brazil	28 (9·8%)	13 (9·0%)	41 (9·5%)
Spain	29 (10·1%)	10 (6·9%)	39 (9·0%)
Argentina	16 (5·6%)	11 (7·6%)	27 (6·3%)
Peru	15 (5·2%)	10 (6·9%)	25 (5·8%)
Turkey	13 (4·5%)	7 (4·8%)	20 (4·6%)
Mexico	14 (4·9%)	4 (2·8%)	18 (4·2%)
United Kingdom	10 (3·5%)	4 (2·8%)	14 (3·2%)
Colombia	7 (2·4%)	3 (2·1%)	10 (2·3%)
France	4 (1·4%)	6 (4·1%)	10 (2·3%)
Germany	5 (1·7%)	4 (2·8%)	9 (2·1%)
Days between onset of symptoms and randomization			
Median (IQR)	11·0 (8·0-14·0)	11·0 (8·0-13·5)	11·0 (8·0-14·0)
Days between diagnosis and randomization			
Median (IQR)	5·0 (3·0-8·0)	5·0 (3·0-7·0)	5·0 (3·0-8·0)
WHO (0-8) clinical status, n			
3 – hospitalized with mild disease (no oxygen therapy [defined as SpO_2 ≥94% on room air])	94 (32·8%)	47 (32·4%)	141 (32·6%)
4 – hospitalized with mild disease (oxygen by mask or nasal prongs)	175 (61·0%)	93 (64·1%)	268 (62·0%)
5 – hospitalized with severe disease (noninvasive ventilation or high-flow oxygen)	17 (5·9%)	5 (3·4%)	22 (5·1%)
Missing baseline clinical status	1 (0·3%)	0	1 (0·2%)
Pneumonia, n	284 (99·0%)	144 (99·3%)	428 (99·1%)
Steroid use, n	170 (59·2%)	79 (54·5%)	249 (57·6%)
Remdesivir use, n	21 (7·3%)	7 (4·8%)	28 (6·5%)

BID=twice daily; BMI=body mass index; RUX=ruxolitinib; SpO_2=oxygen saturation; WHO (0-8)=COVID-19–specific 9-point ordinal scale for clinical status proposed by the World Health Organization (**Appendix**, **Table S1**).

Table 2. Primary, selected secondary, and exploratory efficacy outcomes

	RUX (N=287)	Placebo (N=145)	Comparison (95% CI)
Primary endpoint			
Composite endpoint of death, respiratory failure requiring mechanical ventilation, or ICU care by day 29, n/M[a]	34/284 (12·0%)	17/144 (11·8%)	OR, 0·91 (0·48-1·73) p=0·77
Secondary endpoints			
Mortality rate by day 29, n/M	9/286 (3·1%)	3/145 (2·1%)	OR, 1·21 (0·35-5·11)
Respiratory failure by day 29, n/M[a]	22/286 (7·7%)	10/145 (6·9%)	OR, 0·99 (0·45-2·21)
(post hoc) ICU care by day 29, n/M[a]	30/284 (10·6%)	17/144 (11·8%)	OR, 0·81 (0·42-1·55)
Change in WHO (0-8) clinical status at day 29, n/M[b]			
≥1-point improvement	261/286 (91·3%)	136/145 (93·8%)	OR, 0·79 (0·35-1·79)
≥2-point improvement	252/286 (88·1%)	129/145 (89·0%)	OR, 1·00 (0·52-1·92)
≥1-point deterioration	14/286 (4·9%)	5/145 (3·4%)	OR, 1·18 (0·40-3·49)
(post hoc) Death by baseline clinical status by day 29, n/M[c]			
WHO (0-8) clinical status of 3	2/94 (2·1%)	1/47 (2·1%)	OR, 0·80 (0·10-9·53)
WHO (0-8) clinical status of 4	7/175 (4·0%)	2/93 (2·2%)	OR, 1·35 (0·32-7·89)
Duration of hospitalization, median (95% CI), days[d]	9·0 (8·0-10·0%)	9·0 (8·0-12·0%)	HR, 1·04 (0·84-1·28)
Time to hospital discharge or NEWS2 of ≤2 maintained for 24 hours, median (95% CI), days[d]	4·0 (3·0-4·0)	4·0 (3·0-5·0)	HR, 1·02 (0·84-1·23)
Exploratory endpoints			
(post hoc) Time to recovery (no longer infected, or ambulatory with no or minimal limitations), median (95% CI), days[d]	8·0 (8·0-9·0)	9·0 (7·0-11·0)	HR, 1·10 (0·89-1·36)
Time to independence from non-invasive ventilation, median (IQR), days	19·0 (11·5-25·0)	12·0 (9·0-22·0)	NA[e]
Time to independence from supplementary oxygen, median (IQR), days	5·5 (3·0-10·5)	6·0 (3·0-10·0)	NA[e]

Duration of ICU care, median (IQR), days	9·0 (7·0-13·0)	9·0 (4·0-21·0)	NA[e]
Duration of supplementary oxygen, median (IQR), days	5·0 (2·0-10·0)	6·0 (3·0-10·0)	NA[e]
Duration of invasive mechanical ventilation, median (IQR), days	7·5 (5·0-16·0)	12·0 (5·0-28·0)	NA[e]

HR=hazard ratio; ICU=intensive care unit; NA=not analyzed; NEWS2=National Early Warning Score 2; OR, odds ratio; RUX=ruxolitinib; WHO (0-8)=COVID-19–specific 9-point ordinal scale for clinical status proposed by the World Health Organization (**Appendix**, **Table S1**).

Percentages are based on counts (n) and total number of patients included in the analysis (M) (not model based). ORs are based on logistic regression models incorporating treatment group, region, baseline WHO (0-8) clinical status (≤3, ≥4), age, and sex as covariates. An OR <1 means an event was less likely in the RUX arm (which favored RUX for all bar the positive outcome events assessing ≥1- or ≥2-point improvements in WHO (0-8) clinical status, in which an OR >1 favored RUX). An HR >1, representing higher instantaneous rates of discharge or recovery, favored RUX.

[a] Patients who developed respiratory failure and/or required ICU care at randomization are excluded from the analysis.

[b] Patients with missing data at day 29 are treated as non-responders.

[c] There were no deaths in the ruxolitinib and placebo arms in patients with a baseline WHO [0-8] clinical status of 5.

[d] Patients who did not have the event and did not die were censored at their last assessment date. Median is estimated by Kaplan-Meier method, with deaths being censored at the maximum follow-up time in the study.

[e] Only summary statistics were conducted for these exploratory outcomes; all were evaluated on subsets of patients defined by post-baseline events, which could be confounded with treatment effect.

Table 3. Frequent treatment-emergent adverse events (≥2% in any treatment group) by preferred term

Preferred term, n	RUX (n=281)	Placebo (n=143)
Number of patients with ≥1 AE	173 (61·6%)	93 (65·0%)
Headache	23 (8·2%)	11 (7·7%)
Diarrhea	21 (7·5%)	12 (8·4%)
Alanine aminotransferase increased	17 (6·0%)	6 (4·2%)
COVID-19	12 (4·3%)	3 (2·1%)
Cough	12 (4·3%)	3 (2·1%)
Fatigue	10 (3·6%)	2 (1·4%)
Constipation	9 (3·2%)	7 (4·9%)
Hypokalemia	8 (2·8%)	7 (4·9%)
Transaminases increased	7 (2·5%)	3 (2·1%)
Anxiety	6 (2·1%)	1 (0·7%)
Asthenia	6 (2·1%)	0
Hyperkalemia	6 (2·1%)	6 (4·2%)
Nausea	6 (2·1%)	11 (7·7%)
Neutropenia	6 (2·1%)	4 (2·8%)
Pyrexia	6 (2·1%)	2 (1·4%)
Thrombocytosis	6 (2·1%)	3 (2·1%)
Aspartate aminotransferase increased	5 (1·8%)	3 (2·1%)
Hypoxia	5 (1·8%)	5 (3·5%)
Abdominal pain	4 (1·4%)	4 (2·8%)
Dyspnea	4 (1·4%)	3 (2·1%)
Hyperglycemia	4 (1·4%)	5 (3·5%)
Hypertension	4 (1·4%)	3 (2·1%)
Hypoproteinemia	4 (1·4%)	3 (2·1%)
Leukocytosis	4 (1·4%)	4 (2·8%)
Insomnia	3 (1·1%)	4 (2·8%)

Urinary tract infection	3 (1·1%)	5 (3·5%)
Dizziness	2 (0·7%)	4 (2·8%)
Hyponatremia	1 (0·4%)	3 (2·1%)

AE=adverse event; BID=twice daily; RUX=ruxolitinib.

A patient with multiple AEs is counted only once in the “Number of patients with at least one AE” row.

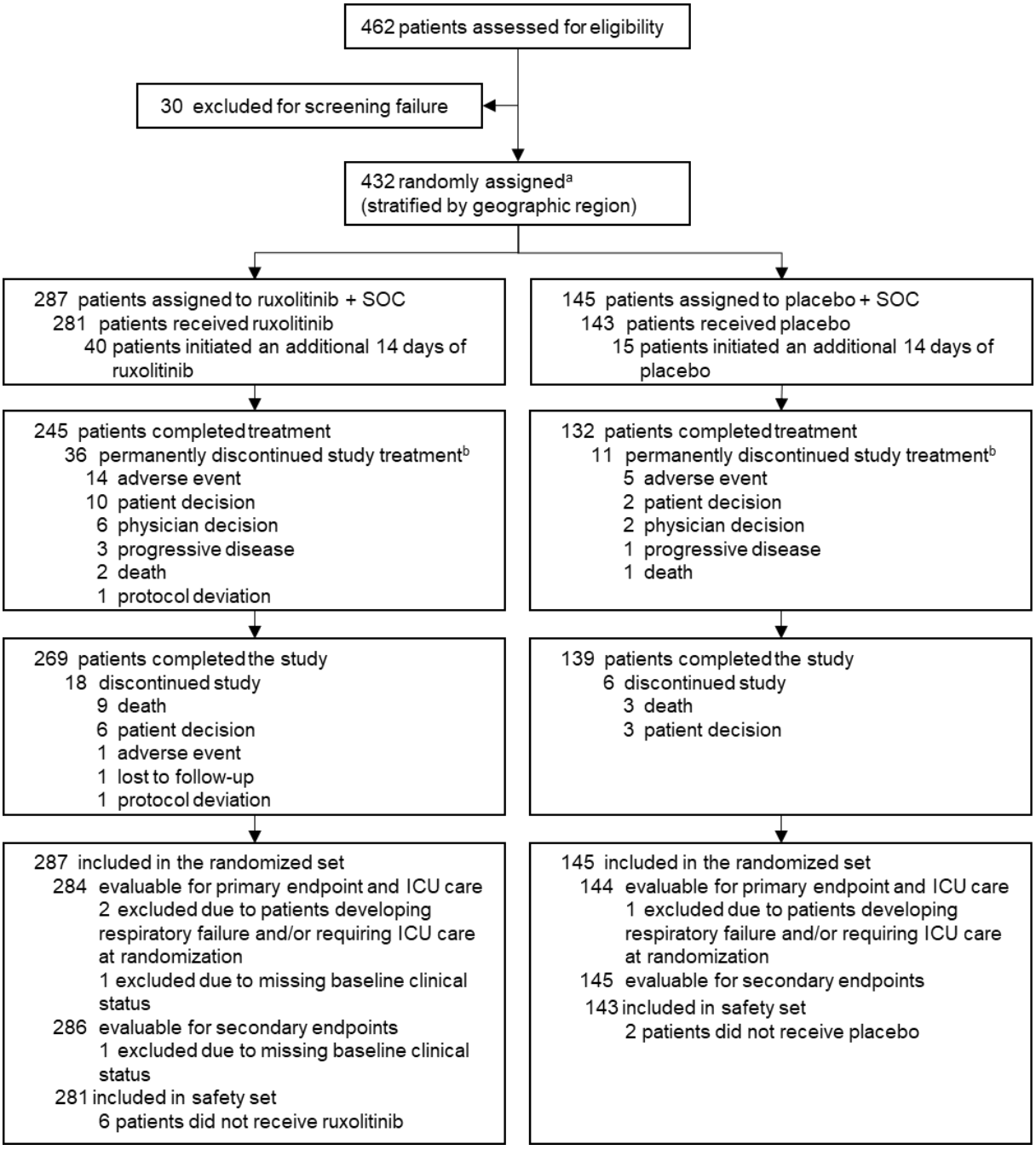
A patient with multiple adverse events within a preferred term is counted only once for that preferred term.

Preferred terms are presented in descending order of frequency in the RUX group.

"COVID-19" relates to AEs of worsening disease.

Figures

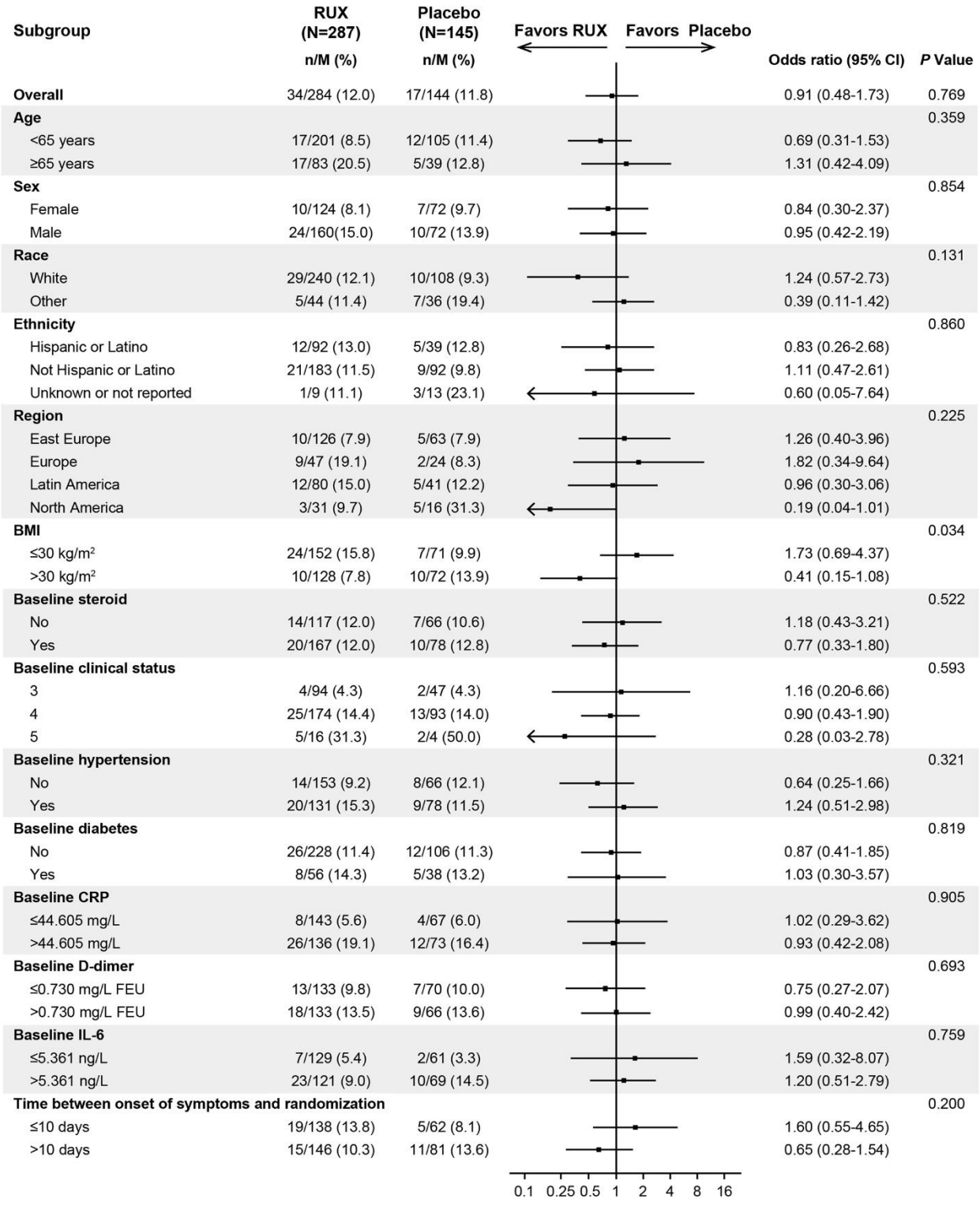
Figure 1. Trial profile



[a] A total of 8 patients were randomized but did not receive treatment due to consent withdrawal (n=4), patient decision (n=3), and misrandomization (n=1).

[b] Includes patients who completed first course of 14-day treatment but discontinued from second course of 14-day treatment.

Figure 2. Primary endpoint according to subgroup analysis (death, respiratory failure, or ICU care by day 29).



Subgroup	RUX (N=287) n/M (%)	Placebo (N=145) n/M (%)	Odds ratio (95% CI)	*P* Value
Overall	34/284 (12.0)	17/144 (11.8)	0.91 (0.48-1.73)	0.769
Age				0.359
<65 years	17/201 (8.5)	12/105 (11.4)	0.69 (0.31-1.53)	
≥65 years	17/83 (20.5)	5/39 (12.8)	1.31 (0.42-4.09)	
Sex				0.854
Female	10/124 (8.1)	7/72 (9.7)	0.84 (0.30-2.37)	
Male	24/160(15.0)	10/72 (13.9)	0.95 (0.42-2.19)	
Race				0.131
White	29/240 (12.1)	10/108 (9.3)	1.24 (0.57-2.73)	
Other	5/44 (11.4)	7/36 (19.4)	0.39 (0.11-1.42)	
Ethnicity				0.860
Hispanic or Latino	12/92 (13.0)	5/39 (12.8)	0.83 (0.26-2.68)	
Not Hispanic or Latino	21/183 (11.5)	9/92 (9.8)	1.11 (0.47-2.61)	
Unknown or not reported	1/9 (11.1)	3/13 (23.1)	0.60 (0.05-7.64)	
Region				0.225
East Europe	10/126 (7.9)	5/63 (7.9)	1.26 (0.40-3.96)	
Europe	9/47 (19.1)	2/24 (8.3)	1.82 (0.34-9.64)	
Latin America	12/80 (15.0)	5/41 (12.2)	0.96 (0.30-3.06)	
North America	3/31 (9.7)	5/16 (31.3)	0.19 (0.04-1.01)	
BMI				0.034
≤30 kg/m^2	24/152 (15.8)	7/71 (9.9)	1.73 (0.69-4.37)	
>30 kg/m^2	10/128 (7.8)	10/72 (13.9)	0.41 (0.15-1.08)	
Baseline steroid				0.522
No	14/117 (12.0)	7/66 (10.6)	1.18 (0.43-3.21)	
Yes	20/167 (12.0)	10/78 (12.8)	0.77 (0.33-1.80)	
Baseline clinical status				0.593
3	4/94 (4.3)	2/47 (4.3)	1.16 (0.20-6.66)	
4	25/174 (14.4)	13/93 (14.0)	0.90 (0.43-1.90)	
5	5/16 (31.3)	2/4 (50.0)	0.28 (0.03-2.78)	
Baseline hypertension				0.321
No	14/153 (9.2)	8/66 (12.1)	0.64 (0.25-1.66)	
Yes	20/131 (15.3)	9/78 (11.5)	1.24 (0.51-2.98)	
Baseline diabetes				0.819
No	26/228 (11.4)	12/106 (11.3)	0.87 (0.41-1.85)	
Yes	8/56 (14.3)	5/38 (13.2)	1.03 (0.30-3.57)	
Baseline CRP				0.905
≤44.605 mg/L	8/143 (5.6)	4/67 (6.0)	1.02 (0.29-3.62)	
>44.605 mg/L	26/136 (19.1)	12/73 (16.4)	0.93 (0.42-2.08)	
Baseline D-dimer				0.693
≤0.730 mg/L FEU	13/133 (9.8)	7/70 (10.0)	0.75 (0.27-2.07)	
>0.730 mg/L FEU	18/133 (13.5)	9/66 (13.6)	0.99 (0.40-2.42)	
Baseline IL-6				0.759
≤5.361 ng/L	7/129 (5.4)	2/61 (3.3)	1.59 (0.32-8.07)	
>5.361 ng/L	23/121 (9.0)	10/69 (14.5)	1.20 (0.51-2.79)	
Time between onset of symptoms and randomization				0.200
≤10 days	19/138 (13.8)	5/62 (8.1)	1.60 (0.55-4.65)	
>10 days	15/146 (10.3)	11/81 (13.6)	0.65 (0.28-1.54)	

Ruxolitinib in addition to standard of care for the treatment of hospitalized patients with COVID-19 (RUXCOVID): results of a randomized, double-blind, placebo-controlled, phase 3 trial

Appendix

Contents

Ruxolitinib dose modifications
Dose reductions or interruptions for patients who did not tolerate the dosing schedule were permitted to allow patients to continue the study treatment. In patients with moderate renal impairment (creatine clearance 30-59 mL/min) or any level of hepatic impairment (Child-Pugh categories A, B, and C) *and* platelet counts between 50 and 100×10^9/L, the dose was reduced to one tablet per day. Once renal/hepatic impairment and platelet count improved to $>100\times10^9$/L, dosing was resumed at one tablet twice daily. Patients with neutropenia were given growth factor supplementation and transfusion as clinically indicated. Patients with grade 3 neutropenia (absolute neutrophil count [ANC] 500 to $<750/mm^3$) had their dose reduced to one tablet per day and were monitored until ANC resolved to grade ≤2 before resuming their initial dose level. Patients with grade 4 neutropenia (ANC $<500/mm^3$) had their dose held until ANC resolved to grade ≤3, at which point they resumed treatment with a reduced dose of one tablet per day. If neutropenia resolved to grade ≤2, patients could resume initial dose level. Patients with platelet counts $<20,0000/mm^3$ had their dose held until the platelet count resolved to $>35,000/mm^3$; treatment was then resumed at a reduced dose level of one tablet per day. If platelet counts remained stable, the dose was cautiously re-escalated. Transfusion support was provided as clinically indicated. Dose reductions or interruptions for nonhematologic toxicity were also permitted. Dose adjustments for aspartate aminotransferase/alanine aminotransferase increase are described fully in the protocol. The dose level was maintained for other nonhematologic grade 1 or 2 events and was held for grade 3 events, until the adverse event (AE) resolved to grade 1 or baseline. Patients with grade 4 events were discontinued from study treatment. All medications used to treat AEs was recorded on the appropriate electronic case report form.

Clinical status
Assessment of clinical status using the 9-category ordinal scale proposed by the World Health Organization (WHO [0-8]; **Table S1**) was recorded at baseline day 1 and then again once daily every morning through day 29 of the study period. If a patient was discharged from the hospital, the assessment was made by phone. On each day, the worst score for the previous day was recorded.
Clinical status analyses included:

- Percentage of patients with a better category (lower number) in clinical status at day 29
- Percentage of patients with at least a 2-point improvement or a 1-point in clinical status at day 29
- Percentage of patients with at least 1-point deterioration in clinical status at day 29
- Time to improvement from baseline category to the next less-severe category of the ordinal scale
- Mean change in the 9-point ordinal scale from baseline to days 15 and 29

National Early Warning Score 2 (NEWS2)
The level of consciousness and the presence/absence of respiratory support were recorded using the NEWS2 scoring system (**Figure S2**). The NEWS2 parameter for respiratory support was the selection of either air or "oxygen," which could include other forms of ventilation to maintain oxygen saturation. These were recorded at the same time points as the vital sign measurements. NEWS2 values were calculated electronically by Novartis based on vital sign parameters and NEWS2-related assessments recorded by the investigator

Vital signs and oxygen saturation
Vital sign measurements included respiratory rate, pulse rate, systolic and diastolic blood pressure, and body temperature. Peripheral oxygen saturation (SpO_2) was to be measured at the same time as vitals. For patients on oxygen by nasal cannula (≤2 L/min), SpO_2 assessment on room air (based on investigator judgment), was also performed at the same time as assessment of vital signs on days 15 and 29 and at discharge. For patients who required supplementary oxygen, the oxygen flow rate (L/min) and/or fraction of inspired oxygen (FiO2) was to be recorded at the same time as the vitals. To allow for assessment of the NEWS2 score, the vital sign parameters and SpO_2 were recorded together once per day for the duration of hospitalization during the study. Following hospital discharge these parameters were measured on days 15 and 29.

In-hospital outcomes
The following hospital outcomes were captured on electronic case report forms: (1) start and end date of mechanical ventilation, (2) start and end date of hospital stay, (3) start and end date of the intensive care unit (ICU) stay, (4) start and end date of supplementary oxygen, (5) start and end date of intubation, (6) start and end date of noninvasive ventilation.

Study discontinuation and treatment

Discontinuation of the study treatment for a participant occurred when study treatment was stopped earlier than the protocol planned duration and could be initiated by either the participant or the investigator. Study treatment was discontinued for a given participant if the investigator believed that continuation would negatively impact the participant's well-being. Study treatment had to be discontinued for the following circumstances: participant/guardian decision, pregnancy, use of prohibited treatment, abnormal liver laboratory results, grade 4 nonhematologic AE attributed to study drug, any situation which might result in a safety risk for the patient, following emergency unblinding, and any laboratory abnormalities in the judgment of the investigator. After study discontinuation, at a minimum the following data were collected at clinic visits or by telephone: new/concomitant treatment and AEs/serious AEs.

Full inclusion/exclusion criteria

Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Patient or guardian/health proxy must provide informed consent (and assent if applicable) before any study assessment is performed.
2. Male and female patients aged ≥12 years (or greater than or equal to the lower age limit allowed by Health Authority and/or Ethics Committee/Institutional Review Board approvals).
3. Patients with coronavirus (SARS-CoV-2) infection confirmed by polymerase chain reaction test or another rapid test from the respiratory tract prior to randomization.
4. Patient is currently hospitalized or will be hospitalized prior to randomization.
5. Patients must meet **at least one** of the below criteria:
    - Pulmonary infiltrates (chest x-ray or chest CT scan)
    - Respiratory frequency ≥30/min
    - Requiring supplemental oxygen
    - Oxygen saturation ≤94% on room air
    - Arterial oxygen partial pressure/fraction of inspired oxygen <300 mm Hg (1 mm Hg=0.133 kPa) (corrective formulation should be used for higher altitude regions [over 1000 m]).

Exclusion criteria

Participants meeting **any** of the following criteria are **not** eligible for inclusion in this study.

1. History of hypersensitivity to any drugs or metabolites of similar chemical classes as ruxolitinib.
2. Presence of severely impaired renal function defined by serum creatinine >2 mg/dL (>176.8 μmol/L) or estimated creatinine clearance <30 mL/min measured or calculated by the Cockcroft-Gault equation or calculated by the updated bedside Schwartz equation.
3. Suspected uncontrolled, active bacterial, fungal, viral, or other infection (besides COVID-19).
4. Current or history of active tuberculosis infection.
5. History of progressive multifocal leukoencephalopathy.
6. Currently intubated or intubated between screening and randomization.
7. In ICU at time of randomization.
8. Patients who are receiving anti-rejection, immunosuppressant, or immunomodulatory drugs (i.e., tocilizumab, ruxolitinib, canakinumab, sarilumab, anakinra).
9. Intubated or in ICU for COVID-19 disease prior to screening.
10. Participating in any other investigational or interventional trials.
11. Unable to ingest tablets at randomization.
12. ALT ≥5 × ULN detected at screening (according to local laboratory reference ranges).
13. Patients who have evidence of liver cirrhosis (Child A to C).
14. Absolute neutrophil count <1000/μL at screening.
15. Platelet count <50,000/μL at screening.
16. Pregnant or nursing (lactating) women.
17. Females ≥12 and <18 years of age and of childbearing potential (e.g., are menstruating) who do not agree to abstinence or, if sexually active, do not agree to the use of highly effective contraception as defined below, throughout the study and for up to 30 days after stopping treatment

OR

Females ≥18 years of age and of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception as defined below, throughout the study and for up to 30 days after stopping treatment. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
- Male sterilization (≥6 months prior to screening). The vasectomized male partner should be the sole partner for that patient.
- Use of oral, injected, or implanted hormonal methods of contraception. Placement of an intrauterine device, intrauterine system, or other forms of hormonal contraception that have comparable efficacy (failure rate of <1%) (e.g., hormone vaginal ring or transdermal hormone contraception; in cases of oral contraception, patients should have been using the same pill at a stable dose for a minimum of 3 months before screening).

Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation ≥6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child-bearing potential.

Table S1. List of PIs by country

Principal investigator	Country
Ricardo Augusto Teijeiro	Argentina
Gabriel Levy Hara	Argentina
Claudio Iastrebner	Argentina
Martti Antila	Brazil
Marina Lima	Brazil
David Machado	Brazil
Carlos Lima	Brazil
Luis Henrique Covello	Brazil
Daniel Santos	Brazil
Cristian Gomez	Colombia
Leonardo Brochado	Colombia
Hugo Macarena	Colombia
Antonie Roquilly	France
Arnaud Desclaux	France
Damien Roux	France
Sébastien Couraud	France
Christian Delafosse	France
Joachim H. Ficker	Germany
Katrin Milger-Kneidinger	Germany
Daniel Droemann	Germany
José Sifuentes-Osornio	Mexico
Norberto Chavez	Mexico
Roberto Ovilla	Mexico
Alfredo Guerreros	Peru
Martin Correa	Peru
Pablo Torres	Peru
Enrique Morello	Peru
Konstantin Trufanov	Russia
Ivan Gordeev	Russia
Alina Agafina	Russia
Alexander Vishnevsky	Russia
Roman Bogdanov	Russia
Anastasia Mochalova	Russia
Tatiana Martynenko	Russia
Tatiana Stepanenko	Russia
Konstantin Zhdanov	Russia
Amparo Lopez Bernus	Spain
Benito Almirante Gragera	Spain
Jose Hernandez	Spain
Jose Garcia	Spain
Carlos Martinez	Spain
Rahmet Guner	Turkey
Fehmi Tabak	Turkey
Gulru Polat	Turkey
Sedat Altin	Turkey
Sinisa Savic	United Kingdom
Ben Parker	United Kingdom
Ashley Whittington	United Kingdom
Mallika Sekhar	United Kingdom
Victoria Potter	United Kingdom
Rachel Ann Bender Ignacio	United States
Mustafa Awili	United States
MeiLan K. Han	United States
Thomas Campbell	United States
Richard Nathan	United States
David Andes	United States
Amesika Nyaku	United States
David Park	United States
Daniel Mogoyoros	United States
Donald Kotler	United States
Brian Pearlman	United States

Table S2. Clinical status: the COVID-19–specific 9-point ordinal scale from the World Health Organization (WHO [0-8])

Ordinal Scale for Clinical Improvement

Patient state	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory (not in hospital or in hospital and ready for discharge)	No limitation of activities	1
	Limitation of activities	2
Hospitalized mild disease	Hospitalized, no oxygen therapy (defined as SpO_2 ≥94% on room air)	3
	Oxygen by mask of nasal prongs	4
Hospitalized severe disease	Noninvasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation plus additional organ support—pressors, renal replacement therapy, extracorporeal membrane oxygenation	7
Dead	Death	8

World Health Organization. Novel Coronavirus: COVID-19 Therapeutic Trial Synopsis (draft February 18, 2020). https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf.

Table S3. Concomitant therapies at baseline by region

Medication, n	Eastern Europe		Western Europe		Latin America		North America	
	RUX (n=127)	**Placebo (n=64)**	**RUX (n=48)**	**Placebo (n=24)**	**RUX (n=80)**	**Placebo (n=41)**	**RUX (n=32)**	**Placebo (n=16)**
Antibiotics	84 (66·1%)	45 (70·3%)	15 (31·3%)	4 (16·7%)	46 (57·5%)	29 (70·7%)	14 (43·8%)	5 (31·3%)
Azithromycin	45 (35·4%)	25 (39·1%)	4 (8·3%)	2 (8·3%)	29 (36·3%)	23 (56·1%)	13 (40·6%)	3 (18·8%)
Antithrombotics	115 (90·6%)	58 (90·6%)	40 (83·3%)	15 (62·5%)	69 (86·3%)	37 (90·2%)	25 (78·1%)	13 (81·3%)
Hydroxychloroquine	25 (19·7%)	11 (17·2%)	1 (2·1%)	1 (4·2%)	1 (1·3%)	0	1 (3·1)	0
Interleukin inhibitors	0	0	0	0	0	0	0	0
Remdesivir	3 (2·4%)	0	9 (18·8%)	3 (12·5%)	0	0	9 (28·1%)	4 (25·0%)
Systemic corticosteroids	59 (46·5%)	28 (43·8%)	25 (52·1%)	9 (37·5%)	63 (78·8%)	31 (75·6%)	23 (71·9%)	11 (68·8%)
Dexamethasone	36 (28·3%)	16 (25·0%)	18 (37·5%)	9 (37·5%)	62 (77·5%)	31 (75·6%)	21 (65·6%)	11 (68·8%)

RUX=ruxolitinib.

Table S4. Concomitant therapies given to ≥10% of patients at any point during the study

	RUX (n=281)	**Placebo (n=143)**	**Total (N=424)**
Dexamethasone	148 (52.7%)	80 (55.9%)	228 (53.8%)
Enoxaparin	150 (53.4%)	78 (54.5%)	228 (53.8%)
Omeprazole	130 (46.3%)	68 (47.6%)	198 (46.7%)
Paracetamol	131 (46.6%)	59 (41.3%)	190 (44.8%)
Enoxaparin sodium	64 (22.8%)	36 (25.2%)	100 (23.6%)
Azithromycin	61 (21.7%)	35 (24.5%)	96 (22.6%)
Ceftriaxone	56 (19.9%)	36 (25.2%)	92 (21.7%)
Ascorbic acid	57 (20.3%)	33 (23.1%)	90 (21.2%)
Levofloxacin	48 (17.1%)	20 (14.0%)	68 (16.0%)
Acetylcysteine	44 (15.7%)	19 (13.3%)	63 (14.9%)
Potassium chloride	40 (14.2%)	18 (12.6%)	58 (13.7%)
Sodium chloride	40 (14.2%)	16 (11.2%)	56 (13.2%)
Amlodipine	32 (11.4%)	20 (14.0%)	52 (12.3%)
Methylprednisolone	36 (12.8%)	16 (11.2%)	52 (12.3%)
Ambroxol	37 (13.2%)	13 (9.1%)	50 (11.8%)
Remdesivir	35 (12.5%)	14 (9.8%)	49 (11.6%)
Atorvastatin	34 (12.1%)	12 (8.4%)	46 (10.8%)
Metformin	30 (10.7%)	15 (10.5%)	45 (10.6%)
Acetylsalicylic acid	29 (10.3%)	15 (10.5%)	44 (10.4%)
Furosemide	29 (10.3%)	14 (9.8%)	43 (10.1%)

RUX=ruxolitinib.

Table S5. Time to recovery by baseline WHO (0-8) clinical status

	n/M	Median time, days (95% CI)	Hazard ratio (95% CI)
Baseline clinical status 3			
RUX	92/94 (97·9%)	9·0 (7·0-10·0)	1·06 (0·76-1·48)
Placebo	45/47 (95·7%)	7·0 (5·0-11·0)	
Baseline clinical status 4			
RUX	158/175 (90·3%)	8·0 (7·0-9·0)	1·12 (0·85-1·48)
Placebo	86/93 (92·5%)	10·0 (7·0-12·0)	
Baseline clinical status 5			
RUX	12/17 (70·6%)	11·0 (6·0-15·0)	1·51 (0·44-5·19)
Placebo	4/5 (80·0%)	15·0 (7·0-NA)	

BID=twice daily; M=number of patients included in the analysis; n=number of patients who recovered; NA=not available; RUX= ruxolitinib; WHO (0-8)=COVID-19–specific 9-point ordinal scale for clinical status proposed by the World Health Organization (**Table S1**).
A hazard ratio >1, representing higher instantaneous rate of recovery, favored RUX.

Table S6. Additional prespecified secondary endpoints

	RUX (n=287)	Placebo (n=145)	Comparison (95% CI)
Secondary endpoints[a]			
Mortality rate by day 15, n/M	6/286 (2·1%)	2/145 (1·4%)	OR, 0·94 (0·20-5·57)
WHO (0-8) clinical status, change from baseline at day 15 and day 29, LS mean (SE)	D15: −1·96 (0·08) D29: −2·61 (0·09)	D15: −1·93 (0·12) D29: −2·69 (0·13)	D15: −0·03 (−0·31 to 0·25) D29: 0·08 (−0·23 to 0·38)
≥1-point improvement at day 15, n/M[b]	250/286 (87·4%)	128/145 (88·3%)	OR, 0·98 (0·51-1·87)
≥2-point improvement at day 15, n/M[b]	206/286 (72·0%)	108/145 (74·5%)	OR, 0·89 (0·55-1·46)
≥1-point deterioration at day 15, n/M[b]	16/286 (5·6%)	9/145 (6·2%)	OR, 0·75 (0·31-1·83)
Time to ≥1 point improvement, median (95% CI), days	9·0 (8·0-10·0)	9·0 (8·0-12·0)	HR, 1·11 (0·90-1·37)
Proportional odds model for better WHO (0-8) clinical status at day 15 and at day 29			D15: OR, 1·12 (0·77-1·63) D29: OR, 0·98 (0·67-1·43)
NEWS2 score, change from baseline, mean (SD)[c]			
Day 3	−0·7 (1·9)	−0·6 (2·1)	NA
Day 5	−1·0 (2·0)	−0·8 (2·2)	NA
Day 8	−1·3 (2·3)	−1·3 (2·6)	NA
Day 11	−1·1 (2·7)	−1·3 (2·7)	NA
Day 15	−1·9 (2·3)	−2·2 (2·4)	NA
Day 29	−2·3 (2·4)	−2·5 (2·2)	NA
SpO_2/FiO_2 ratio, change from baseline at day 15 and day 29, mean (SD)	D15: 90 (104) D29: 106 (98)	D15: 107 (101) D29: 110 (95)	NA
Proportion of patients not on oxygen therapy (SpO_2 ≥94%) at day 15 and day 29, n/M	D15: 255/274 (93·1%) D29: 262/269 (97·4%)	D15: 133/140 (95·0%) D29: 136/139 (97·8%)	D15: OR, 0·61 (0·23-1·63) D29: OR, 1·22 (0·25-5·40)

HR=hazard ratio; ICU=intensive care unit; NA=not analyzed; NEWS2=National Early Warning Score 2; OR, odds ratio; RUX=ruxolitinib; WHO (0-8)=COVID-19–specific 9-point ordinal scale for clinical status proposed by the World Health Organization (Appendix, Table S1).

Percentages are based on counts (n) and total number of patients included in the analysis (M) (not model based). ORs are based on logistic regression models incorporating treatment group, region, baseline WHO (0-8) clinical status (≤3, ≥4), age, and sex as covariates. An OR of <1 means an event was less likely in the RUX arm (which favored RUX for all except the positive outcome events assessing ≥1- or ≥2-point improvements in WHO (0-8) clinical status and the proportional odds model for better WHO (0-8) clinical status, in which an OR >1 favored RUX). An HR of >1, representing higher instantaneous rates of discharge or recovery, favored RUX.

[a] Patients who developed respiratory failure and/or required ICU care at randomization are excluded from the analysis.

[b] Patients with missing data at day 15 are treated as non-responders.

[c] At each visit, only patients with a value at both baseline and the respective visit are included.

Table S7. Overall summary of treatment-emergent AEs

	RUX (n=281)		Placebo (n=143)		Total (N=424)	
Category	All grades, n	Grade ≥3, n	All grades, n	Grade ≥3, n	All grades, n	Grade ≥3, n
AEs	173 (61·6%)	35 (12·5%)	93 (65·0%)	23 (16·1%)	266 (62·7%)	58 (13·7%)
Treatment related	36 (12·8%)	4 (1·4%)	17 (11·9%)	4 (2·8%)	53 (12·5%)	8 (1·9%)
SAEs	31 (11·0%)	31 (11·0%)	15 (10·5%)	14 (9·8%)	46 (10·8%)	45 (10·6%)
Treatment related	0	0	2 (1·4%)	2 (1·4%)	2 (0·5%)	2 (0·5%)
Fatal SAEs	9 (3·2%)	9 (3·2%)	3 (2·1%)	3 (2·1%)	12 (2·8%)	12 (2·8%)
Treatment related	0	0	0	0	0	0
AEs leading to treatment discontinuation	16 (5·7%)	9 (3·2%)	6 (4·2%)	5 (3·5%)	22 (5·2%)	14 (3·3%)
Treatment related	6 (2·1%)	0	4 (2·8%)	3 (2·1%)	10 (2·4%)	3 (0·7%)
SAEs leading to treatment discontinuation	8 (2·8%)	8 (2·8%)	4 (2·8%)	4 (2·8%)	12 (2·8%)	12 (2·8%)
Treatment related	0	0	2 (1·4%)	2 (1·4%)	2 (0·5%)	2 (0·5%)
AEs leading to dose adjustment/interruption	6 (2·1%)	3 (1·1%)	5 (3·5%)	1 (0·7%)	11 (2·6%)	4 (0·9%)
AEs requiring additional therapy	102 (36·3%)	28 (10·0%)	61 (42·7%)	13 (9·1%)	163 (38·4%)	41 (9·7%)

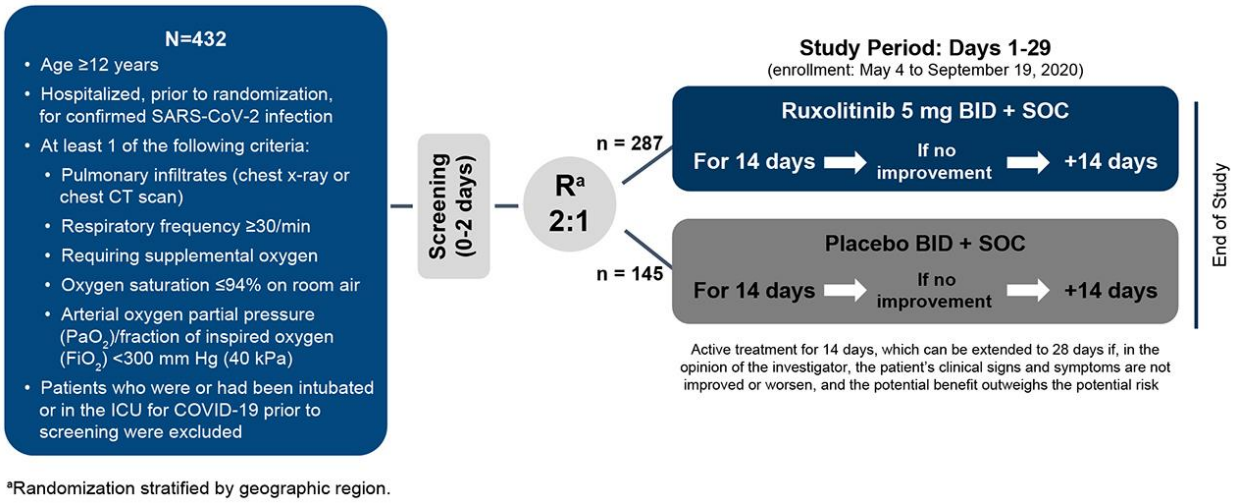
AE=adverse event; BID=twice daily; RUX=ruxolitinib; SAE=serious adverse event.

Table S8. Most frequent treatment-emergent SAEs (≥1% in any treatment group) by preferred term

Preferred term, n	**RUX (n=281)**	**Placebo (n=143)**
Number of patients with ≥1 SAE	31 (11·0%)	15 (10·5%)
COVID-19	8 (2·8%)	3 (2·1%)
Acute respiratory failure	4 (1·4%)	1 (0·7%)
Hypoxia	4 (1·4%)	4 (2·8%)
Pneumonia	3 (1·1%)	0
Respiratory failure	2 (0·7%)	2 (1·4%)

BID=twice daily; RUX=ruxolitinib; SAE=serious adverse event.

Figure S1. Study design



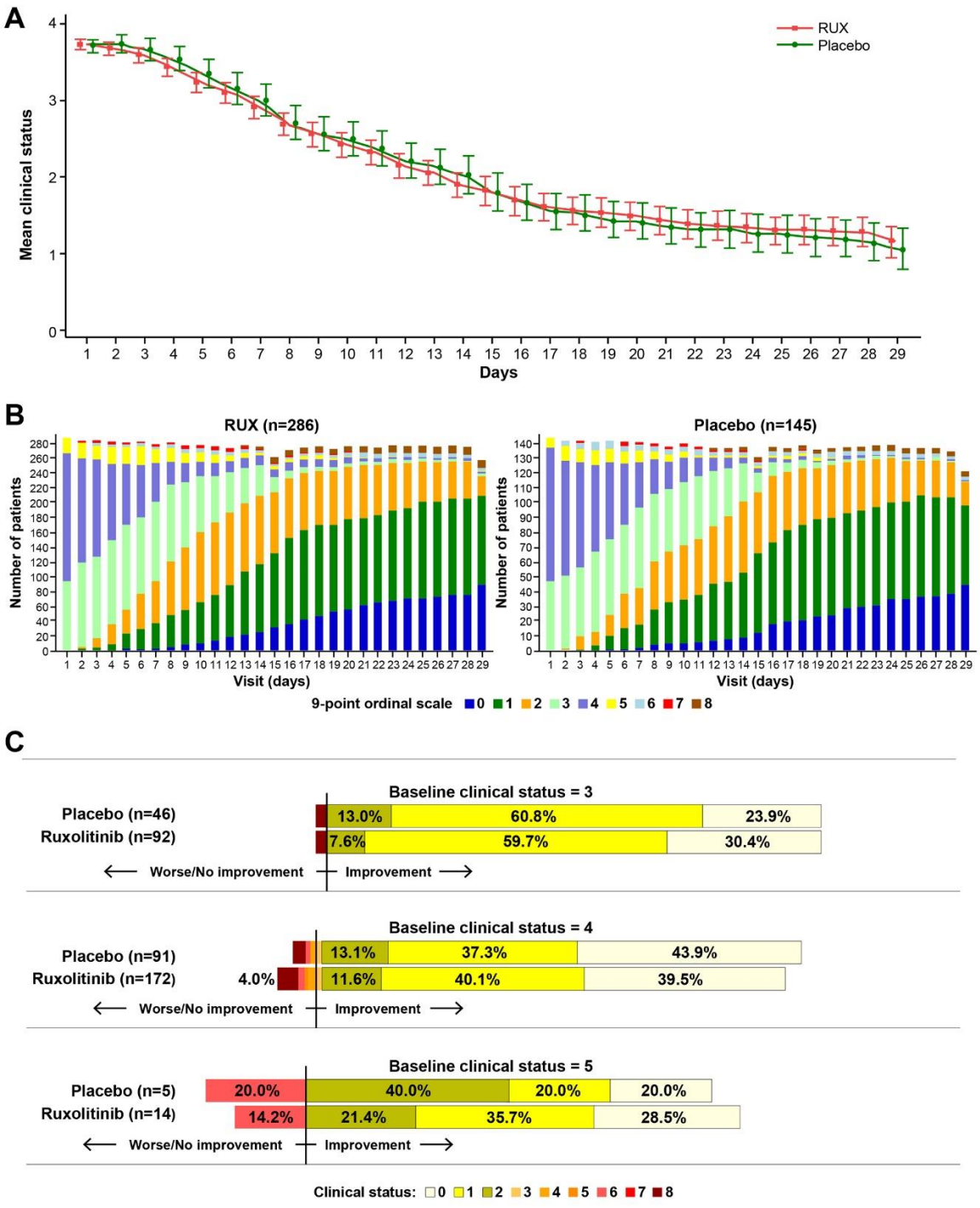
[a]Randomization stratified by geographic region.

Figure S2. NEWS2 score

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35·0		35·1–36·0	36·1–38·0	38·1–39·0	≥39·1	

Reproduced from: Royal College of Physicians. National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS. Updated report of a working party. London: RCP, 2017 (© Royal College of Physicians 2017).

Figure S3. Change in WHO (0-8) clinical status over time. (A) Mean WHO (0-8) clinical status over time by treatment arm. (B) Change in WHO (0-8) clinical status over time. (C) Change in WHO (0-8) clinical status by day 29 by baseline clinical status



WHO (0-8)=COVID-19 specific–9-point ordinal scale for clinical status proposed by the World Health Organization (**Table S1**).

Figure S4. Change in inflammatory biomarkers over time