Clinical Study Protocol

A proof-of concept study of the use of Janus Kinase 1 and 2 Inhibitor, Baricitinib, in the treatment of COVID-19-related pneumonia

Baricitinib for coRona virus pnEumonia: a THerapeutic trial (BREATH trial)

Study type: Exploratory, single-arm proof of concept Phase IIa study

Study categorization: risk category according to HRA: B

Registration number:

Clinical trials.gov: tbd

Study identifier: EudraCT: 2020-001185-11

Principal Investigator: Prof. Carlomaurizio Montecucco

Co-principal Investigator: Prof. Raffaele Bruno

Department of Rheumatology, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; and Department of Infectious and Tropical Diseases, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy.

Viale Camillo Golgi, 19; 27100 Pavia, Italy

(+39) 0382501878

e-mail: c.montecucco@smatteo.pv.it

Coordinating centres:

Department of Rheumatology, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy

Prof. Carlomaurizio Montecucco, Dr.ssa Sara Monti; Medical staff from the Rheumatology Department, Pavia, Italy

Department of Infectious and Tropical Diseases, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy

Prof. Raffaele Bruno, Dr.ssa Valentina Zuccaro; Dr. Paolo Sacchi; Medical staff from the Infectious and Tropical diseases Department, Pavia, Italy

Unit of Clinical Epidemiology and Biometry, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy

Dr.ssa Catherine Klersy, Dr.ssa Valeria Musella

Sponsor: Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy
Investigational product: Baricitinib (Olumiant)
Protocol version: 3.0; 16th April 2020
Funding: IRCCS Policlinico S. Matteo; Lilly

Signature Page

Study number: tbd

Study Title: ***B**aricitinib for co**R**ona virus pn**E**umonia: a **TH**erapeutic trial (BREATH trial)*

The Sponsor-Investigator and trial statistician have approved the protocol version [3.0 dated 16.04.2020] and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Sponsor-Investigator: Prof. Carlomaurizio Montecucco

Pavia, 16/04/2020
   Place/Date   Signature

STUDY SYNOPSIS

Since December 2019 there has been an outbreak of coronavirus-2 (CoV-2) disease (COVID-19) responsible for a severe acute respiratory syndrome, often requiring hospital admission for

ventilatory and medical support. There are no currently approved treatments for COVID-19 infection. Treatment with anti-viral agents combined with Hydroxychloroquine has been often used based on the available pre-clinical evidence and clinical experience collected since the infection outbreak. Despite these treatment measures, approximately 10-20% of patients worsen and develop acute respiratory distress syndrome (ARDS) requiring continuous positive airway pressure therapy or mechanical ventilation with admission to the intensive care units (ICU). The mechanisms underlying the occurrence of ARDS have been related to a cytokine storm leading to an aberrant inflammatory response perpetuating the pulmonary damage, suggesting a role for immunomodulatory/immunosuppressive treatments. Potential new candidate treatments for COVID-19 acute respiratory disease have been identified by means of machine learning techniques by connecting medical information regarding therapies that could block the viral infection interaction with the host cells. Amongst the drugs Baricitinib has been proposed as the most promising one. Baricitinib is a high-affinity inhibitor of the receptor used by CoV-2 to enter lung cells and has the potential to inhibit the endocytosis of the virus and the intracellular assembly of viral particles. Moreover, its action in controlling cytokine signaling involved in inflammation could be useful in the prevention and control of the aberrant host inflammatory response hypothesized to lead the ongoing lung damage and subsequent mortality in severe cases of COVID-19.

The objective of the study is to assess the efficacy and safety of Baricitinib in the treatment of patients with COVID-19 pneumonia.

This will be a proof-of-concept trial with an exploratory single-arm proof of concept Phase IIa study to assess the efficacy and safety profile of Baricitinib in a limited number of patients with severe acute respiratory syndrome (SARS)-CoV-2 pneumonia. If the initial proof of concept phase will lead to favourable results, an open-label, Phase II, randomized controlled trial will be then designed and performed to confirm the results obtained in the proof of concept phase. The proof-of-concept phase guarantees that no safety issues arise on a limited number of patients in the use of a drug new to the current condition being treated.

Baricitinib 4 mg/daily will be prescribed for 7 days to eligible patients showing signs of acute inflammatory response activation. The primary outcome of the study will be the response to treatment. A patient is considered responder in the absence of either moderate to severe oxygenation impairment or death, whichever occurs first, within 8 days from enrolment. The main secondary outcomes will include the responder rate and mortality at 15 days, the

quantification of patients experiencing moderate to severe oxygenation impairment, rate of patients admitted to the ICU, length of hospitalization, mortality at 28 days, rate of re-admission, and adverse events. The duration of the study will be 28 days. In the proof of concept phase, 13 patients will be enrolled; if the responders will be at least 4 patients without safety issues, Baricitinib will be considered for further studies.

ABBREVIATIONS

ABG: arterial blood gas test

ARDS: acute respiratory distress syndrome

CoV: coronavirus

CoV-2: coronavirus-2

COVID-19: coronavirus disease 2019

C-PAP: continuous positive airway pressure

CRP: c-reactive protein

CRS: cytokine release syndrome

DVT/PE: deep venous thrombosis/pulmonary embolism

HIV: human immunodeficiency virus

JAK: Janus Kinase

PaO2/FiO2: ratio of arterial oxygen partial pressure to fractional inspired oxygen

SARS: severe acute respiratory syndrome

SpO2: peripheral capillary oxygen saturation

STUDY SCHEDULE

Study Period:	Screening	Baseline	Treatment period	Follow-up period	End of study
Day	Day -1	Day 0	Days 0-7	Day 8 – day 15	28 days
Informed Consent	X	X			

Inclusion/Exclusion Criteria	X	X			
Demographics	X	X			
Medical History	X	X			
Physical examination	X	X	X	X	
Vital signs	X	X	X	X	
Hematology	X	X	X	X	
Biochemistry (including ferritin)	X	X	X	X	
D-Dimer	X	X	X		
Hepatitis B, C tests, HIV	X	X			
Imaging tests	X	X		X	
ABG	X	X	X	X	
Adverse events			X	X	X
Blood sample collection for storage (additional cytokine analysis and exploratory biomarkers analysis in future)		X	X		

Summary

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor-Investigator

Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, is the sponsor of this investigator initiated study.

1.2 Principal Investigator(s)

Prof .Carlomaurizio Montecucco
Prof. Raffaele Bruno (co-PI)

Department of Rheumatology, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; Department of Infectious and Tropical Diseases, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy. Viale Camillo Golgi, 19; 27100 Pavia, Italy; (+39) 0382501878

1.3 Co-investigators

Dr.ssa Sara Monti
Dr.ssa Valentina Zuccaro
Department of Rheumatology and Department of Infectious and Tropical Diseases, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; Viale Camillo Golgi, 19

1.4 Statistician ("Biostatistician")

Dr.ssa Catherine Klersy (biostatistician)
Dr.ssa Valeria Musella (database manager)

Unit of Clinical Epidemiology and Biometry, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; Viale Camillo Golgi, 19; (+39) 0382503557

1.5 Laboratory

Laboratory of Virology
Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; Viale Camillo Golgi, 19

1.6 Monitoring institution

Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; Viale Camillo Golgi, 19

1.7 Data Safety Monitoring Committee

Prof. Lorenzo Cavagna[1]
Dr.ssa Laura Bogliolo[1]
Dr. Paolo Sacchi[2]

1. Department of Rheumatology, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy
2. Department of Infectious and Tropical Diseases, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy

The data safety monitoring committee has no competing interests.

2. ETHICAL AND REGULATORY ASPECTS

2.1 Study registration

The study has been registered on EUDRACT and is planned to be registered on Clinical

trials.gov as soon as ethical approval has been obtained.

2.2   Competent Ethics Committee (CEC)

The responsible investigator will ensure that approval from the Competent Ethics Committee (CEC) is sought for the clinical trial.

The principal investigator will monitor, together with the DSMC on the safety of the study to assess the need of a premature study end. The principal investigator will ensure that no changes are made to the protocol without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants. Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.9.

2.3   Competent Authorities (CA)

The Sponsor will obtain approval from the competent authority (AIFA) before the start of the clinical trial. Premature study end or interruption of the study is reported within 15 days to the CA. The regular end of the study is reported to the CA within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.9.

2.4   Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the Italian Law and Italian regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.5   Declaration of interest

No conflict of interest (independence, intellectual, financial, proprietary) to declare.

2.6   Patient Information and Informed Consent

Patients will be informed about the study by the treating medical physician upon admission. Patient will be informed that no compensation is provided for participation to the study. The

treating physician will illustrate the nature of the study, its purpose, all study procedures, duration of the study, alternative therapies, benefits and risks, and any discomfort it may entail to the patient. Patients will be informed about the limitations of existing knowledge regarding Baricitinib's efficacy in the management of COVID-19, and the precautions indication as well as the presence of known risk of being treated with Baricitinib while the subject of an active infection. Patients will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The participant will be informed that his/her medical records may be examined by authorised individuals other than their treating physician. All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. The patient will have time (up to 24 hours) to consider the study and ask all questions.

Eligible patients will provide written informed consent at screening visit provided by the treating physician before the patient is submitted to any study procedure. A copy of the signed informed consent will be given to the patient. The consent form must also be signed and dated by the investigator (or his designee) at the same time as the participant sign, and it will be retained as part of the study records.

Patients will have the possibility to withdraw informed consent at any time during the study period. Data collected up to the withdrawal of consent to participate in the study will be used for the final analyses.

2.7 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Anonymity of the participants will be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files. For data verification purposes, authorised representatives of the Sponsor (-Investigator), a competent authority (e.g. AIFA), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical

history. The investigators will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections, providing direct access to source documents.

2.8   Early termination of the study

The Sponsor-Investigator (and any competent authority) may terminate the study prematurely when the safety of the participants is doubtful or at risk, when alterations in accepted clinical practice arise that make the continuation of a clinical trial unwise, or in case of early evidence of harm of the experimental intervention.

2.9   Protocol amendments

The principal investigator will be allowed to amend the protocol or to provide suggestions for a protocol amendment. Important protocol modifications will be communicated to relevant parties (investigators, CEC, competent authorities, trial participants, trial registries). Substantial amendment will only be implemented after approval of the CEC and CA respectively. These procedures will be put in place prior to proceeding to the second part of the study, in case of successful completion of the proof of concept phase.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC/CA. Such deviations shall be documented and reported to the sponsor and the CEC/CA as soon as possible.

All non-substantial amendments are communicated to the CA as soon as possible if applicable and to the CEC within the Annual Safety Report (ASR).

3.   BACKGROUND AND RATIONALE

3.1   Background and Rationale

Since December 2019 there has been an outbreak of coronavirus-2 (CoV-2) disease (COVID-19) responsible for a severe acute respiratory syndrome, often requiring hospital admission for ventilatory and medical support (1). The outbreak originated in Wuhan city, in China but has subsequently spread to Europe from February 2020. Reports from the Chinese Centre for Disease Control (China CDC) has reported the isolation of 44672 cases, with the majority belonging to the age group 30-79 years old. The mortality rate amongst these cases was 2.3%

(1023 deaths). Mortality was associated with increasing age (> 70 years of age), the presence of comorbidities (including hypertension, diabetes, chronic cardiovascular or pulmonary disorders, neoplastic comorbidities), and the severity of the clinical presentation. Mortality was as high as 49% amongst critical cases (2,3).

Italy, and particularly the Northern region, Lombardia, has initially been the centre of the most numerous reports of confirmed cases of COVID-19 since the spread of the infection to Europe, reaching 5469 cases out of 9172 total cases in Italy (corresponding to 0.054% of the region population) within 2 weeks from the identification of the first Italian case at the end of February 2020. Data updated at the 9th of March 2020 reported 463 deaths out of 9172 cases in Italy (4–6). The overall number of patients requiring admission to hospital reached 4316, with another 733 needing intensive care unit (ICU) management. Only in Lombardia, within two weeks of the onset of the epidemic, the patients admitted were 2802, with 440 in ICU.

From the data available to date, the clinical presentation of the disease varies from asymptomatic or pauci-symptomatic cases, resolving spontaneously within a few days, to the severe cases with interstitial viral pneumonia, hypersensitivity pneumonitis, and respiratory failure leading to the epidemiological data described above (1,7).

There are no currently approved treatments for COVID-19 infection, however, therapeutic strategies based on the available pre-clinical evidence, reported case-series described since the infection outbreak, and data obtained from previous SARS-CoV and MERS-CoV infections are usually being applied. These include supportive measures (including oxygen supplementation, and fluid management) (8), and the early use of antiviral agents (3). Antimicrobial therapy is usually associated. Chloroquine, and probably more effectively, hydroxychloroquine has been used in patients diagnosed with COVID-19 during the Chinese outbreak for its potential antiviral efficacy through the modification of the cell membrane surface pH, necessary for the interaction virus-host cells, and its immunomodulatory action (9). Despite these treatment measures, approximately 10% of patients worsen and develop acute respiratory distress syndrome (ARDS) requiring continuous positive airway pressure therapy or mechanical ventilation. The mechanisms underlying the occurrence of ARDS have been related to a cytokine storm leading to an aberrant inflammatory response perpetuating the pulmonary damage, not necessarily strictly related to the viral load (10,11). When this immune response is activated, antiviral agents might need to be combined with anti-inflammatory and immunomodulatory treatments in order to obtain an improvement in the outcome (12). The

aberrant inflammatory pulmonary response is considered to be similar to that of cytokine release syndrome (CRS) occurring in the setting of T cell-engaging immunotherapies (CAR-T), hence suggesting the rationale for immunomodulatory/immunosuppressive drugs being tested in severe cases of COVID-19, such as Tocilizumab and systemic glucocorticoids. CRS in triggered by interferon-gamma and excessive interleukin (IL)- 6, tumor necrosis factor alpha (TNF-a), and IL-10 production (13).

3.2   Investigational product, preclinical evidence, clinical evidence to date

Given the scale and rapidity of the COVID-19 spread, despite the standard therapeutic strategies being applied, and the limitations of resources and capability of the National health systems to face the disease, there is an urgent need to identify novel treatment options that would halt the rapid deterioration of severely affected patients.

In a recently published correspondence article on The Lancet (14), potential new candidate treatments for COVID-19 acute respiratory disease have been identified by connecting medical information regarding therapies that could block the viral infection process by means of machine learning techniques. Amongst the drugs with the ability to modify the mechanisms through which the virus enters the host pulmonary cells, Baricitinib, a janus kinase inhibitor (JAK 1/2) approved for the treatment of rheumatoid arthritis, has been proposed as the most promising one. Baricitinib was selected as a high-affinity inhibitor of the receptor used by 2019-CoV to enter lung cells (epithelial cells ACE2), the AP2-associated protein kinase 1 (AAK1). Through the inhibition of AAK1, Baricitinib has the potential to inhibit the endocytosis of the virus and the intracellular assembly of viral particles (14,15). Of the six identified AAK1-binding therapies, Baricitinib also binds to another regulator of viral endocytosis, the G-associated kinase. Baricitinib was reported to inhibit AAK1 already at therapeutic doses of 2-4 mg/daily (14). Moreover, Baricitinib has an action in controlling cytokine signaling involved in inflammation with a wide action on multiple pathways through the inhibition of JAK1 and JAK2 (16). Baricitinib regulates the signaling through receptors of the IL-6, IL-10, IL12, IL-23, interferon families cytokine receptors and the downstream related inflammatory pathways (17). Baricitinib mechanisms of action seem particularly promising in regulating both CoV-2 virulence on the host cells, and the inflammatory response hypothesized to lead the ongoing lung damage and subsequent mortality in severe cases of COVID-19. Baricitinib offers a number of other advantages outlined in the following sections.

3.3   Dose rationale

Baricitinib can be administered orally, once daily. The approved dose for rheumatoid arthritis is 4 mg/daily, however, this can be reduced to 2 mg/daily in specific conditions. The safety profile is acceptable and the interaction with other drugs is very low, making it compatible with the antivirals used in the treatment of COVID-19 (12). The drug has demonstrated rapidity in action, and is characterized by a short half-life, being particularly flexible in the management of seriously ill patients in whom further infectious complications or changes in the general conditions might occur in a short period of time. A systematic literature review and meta-analysis of the infection risk related to JAKI in the treatment of rheumatoid arthritis including data on 3520 patients who received Baricitinib reported incidence rates per 100 person year of 3.16 (95% CI: 2.07; 4.63), with no statistically different rates compared to placebo.

3.4   Risks/benefits

A potential source of concern related to Baricitinib is the reported higher incidence of herpes zoster infections [incidence rates of Baricitinib compared to placebo of 2.86 (95%CI: 1.26; 6.50)]. Potential confounders for these observations have been identified such as older age, ethnicity (with herpes zoster infections being highest in Asian patients (18), concomitant medications including glucocorticoids or other concomitant immunomodulatory treatments for the underlying condition) (19). Similarly, reports of hepatitis B virus reactivation in patients with prior infection (HbcAb positive) have been reported suggesting the need for monitoring and initiation of antiviral treatment when necessary (20). Deep vein thrombosis/pulmonary embolism (DVT/PE) has been reported in a minority of patients receiving Baricitinib 4 mg compared to placebo (incidence 0.5/100 patients-years) (21,22); associated risk factors are older age, obesity, a previous history of DVT/PE, or patients undergoing surgery or immobilization. The risk of DVT/PE is of concern in the study population and needs to be taken-into-account in each patient. Current standard treatment in hospitalized patients includes prophylactic low molecular weight heparin to prevent thromboembolism. The individual patient's risk/benefit ratio is evaluated in all patients to assess the need to further implement anticoagulant therapy. The risk of DVT/PE in patients with COVID-19 is particularly relevant, based on the observations of patients treated to date, in those requiring continuous positive airway pressure (c-PAP). This can be partly related to the effect of the armpit braces promoting

venous stasis and higher risk of DVT. However, patients requiring c-PAP are excluded from the current study, therefore this higher-risk population will not receive Baricitinib.

In general, Baricitinib has been confirmed to have a good safety profile during previous use in patients with rheumatoid arthritis, with no excessive risk of death, malignancies, major adverse cardiovascular events, even after long-term exposure to Baricitinib.

3.5   Justification of choice of study population

Based on the clinical information regarding COVID-19 available to date, and the clinical course of patients assessed at our institution since the outbreak, a number of factors being associated with the activation of a systemic inflammatory response are often associated with a clinical deterioration. A consensus of experts managing patients with COVID at Policlinico S. Matteo, Pavia, has defined these parameters such as c-reactive protein (CRP) > 10 mg/dl or ferritin levels > 900 ug/L as being the expression of inflammatory activation.

4.   STUDY OBJECTIVES

4.1   overall objective

To assess the efficacy and safety of Baricitinib in the management of patients admitted for COVID-19 pneumonia.

4.2   primary objective

The primary objective will be the efficacy of the experimental treatment.

4.3   secondary objectives

Secondary objective will be the safety of the experimental treatment and the quantification of the efficacy parameters.

4.4   safety objectives

Safety of Baricitinib, including drug-related toxicity, infections, and laboratory abnormalities will be assessed throughout the study duration.

5. STUDY OUTCOMES

5.1 primary outcome

The primary outcome of the study will be the response to treatment. A patient is consider responder in the absence of either moderate to severe oxygenation impairment according to Berlin criteria (23) or death, whichever occurs first, within 8 days from enrolment.

5.2 Secondary outcomes

1. To quantify the rate of each of: moderate or severe oxygenation impairment within 8 days
2. To quantify the mortality within 8 days
3. To quantify the rate of each of: moderate or severe oxygenation impairment within 15 days
4. To quantify the mortality within 15 days
5. Peripheral capillary oxygen saturation (SpO2)
6. PaO2/FiO2
7. To assess the rate of patients admitted to the ICU
8. To measure the length of hospital stay
9. To quantify 28-day mortality
10. To quantify the rate of re-admission within 28 days
11. To quantify the cumulative incidence and severity of adverse events

5.3 safety outcomes

Adverse events and drug-related reactions will be assessed throughout the duration of the study. The occurrence of serious infections and herpes zoster reactivation will be recorded. Significant laboratory abnormalities will be assessed.

5.4 exploratory outcomes

Serial serum samples analyzed for cytokines and biomarkers (including IL-6) to assess the correlation between reduced cytokine/inflammatory mediators and anti-viral effects of ancillary Baricitinib treatment in responders and non-responders.

5.5 Definitions for inclusion of participants and outcomes

Confirmed SARS-CoV-2

Defined as the identification of unique sequences of virus RNA by nucleic acid amplification tests, such as real-time reverse transcription polymerase chain reaction (RT-PCR) on respiratory specimens.

Acute Respiratory Distress Syndrome

The Berlin Definition (23) will be used to define moderate and severe oxygenation impairment as follows:

-Moderate: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg

-Severe: PaO2/FiO2 ≤ 100 mmHg

6. STUDY DESIGN

6.1 general study design

This will be a single-arm proof of concept Phase IIa study to assess the efficacy and safety profile of Baricitinib in a limited number of patients with severe acute respiratory syndrome (SARS)-CoV-2 pneumonia. This will include 13 consecutive patients with a confirmed SARS-CoV-2 pneumonia satisfying the inclusion and exclusion criteria and willing to participate. Baricitinib 4 mg/daily will be administered for 7 days in adjunction to standard therapy.

The proof-of-concept phase guarantees that no safety issues arise on a limited number of patients in the use of a drug new to the current condition being treated. The study will have a duration of 28 days.

6.2 methods of minimizing bias

The proof of concept one arm study. Objective measure of the response is the main bias mitigation method used.

7. STUDY POPULATION

7.1 eligibility criteria

Patients fulfilling all of the following inclusion criteria are eligible for the study

Inclusion criteria

- Ability to obtain informed patient consent noting the limitations of existing knowledge regarding Baricitinib's efficacy *and the labeled warning and precautions* as the proposed use is outside the approved indication, as well as the presence of known risk of being treated with Baricitinib while the subject of an active infection

- informed Consent as documented by signature

- patients with a confirmed SARS-CoV-2 pneumonia

- adult patients aged 18-74 years old

- infiltrates at chest radiography

- c-reactive protein level greater than 10 mg/dl or ferritin level > 900 ug/L

- Lymphocyte count less than 1500/mmc

- > 200 PaO2/FiO2 ≤ 300

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:
Exclusion criteria:

- patients aged < 18 years old and ≥ 75 years old

- concomitant bacterial infection

- lymphopenia less than 200/mmc

- hemoglobin < 8 g/dl

- absolute neutrophil count < 1×10^9 cells/L

- requiring continuous positive airway pressure (C-PAP) or mechanical ventilation

- sudden clinical deterioration requiring ICU access

Exclusion criteria (Drug-related)

- known hypersensitivity or allergy to the study drug

- Creatinine clearance < 30 mL/min; if the creatinine clearance is between 30 and 60 mL/min the dose of Baricitinib should be reduced to 2 mg/daily

- Severe hepatic impairment (no dose adjustment of Baricitinib is required in mild or moderate hepatic impairment)

- Pregnant or breast-feeding

- Active tuberculosis

- Evidence of active HBV (HbsAg positive) or with detectable HCV-RNA, HIV

- Ongoing, acute diagnosis of DVT/PE

- Previous diagnosis of DVT/PE

7.2 recruitment and screening

Patients will be identified and recruited by the treating physician at the Infectious and Tropical Disease ward at the Policlinico S. Matteo, IRCCS Fondazione, Pavia, Italy. The study will be conducted in the setting of an academic hospital.

7.3 Criteria for withdrawal/discontinuation of participants

Patients will be withdrawn from the study in case significant safety issues or drug toxicity might arise. Dropouts are not expected. In case they would occur, they will be replaced by an additional patient.

8. STUDY INTERVENTION

8.1 identity of investigational products

Baricitinib (Olumiant) 4 mg/once daily will be administered orally for 7 days.

Baricitinib will be prescribed in adjunction to supportive therapy according to local protocols according to Hospital Policy and National Agency directives according to the updated treatment for COVID-19 based on the available evidence. All patients will receive anti-thrombotic prophylaxis; risk/benefit ratio to further implement anticoagulant therapy in patients with risk factors for venous thromboembolism is recommended.

8.1.1 Experimental intervention

Baricitinib (Olumiant) will be administered orally in the form of pink, round-shaped, film-coated tablets.

8.1.2   Packaging, labelling and supply

Each package will contain 28 tablets of the study drug. There will be no deviations from the available commercial product distributed by Lilly pharma company.

8.1.3   storage conditions

Investigational product does not require any particular storage conditions. The product will be stored at room temperature in a secure, limited access storage area under the recommended storage conditions.

8.2   administration of experimental interventions

Baricitinib will be administered to inpatients by the medical and nurse teams.

Baricitinib (Olumiant) 4 mg/once daily will be administered orally for 7 days with or without concomitant food.

8.3   dose modifications

Baricitinib dose will be reduced to 2 mg/daily in case of reduction of the glomerular filtration rate < 60 ml/min.

Baricitinib will be reduced to 2 mg/daily in patients treated with probenecid (a potent OAT3 inhibitor).

In case of clinical deterioration or toxicity suspected to be secondary to the study drug, this will be discontinued and standard therapy according to local protocols will be continued as salvage therapy.

Baricitinib will be withdrawn in case of drug-related toxicity: occurrence of severe drug-induced liver injury, lymphopenia less than 200/mmc, occurrence of severe bacterial infection, acute diagnosis of DVT/PE, creatinine clearance < 30 ml/min, pregnancy. Baricitinib interruption will be considered if: hemoglobin < 8 g/dl, absolute neutrophil count < 1 x 10^9 cells/L.

8.4   compliance with study intervention

The treatment will be administered during hospital stay, under the supervision of a nurse.

Lack of compliance is not expected to be an issue.

8.5 data collection and follow-up for withdrawn participants

Patients will have the possibility to withdraw informed consent at any time during the study period. Data collected up to the withdrawal of consent to participate in the study will be used for the final analyses.

8.6 trial specific preventive measures

Concomitant treatments allowed according to local protocols (updated according to accumulated evidence on COVID-19 management), including antibiotic if indicated, antiviral, oxygen support (low and high flow until requiring C-PAP or mechanical ventilation), glucocorticoids, appropriate anticoagulant therapy in patients with risk factors for venous thromboembolism.

Treatments not allowed: any other concomitant immunosuppressive and/or drug agent targeting cytokines. If a patient is treated with probenecid (a potent OAT3 inhibitor), the 2-mg dose of Baricitinib should be utilized.

8.7 concomitant interventions (treatments)
Oxygen support

Low (cannula and simple masks) and high flow (Venturi and reservoir masks) oxygen support will be provided according to the level of hypoxia.

8.8 study drug accountability

Records of the drug use and accountability will be kept, including lot/batch number and quantities received and used.

8.9 return or destruction of study drug

Unused study drug will be shipped back to Sponsor.

9. STUDY ASSESSMENTS

The following variables will be collected, including demographic data, previous medical history (including the presence and type of comorbidities, smoking history, ongoing treatments), clinical presentation (date and type of symptoms onset leading to the admission to hospital), laboratory

parameters (biochemistry, full blood count, ferritin levels, D-Dimer, CRP). Microbiological analyses will be performed to exclude concomitant bacterial infections. Arterial blood gas test (ABG) will be performed. The ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2) will be calculated. Chest radiography (x-ray) will be performed. Serum samples for storage and future assessment of cytokines, including IL-6 and other exploratory biomarkers. IL-6 assessment is part of common clinical practice for the evaluation of these patients.

9.1 table of study procedures and assessments

Study Period:	Screening	Baseline	Treatment period	Follow-up period	End of study
Day	Day -1	Day 0	Days 0-7	Day 8 – day 15	28 days
Informed Consent	X				
Inclusion/Exclusion Criteria	X	X			
Demographics	X				
Medical History	X				
Physical examination	X	X	X	X	
Vital signs	X	X	X	X	
Hematology	X	X	X	X	
Biochemistry (including ferritin)	X	X	X	X	
D-Dimer	X		X		
Hepatitis B, C tests, HIV	X				
Imaging tests	X			X	
ABG	X	X	X	X	
Adverse events			X	X	X
Blood sample collection for storage (additional cytokine analysis and exploratory biomarkers analysis in future)	X		X		

9.2   assessments of outcomes

The primary outcome will be assessed by monitoring the oxygenation status of the patient with the PaO2/FiO2 ratio. This will require BGA to obtain the PaO2 value. This will be assessed at entry, then every 48 hours until day 8, and at day 15. Mortality will be assessed up to day 28.

9.3   assessment of secondary outcomes

Monitoring the oxygenation status of the patient with the PaO2/FiO2 ratio will be applied to quantify the rate of moderate or severe oxygenation impairment within 8 days (by assessments performed at entry and every 48 hours), and day 15. This will require BGA to obtain the PaO2 value. PaO2 value, CRP measurements, lymphocyte count will be monitored every 48 hours. SpO2 will be monitored over the whole duration of the study. Chest x-ray will be performed at admission and at the end of the treatment period or in case of clinical deterioration. The length of hospital stay will be assessed by the number of days from admission to discharge of the patient or death. Re-admission for complications or relapses of the disease will be assessed up to day 28.

9.4   assessment of safety outcomes

Adverse events and drug-related reactions will be assessed throughout the duration of the study. The occurrence of serious infections and herpes zoster reactivation will be diagnosed clinically or through microbiological tests and recorded. Significant laboratory abnormalities will be assessed. This will include monitoring (every 48 hours or in case of clinical conditions deterioration) full blood count, biochemistry (including liver transaminases), renal function through creatinine values and glomerular filtration rate.

In case of adverse events, information regarding the time of onset, duration, resolution, action to be taken, assessment of intensity, relationship with the study treatment will be recorded.

9.4.1   assessment in participants who prematurely stop the study

Participants who will prematurely withdraw from the study will be followed to assess and record any adverse event related to the study that might occur during follow-up until day 28.

9.5   procedures at each visit

Screening visit. Patients will be screened for eligibility to the study after signing an approved informed consent form. As part of the screening, patient's previous medical history will be recorded. Inclusion/exclusion criteria will be assessed. Vital signs will be recorded (blood pressure, pulse, temperature, respiratory rate, body weight and height). Physical examination and routine laboratory tests will be performed.

Prior and ongoing medications will be recorded. All patients will undergo screening test for the initiation of Baricitinib: exclusion of active tuberculosis, HBV serology, HCV serology and if positive, HCV-RNA, HIV. Imaging studies will include chest X ray. ABG will be performed.

Baseline visit. From baseline visit all eligible patients witll receive Baricitinib.

Treatment period. Days 0-7. Patients will receive the active treatment while their inpatient stay. Vital signs will be recorded every 8 hours. Physical examination will be performed every day, while laboratory tests, ABG and re-evaluation of the clinical picture will be performed every 48 hours. Additional assessments will be performed in case of symptoms deterioration.

Follow-up period. Days 8-15. Patients will be continuously monitored daily until the resolution of COVID-19 infection, or the occurrence of death.

End of study. Patients will be followed up to day 28.

10. SAFETY

<u>*Definitions of adverse events*</u>*: defined* according to Regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 for definitions of AE, adverse reactions and reporting including causality.

For the purposes of this study, AE will be classified into the following categories:

-AE: any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment;

-Adverse Drug Reaction (ADR): "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man". The phenomenon is to be intended as noxious (an unexpected therapeutic response, may be a side effect but not an adverse reaction).

-Serious Adverse Event (SAE): any untoward medical occurrence that at any dose requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death;

-Unexpected Serious Adverse Event: serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference drug safety information;

-Unexpected Adverse Event: an event, the nature or severity of which is not consistent with applicable product information.

Safety reporting:

Reporting of AEs and SAEs during the study will be performed using the common terminology criteria for AE (CTCAE) v5.

Exceptions to AE reporting:

The following events are expected following Baricitinib treatment, and will be recorded only if of significant grade ≥ 3 (laboratory):

- mild to moderate increase in liver function tests

-increase in lipid parameters

-significant elevation of creatine kinase (CPK) (no need for monitoring except for other clinical reasons)

- decrease of absolute neutrophil count to levels < 1 x 10^9 cells/L

-decrease of lymphocyte count to levels < 200 cells/L

-decrease of haemoglobin to levels < 8 g/dL

Reporting of AE and SAE by the investigator to the sponsor:

The investigator will record AEs and laboratory abnormalities according to the protocol as critical to the safety assessment, and will report them to the sponsor in accordance with the

reporting requirements. SAE will be reported within 24 hours from AE identification and acknowledgment.

The investigator will record and document all AEs, unless differently specified in the protocol.

Where relevant, the investigator will provide a follow-up report to determine whether the SAE has an impact on the benefit-risk ratio of the clinical trial.

The sponsor will keep detailed records of all AE communicated by the investigator.

In case of SAEs occurring after the end of the trial, but with suspected causal relationship to the investigational drug, the investigator will, without undue delay, report the AE to the sponsor.

Exceptions from SAE reporting:

Hospitalization for regular therapy as stated in the clinical trial plan. It is assumed that patients will be hospitalized at least from day -2 to day + 7.

Regular follow-up of instrumental or biochemical tests.

Reporting of Suspected Unexpected Serious Adverse Reactions:

The sponsor should report to the Eudravigilance database, without delay, all relevant information related to suspected SAE, including all suspected unexpected SAE to the investigational drug product occurring in the clinical trial; all suspected unexpected serious adverse reaction related to the drug product occurring in any subject of the clinical trial, even after the end of the trial.

The period for the reporting of suspected unexpected serious adverse reaction by the sponsor to the Agency shall take account of the seriousness of the reaction and shall be as follows:

(a) in the case of fatal or life-threatening suspected unexpected serious adverse reactions, as soon as possible

and in any event no later than seven days after becoming aware of the reaction;

(b) in the case of non-fatal or non-life-threatening suspected unexpected serious adverse reaction, no later than 15 days after becoming aware of the reaction;

(c) in the case of a suspected unexpected SAE which was initially considered to be nonfatal

or non- life threatening but which turns out to be fatal or life-threatening, as soon as possible and in any

event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening.

Where necessary to ensure timely reporting, the sponsor may submit an initial incomplete report followed up by a complete report.

Adverse Events and Causality:

Medication errors, pregnancy and uses outside what is specified in the protocol, including misuse and abuse of the product, shall be subject to the same obligation to report as adverse reactions.

In determining whether an AE is to be considered as an adverse reaction, consideration shall be given to whether there is a reasonable possibility of establishing a causal relationship between the event and the investigational medicinal product based on an analysis of available evidence. Information on causality should be provided by the investigator when reporting to the sponsor. The causality assessment given by the investigator shall not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor shall be provided with the report.

Causality will be defined according to criteria listed in the ICH E2A guidelines.

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Information for the reporting of suspected unexpected serious adverse reactions:

The report should include:

   a) a valid trial reference number

   b) the patient identification code

   c) an identifiable reporter

d) details on the suspected unexpected adverse reaction

e) a suspect investigational drug product

f) a causality assessment

g) the date of the initial information from the primary source

h) the date of the receipt of most recent information

i) the unique case identification number

j) the sender identifier

Infections:

Infections will be classified, as far as possible, by pathogenic agent, clinical syndrome, localisation and severity. Date of onset, duration, treatment and outcome will also be recorded.

Cause of death:

Investigators should define death as being caused by SARS-CoV-2 or related to other causes. The cause of death, when identified, should always be reported.

Medical monitoring:

It is the responsibility of the local institutional Principal Investigator to oversee the safety of the trial at the site. The safety monitoring will include assessment and reporting of AE as previously noted, as well as the implementation of a site data and safety monitoring plan. A regular assessment of the number and type of SAE will be part of the medical monitoring.

Contact for pharmacovigilance

The PI delegates the pharmacovigilance collection and reporting (annually and at the end of the study) in accordance with current GCP rules to:
Dr Laura Bogliolo
Dr Paolo Sacchi
The person responsible for Eudravigilance: Dr.sa Barbara Croesi
Phone: (+39) 0382503470
Email: b.croesi@smatteo.pv.it

11. STATISTICAL METHODS

11.1 hypothesis

The null hypothesis is of no effect of the experimental drug.

11.2 determination of sample size

Assuming a spontaneous rate of improvement of clinical conditions related to COVID-19 infection of 10%, a power of 80%, a 2-sided type I error of 5%, 13 patients will be required to show a response rate to the intervention of 40%. Moreover, if the number of responders is 4 or more, the H_0 hypothesis of no effect will be rejected.

The sample size has been computed with Stata 16 (StataCorp, College Station, TX, USA). using the following code "*sampsi_fleming, p0(0.1) p1(0.40) a(0.05) p(0.8)*"

11.3 statistical criteria of termination of trial

The trial will be prematurely stopped in case safety issues arise.

Dropouts are not expected. In case they would occur, they will be replaced by an additional patient.

11.4 planned analyses

Computations will be performed with the software Stata 16 (StataCorp, College Station, TX, USA). Patients clinical characteristics will be summarized with the mean and standard deviation or the median and 25th-75th percentiles if continuous and as counts and percent if categorical.

11.4.1 datasets to be analysed, analysis populations

Intention to treat analysis will be performed.

11.4.2 primary analysis

The proportion of responders, computed as the number of responders over the number of valid patients enrolled (ITT population) will be computed together with its exact binomial 95% confidence interval (95%CI).

The response rate will be assessed at day 8, after having completed the full course of Baricitinib treatment (administered for 7 days). This is in line with the typical duration of the acute disease phase based on clinical experience available to date.

11.4.3 secondary analyses

(1) the rate of each component

1. the ratio of the number of patients with moderate or severe oxygenation impairment within 8 days will be computed over the number patients enrolled, together with its 95%CI

2. the mortality within 8 days will be computed as the number of patients dying over the number patients enrolled, together with its 95%CI

3. the ratio of the number of patients with moderate or severe oxygenation impairment within 15 days will be computed over the number patients enrolled, together with its 95%CI

4. the mortality within 15 days will be computed as the number of patients dying over the number patients enrolled, together with its 95%CI

5. SpO2 will be assessed with the median and 25th-75th percentiles

6. PaO2/FiO2 will be assessed with the median and 25th-75th percentiles

7. The rate of patients admitted to the ICU will be computed as the number of patients over the number of patients enrolled, together with its 95%CI

8. the length of hospital stay will be described with the median and 25th-75th percentiles

9. The 28-day mortality will be computed as the number of patients dying over the person time, together with its 95%CI. Overall survival will be plotted using the Kaplan Meier Curve

10. the rate of re-admission within 28 day will be computed as the number of patients readmitted over the number patients enrolled, together with its 95%CI

11. the number, type, and severity of adverse events will be tabulated. The cumulative incidence and its Poisson 95%CI will be reported.

11.4.4 interim analyses

No interim analyses for efficacy will be performed.

However, repeated interim analyses will be performed to confirm the safety of Baricitinib in the included population. In particular, every 3 enrolled patients the rate of toxicity, defined by new and worsening adverse events suspected to be correlated with the investigational treatment, will be assessed and examined by a data safety monitoring board (DSMB) of clinicians who are not involved in the study who might advice for the interruption of the study based on safety reasons, if more than 1/3 patients show toxicities.

Toxicity leading to the need to discontinue Baricitinib has been defined in the intervention section.

11.4.5 safety analysis

Patients will be monitored for treatment- or disease related-AE throught the duration of the study. Particular attention will be given to Baricitinib well-known AE, including the occurrence of infections (including herpes zoster or other serious infections) or laboratory abnormalities.

11.5 handling of missing data and drops-out

No dropout is expected, thus no formal missing data imputation will be performed. However, in a sensitivity analysis we will conservatively consider patients who dropped out to be non-responders.

12. QUALITY ASSURANCE AND CONTROL

The sponsor is responsible for implementing and maintaining quality assurance with working instructions and adherence to the study protocol.

12.1 data handling and record keeping/archiving

12.1.1 case report forms

Data collection will be performed by the treating physician. Data will be recorded on paper case report forms (CRF) and transferred to electronic CRFs. Participants will not be identified in the CRF by name or initials and birth date. Appropriate coded identification will be used.

12.1.2 specification of source documents

Source data will be available at site to document the existence of the study participants. Source data must include the original documents relating to the study, the medical treatment and medical history of the participant. Source documents will be the CRFs, information on AE, SAE, concomitant medications.

12.1.3 record keeping/archiving

Upon completion of the study, data will be archived for a minimum of 10 years on the anonymized dataset. Confidentiality of collected information will be ensured throughout the trial duration.

12.2 data management

Data will be pseudo-anonymized and they will be collected in a secured web-based database in REDCap that will be built and maintained by the Clinical Epidemiology & Biometry Unit on a dedicated server of the Scientific Direction. The Unit will also monitor data quality and completeness and will use the REDCap query facility for interaction with the clinical investigators.

12.2.1 data management system

Data will be collected on a secured web-based database in REDCap that will be built and maintained by the Clinical Epidemiology & Biometry Unit on a dedicated server of the Scientific Direction.

12.2.2 data security, access and back-up

Access to the database will be granted nominally to the investigator(s), who will access via username and password (to be renewed every 2 months). No identification data will be recorded in the database. It will be the responsibility of the principal investigator to maintain an updated list of the patient identification data enrolled in the study together with their enrolment number. Regular back up of the database information will be performed automatically.

12.2.3 analysis and archiving

Data will be extracted through REDCap software. The dataset will be stored by the Clinical Epidemiology & Biometry Unit on a dedicated server of the Scientific Direction.

12.2.4 electronic and central data validation

Single data entry will be performed. Predefined lists of values will be provided for categorical variables; the range for plausible values will be defined for continuous variables. Remote monitoring of missingness will be performed and queries will be sent to the investigator.

12.3 monitoring

Formal monitoring will be performed by the Clinical Trial Quality Team (CTQT) of the Fondazione IRCCS Policlinico San Matteo. Source documents will be accessible to monitors and questions answered during monitoring.

12.4 audits and inspections

The study documentation and data source will be made accessible to auditors/inspectors if needed. All involved parties will keep the participant data strictly confidential.

12.5 confidentiality, data protection

Direct access to source documents will be permitted for purposes of monitoring, audits and inspections. Investigators involved in the trial and the principal investigator will have access to the final set of anonymized data.

12.6 storage of biological material and related health data

Serum samples will be stored in a biobank located at Policlinico S. Matteo, IRCCS Fondazione, Pavia, Italy. Coded samples without recognizable patients information will be stored with the participants consent.

13. PUBLICATION AND DISSEMINATION POLICY

Results will be presented and disseminated to the public and at rheumatology or infectious diseases scientific meetings; manuscripts derived from the project will be published on peer-reviewed international journals. Authorship eligibility will be defined according to the ICMJE recommendations.

14. FUNDING AND SUPPORT

Funding will be provided by Policlinico S. Matteo, IRCCS Fondazione, Pavia, Italy.

15. INSURANCE

Insurance will be provided by the Sponsor.

16. REFERENCES

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. :9.

2. Chinese Center for Disease Control and Prevention [Internet]. [cited 2020 Mar 10]. Available from: http://www.chinacdc.cn/en/COVID19/

3. Simit [Internet]. [cited 2020 Mar 10]. Available from: http://www.simit.org/IT/index.xhtml

4. EpiCentro. Focolaio di infezione da nuovo coronavirus SARS-CoV-2: la situazione in Italia [Internet]. [cited 2020 Mar 10]. Available from: https://www.epicentro.iss.it/coronavirus/sars-cov-2-italia

5. Coronavirus in Italia, i dati e la mappa [Internet]. www.ilsole24ore.com. [cited 2020 Mar 10]. Available from: https://lab24.ilsole24ore.com/coronavirus/

6. Salute M della. Covid-19 - Situazione in Italia [Internet]. [cited 2020 Mar 10]. Available from: http://www.salute.gov.it/portale/nuovocoronavirus/dettaglioContenutiNuovoCoronavirus.jsp?lingua=italiano&id=5351&area=nuovoCoronavirus&menu=vuoto

7. Clinical Characteristics of Coronavirus Disease 2019 in China | NEJM [Internet]. [cited 2020 Mar 10]. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2002032

8. WHO | World Health Organization [Internet]. [cited 2020 Mar 10]. Available from: https://www.who.int/

9. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis [Internet]. [cited 2020 Mar 10]; Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa237/5801998

10. Park WY, Goodman RB, Steinberg KP, Ruzinski JT, Radella F, Park DR, et al. Cytokine balance in the lungs of patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2001 Nov 15;164(10 Pt 1):1896–903.

11. Hagau N, Slavcovici A, Gonganau DN, Oltean S, Dirzu DS, Brezoszki ES, et al. Clinical aspects and cytokine response in severe H1N1 influenza A virus infection. Crit Care. 2010 Nov 9;14(6):R203.

12. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis [Internet]. 2020 Feb 27 [cited 2020 Mar 10];0(0). Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30132-8/abstract

13. Wang Z, Han W. Biomarkers of cytokine release syndrome and neurotoxicity related to CAR-T cell therapy. Biomark Res. 2018;6:4.

14. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet Lond Engl. 2020 15;395(10223):e30–1.

15. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov | bioRxiv [Internet]. [cited 2020 Mar 10]. Available from: https://www.biorxiv.org/content/10.1101/2020.01.26.919985v1

16. Kubo S, Nakayamada S, Sakata K, Kitanaga Y, Ma X, Lee S, et al. Janus Kinase Inhibitor Baricitinib Modulates Human Innate and Adaptive Immune System. Front Immunol. 2018;9:1510.

17. Dowty ME, Lin TH, Jesson MI, Hegen M, Martin DA, Katkade V, et al. Janus kinase inhibitors for the treatment of rheumatoid arthritis demonstrate similar profiles of in vitro cytokine receptor inhibition. Pharmacol Res Perspect [Internet]. 2019 Nov 15 [cited 2020 Mar 10];7(6). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6857076/

18. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol. 2017 Apr;13(4):234–43.

19. Bechman K, Subesinghe S, Norton S, Atzeni F, Galli M, Cope AP, et al. A systematic review and meta-analysis of infection risk with small molecule JAK inhibitors in rheumatoid arthritis. Rheumatol Oxf Engl. 2019 Oct 1;58(10):1755–66.

20. Harigai M, Winthrop K, Takeuchi T, Hsieh T-Y, Chen Y-M, Smolen JS, et al. Evaluation of hepatitis B virus in clinical trials of baricitinib in rheumatoid arthritis. RMD Open. 2020 Feb;6(1).

21. Smolen JS, Genovese MC, Takeuchi T, Hyslop DL, Macias WL, Rooney T, et al. Safety Profile of Baricitinib in Patients with Active Rheumatoid Arthritis with over 2 Years Median Time in Treatment. J Rheumatol. 2019;46(1):7–18.

22. van Vollenhoven R, Helt C, Arora V, Zhong J, Correia AP, de la Torre I, et al. Safety and Efficacy of Baricitinib in Patients Receiving Conventional Synthetic Disease-Modifying Antirheumatic Drugs or Corticosteroids. Rheumatol Ther. 2018 Dec;5(2):525–36.

23. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012 Jun 20;307(23):2526–33.