Protocol Title: BARICIVID-19 STUDY: MultiCentre, randomised, Phase IIa clinical trial evaluating efficacy and tolerability of Baricitinib as add-on treatment of in-patients with COVID-19 compared to standard therapy

Investigational Compound: Baricitinib

Short Title: Baricitinib in COVID-19/SARS-CoV2 pneumonia

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PROTOCOL AUTHORIZATION PAGE

I have read this study protocol and agree that it contains all the information required to conduct the study. I agree to conduct the study as set out in this protocol. In particular, I agree to adhere to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the guidelines on Good Clinical Practice and the appropriate national laws.

Local Investigator

_____ _____

Date

Trial Promoter Coordinating Centre

_____ _____

Date

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1. Synopsis

Protocol Title: BARICIVID-19 STUDY: Multi Centre, randomised, Phase IIa clinical trial evaluating efficacy and tolerability of Baricitinib as add-on treatment of in-patients with COVID-19 compared to standard therapy

Short Title: Baricitinib in COVID-19/SARS-CoV2 pneumonia

Rationale

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with droplets and contact as the main means of transmission[1-3]. Since the first case appeared in Wuhan, China, in December 2019, the outbreak has gradually spread nationwide, inducing worldwide concern. A bilateral interstitial pneumonia is the most frequent and serious complication of COVID-19.

SARS-CoV-2 infection induces an excessive and aberrant host immune response that is associated with an acute respiratory distress syndrome, with typical radiological findings and, in most critical patients, with a so-called "cytokine storm", characterized by the plasma increase of many cytokines that produce long-term damage and fibrosis of lung tissue[4-5].

The optimal treatment of COVID-19 has not been well established. COVID-19 does not have specific antiviral drug treatment currently, so the treatment of the disease is mainly focused on symptomatic treatment and oxygen therapy.

Inflammatory factors and lymphocyte subsets are recommended to be monitored during the disease. Lymphopenia and increase in inflammatory cytokines (including IL-6) occur during COVID-19.

Ongoing research about therapy of patients with COVID-19 is based on one hand on the identification of an antiviral that may reduce the viral load and on the other hand aims to identify drugs potentially reducing the inflammatory response of the host. Thus, several studies about anti-inflammatory drugs in patients with COVID-19 are ongoing. Baricitinib has been identified as a molecule potentially useful in patients with COVID-19, because of a double action of mitigate inflammatory cascade and reduce viral entry in the lung cells.

The receptor that 2019-nCoV uses to infect lung cells might be ACE2, a cell-surface protein on cells in the kidney, blood vessels, heart, and, importantly, lung AT2 alveolar epithelial cells. These AT2 cells are particularly prone to viral infection. One of the known regulators of endocytosis is the AP2-associated protein kinase 1 (AAK1)[6].

A recent correspondence published on Lancet Infectious Disease identified baricitinib as potential treatment for 2019-nCoV acute respiratory disease using a scientific review by machine learning.

Among other AAK1 inhibitors, the authors identified baricitinib as a “trialled” molecule for different reasons: baricitinib is a high-affinity AAK1-binding drug. Disruption of AAK1 might, in turn, interrupt the passage of the virus into cells and also the intracellular assembly of virus particles. It also binds the cyclin G-associated kinase, another regulator of endocytosis. Thus, baricitinib may be useful for both reducing inflammatory response and reduce viral endocytosis[6-7].

Based on the previous findings, at University of Pisa we treated a small number of patients (about 20) with COVID-19 and severe pneumonia with baricitinib as adjunctive therapy. We observed a rapid improvement in blood gas analysis, with an increase in P/F ratio of about 50% in the subsequent 96 hours. The majority of these patients do not require invasive mechanical ventilation, despite the presence of parameters of clinical severity before the start of the drug.

Objectives and Endpoints

Primary
Efficacy of baricitinib in reducing the number of patients requiring invasive ventilation after 7 and 14 days of treatment

Secondary

1. Mortality rate after 14- and 28-days from randomization
2. Time to invasive mechanical ventilation (days)
3. Time to independence from non-invasive mechanical ventilation (days)
4. Time to independence from oxygen therapy (days)
5. Time to improvement in oxygenation for at least 48 hours (days)
6. Length of hospital stay (days)
7. Length of ICU stay (days)
8. Instrumental response (pulmonary echography)
9. To describe the toxicity of baricitinib

Overall Design

This study is a multicenter randomized controlled PoC (phase IIa) clinical trial for evaluating efficacy, safety and tolerability of baricitinib added to the usual care treatments in reducing the number of patients requiring invasive ventilation after 7 and 14 days of treatment, in comparison with the usual care treatments, enrolling patients with COVID-19 /SARS-CoV2 pneumonia.
A total number of 126 patients will be enrolled. All patients enrolled are treated with the usual care treatments. One group of 63 patients are adding with baricitinib by oral route, while one group of 63 patients are continuing the usual care treatments. Seven-days and 14-days number of patients requiring invasive ventilation is the primary end-point. From available data, it can be assumed that about 30% of patients with Covid19 pneumonia administered with usual care treatments defined by the inclusion/exclusion criteria are requiring invasive ventilation (P0). To verify the hypothesis that the experimental treatment baricitinib may produce a reduction of 60% of patients requiring invasive ventilation (from 30% to 12%, P1), 126 patients are needed with a 80%power and a 5% bilateral alpha error.

Treatment and Duration

Patients will receive Baricitinib 4 mg film-coated tablets by oral route, 1 tablet a day for 14 consecutive days. For patients with eGFR between 30 and 60 ml/min and for patients with age >75 years old, the dosage will be half a tablet a day (2 mg/day) for 14 days.

2. Schedule of assessments

Procedure	Day 1 Baseline before first Baricitinib administration	Day 1-14 Baricitinib administration	Treatment and hospitalization period		Discharge	Follow-up On day 30
			Day7	Day14		
Informed consent	x					
Inclusion and exclusion criteria	x					
Pregnancy Test (Female)	X					
Demography	x					
Full physical examination including height and weight	x					
Medical history (includes past and current medical conditions, and substance usage)	x					
Baricitinib administration and drug accountability		x	x	x		
Arterial Blood Gas Analysis[1]	x	x	x	x	x	
Respiratory assistance assessment	x		x	x	x	
Laboratory assessments[2]	x		x	x	x	
12-lead ECG	x		x	x	x	
Vital signs	x	x	x	x	x	
SOFA score[3]	x	x	x	x	x	
Pulmonary Echography	x		x	X	X	

Thoracic CT scan or Chest xR[4]	x				x	
AE review	x	x	x	x	x	x
Concomitant medication review	x	x	x	x	x	
Survival follow-up					x	x

[1]at least once daily

[2]At least blood count, bilirubin, AST, ALT, creatinine, PT, PTT, LDH, D-dimer

[3]SOFA score is calculated considering PaO2/FiO2, Glasgow coma scale, mean arterial pressure, and bilirubin, platelet and creatinine levels.

[4]Radiological evaluation is optional. If baseline evaluation (CT or xR) is available a re-evaluation is planned on day 7 and subsequently if clinically indicate

3. Introduction

Baricinitib is an oral, targeted synthetic DMARD that inhibits Janus kinase (JAK) inhibitors, JAK1 and JAK2, which are intracellular enzymes that transmit signals from cytokine or growth factor receptor interactions implicated in hematopoiesis and immune cell function. It also modulates the signaling pathway at the point of JAKs, thereby blocking the phosphorylation and the activation of signal transducers and activators of transcription (STATs); these STATs regulate intracellular activity, including gene expression. The drug is approved for use as monotherapy or in combination with methotrexate in the treatment of adults with moderately to severely active rheumatoid arthritis.

3.1. Background

3.1.1. SARS-CoV-2 Pneumonia

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with droplets and contact as the main means of transmission. Since the first case appeared in Wuhan, China, in December 2019, the outbreak has gradually spread nationwide, inducing worldwide concern. A bilateral interstitial pneumonia is the most frequent and serious complication of COVID-19.

SARS-CoV-2 infection induces an excessive and aberrant host immune response that is associated with an acute respiratory distress syndrome, with typical radiological findings and, in most critical patients, with a so-called "cytokine storm", characterized by the plasma increase of many cytokines that produce long-term damage and fibrosis of lung tissue.
The optimal treatment of COVID-19 has not been well established. COVID-19 does not have specific antiviral drug treatment currently, so the treatment of the disease is mainly focused on symptomatic treatment and oxygen therapy.
Inflammatory factors and lymphocyte subsets are recommended to be monitored during the disease. Lymphopenia and increase in inflammatory cytokines (including IL-6) occur during COVID-19.
Ongoing research about therapy of patients with COVID-19 is based on one hand on the identification of an antiviral that may reduce the viral load and on the other hand aims to identify drugs potentially reducing the inflammatory response of the host. Thus, several studies about anti-inflammatory drugs in patients with COVID-19 are ongoing.

3.1.2. Baricitinib mechanism of action

Baricitinib has been identified as a molecule potentially useful in patients with COVID-19, because of a double action of mitigate inflammatory cascade and reduce viral entry in the lung cells.
The receptor that 2019-nCoV uses to infect lung cells might be ACE2, a cell-surface protein on cells in the kidney, blood vessels, heart, and, importantly, lung AT2 alveolar epithelial cells. These AT2

cells are particularly prone to viral infection. One of the known regulators of endocytosis is the AP2-associated protein kinase 1 (AAK1). Disruption of AAK1 might, in turn, interrupt the passage of the virus into cells and also the intracellular assembly of virus particles. Baricitinib is a high-affinity AAK1-binding drug. It also binds the cyclin G-associated kinase, another regulator of endocytosis. Thus, baricitinib may be useful for both reducing inflammatory response and reduce viral endocytosis.

3.1.3. Baricinib experience in COVID-19 patients

Based on the previous findings, at Infectious Disease Unit of Pisa University, a small number of patients (about 10) with COVID-19 and severe pneumonia were treated with baricitinib as adjunctive therapy. It was observed a rapid improvement in blood gas analysis, with an increase in P/F of about 50% in the subsequent 96 hours. The majority of these patients do not require invasive mechanical ventilation, despite the presence of parameters of clinical severity before the start of the drug.

3.2. Study Rationale

Baricitinib is a high-affinity AAK1-binding drug. It also binds the cyclin G-associated kinase, another regulator of endocytosis. Thus, baricitinib may be useful for both reducing inflammatory response and reduce viral endocytosis.

3.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected adverse events of Baricitinib may be found in the Summary of Product Charactheristics of the product.

In the Pisa University experience of Baricitinib in COVID-19 patients no toxic death and no serious adverse event was reported. A risk of Deep Vonous Thrombosis/Pulmonary Embolism is known to be associated with the use of Baricitinib. In order to avoid/minimize this risk, patients at risk of DVT/PE are excluded from the study.

4. Objectives and Endpoints

Objectives	Endpoints
Primary	
Efficacy of baricitinib in reducing the number of patients requiring invasive ventilation after 7 and 14 days of treatment	Number of patients with respiratory failure requiring invasive mechanical ventilation at 7 and 14 days of treatment
Secondary	
To evaluate: 1) Mortality rate after 14- and 28-days from randomization 2) Time to invasive mechanical ventilation 3) time to independence from non-invasive mechanical ventilation 4) time to independence from oxygen therapy 5) Time to improvement in Oxygenation for at least 48 hours 6) Length of hospital stay 7) Length of ICU stay 8) Instrumental response 9) To describe the toxicity of baricitinib	1) Mortality rate at day 14 and 28 2) days to intubation 3) days to independence from non-invasive mechanical ventilation 4) days to independence from oxygen therapy 5) Hours from randomization to increase of P/F 50% or greater with respect of nadir of P/F 6) Days of hospitalization 7) Days of ICU 8) Pulmonary Echography response 9) Rate of adverse events codified by Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0

5. Study Design

5.1. Preamble

This project is written at the time of the coronavirus pandemia and while in Italy the number of people who get infected or is hospitalized for respiratory complication is dramatically increasing. Therefore, the clinical and operational scenario is extremely variable and it is expected that it will remain so for an unforeseeable time. In addition, very few solid evidence is available on the course of the disease and on the significance of intermediate end-points, before the use of the experimental drug.

Therefore, it is accepted in advance that the present protocol may need repeated amendments to comply with evolving knowledge on the pandemia, the rate of complications, and the therapeutic scenario for patients who develop pneumonia. A high degree of adaptivity is therefore planned, that will be strictly discussed with the Independent Data Monitoring Committee that will be nominated soon after the approval of the protocol.

5.2. Overall Design

The study is a multicenter randomized controlled clinical Proof of Concept (PoC) phase IIa clinical trial enrolling patients with COVID-19 pneumonia. A total number of 126 patients will be enrolled. All patients enrolled are treated with the usual care treatments. One group of 63 patients are adding with baricitinib by oral route, while one group of 63 patients are continuing the usual care treatments. The number of patients with respiratory failure requiring invasive ventilation at day 7 and 14 is the primary end-point. From available data, it can be assumed that about 30% of patients with Covid19 pneumonia administered with usual care treatments defined by the inclusion/exclusion criteria are requiring invasive ventilation (P0). To verify the hypothesis that the experimental treatment baricitinib may produce a reduction of 60% of patients requiring invasive ventilation (from 30% to 12%, P1), 126 patients are needed with a 80%power and a 5% bilateral alpha error.

5.3. End of Study Definition

A participant is considered to have completed the study if he/she has completed the last scheduled procedure shown in the Schedule of assessments. The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of assessments for the last participant in the trial globally.

6. Study Population

6.1. Inclusion Criteria

Participants are eligible to be included in the study if the following criteria apply:

1. Any gender
2. Age > 18 years on day of signing informed consent
3. Informed written consent for participation in the study
4. Virological diagnosis of SARS-CoV-2 infection (real-time PCR)
5. Hospitalized due to clinical instrumental diagnosis of pneumonia
6. Oxygen saturation at rest in ambient air ≤93% or P/F ratio <250
7. Able to be administered by oral route drugs
8. Patients who receive O2 therapy or who need non-invasive mechanical ventilation
9. In case of female patients at childbearing potential, they should agree to use highly effective methods of birth control at least till 7 days after the termination of the treatments

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Known hypersensitivity to Baricitinib or its excipients
2. Patients with Creatinine Clearance < 30 ml/min
3. Patients with active Tuberculosis (TBC)
4. Patients with known HBV or HCV infection
5. Patients with deep vein thrombosis (DVP) or Pulmonary Embolism (PE)
6. Patients with ALT or AST> 5 times the upper limit of the normality
7. Neutrophils <1000/mmc
8. Platelets <50.000/mmc
9. Hb< 8g/dl
10. Bowel diverticulitis or perforation
11. Patients who receive invasive mechanical ventilation
12. Documented bacterial infection at time of randomization
13. Patients with “do not resuscitate order”
14. Patients receiving immunosuppressants or anti-rejection drugs
15. Pregnancy or breastfeeding

7 Withdrawal of patients from treatment or study

7.1 Withdrawal from treatment

A patient should be withdrawn from the study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient.

When a patient is withdrawn, the date of last investigational medicinal product administration and the date and reason for treatment withdrawal should be clearly described in the relevant sections of the CRF. If a patient is removed from treatment because of an adverse event (AE), the reason for treatment withdrawal should always be stated as 'adverse event' irrespective of whether this was the investigator's or the patient's decision.

The patient will continue to participate in the study without taking study treatment.

7.2 Withdrawal from study

Whenever possible and irrespective of the reason for withdrawal, the patient should be examined as soon as possible. The CRF should be completed as far as possible. Date and reason for the study withdrawal should be clearly described in the CRF.

7.3 Replacement of withdrawn patients

Patients withdrawn from the study will not be replaced.

8. Treatments

8.1. Treatments Administered

Study Treatment Name:	Baricitinib
Dosage formulation:	4 mg film-coated tablets
Unit dose strength(s)/Dosage level(s):	4 mg film-coated tablets

Route of Administration	Oral Route
Dosing instructions:	1 tablet a day for 14 days. For patients with eGFR between 30-60 ml/ min and for patients with age >75 years, the dosage will be half a tablet a day (2mg/day) for 14 days
Packaging and Labeling	Drugs will be provided in blister containing 14 tablet in one box. Label is according to country requirement for clinical practice.
Manufacturer	Ely Lilly

8.2. Storage/Accountability

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Specific forms for drug accountability will be provided by the promoter.

8.3. Treatment Compliance

The effective doses of study drugs received by each participant during the study will be recorded.

8.4. "Standard" Usual Therapy

Currently, there is no "standard" treatment available for Covid19 infection.
All patients, required by the assignment arm, will continue to receive therapy already in place, including that for Sars-CoV2 infection. Local treatment protocols, including chloroquine/idrossichloroquine and low-molecular weight eparin (LMWH) eventually associated with ritonavir/lopinavir or darunavir/ritonavir will be allowed for all included patients.
For the duration of the study, the following will not be allowed:
 the concomitant use of IL-1 or IL-6 blockers, JAK inhibitors and TNF inhibitors
 the start of the steroid in the two weeks of study. The steroid will be continued if the patient already takes steroid at the time of admission.

8.5. Concomitant Therapy

In case of suspected or demonstrated concomitant infections that can be successfully treated with antimicrobials in order to make the patient eligible, such treatments are allowed.

However, any medication that the participant is receiving at the time of enrollment or receives during the study will be recorded along with:
- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

8.6. Rescue Therapy

Patients will be constantly monitored in the hospital according to the usual procedures. Any clinical situation will be managed according to the usual clinical practice. In patients showing worsening of clinical condition, the Investigator is completely free to decide to introduce any drug considered necessary for a given patient as rescue treatment.

9. Study Assessments and Procedures

Screening evaluations must be completed and reviewed to confirm that potential participants meet eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before informed consent may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria.

9.1. Screening procedures

- Informed Consent Form
- Demography (age, gender, ethnicity)
- Standard Pregnancy Test
- Medical history (previous and current diseases, all medications started within 14 days prior to screening visit)
- Full physical examination including height and weight.
- Arterial Blood Gas (ABG) Analysis once daily
- Respiratory assistance assessment
- Laboratory assessments: At least blood count, bilirubin, AST, ALT, creatinine, PT, PTT, LDH, D-dimer
- 12-lead ECG
- Vital signs (respiratory rate, pulse, blood pressure and temperature) will be obtained as appropriate
- SOFA score is calculated considering PaO2/FiO2, Glasgow coma scale, mean arterial pressure, and bilirubin, platelet and creatinine levels.
- Pulmonary Echography evaluation
- Thoracic CT scan or Chest XR (if clinically indicated)
- AE review (including SAEs)
- Concomitant medication review

9.2. Treatment and procedures during hospitalization period

- Arterial Blood Gas (ABG) Analysis at least once daily
- Respiratory assistance assessment
- Laboratory assessments: At least blood count, bilirubin, AST, ALT, creatinine, PT, PTT, LDH, D-dimer
- 12-lead ECG

- Vital signs (respiratory rate, pulse, blood pressure and temperature) will be obtained as appropriate
- S0FA score is calculated considering Pa02/Fi02, Glasgow coma scale, mean arterial pressure, and bilirubin, platelet and creatinine levels
- Instrumental Evaluation (Pulmonary Echography)
- Thoracic CT scan or Chest XR (if baseline evaluation (CT or XR) is available a re-evaluation is planned on day 7 and then if clinically indicated)
- Treatment with Baricitinib
- AE review (including SAEs)
- Concomitant medication review

9.3. Procedures before discharge

- Arterial Blood Gas (ABG) Analysis
- Respiratory assistance assessment
- Laboratory assessments: At least blood count, bilirubin, AST, ALT, creatinine, PT, PTT, LDH, D-dimer
- 12-lead ECG
- Vital signs (respiratory rate, pulse, blood pressure and temperature) will be obtained as appropriate
- S0FA score is calculated considering Pa02/Fi02, Glasgow coma scale, mean arterial pressure, and bilirubin, platelet and creatinine levels
- Instrumental Evaluation (Pulmonary Echography)
- Thoracic CT scan or Chest XR if clinically indicated
- AE review (including SAEs)
- Concomitant medication review

9.4. Follow up (30 days) procedures

- Follow-up information may be collected via telephone calls, patient medical records and/or clinical visits
- AE review (including SAEs)

9.5. Efficacy Assessments

9.5.1. Pa02/Fi02 ratio

Pa02/Fi02 ratio (or P/F ratio for brevity) represents the ratio between the arterial blood partial pressure of the oxygen (Pa02) and the percentage of oxygen supplied (fraction of inspired oxygen, Fi02). This parameter is calculated from arterial blood gas analysis and is commonly used for the definition of ARDS. A P/F ratio of 300 to 200, indeed, identifies Mild ARDS, 200 to 100 Moderate ARDS, and a respiratory failure featuring a P/F less than 100 is suggestive for Severe ARDS.

9.5.2. Laboratory assessment

Lymphocyte count, C-reactive protein (CRP) are assessed by routinely used determination of blood count and CRP.

IL-panel levels will be assessed using commercial ELISA method.

9.5.3. Sequential 0rgan Failure Assessment (S0FA) score

S0FA is a morbidity severity score and mortality estimation tool designed for evaluating organ dysfunction and morbidity. It evaluates 6 variables, each representing an organ system (one for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems), and scored from 0 (normal) to 4 (high degree of dysfunction/failure). Thus, the maximum score may range from 0 to 24. The tool can be used for estimating mortality risk.

9.5.4. Instrumental Assessment

Evaluation of the improvement of Pulmonary Echography parameters at 7, 14 days after the starting of the therapy. Lung ultrasound parameters will be : the number of B-lines for each given explored region; the presence of lung consolidation and the presence and the pattern of lung aeration areas. An echo-score will be calculated for each patient.

9.6. Adverse Events

9.6.1 Definitions

An AE is any untoward medical occurrence in a study participant administered the medicinal products and which does not necessarily have a causal relationship with this treatment.An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or

disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse reaction (AR)is an untoward and unintended response to the investigational medicinal products related to any dose administered, judged by either the investigator or the promoter.

An unexpected adverse reaction (UAR) is an adverse reaction, the nature or severity of which is not consistent with the applicable products information (investigator's brochure).

A Serious Adverse Event (SAE) is untoward medical occurrence or effect that at any dose results in death, risk of death, permanent disability/incapacity, hospitalisation or prolongation of existing hospitalization or need for urgent medical treatment, or another medically important serious event as judged by the investigator. Further, any unexpected changes in relation to the toxicity profile of the drugs used of gradeD 3, as well as adverse event(s) which, although not falling within this definition, are considered unexpected and serious by the Investigator should be reported.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to the coordinating centre.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is an unexpected adverse reaction judged serious by the Investigator and/or Promoter, that is not consistent, either in nature or in severity, with the applicable product information.

9.6.2. Collection and reporting of adverse events

All adverse events recorded from time of signature of informed consent, throughout the treatment and observation period up to 30 days following registration, have to be reported in the toxicity case report form, graded according to the corresponding CTCAE term (Version 5.0).

The Investigator must immediately report to the promoter all serious adverse events. The report should be made using the SAE report form online or by sending the paper copy by fax to the coordinating office immediately and not exceeding 24 hours following knowledge of the event. All SAE must be also reported in the toxicity case report form within the corresponding CTCAE term.

During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion. The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

9.6.3. Causality assessment between treatment and event

The following criteria will be used for causality assessment:

Term	Description
CERTAIN	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals.
PROBABLE/ LIKELY	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to the concurrent disease or other drugs or chemicals.
POSSIBLE	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals.
UNLIKELY	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
NOT RELATED	There is no causal relationship between the treatment and the event
CONDITIONAL/ UNCLASSIFIED	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
UNASSESSIBLE/ UNCLASSIFIABLE	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

9.6.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the promoter of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The promoter will review all adverse events and issue queries directly to the Investigator reporting the event. The promoter will determine if an event qualifies as a SUSAR.
- The Reference Safety Information (RSI) necessary to classify an adverse reaction as SUSAR, based on the nature and seriousness, including the frequency, represented by the Investigator's brochure/ approved RCP of Baricitinib
- The promoter has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation.

The promoter will report all SUSARs to Eudravigilance through the EVCTM, to all participating Investigators, to all Ethical Committees of participating centres, within the timelines of the article 17 of the European Directive 2001/20/EC. The study protocol will be also submitted to the Manufacturer.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the promoter will review and then file it along with the Investigator's Brochure.
- The promoter will provide an annual Development Safety Update Report, including all Serious Adverse Events occurring in the Study, to the Regulatory Agency, all participating Investigators, and to the Ethical Committees of participating centres.
- The Investigators are responsible for informing their Ethics Committee of the SAE reported in their centre, as per local requirements.

The Promoter is responsible for informing immediately (within one working day) the Manufacturer about the evenience of any serious adverse event.

9.7. Safety Assessments

Planned time points for all safety assessments are provided in the schedule of assessments table. The scientific committee will review safety data periodically in order to evaluate the benefit/risk ratio of the study.

9.8. Stopping Rules

The Scientific Committee as well as the independent Data monitoring Committee will review periodically (weekly) and safety data concerning patients participating in the study with a continuous evaluation of the Benefit/risk ratio of the use of Baricitinib as add-on treatment. In case of severe adverse reaction or improvement of patients not clinically significant, that change the benefit/risk ratio evaluation, the trial will be stopped.

10. Statistical Considerations

10.1. Sample Size Determination

The study is designed as a double-arm single-stage phase 2 study with 7days and 14-days number of invasive ventilation as primary endpoint.

Expected 7-days and 14-days invasive

ventilation (P_0):30%

Auspicated 7-days and 14-days invasive

ventilation (P_1):12%

Statistical power: 80%

Bilateral alpha error: 5%

Sample size needed: 63 patients for each group

10.2. Randomization

Being a parallel, multicenter, open-label study, the assignment of patients to one of the two treatment groups will take place via a randomization list.
The randomization list will be computer-generated by the PLAN procedure of the validated SAS/STAT® software.
It will be stratified by centre allocating several whole blocks to each centre.
After checking for the patient incl/ex criteria, in case of an eligible patient, the investigator will assign randomization the code sequentially following the randomization list of its own centre.

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF and are registered
Evaluable	All participants enrolled (Intention-to-treat)
Safety	All participants who take at least 1 dose of study treatment.

10.4. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

Primary and secondary analyses will be stratified by age categories, gender and eventually other clinically relevant factors (comorbidities, smoke habits etc.).

10.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	7-days and 14-days number of patients with invasive ventilation is defined as the ratio of patients who will have invasive ventilation after 7-days and 14-days from study start out of those registered at baseline and will be described with its 95% confidence interval between the group of patients treated with Baricitinib in comparison with patients administered with standard treatment. In addition, the primary end point will be described separately by age group and gender.
Secondary	All the analysis will be descriptive.

10.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	Toxicity. For each patient and for each type of toxicity described according to CTCAE, the worst degree ever suffered during treatment will be used for descriptive analysis.

11. Ethics, Quality Assurance and Monitoring

The procedures set out in this study protocol are designed to ensure that the promoter and the Investigators abide by the principles of the Good Clinical Practice guidelines of the International Conference on Harmonization (ICH) and the Declaration of Helsinki in the conduct, evaluation and documentation of this study. The study will be carried out adhering to local legal requirements and the applicable national law, whichever represents the greater protection for the individual.

Study protocol, patient information and informed consent will be submitted to the appropriate Ethical Committee for approval. The promoter will inform the appropriate Ethical Committee about any changes in the study protocol which could interfere with the patient's safety.

The monitoring activities during pandemia will be primarily or exclusively performed without peripheral visits. Remote monitoring will be performed through periodic, comprehensive connections through the web or the telephone with all participating centres by promoter personnel or representatives.

11.1. Informed Consent Process

The physicians treating the hospitalized patient are responsible for information of the patient and obtaining of the Informed Consent.

A written informed consent is required.

The same procedure apply to the information of the patient and providing of consent to the processing of personal data according to the European Regulation n. 679/2016 on the Protection of Personal Data, the Personal Data Protection Code (Legislative Decree 196/03) and subsequent amendments and additions, and to the provisions, guidelines and general authorizations of the National Guarantor for Personal Data Protection.

12. Data Monitoring Committee

An Independent Data Monitoring committee (IDMC) will be nominated to warrant the quality of the study management and analysis. The IDMC will be made of 3 to 5 members, selected among statisticians, trialists and experts in Infectivology and Resuscitation.

The IDMC will be responsible for:

- reviewing activity and safety data through progress reports produced by the promoter and recommending for example modifications in case of unexpected or unexpectedly severe toxicities for study treatment, or in case of preliminary data suggesting inactivity or surprisingly positive efficacy in specific subgroups of patients. These corrections may be modifications of the treatment, the inclusion criteria or conditions for retreatment, or the sample size, or the study procedures or early study termination.
- evaluating the effect on the study of possible changes in scientific evidence, such as results of other studies, and recommending modifications as above on the basis of such external data.

Considering the setting of the present study, which apply to a health emergency situation, progress report will be produced weekly and the IDMC will examine all the reports produced, in collaboration with the steering committee and/or within closed meetings, and will suggest possible modifications as described above.

13. Data collection procedures

Patient registration and data collection are performed at the university of Pisa, Infection Disease Unit and ICU Unit

14. Administrative aspects

This is a non-profit investigator initiated trial. The study protocol will be submitted to Manufacturer (Eli Lilly).

Study protocol, patient information, and informed consent at beginning and at each required amendment will be submitted to the Area Vasta Nord-Ovest Tuscany Ethical Committee for approval.
Coverage for any damage resulting from the participation of the subjects in the clinical trial is included in the general insurance of the individual participating clinical centers.

15. Coordinating centre contacts

University of Pisa

Medical contacts
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