Protocol title

A multicenter randomized trial to evaluate the efficacy of tocilizumab in patients with severe Coronavirus Disease 2019 (Covid-19) pneumonia failing glucocorticoids (*Anticipant Study*)

Promoter: AOU di Modena, via del Pozzo 71, 41124 Modena MO, Italy

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Sommario

BACKGROUND AND RATIONALE

After 10 months of SARSCOV2 pandemic it is still unclear which should be the best standard of care for the treatment of COVID19. On the basis of large randomized clinical trials, only glucocorticoids were shown to be able to reduce mortality especially among patients undergoing mechanical ventilation (1). Nevertheless, mortality rate in the RECOVERY trial remained high at 20% meaning that we need a salvage therapy after the failure of these treatment (1). At present, data on the percentage of patients with severe COVID19 who deteriorate after glucocorticoids has not been published, nevertheless we have conducted an analysis on our almost 400 patients finding this percentage to be around 30% and a treatment for these patients is essential. A few immunomodulatory agents, mainly tocilizumab, anakinra and baricitinib, have been tested in observational studies on the basis of their possible activity against the cytokine storm characterizing more severe COVID19 clinical pictures and results have been encouraging (2-5). Indeed, baricitinib showed to be effective in combination with remdesivir and has been recently approved by FDA (6). Tocilizumab (TCZ) is a recombinant humanized monoclonal antibody, of the IgG1 class, directed against both the soluble and the membrane bound IL-6 receptor (7). A systematic review and meta-analysis of 10 observational studies including 1358 patients demonstrated that mortality was 12% lower for COVID-19 patients treated with tocilizumab compared to patients who were not treated. The number needed to treat was 11, suggesting that for every 11 COVID-19 patients treated with tocilizumab, 1 death could be prevented (8).

Tocilizumab was also tested in randomized clinical trials with discordant results. A pharmaceutical company press releases showed no evidence for clinical improvement and reduced risk of mortality when comparing patients treated with tocilizumab vs. placebo in the double-blind COVACTA trial (9). In contrast, a 44% reduced risk of mechanical ventilation in people treated with tocilizumab was observed in the EMPACTA trial which included patients with a greater severity of disease at enrollment and a significant enrichment in Hispanic, Native American and Black ethnic minorities as compared to the target population examined in COVACTA (10).

Additionally, CORIMUNO, a French multi-centre randomized clinical trial including 129 patients (65 standard of care + 64 tocilizumab) with severe COVID19 pneumonia, was recently published showing a beneficial effect of tocilizumab vs. standard of care in reducing mechanical ventilation and/or mortality at 14 days (11). Recently, a press release of the REMAP-CAP trial stated that the trial data yielded an estimated odds ratio of 1.87 for a better outcome with tocilizumab compared to no immune modulation, with a high degree of statistical certainty (99.75% probability that tocilizumab is superior to no immune modulation) (12). At present, what seems clear is that tocilizumab is not effective in patients with moderate diseases, thus in presence of a PaO_2/FiO_2 ratio <300 mmHg since 3 studies conducted in patients with a non-severe COVID-19 pneumonia showed that the drug was non-effective (13-15).

Discordant results may be explained by different inclusion criteria, drug doses, study methods and overall clinical competence in managing severe COVID-19 patients. Actually, the drug is largely used in clinical practice as salvage treatment for critical pneumonia in patients failing standard of care.

STUDY AIMS

Primary aim

Evaluate the efficacy of tocilizumab in preventing intubation or death in patients with COVID-19 severe pneumonia who are deteriorating their respiratory function on glucocorticoids.

Secondary aims

Evaluate the correct timing for tocilizumab administration.

Evaluate the safety of tocilizumab after glucocorticoids.

STUDY DESIGN

This is a prospective, multicentre, randomized, open-label Phase 3 interventional trial evaluating the efficacy of tocilizumab in patients with COVID-19 pneumonia failing glucocorticoids.
Patients with advanced COVID-19 pneumonia admitted to hospital requiring oxygen and with a PaO_2/FiO_2 ratio between 250 and 150 mmHg_will receive Low-Molecular-Weight Heparin (LMWH) at a prophylactic dose and dexamethasone 6 mg per day for 10 days.

In case patients PaO_2/FiO_2 ratio in room air decreases by more than 20% from baseline value (at time of dexamethasone initiation) and/or respiratory distress (RR> 30 bpm and/or use of accessory respiratory muscles) occurs despite treatment after 36 hours from first dexamethasone dose(based on clinical experience), patients will be randomized to receive or not tocilizumab 2 doses 12 hours apart at the dose of 8 mg/kg maximum dose 800 mg per administration.
Due to the high risk of Herpes Simplex Virus (HSV) re-activation, patients receiving glucocorticoids + tocilizumab will be prescribed acyclovir 400 mg twice daily.
COVID-19 patients will be recruited in 42 Italian clinical centres.

STUDY POPULATION

The study population includes patients with COVID-19 severe pneumonia who require hospital care.

The inclusion criteria are:

- age>= 18 years;
- Informed consent for participation in the study;
- Polymerase Chain Reaction (Real-time PCR) diagnosis of Sars-CoV2 infection;
- Hospitalization;
- Clinical/instrumental diagnosis (high resolution chest computed tomography scan or chest x-ray or pulmonary ultrasound) of COVID-19 pneumonia;
- PaO_2/FiO_2 ratio in room air <250 mmHg and decreased by more than 20% and/or respiratory distress (RR> 30 bpm and/or use of accessory respiratory muscles) occurs despite treatment at least 36 hours from first dexamethasone dose. The

interval has been chosen on the basis of clinical experience with the timing of clinical improvement after starting this treatment.

- An hyperinflammation condition defined by the presence of at least two of the following criteria at any time from admission: a) blood lymphocytes < 1000/mmc; b) ferritin > 500ng/mL; c) LDH > 300 U/L; d) D-dimers > 1000 ng/mL; e) C-reactive protein > 3mg/dL (16).

The exclusion criteria are:

- Patient with acute respiratory distress syndrome with PaO_2/FiO_2 ratio > 250 mmHg;
- Invasive ventilation (oro-tracheal intubation);
- Known hypersensitivity to TCZ or its excipients;
- Clinical conditions that contraindicate TCZ and cannot be treated or resolved according to the physician's judgment: e.g. Glutamate-pyruvate transaminase (GPT) or glutamine oxaloacetic transaminase (GOT) > 5 times the upper limit of the norm, Neutrophils < 500/mmc, Platelets < 50.000/mmc, Diverticulitis or intestinal perforation, suspicion of latent tuberculosis;
- Previous or concomitant use of other immune-modulants for COVID-19: anti-IL-1, JAK-inhibitors, other anti-IL-6.
- PCT > 0.5 ng/mL

TREATMENT PROTOCOL

Experimental therapy with TCZ. Duration, dosage, and treatment schedule

Given the little experience and in analogy with the Cytokine release syndrome after CAR-T therapy in which most of the responses occur after two administrations, the following dosage schedule will be applied to the population in the experimental arm:

1. Tocilizumab 8 mg/kg (maximum dose per single infusion: 800 mg) to be administered by intravenous infusion lasting 60 minutes according to the following dosage schedule:

- 1st infusion within 4 hours after randomisation
- 2nd infusion 12 hours after the first infusion

Standard of care

On the basis of the RECOVERY trial, Dexamethasone will be administered at the dose of 6 mg per day for 10 days+ LMWH at prophylactic dose will be administered to all patients. Standard of care could be changed by the Investigator during the study in relation to patient clinical conditions.

Remdesivir may be added depending on AIFA approval, at dosage of 200 mg on day 1 followed by 100 mg on days 2-5.

For the duration of the study, the following treatments will not be allowed:

- the concomitant use of IL-1 blockers, Janus Kinase Inhibitor (JAK) inhibitors, IL-17 inhibitors and TNF inhibitors;
- the concomitant use of hydroxychloroquine or colchicine;
- the concomitant use of hyperimmune serum.

ENDPOINTS OF THE STUDY

The primary endpoint is defined by the occurrence, within 4 weeks of randomization, of one of these 3 events:

a) entry into ICU (Intensive Care Unit) with invasive mechanical ventilation;
b) death from all causes;
c) reaching a PaO_2/FiO_2 <130 mmHg in room air

The assessment of secondary endpoints is done in the order in which the secondary objectives of the study are presented:

1) entry into ICU with invasive mechanical ventilation;
2) all-cause mortality;
3) duration of oxygen support;
4) duration of non-invasive ventilation;

5) duration of hospitalization;
6) toxicity measured according to internationally recognized standard;
7) evaluation of IL-6 and serum C-Reactive Protein (CRP) levels and their correlation with the outcome;
8) evaluation of ferritin, Lactate Dehydrogenase (LDH) and D-dimer levels and their correlation with the outcome;
9) evaluation of the progress of the PaO_2/FiO_2 ratio in room air and its correlation with the outcome.

CLINICAL ASSESSMENTS

Evaluations are scheduled in the four weeks of the study or until the patient withdraws from the study due to death, transition to intensive care unit or clinical aggravation.

Day 1 is the day of randomization, regardless of the time it is made (00-24). The exams done for the assessment of eligibility prior to randomization can be used for day 1. The required exams are those required by the protocol. The clinician is free to prescribe additional tests at his/her discretion. In case of early termination of the study due to ICU transfer or clinical aggravation, the evaluations foreseen by the protocol are suspended.

Timing of the programmed arterial EGAs and laboratory evaluations are described in Appendix 1. During the planned days of assessments, temperature, saturation and respiratory frequency will be collected for all patients.

REGISTRATION AND RANDOMISATION PROCEDURES

Eligible patients will be registered in a centralized database. Randomisation will take place on a competitive and balanced basis by participating clinical centers.
Randomisation lists, stratified by center, will be prepared using permuted blocks of various sizes in random order. Randomisation will be carried out by the CRO 7 days a

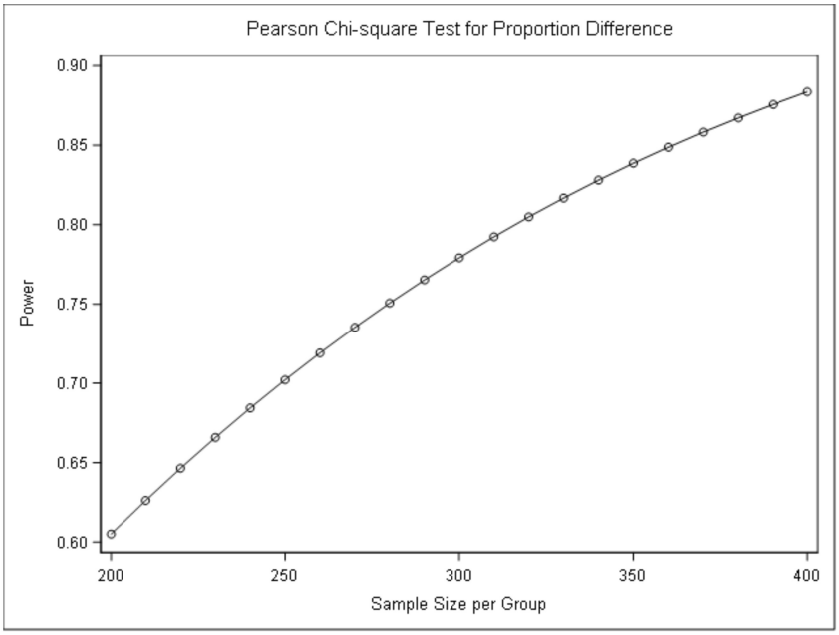
week, 24 hours a day. This operation also determines the registration of enrolled patients.

SAMPLE SIZE

The sample size is calculated using the Pearson's chi-square statistics for a difference in proportions. The assumptions are that the baseline probability of developing the primary composite outcome by 28 days from randomisation (when PaO_2/FiO_2 ratio has dropped by >20% from the level at initiation of standard of care (SoC) in hospital) is 22.0% for people who have failed treatment with SoC (dexamethasone or other currently recommended first line treatment) and that initiation of tocilizumab will reduce this probability to 13.5%. Therefore, we assume a risk reduction of 8.5% and a risk ratio (RR) of 0.61. These assumptions are based on the minimum clinical effect that we do not want to miss and on previous risk estimates observed in randomised clinical trials (17). The baseline risk combining all studies in a recent meta-analysis of RCTs was of 22%. In the Corimuno trial, the risk difference was 11.1% and the RR=0.61 while in the Covacta trial the risk difference was 13.3% and the RR=0.69. Because Covacta included patients with less severe disease compared to our target enrolled, we believe that it is reasonable to expect that tocilizumab will have a slightly larger impact in our study population on the RR scale. In the recently published EMPACTA trial, which enrolled patients more similar to our target population, the day28 risks were 19.3% in placebo vs. 12.0% in tocilizumab with a HR=0.56 (95% CI:0.33-0.97) (10). In terms of risk difference the study is conservative. Also the baseline risk is conservative as plausibly people failing SoC might have an higher underlying risk than that seen in RCTs. We also assume a two-sided test (with a null hypothesis of no difference between starting tocilizumab or not), and type I error=5%. The calculation of the estimates of the risk for the single components of the composite endpoint is complicated because each of these are competing risks. The composite outcome was indeed chosen to remove this complication.

The graph below (Figure 1) shows that in order to have at least 80% statistical power, 320 patients per group will need to be recruited (640 total). Because we are planning to recruit from 42 clinical sites across Italy, this amounts to an average of 15 patients enrolled per participating site which we believe is a realistic target over the current and subsequent pandemic waves (see Appendix for list of participating sites). Even if the number of active sites will drop by 26% to 31 sites, an average enrolment of 21 patients per center will be sufficient to reach the target.

Figure 1. Sample size per group for a given power



Statistical analysis plan

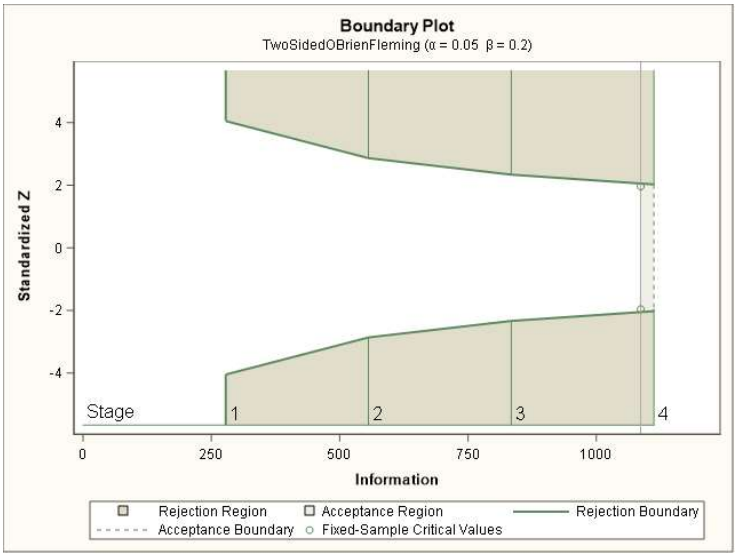
The proportion of people experiencing the composite primary endpoint will be compared using Pearson's chi-square statistics. In case of random imbalances between the group, residual confounding will be controlled using propensity score matching and a logistic regression model. The treatment effect will be shown as difference in risk and risk ratio between the two groups with 95% confidence interval. In case of effectiveness of

tocilizumab it will be expressed also as number of patients needed to be treated to avoid one event of PaO_2/FiO_2 ratio drop below 130, mechanical ventilation or deathand the number of people who needs to be treated with tocilizumab to prevent 1 death (secondary endpoint). Besides the stratification by site, we are not planning to perform stratified analysis so standard block randomisation will be performed within each site and the study is not powered to detect differences in sub-groups. Nevertheless, post-hoc subgroup analyses might be conducted to guide future research .

Plan for interim analysis (frequentist approach)

This section is drafted using the minimum power of 80% for the primary endpoint. as calculated above, this will be reached after 320 people are enrolled and follow-up for 28 days. A minimum of three interim analyses are planed approximately every n=80 patients enrolled in the trial and follow-up for 28 days. The O'BrienFleming error spending method was used to create boundaries for this sequential design as shown in the Figure 2 below .

Figure 2. Boundary plot for 3 pre-planned interim analyses



This plot will be created and shared with the DSMB committee that will periodically monitor safety and efficacy data of the trial. The boundaries should assist the DSMB in the recommendation that the trial should be stopped for safety concerns (such as an unacceptable toxicity level) or for efficacy. In contrast to a fixed-sample trial, a group sequential trial provides for interim analyses before the completion of the trial while maintaining the specified overall Type I and Type II error probabilities. A group sequential trial is most useful here as it is important to monitor the trial to prevent unnecessary exposure of patients to tocilizumab, or alternatively to lack of treatment intensification if the tocilizumab shows significant improvement. In most cases, if a group sequential trial stops early for safety concerns, fewer patients are exposed to the new treatment than in the fixed-sample trial. If a trial stops early for efficacy reasons, the new treatment is available sooner than it would be in a fixed-sample trial. Early stopping can also save time and resources.Detailed specifications for our group sequential trial are the following: there will be a minimum of 4 total number of stages (3 interim stages plus a final stage). The boundaries in the figure provide critical values, sample size and stopping criterion to reject the null hypothesis at each interim stage (Tables 1,2).

Table 1. Sample size at each interim analysis

Sample Sizes (N) Two-Sample Z Test for Proportion Difference								
	Fractional N				Ceiling N			
Stage	N	N(Grp 1)	N(Grp 2)	Information	N	N(Grp 1)	N(Grp 2)	Information
1	160.37	80.19	80.19	278.1	162	81	81	280.9
2	320.75	160.37	160.37	556.1	322	161	161	558.3
3	481.12	240.56	240.56	834.2	482	241	241	835.7
4	641.49	320.75	320.75	1112.3	642	321	321	1113.1

Table 2. Boundaries defining Z-scores at each interim stage

Ceiling-Adjusted Design Boundary Information (Standardized Z Scale) Null Reference = 0							
				Alternative		Boundary Values	
	Information Level			Reference		Lower	Upper
Stage	Proportion	Actual	N	Lower	Upper	Alpha	Alpha
1	0.2523	280.8843	162	-1.42457	1.42457	-4.03024	4.03024
2	0.5016	558.3008	322	-2.00841	2.00841	-2.85864	2.85864
3	0.7508	835.7174	482	-2.45725	2.45725	-2.33649	2.33649
4	1.0000	1113.134	642	-2.83591	2.83591	-2.02451	2.02451

In practice, at each interim stage, all the data collected up to that point are analysed, and statistics such as a maximum likelihood test statistic and its associated standard error are computed. The Z test statistic is then compared with critical values generated from the sequential design, and if the Z-score falls inside the boundaries the trial (shown in Figure 2) is continued, otherwise the DSMB will be consulted for advice over possible early termination. If a trial continues to the final stage, the null hypothesis is either rejected or we will conclude that we have no enough evidence to reject it.

Bayesian approach for unplanned looks

In addition, to further supplement the DSMB with indications for the effect of treatment, for ad-hoc unplanned interim analyses after any number of new persons enrolled and with complete follow-up of 28 days , posterior probabilities for the parameters of the logistic model will also be calculated under non informative priors as shown below following the methodology illustrated here (http://hbiostat.org/doc/bbr.pdf).

- Prior P(OR>1)=P(OR<1)=0.5 (equally likely harmful as beneficial)
- Prior P(OR>2)=P(OR<12)=0.025 (two-fold difference in effect in either direction unlikely)

Specifically, we will calculate the probability P1 that the OR for the primary outcome associated with use of tocilizumab is <1 (any benefit of tocilizumab) and P2 = Pr(OR<0.61) (value of the OR under the alternative hypothesis of at least a 39% reduction in risk, so moderate to high benefit).

For this study, example action triggers are:

- Stop the RCT with evidence for efficacy if P1>99%

- Stop the RCT with evidence for moderate or greater efficacy if P2>95%

In other words, if the DSMB finds at any point in the trial that there is at least 95% chance that the effect of risk reduction with tocilizumab is at least 39% they might suggest to stop the study for established efficacy. These probabilities can be calculated every time there is a new participant in the trial and the new value oversees the previous estimate.

SAFETY AND PHARMACOVIGILANCE

Any adverse event (AE) that the Investigator becomes aware of after completing the observation and clinical evaluation period and that is judged as possibly related to the treatment must be reported until the closure of the study.
During the study, all adverse events and associated adverse events should be followed proactively. Every effort should be made to obtain a resolution for all events, even if the events continue after the interruption / completion of the study. The investigator is responsible for following all Serious Adverse Events (SAEs) until resolution, until the subject returns to basic status or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond participation in the study.
The reference safety information necessary to evaluate and classify an adverse reaction, based on nature and severity, including frequency, is included in the updated Investigator's Brochure for Tocilizumab and provided by the marketing authorization holder.

Data Safety Monitoring Committee (DSMC)

The study has a committee of independent experts who will evaluate the conduct of the study, the safety data and, if necessary, the critical efficacy endpoints on a weekly basis. Based on its assessment, the DSMC provides the sponsor with recommendations regarding the modification, continuation or conclusion of the study.

Detection of adverse events

Any adverse event of which the Investigator becomes aware after completion of the observation and clinical evaluation period and which is judged as possibly related to treatment should be reported until the end of the study.

During the course of the study, all adverse events and associated adverse events should be followed proactively. Every effort should be made to achieve a resolution for all events, even if the events continue after the interruption/completion of the study. The investigator is responsible for following all severe adverse events until resolution, until the subject returns to the baseline state or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond participation in the study.

DEFINITIONS

Adverse Event (AE)

Any harmful clinical event occurring in a trial subject who has been administered the experimental treatment and who does not necessarily have a causal relationship with it. This definition includes effects resulting from therapeutic error, abuse, misuse, overdose, related toxicity or hypersensitivity reactions. An adverse event may therefore be a harmful and unwanted sign (including an abnormal laboratory test result), symptom or disease concomitant with the treatment, but not necessarily related to it. An adverse event may occur during both treatment and follow-up periods. An abnormal laboratory value is considered an adverse event if the abnormality:

- determines the definitive suspension of treatment;
- requires modification / discontinuation of treatment, or any other intervention;
- is judged to be of significant clinical importance.

Adverse Reaction (AR)

Any harmful and unwanted reaction to the experimental treatment, regardless of the dose administered.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Any adverse event or reaction that, regardless of dose:
- requires hospitalization;
- prolongs ongoing hospitalization;
- results in severe or prolonged disability;
- results in a congenital abnormality;
- endangers the subject's life or causes death.

Serious Unexpected Adverse Event (SUSAR)

Any unforeseen serious adverse event deemed serious by the Investigator and/or the Promoter, which is inconsistent, either in nature or severity or frequency, with the relevant security information (CSR).

ASSESSMENT OF AN ADVERSE EVENT

The Investigator (or other physician trained in the registration and notification of EAs) is responsible for evaluating an adverse event with regard to seriousness, severity, correlation, predictability and outcome of the event.

Seriousness

The seriousness of an event defines the obligations and timing of notification. The criteria according to which the Investigator will assess the seriousness of the AE are those set out in the definition of “Serious Adverse Event (SAE)”.

Severity/Gravity

The criterion of severity should not be confused with the criterion of seriousness which is the guide for the definition of reporting obligations. If a severity assessment toxicity occurs, reference should be made to NCI Common Toxicity Criteria, - NCI CTCAE term (Version 5.0).

The severity of adverse events not listed on the NCI CTCAE term toxicity scale (Version 5.0) will be assessed at the following levels:

1. mild: the adverse event is easily tolerated by the subject, causing minimal discomfort and no interference with daily activities; does not require specific treatment;
2. moderate: the adverse event is discouraging enough to interfere with normal daily activities and is improved by therapeutic intervention;
3. severe: the adverse event prevents normal daily activities and requires specific therapeutic intervention;
4. life threatening: immediate risk requiring hospitalization and clinical intervention;
5. death.

Correlation

The Investigator will assess the correlation between AE and treatment against the reference safety information (RSI), regardless of the dose administered:

- Unrelated: when AE is not considered to be related to treatment;

- Possible/probable correlation (or correlated): when the causal link between the EA and treatment is made possible/probable by the temporal relationship, nature of the event and dependence on discontinuation/restart of treatment, while the relationship of the EA with concomitant drugs or underlying diseases or any specific procedures is considered unlikely.

The Investigator should also consider events that are generated by therapy errors and uses not foreseen in the protocol, including misuse or abuse of the product and interaction with a treatment, as related to treatment.

Predictability

If the AE is judged to be related to the treatment, the Investigator will assess predictability against known safety information. The AE will be classified as:

- Expected: the reaction is consistent with the treatment toxicity information listed as reference safety information (RSI).

- Unexpected: The reaction is NOT consistent with the toxicity information of the listed treatment as reference safety information (RSI). An increase in the frequency or severity

of a known and already documented serious adverse reaction is considered unexpected.

Outcome of the event

The Investigator will indicate the actions taken with regard to the treatment (temporary suspension, reduction or interruption of treatment) and will indicate whether additional actions not foreseen in the protocol were necessary for the management of the event.

The Investigator is responsible for adequate clinical follow-up of the EFA until full or partial resolution, stabilization, aggravation or death (due to the event itself). This may mean that in some circumstances the follow-up continues after the end of the study.

RECORDING OF AN ADVERSE EVENT

The Investigator (or other Physician trained in the registration and notification of EAs) will register EAs and SAEs in both CRF and health records and update the permanent EAs register.

In this study, all EAs will be registered in the CRF except for:

- Any medical conditions in the patient reported at baseline assessment, prior to the start of treatment in the study (worsening of these conditions during the study will be recorded as an EAs).

- An abnormal laboratory value that is clinically non-significant (not leading to exit from the study, specific treatment, modification or discontinuation of treatment in the study, other therapeutic interventions) or that in the opinion of the Investigator is not clinically important. If the laboratory parameter is part of a disease state, only the diagnosis of the disease should be reported as AE within the CRF. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result.

Within the CRF, the Investigator should describe the AE in medical terms, detail the required information as defined against the event evaluation criteria, and record the duration of the AE (date of submission and outcome).

A resolved AE that recurs or increases in severity should be recorded as a new event.

Procedures for reporting a serious adverse event

All SAE/SUSARs should be reported by the Investigator immediately and no later than 24 hours after the Investigator becomes aware of the event to the Promoter. The event will be verified against EVCTM (EudraVigilance clinical trials module) reporting requirements in addition to specific section CRF registration.

In case of death, the relevant Ethics Committee will also be notified.

Collection and reporting of adverse events

The Promoter will notify all SUSARs that could adversely affect the safety of Eudravigilance participants (through EVCTM), all the Experimenters and Ethics Committees of the participating centres and the holder of the marketing authorisation (F. Hoffmann-La-Roche), within the terms of Article 17 of the European Directive 2001/20 / EC:

- Fatal or life-threatening SUSARs within 7 days
- all the other SUSARs within 15 days.

The promoter will prepare an Annual Safety Report (DSUR) in accordance with applicable legislation.

ETHICAL ASPECTS

This study will be conducted in full compliance with the principles of the Helsinki Declaration, or Italian laws and regulations, whichever is the greater protection for the individual.

DATA PROTECTION

The AOU of Modena, as promoter, affirms the right of the subject to protection against the violation of privacy and applies the rules for the protection of fundamental rights and freedoms of natural persons (participants) in relation to the processing of personal data in accordance with the GCP and European and local regulations. All information

identifying the patient will be kept confidential and, to the extent permitted by applicable laws and/or regulations, will not be made publicly available.

If the patient's name or other potentially identifying patient information appears on any study document, it must be deleted before a copy of the document is shown to the Promoter or its representatives (pseudo-anonymization). According to Directive 95/46 / EC (General Data Protection Regulation, GDPR), the pseudo-anonymization of the participant's data implies the replacement of any identifying characteristic of the data with a value that does not allow the person concerned to be directly identified. The code key (patient ID) remains at the Clinical Centre and is covered by the confidentiality obligation.

The names of the trial participants or any other data allowing their identification will not be collected and recorded in the Case Report Form (CRF). Only the participant's code (i.e. patient ID) will be recorded in the CRF. All information collected in the CRF will be made accessible to investigators authorized by the PI as treatment manager in the study delegation log of each clinical centre and access will be possible only through the username and password provided to each investigator participating in the study. Study results collected on a study-specific database will be stored in accordance with data protection laws and in accordance with the Integrated Addendum to ICH E6 (R1) E6R2. This central database will be available and shared with all participant sites.

The Company as data controller will ensure that:

- patients enrolled in the study receive detailed information on why their data is needed and how it will be used;
- a procedure is in place to respond to requests for information from trial subjects;
- a procedure is in place to promptly process any request for information on the management of personal data or request for access within the terms and conditions established by applicable legislation;

and that properly identified data controllers will ensure that:

- clinical data are processed only for the management for which they are collected, as specified in the study protocol;
- all those who process personal data are responsible for compliance with good data protection practices and are adequately trained and supervised.

In accordance with GCP, study information will be kept safe by appropriate physical, technical, organizational, and other measures to safeguard study data and prevent unauthorized or unlawful reproduction or processing or accidental loss or destruction. Study information will be accessible only to authorized personnel and will be retained only for as long as necessary.

The sites will take appropriate measures to ensure that adequate technical and security measures are in place during the transfer of study data within the data management unit and that such data transfers are carried out in accordance with applicable local law. Quality assurance will regularly assess the process and performance in relation to the management of personal information. This policy will be updated as necessary to reflect best practices in data management, security and control.

All the above responsibilities are supervised by the Data Protection Officer, as defined in Regulation Article 37 EU 2016/679 (GDPR).

PARTICIPATING CENTERS

1. Clinic of Infectious Diseases Modena
2. Clinic of Infectious Diseases Bologna
3. Clinic of Infectious Diseases Parma
4. Clinic of Infectious Diseases Tor Vergata Rome
5. Clinic of Infectious Diseases Latina
6. Clinic of Infectious Diseases Hospital San Paolo Milan
7. Clinic of Infectious Diseases Sacco Hospital Milan
8. Clinic of Infectious Diseases Ferrara
9. Clinic of Infectious Diseases Caserta
10. Clinic of Infectious Diseases Policlinico Milan
11. Infectious Disease Unit Piacenza
12. Infectious Disease Unit Reggio Emilia
13. Infectious Disease Unit Niguarda Hospital Milan
14. Infectious Disease Unit Cotugno Hospital Naples

15. Infectious Disease Unit Padua
16. Clinic of Infectious Diseases Turin
17. Clinic of Infectious Diseases Pisa
18. Clinic of Infectious Diseases San Raffaele Hospital Milan
19. Infectious Disease Unit Bergamo
20. INMI L. Spallanzani, Rome
21. Clinic of Infectious Diseases Pescara
22. Clinic of Infectious Diseases, Palermo
23. Clinic of Infectious Diseases, Foggia
24. Clinic of Infectious Diseases, Bari
25. Unit of Infectious Diseases, Ravenna
26. Clinic of Infectious Diseases, Perugia
27. Clinic of Infectious Diseases, Ancona
28. Clinic of Infectious Diseases, Catania
29. Unit of Infectious Diseases, Siracusa
30. Unit of Infectious Diseases, Rimini
31. Clinic of Infectious Diseases, Sassari
32. Clinic of Infectious Diseases, Gemelli Hospital, Rome
33. Clinic of Infectious Diseases, Pesaro
34. Clinic of Infectious Diseases, Vanvitelli University Napoli
35. Unit of Infectious Diseases, Ancona
36. Unit of Infectious Diseases, Bolzano
37. Clinic of Infectious Diseases, Udine.
38. Covid 19 Hospitals, ASL Bari
39. Unit of Infectious Diseases, Firenze Santa Maria Annunziata
40. Unit of Infectious Diseases, Pistoia
41. Clinic of Infectious Diseases, Trieste
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APPENDIX 1: SCHEDULE OF ACTIVITIES (SOA)

Study Procedure	**Screening Visit[1]**	**Baseline Visit[1]**	**Daily Follow-up Until Hospital discharge**					**EOS[2]**	**Discharge Before Day 29[3,4]**
	Day -1 or 1	Day 1	Day 4	Day 7	Day 15	Day 21	Day 28_3	Day 60	
Window (day)								+- 7	
Screening/baseline									
Inclusion/Exclusion	X								
Informed Consent	X								
Demographics and Medical History	X								
Randomization		X							
Treatment									
Study drug administration		X							
Assessments:									
Efficacy									
Body temperature	X (2 times a day)	Day 1-3: 4 times a day; Day Day 4-29: 2 times a day							
Oxygen Delivery and Oxygenation	X	Day 1-3: 4 times a day; Day Day 4-29: record results as assessed							
Resting SpO_2[5]	X	Day 1-3: 4 times a day; Day Day 4-29: record results as assessed							
Clinical Daily	X	Daily until discharge							

Assessment (including 7-point ordinal scale)									
Vital Status (and cause of death)		Daily until discharge						X	
Arterial blood gas results (as available)	X	X							
Vital signs (other than temperature and SpO_2)	X	Daily until discharge							
Electrocardiogram[6]	X								
Record Concomitant Therapy	X	Daily until discharge							
Adverse Events[7]	X	X							
Pregnancy Test (WOCBP)[8]	X								
Bacterial infection testing, fungal infection testing, HSV1 PCR (blood)				X	X				
Laboratory Testing Standard-of-Care:									
Hematology Results[9]	X	X	X	X	X	X	X		
Blood Chemistry Results[10]	X	X	X	X	X	X	X		
Urinalysis culture Results (as available)	X	X							

C-Reactive Protein Results	X	X	X	X	X	X	X		
D-Dimer Results[11]	X								
Serum sIL-6R[12] (optional)		X	X			X	X		

EOS: end of study; SpO2: oxygen saturation; ECG: electrocardiogram; WOCBP: women of childbearing potential.

1. Screening and baseline may occur within the same day. Assessments that are noted for both visits should only be assessed once. All samples should be collected before study drug administration at baseline visit except post-infusion PK and sIL-6R samples.
2. Patients will have an end of study (EOS) assessment to collect data on survival and history of hospital re-admission. This assessment may be performed by phone.
3. Patients discharged prior to Day 28 will have a follow-up phone call on Day 28 to collect data on serious adverse event and history of hospital re-admission.
4. Patients discharged prior to day 28 should have a sample collected on or before day of discharge.
5. Must be measured after 5 minutes of rest (sitting or supine), and must be measured simultaneously with oxygen delivery and ventilation data.
6. Historical ECG from current hospital admission acceptable.
7. Only SAEs (serious adverse events) and AESIs (adverse events of special interest) will be recorded in CRF.
8. Pregnancy testing to be performed locally in women of childbearing potential (WOCBP) only. Serum or urine pregnancy test are both acceptable.
9. Hematology: refer to Appendix 2 of the protocol for details.
10. Blood Chemistry: refer to Appendix 2 of the protocol for details.
11. D-dimer: refer to Appendix 2 of the protocol for details.
12. If available.

APPENDIX 2: CLINICAL LABORATORY TESTS

The tests detailed in table 1 will be performed by the local laboratory.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Pregnancy testing: Pregnancy testing to be performed locally in women of childbearing potential (WOCBP) only. Serum or urine pregnancy test are both acceptable.

Table 1 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit <u>RBC indices:</u> MCV MCH %Reticulocytes <u>White blood cell (WBC) count with differential</u>:

	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a]	
	Blood urea nitrogen (BUN)
	Creatinine
	Glucose (fasting or nonfasting)

Laboratory assessments	
Parameters	
	Potassium
	Sodium
	Calcium
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase
	Total and direct bilirubin
	Total protein
Routine urinalysis	Specific gravity pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick

	Microscopic examination (if blood or protein is abnormal)
Other tests	Highly sensitive [Serum or urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)a C reactive protein D dimer Bacterial and fungal blood culture HSV1 PCR Serum IL-6 SARS-CoV-2 (Blood and NP swab) (Mandatory at screening only) Blood for DNA/RNA (optional)

NOTES :

a Details of liver chemistry and follow-up assessments are given in Section [8.3.6]

b Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

The results of each test must be entered into the CRF.

Investigators must document their review of each laboratory safety report.