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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

_____ _____

Contents

1. Synopsis

Protocol Title: "ColcHicine in patients with COVID-19: a home CarE study"

Short Title: Colchicine in COVID-19

Rationale

1.1 Introduction

The outbreak of the 2019-coronavirus (SARS-CoV-2) has posed the world at a pandemic risk (1). The disease (COVID-19) is characterized by an acute respiratory distress and there is an immediate need for any agent before the development of a vaccine. So far, therapeutic regimes include a combination of anti-viral drugs such as lopinavir plus ritonavir. Moreover, preliminary in vitro experiments have suggested that chloroquine/hydroxychloroquine have anti-viral activity. Chloroquine may inhibit the glycosylation process of angiotensin-converting enzyme (ACE)-2 and hamper the phosphorylation of p38 mitogen-activated protein kinase (MAPK), thus contributing to the inhibition of virus cell entry and replication. Moreover, chloroquine/hydroxychloroquine may have an immunomodulatory effect on TNFα, IL-1β and IL-6. Tocilizumab, an anti-IL-6 monoclonal antibody, has been used with encouraging results in particularly ill patients since there may be a massive release of pro-inflammatory cytokines, especially IL-6, by lung epithelium in severe cases. Indeed, a pro-inflammatory status with high levels of IL-1B, IL-1RA, and TNF-α characterizes the diseases, and higher levels of IL-2, IL-10, and TNF-α have been observed in intensive-care-unit patients. Colchicine is the main treatment of several rheumatic conditions in which the activation of the inflammasome and release of pro-inflammatory cytokines are the key pathogenic events. It alters the organization of actin cytoskeleton by binding to tubulin monomers and inhibits polymer formation. This drug has shown clear anti-inflammatory effects, more pronounced on IL-1/IL-6. Moreover, colchicine has anti-viral properties against flaviviridae and against the recombinant demyelinating strain of mouse hepatitis virus RSA59 as demonstrated reducing virus replication since microtubules are crucial in cell entry and blocking neuronal transport. It inhibits respiratory syncytial virus replication reducing IL-6 and TNF-α levels. A rational of colchicine as an anti-HIV agent has been proposed too. Certain subsets of the 2003-SARS coronavirus replication machinery have been shown to activate the inflammasome and to move in the cell in a manner that corresponds with microtubule-associated transport, inducing the formation of double-membrane vesicles in infected cells. The question may be whether this occurs during SARS-CoV-2 infection and if microtubule disruption may influence viral genome replication levels.
A dysregulated activation and inflammatory activity of myeloid cells is one the main pathogenic events characterizing the infection by coronaviruses. Due to its anti-neutrophilic properties, colchicine was proposed as an anti-viral agent as an adjuvant treatment for RSV bronchiolitis. Thus, colchicine has broad anti-inflammatory effects, anti-viral properties and it is not hampered by an immunosuppressant effect. Unlike other proposed treatments, colchicine is inexpensive and with known side effects.

1.2 Objectives and endpoints

Primary	
To evaluate the efficacy of colchicine by describing:	
1. Rate of hospitalization (30 days)	a. Need for hospitalization (at 30 days after randomization)
Secondary	
To describe:	
1. Hospital-free days 2. Death 3. Clinical remission 4. Toxicity of Colchicine	1. Hospital-free days (at 30 days after randomization). 2. Rate of death (at 30 days after randomization) 3. Rate of disappearance of symptoms and two consecutive negative swabs at 24 hours (at 30 days after randomization) 4. Rate of adverse events codified by Common Terminology Criteria for Adverse Events (CTCAE) v5.0

1.3 Overall Design

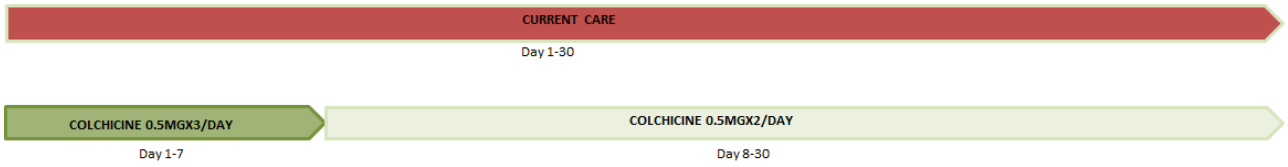
This is an interventional, multicenter, double-arm, randomized, open-label, phase 3 study, enrolling patients with COVID-19 disease.

Phase 3 cohort study
One-month rate of hospitalization is the primary endpoint. From available data (http://www.salute.gov.it/imgs/C_17_notizie_4640_0_file.pdf), it can be assumed that 1-month rate of hospitalization for the population defined by the selection criteria is around 18.4% (P0). To verify the hypothesis that the experimental drug may produce a halving of the rate of entering the critical stage (from 18.4% to 9.2%, P1), 438 patients are needed with an 80% power and a 5% bilateral alpha error. The two arms will be randomized with 219 patients treated with current care and 219 with colchicine added to the current care.

1.4 Treatment and Duration

Participants in arm 1 will receive current care from day 1 to day 30 plus colchicine 0.5 mg every 8 hours from day 1 to day 7, then colchicine 0.5 mg every 12 hours from day 8 to day 30.
Participants in arm 2 will receive current care from day 1 to day 30.
Colchicine may be lowered at 0.5 mg every 12 hours during the first week or at 0.5 mg every 24 hours during the entire month of treatment in case of gastrointestinal symptom appearance at discretion of the Investigator. Colchicine may cause gastrointestinal side effects, particularly diarrhea, in about 9.6% of patients that usually do not require treatment discontinuation.
The maximum dose is the same approved by EULAR for the treatment of Gout and FMF.
Treatment can be withdrawn in both arms in case of clinical remission (disappearance of symptoms and two consecutive negative swabs at 24 hours) occurring prior of the 30 days after randomization.

ARM 1.



ARM 2.

Procedures	**Baseline before randomization**	**Telephone monitoring (every 7 days)**	**End of the study**
Informed consent	X		
Inclusion and exclusion criteria	X		
Demography	X		
Physical parameters including height and weight, blood pressure, SpO_2 at rest, temperature, respiratory rate at rest*	X	X	X
Medical history (includes past and current medical conditions, and substance usage)	X		
Laboratory assessments[1]	X	X	X
Pharyngeal swab[2]	X		X
12-lead ECG [3]	X		
Thoracic CT scan or Chest XR[4]	X	X	X
AE review	X	X	X
Concomitant medication review	X	X	X

* blood pressure, SpO_2 at rest, temperature, respiratory rate at rest when available
[1] Laboratory assessment is optional
[2] At the end of the study perform at least 2 separated by 24 hours
[3] 12-lead ECG evaluation is optional.
[4] Radiological evaluation is optional.

2. Introduction

Colchicine is an inexpensive, orally administered, potent anti-inflammatory medication that was initially extracted from the autumn crocus and has been used for centuries. Its mechanism of action is through the inhibition of tubulin polymerization and microtubule generation and, possibly, effects on cellular adhesion molecules, inflammatory chemokines, and the inflammasome (2, 3). Colchicine is currently indicated for the treatment of gout, familial Mediterranean fever, and pericarditis (4-6).

3. Background

The outbreak of the 2019-coronavirus (SARS-CoV-2) has posed the world at a pandemic risk. The disease (COVID-19) is characterized by an acute respiratory distress and there is an immediate need for any agent before the development of a vaccine. Coronavirus-19 disease (COVID-19) is an infectious disease caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), a β-coronavirus that belongs to the same family as SARS and MERS, which causes pneumonia, requires intensive care unit hospitalization in about 10% of cases and can lead to a fatal outcome (7-10).

To date, there is no registered molecule for the treatment of COVID-19 patients. However, there are ongoing trials on the use of some antivirals and immunosuppressive or immunomodulating drugs that have demonstrated efficacy on COVID-19 both in vitro and on animal models as well as in small cases series.

Certainly, previous experiences on viruses belonging to the same β-coronavirus family have formed the cornerstones of the current therapeutic strategy (11, 12). The emergency facing the scientific community in addressing the pandemic from COVID-19 provides the rationale for the use of drugs that have not yet been approved and with still preliminary scientific evidence.
So far, therapeutic regimes include a combination of anti-viral drugs. Moreover, preliminary in vitro experiments have suggested that CQ/HCQ have anti-viral activity by inhibition of cell virus entry and viral replication (13, 14). Tocilizumab, an anti-IL-6 monoclonal antibody, has been used with encouraging results in particularly ill patients since there may be a massive release of pro-inflammatory cytokines, especially IL-6, by lung epithelium in severe cases (15). Trials to test the efficacy of Tocilizumab on severe COVID-19 patients are being tested in China and in Italy (16, 17).

Indeed, a pro-inflammatory status with high levels of IL-1β, IL-1RA, and TNF-α characterizes the diseases, and higher levels of IL-2, IL-10, and TNF-α have been observed in intensive-care-unit patients (18). Authors recently documented that SARS-CoV and its accessory protein are potent activators of pro-IL-1β gene transcription and protein maturation, and thus are able to activate the NLRP3 inflammasome. Colchicine is the main treatment of several rheumatic conditions (19-21) in which the activation of the inflammasome and the release of pro-inflammatory cytokines is the key pathogenic event. It alters the organization of actin cytoskeleton by binding to tubulin monomers and inhibits polymer formation (22).

3.1 Rationale for colchicine in COVID-19 infection

Colchicine drug has shown clear anti-inflammatory effect more pronounced on IL-1/IL-6, as evident from *in vivo* studies at therapeutic dosage (20). For instance, colchicine has demonstrated a protective effect after myocardial infarction at only 0.5 mg/day in terms of incidence of strokes and urgent hospitalizations for angina leading to coronary revascularization (19). It reduced the C-reactive protein level in these patients similarly to an anti-IL-1 drug, canakinumab. Colchicine is effective in preventive atherosclerosis in multiple ways (23). Indeed, it is highly concentrated in neutrophils and macrophages prolonging its action (24). Its ability to bind tubulin achieves multiple cellular actions, including inhibition of the assembly of the NLRP3 inflammasome. In addition to its effect on neutrophils (25, 26), colchicine impairs the release of IL-1b into NETs (27). Many of the actions have been demonstrated in patients with coronary disease (28, 29).

Colchicine blocks the NLRP3 inflammasome, a cytosolic complex responsible for the production of IL-1β and IL-18. In patients with acute coronary syndromes, in which IL-1β, IL-18, and downstream IL-6 that are key inflammatory cytokines in the pathogenesis of this condition, colchicine administration was able to significantly reduce transcoronary gradients of all 3 cytokines in by 40% to 88% (29). A similar reduction in IL-6, but also in IL-8 or TNF-α levels can be observed in mucocutaneous Behçet's disease patients (30).

Moreover, colchicine has anti-viral properties against flaviviridae and against the recombinant demyelinating strain of mouse hepatitis virus RSA59 as demonstrated reducing virus replication since microtubules are crucial in cell entry and blocking neuronal transport (31, 32). It inhibits respiratory syncytial virus (RSV) replication reducing IL-6 and TNF-α levels (33). A rational of colchicine derivatives as an anti-HIV agent has been proposed too (34). Certain subsets of the 2003-SARS coronavirus replication machinery have been shown to move in the cell in a manner that corresponds with microtubule-associated transport, inducing the formation of double-membrane vesicles in infected cells (35). The question may be whether this occurs during SARS-CoV-2 infection and if microtubule disruption may influence viral genome replication levels (35). As abovementioned, as SARS-CoV, it is likely that also SARS-CoV-2 activates the inflammasome, an effect directly inhibited by colchicine (36). Moreover, a dysregulated activation and inflammatory

activity of myeloid cells is one the main pathogenic events characterizing the infection by coronaviruses (37, 38). Colchicine is a well- known inhibitor of the pro-inflammatory mechanisms induced by neutrophils thus it was proposed as an adjuvant treatment for RSV bronchiolitis (39).

3.2. Benefit/Risk Assessment

Colchicine has broad anti-inflammatory effects, anti-viral properties and is not hampered by an immunosuppressant effect. Colchicine is also inexpensive. Detailed information about the known and expected benefits and risks and reasonably expected adverse events of the drug may be found in the Investigator's Brochure. Colchicine may cause gastrointestinal side effects, particularly diarrhea, in about 9.6% of patients that usually do not require treatment discontinuation.

4. Study Design

4.1. 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 evidences are 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.

4.2. Overall Design

This is an interventional, multicenter, double-arm, randomized, open-label, phase 3 study, enrolling patients with COVID-19 disease.

One-month rate of hospitalization is the primary endpoint. From available data (http://www.salute.gov.it/imgs/C_17_notizie_4640_0_file.pdf), it can be assumed that 1-month rate of hospitalization for the population defined by the selection criteria is around 18.4% (P0). To verify the hypothesis that the experimental drug may produce a halving of the rate of entering the critical stage (from 18.4% to 9.2%, P1), 438 patients are needed with an 80% power and a 5% bilateral alpha error. The two arms will be randomized with 219 patients treated with colchicine added to the current care and 219 treated with current care.

The trial will be conducted in the Italian regions currently reported having the higher prevalence of COVID-19: Lombardia, Piemonte, Liguria, Veneto, Trentino, Emilia-Romagna, Marche.

Patients will be screened for having COVID-19 disease due to positive swab in the 96 hours prior to randomization and typical symptoms occurring in the 10 days prior to randomization.

General practitioners (GP) will screen the patients that will be randomized in one of the two arms (see section 9.2). In case the patient will be assigned to the colchicine arm, the patient will have the prescription from the GP and the drug will be provided in pharmacies where it is easy to be found. In case there is any impediment to providing the drug for any reason (economic, incapacitation to reach the pharmacy, etc.) the drug will be directly provided by ACARPIA Farmaceutici S.r.l. at no expenses directly at the residency address of the patient via certified express courier.

Then, the patients will be followed at home via weekly telephone interviews by general practitioner. In case of disease worsening and suspect of need of hospitalization the general practitioner will request the reference PS/DS to schedule a specialist home evaluation when available or either activate 118 for hospitalization if the clinical situation requires it.

4.3 Authorship
Besides the abovementioned promoting centers, any general practitioner that will enroll at least 10 patients is entitled, in case of publication, of 1 co-author.

4.4 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.
Any available *rescue therapy* will be adopted if required in all the three arms.
The trial will be concluded when at least 438 patients will be enrolled and ended the study protocol.

5. Study Population
5.1. Inclusion Criteria
Participants are eligible to be included in the study if the following criteria apply:
1. Any gender
2. ≥18 years old
3. Informed consent for participation in the study
4. Virological diagnosis of SARS-CoV-2 infection (real-time PCR) with positive swab within 96 hours from randomization
5. First symptom appearance likely to be associated with SARS-CoV-2 infection within 10 days from randomization
6. Presence of at least two of the following:
a. Fever ≥ 37°C
b. Breath frequency at rest ≥ 19 ≤23
c. Dry cough, dyspnoea, pharyngodynia, dysgeusia, anosmia, burning eyes, arthromyalgias or diarrhea
d. Oxygen saturation at rest in ambient air >94%

5.2. Exclusion Criteria
Participants are excluded from the study if any of the following criteria apply:
1. Known hypersensitivity to colchicine or its excipients
2. Patients who cannot take oral therapy
3. Pregnant and lactating patients
4. Hospitalized patients or under immediate consideration for hospitalization
5. Patient with pre-existent progressive neuromuscular disease and CPK > 2 times the normal limits
6. Patients with severe cardiac, renal insufficiency (Estimated Glomerular filtration rate (eGFR), using the MDRD (or EPI CKD) equation for all subjects being considered for enrollment, with a cut-off of < 30 mL/m in/1.73m2)
7. Patient with a history of cirrhosis, chronic active hepatitis or severe hepatic disease;
8. Patient currently taking colchicine for other indications (gout, pericarditis, familiar Mediterranean fever, other autoinflammatory diseases)
9. Patients taking drugs that have a strong interaction with the CYP3A4 enzyme or with P-glycoprotein (including lopinavir, ritonavir, darunavir/cobicistat, ketoconazole, cyclosporine, verapamil, quinidine and clarithromycin)
10. Other known clinical condition that contraindicate colchicine and cannot be treated or solved according to the judgement of the clinician

11. Patients with known history of neutropenia (neutrophils<1.000/mmc) and thrombocytopenia (platelets <50.000 / mmc)
12. Patients with inflammatory bowel disease and diverticulitis
13. Patients already enrolled in other clinical trials

6. Treatments

6.1. Treatment Administered

Study Treatment Name:
Colchicine
Dosage formulation:
Colchicina LIRCA
1 mg Unit dose
strength(s)/Dosage level(s):
Colchicine up to 1.5 mg/day
Such dose is same approved by EULAR for the treatment of Gout and FMF
Route of Administration orally
Dosing instructions: 0.5 mg every 8 hours
Packaging and Labeling
Marketing Authorization Holder
ACARPIA Farmaceutici S.r.l.
Via Vivaio, 17- 20122 Milano (Italia),
AIC: 009964038
Excipients: lactose, gum arabic, sucrose, magnesium stearate.

6.2. Treatment Compliance

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

6.3. Concomitant Therapy

There is no contraindication to concomitant treatment (excluding any drug administered in the course of another clinical trial or any drug strongly interfering with CYP3A4 or p-glycoprotein) that can be defined in advance given the severity of the disease. It is likely that several patients will be treated with hydroxychloroquine at the time of the study entry. In this context, a synergistic anti-viral effect may be expected. However, although few data exist on pharmacological interactions between hydroxychloroquine and colchicine, the available data suggest that this pharmacological association is safe. To prevent the rare but reported occurrence of myopathy, patients with pre-existent progressive neuromuscular disease and CPK > 2 times the normal limits will be excluded (40-42).
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

7. 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.

7.1. Screening procedures
- Informed Consent Form
- Demography (age, gender, ethnicity)
- Medical history (previous and current diseases, all medications started within 14 days prior to screening visit)
- Height and weight
- Respiratory rate, Blood pressure, SpO2 saturation, temperature (when available)
- Laboratory assessments (when available record at least blood count, bilirubin, AST, ALT, creatinine, ferritin, LDH, CRP levels)
- Pharyngeal swab for SARS-CoV-2
- 12-lead ECG (when available)
- Thoracic CT scan or Chest XR (when available)
- AE review (including SAEs)
- Concomitant medication review

7.2. Procedures through weekly telephone interview
- Respiratory rate, Blood pressure, SpO_2, temperature (when available)
- Laboratory assessments (when available record at least blood count, bilirubin, AST, ALT, creatinine, ferritin, LDH, CRP levels)
- AE review (including SAEs)
- Concomitant medication review

7.3. Procedures at the end of the study
- Respiratory rate, Blood pressure, $sSpO_2$, temperature (when available)
- Laboratory assessments (when available record at least blood count, bilirubin, AST, ALT, creatinine, ferritin, LDH, CRP levels)
- Pharyngeal swab for SARS-CoV-2 (perform at least 2 separated by 24 hours)
- 12-lead ECG (when available)
- Thoracic CT scan or Chest XR (when available)
- AE review (including SAEs)
- Concomitant medication review

7.4. Efficacy Assessments
The patient will perform a self-assessment of objective measures (when available) including respiratory rate, SpO_2 and temperature which will be telephonically reported to the General Practitioner. Rate of hospitalization for any reason due to COVID-19 is the final outcome measure.

8. Adverse Events

8.1 Definitions

An adverse event (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 brochures). A Serious Adverse Event (SAE) is untoward medical occurrence or effect that at any dose results in death, risk of death, permanent disability/incapacity, hospitalization 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 grade≥ 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 center. 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. Adverse events of special interest (AESI)- The following adverse events have been identified as AESI for this study and require prompt reporting to Safety desk for the study immediately and no more 24h of the Investigator becoming aware of the event (expedited reporting), even if the events can be considered non-serious according to the usual regulatory criteria as they may be subject to expedited submission to regulatory authorities:

- Cases of potential drug-induced liver injury (DILI) that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law.
- Suspected transmission of an infectious agent by the study drug (STIAMP), defined as any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, that is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

8.2. 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 (+39075045569) 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.

8.3. 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
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.

8.4. 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, is located in the specific section of the Investigator's Brochure of colchicine (section 6.4.1 as of the version 21 released in September 2019).
- 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, and to the manufacturer, within the timelines of the article 17 of the European Directive 2001/20/EC.

- 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.

8.5. Safety Assessments

Planned time points for all safety assessments are provided in the schedule of assessments table.

9. Statistical Considerations

9.1. Sample Size Determination

The study is designed as a double-arm single-stage phase 3 study with 1-month rate of hospitalization as primary endpoint.
Expected 1-month rate of hospitalization (P0): 18.4%
Auspicated 1-month rate of hospitalization (P1): 9.2%
Statistical power: 80%
Bilateral alpha error: 5%
Sample size needed: 438 patients

9.2 Randomization

To maintain confidentiality, patients who sign the Informed Consent Form will be assigned a screening number (2-digit site number and 3-digit progressive number for each site). This number will be used to identify the patient during screening procedures. For all patients who successfully fulfill all screening procedures and meet Inclusion/Exclusion Criteria, a unique "Randomization number" corresponding to the treatment number will be assigned (4-digit). These patients are identified as "Randomized Patient". Allocation of each patient to a given treatment will be listed in a randomization list. The randomization list will be prepared using the SAS System software version 9.4. The randomization will be made with a sample allocation ratio of 1:1 using an appropriate block size. Eligible patients will be assigned to the next lowest randomization number available. Should a patient be withdrawn from the study, neither his/her screening number nor the randomization number will be reallocated.

9.3. 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.

9.4. 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.).

Endpoint	**Statistical Analysis Methods**
Primary	1-month rate of hospitalization is defined as the ratio of patients who will be hospitalized from study start out of those registered at baseline and will be described with its 95% confidence interval.
Secondary	All the analysis will be descriptive.

9.4.1. 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.

10. 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 pandemic will be 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.

10.1. Informed Consent Process

The general practitioners treating the patient are responsible for information of the patient and obtaining of the Informed Consent. The consent can be oral if a written consent cannot be expressed and written will be obtained as soon as the conditions will allow. Consent to remain in the research should be sought as soon the conditions of the patient will allow it. The same procedure applies 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.

11. Data collection procedures

Patient registration and data collection will be centralized. The CRF design will be performed by LB (Evidence®), data collection is electronic through the Nubilaria's ACTide eCRF Platform which is GAMP5, FDA Part 11, ICH/GCP, GDPR and ISO 9001 & 27001 compliant. The platform will be available at https://trials.actide.com/lb/choice19.

12. Administrative aspects

This is a non-profit investigator initiated trial.
Study protocol, patient information, and informed consent at beginning and at each required amendment will be submitted to the appropriate Ethical Committee for approval. After the first approval the study will be started at identified territories in Italy requiring to participate and such participation will be notified.
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.

13. Coordinating centre contacts

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CHOICE-19

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