CONVINCE

Short title:
CorONa VIrus edoxabaN ColchicinE (CONVINCE)

Full Title:
Efficacy and Safety of Edoxaban and or Colchicine for patients with SARS-CoV-2 infection managed in the out of hospital setting (COVID 19)

Prepared by **M. Valgimigli, P. Vranckx, N. Morici**

Study Type:	Clinical trial with Investigational Medicinal Product (IMP)
Study Registration:	clinicaltrial.gov NCT04516941
Study Identifier:	CONVINCE / EudraCT number 2020-002234-32
Sponsor:	InselGruppe AG, Bern University Hospital Department of Cardiology Freiburgstrasse, 3010 Bern, Switzerland
Co-Sponsor:	Azienda Socio-Sanitaria Territoriale (ASST) of Lecco Via dell'Eremo 9/11, 23900, Lecco, Italy
Investigational Product:	Edoxaban, Colchicine
Protocol Version and Date:	V2/ 31.08.2020

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Protocol approval page

CONVINCE

Protocol version: 2.0, dated on 31.08.2020

We, the undersigned, have read and approved the protocol specified above, and agree upon the contents:

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Coordinating Principal Investigator and Principal Investigator

Date 21/09/2020

Pascal Vranckx, Hasselt, Belgium
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Date 17/09/20

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Protocol Signature Page

CONVINCE Protocol Version 2.0 dated on 31.08.2020

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Site Name and Address: _____

Printed Name of Principal Investigator: _____

Date: _____

Signature: _____

1. PROTOCOL SUMMARY

Background	There is emerging evidence that patients with SARS-CoV-2 infection are affected by increased coagulopathy, including in the most advanced forms, a fully blown disseminated intravascular coagulation, leading to multi organ failure (MOF). Post-Morten observations from patients who died because of SARS-CoV-2 infection in Bergamo, Italy and other places have revealed the presence of diffuse venous, arterial and microcirculatory thrombosis, not only restricted to the lung but also involving the kidneys, heart and gut. Moreover, elevated D-dimers or low platelet count are independent predictors of morbidity and mortality among SARS-CoV-2 infected patients. The molecular mechanisms for coagulopathy among SARS-CoV-2 infected patients have not been identified yet. SARS-CoV-2 infects the host using the angiotensin converting enzyme 2 (ACE2) receptor, which is expressed in several organs, including the lung, heart, kidney, and intestine. ACE2 receptors are also expressed by endothelial cells. Whether vascular derangements in COVID-19 are due to endothelial cell involvement by the virus is currently unknown. Intriguingly, SARS-CoV-2 can directly infect engineered human blood vessel organoids in vitro. A recent case series demonstrated endothelial cell involvement across vascular beds of different organs in a series of patients with COVID-19. Inflammation and haemostasis are tightly interrelated pathophysiologic processes that considerably affect each other. In this bidirectional relationship, inflammation leads to activation of the haemostatic system that in turn also considerably influences inflammatory activity. Inflammation shifts the haemostatic activity towards procoagulant state by the ability of proinflammatory mediators to activate coagulation system and to inhibit anticoagulant and fibrinolytic activities. Once the activation of haemostatic system occurs in inflammatory states, amplification of the haemostatic disorder can result in thrombosis and organ damage. In turn, uncontrolled activation of the haemostatic system can also amplify the initial inflammatory response thus causing additional organ injury. Such, the haemostatic system acts in concert with the inflammatory cascade creating an inflammation-haemostasis cycle in which each activated process promotes the other and the two systems function in a positive feedback loop. Thrombin plays a central role in mediating clot forming as well as in mediating inflammation. Colchicine is an inexpensive (generic drug), orally administered, potent anti-inflammatory medication that was initially extracted from the autumn crocus and has been used for centuries. Colchicine is also used for other inflammatory conditions, primarily calcium pyrophosphate crystal disease and familial Mediterranean fever. Cardiologists also regularly prescribe colchicine in pericarditis for short-term use. 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. In the recent ESC guidelines, it is suggested that it may be administered for the prevention of post-pericardiotomy syndrome and in a consensus document it is suggested that it may be used for prevention of atrial fibrillation recurrence after cardiac surgery or ablation procedures. Beyond these, colchicine has been administered in numerous research protocols with various clinical settings, including acute myocardial infarction, showing a favourable safety profile and promising results. SARS-CoV-2 entry in cells is dependent on the connection of viral proteins S with cellular receptors and activation of viral proteins by proteases of host-cells. Therefore, factors that may have an effect on clathrin-mediated endocytosis (a procedure that is – in part – regulated by microtubules remodeling) would potentially decelerate viral infection of cells. Therefore, Colchicine may exert anti-inflammatory as well as direct anti-viral effects among patients with SARS-CoV 2.

Objectives	The aim of the CONVINCE study is therefore to assess the safety and efficacy of edoxaban and/or colchicine administration in SARS-CoV-2 infected patients who are managed outside the hospital with respect to the occurrence of fatalities, hospitalization, major vascular thrombotic events or the SARS-CoV-2 clearance rate under RT PCR.
Study Design	An Investigator-initiated, multi-center, randomized 2X2 factorial design clinical trial in SARS-CoV-2 positive patients managed outside the hospital.
Inclusion criteria	Patients ≥ 18 years old with symptoms compatible with active Coronavirus infection and laboratory confirmed SARS-CoV-2 infection (under RT PCR) who are managed at home or in another out-of-hospital setting.
Exclusion criteria	• Hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including Child-Pugh C cirrhosis with portal hypertension. • Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. • Uncontrolled severe hypertension. • Ongoing or planned treatment with parenteral or oral anticoagulants • Unilateral or bilateral above knee lower extremity amputation. • Inability to take oral medication or otherwise unable or unwilling to undergo/perform study-specified procedures • Have received or will receive an experimental drug or used an experimental medical device within 30 days before the planned start of treatment • Pregnancy or breast-feeding or any plan to become pregnant during the study. Women (and men, for Colchicine group only) with child-bearing potential not using adequate birth control method (note: as adequate method of birthcontrol oral contraception is recommended. If oral contraception is not feasible, both partners should use adequate barrier birth control). • Need for dual anti-platelet therapy consisting of aspirin and an oral P2Y12 inhibitor • Inflammatory bowel disease or chronic diarrhea or neuromuscular disease • Creatinine clearance (CrCl) <15 ml/min • Anticipated use of Hydroxychloroquine • Participation in any other clinical trial • Inability to understand the requirements of the study and to provide informed consent
Informed consent	Eligible patients can be consented and randomised at any within 7 days from first SARS-CoV-2 positive diagnosis
Randomization	Randomization is performed within seven days from first SARS-CoV-2 positive diagnosis. Patients are randomized to edoxaban or no edoxaban and to colchicine or no colchicine. Randomization is stratified per site and sex.
Edoxaban	Edoxaban 60 mg q.d., or 30 mg q.d. in patients with CrCl = or <50 ml/min or body weight equal, less than 60 kg and concomitant prescription of ciclosporin, dronedarone, erythromycin, ketoconazole, from randomization to end of study visit at day 25 (+/-3).
Colchicine	Colchicine at 0.5 mg per os (PO) twice daily for the first 3 days and then once daily from randomization to study visit FU at day 14 (+/-3) days. Treatment could be continued to the day 25 (+3/-3 days). If the creatinine clearance (CrCl) is between 15-30 ml/min the loading dosage will be 0.5 mg once daily while the maintenance dosage will remain unchanged.

Concomitant Treatment(s)	As per local standard of care. If P-gp inhibitors such as ciclosporin, dronedarone, erythromycin, or ketoconazole need to be implemented, the recommended dose is 30 mg edoxaban once daily. If P-gp inhibitors and/or CYP3A4 inhibitors (such as erythromycin and clarithromycin) the prescription of colchicine will be interrupted.
Treatment and Follow-up	Patients are treated according to the randomized regimen until maximum 28 days after randomization. Clinical follow-up is performed at day 14 (+/-3) and 25 (+/-3) days after randomization. Two phone calls will be performed at day 7±3 days post randomization and day 21±3 days post randomization.
Primary endpoints	This study has 2 primary endpoints, one each randomization as follows: **Edoxaban vs. no active treatment** To assess the effect of edoxaban versus no active treatment on the composite endpoint of asymptomatic proximal deep-vein thrombosis, symptomatic proximal or distal deep-vein thrombosis, symptomatic pulmonary embolism or thrombosis, myocardial infarction, ischemic stroke, non-CNS systemic embolism or death at day 25 (+/-3) after randomization. **Colchicine vs no active treatment** To assess the effect of colchicine versus no active treatment on the SARS-CoV-2 clearance rates under RT PCR or freedom from death or hospitalisation at day 14 (+/-3) after randomization.
Major Secondary endpoints	The secondary endpoints of the study are the following: 1) Each component of the co-primary endpoints 2) Need for non-invasive or invasive ventilation 3) Need for oxygen therapy 4) Body temperature kinetics 5) Need for analgesics including NSAIDs and/or paracetamol 6) Need for hospitalisation and total days in the hospital 7) Any combination of the above endpoints 8) Each component of the primary endpoint as well as pre-specified composite endpoints at the time all SAEs have come to a resolution 9) Impact of either intervention on coagulation and inflammatory biomarkers including IL-6, CRP, D-dimers, sCD40L, Fibrinogen, Factor X activity and Factor XIa 10) EKG analyses for QT segment measures and for detection of EKC changes associated to myo-pericarditis. 11) HsTroponin levels 12) Bleeding endpoints according to the Bleeding Academic Research Consortium (BARC) 2, 3 or 5 and ISTH major and clinically relevant non-major bleeding
Statistical Hypotheses	The study was designed to test the following hypotheses 1) The edoxaban regimen is superior to no edoxaban treatment for the composite of major vascular thrombotic events (MVTE) or death. 2) The colchicine regimen is superior to no colchicine treatment for the SARS-CoV-2 clearance rates under RT PCR or freedom from death or hospitalisation. These hypotheses are tested independently. Rates of primary endpoints are estimated as the cumulative incidence between randomization and end of study visit by Kaplan-Meier.
Sample size	A total of 420 patients will be recruited based on the following considerations: 204 patients per group will provide 80% power to assess the superiority of edoxaban as compared to no edoxaban on the composite endpoint of asymptomatic proximal deep-vein thrombosis, symptomatic proximal or distal deep-vein thrombosis, symptomatic pulmonary embolism/thrombosis or all-cause death, at day 25 (+/-3) after randomization in the mITT population assuming an event rate of 8% and 2% in the no edoxaban and edoxaban group, respectively with an alpha error set at 5.0%. 167 patients per group will provide 80% power to assess the superiority of colchicine as compared to no colchicine on the SARS-CoV-2 clearance rates under RT PCR or freedom

	from death or hospitalisation at day 14 (+/-3) after randomization in the mITT population assuming an event rate of 50% and 35% in the no colchicine and colchicine group, respectively, with an alpha error set at 5.0%.
Study sites	Up to 30 Centers in Switzerland, Italy, Belgium and Spain
Time-lines	Approximately 2 months for setting up the study organization, an expected enrolment period of approximately 6 months. For each patient, the expected duration of participation is 25 (+/-3) days.
Contact	**Sponsor:** Insel Gruppe AG, Bern University Hospital, Department of Cardiology, Freiburgstrasse, 3010 Bern, Switzerland **Coordinating Principal Investigators:** Marco Valgimigli, Lugano, Switzerland Pascal Vranckx, Hasselt, Belgium Nuccia Morici, Milan, Italy **Clinical Research Organization:** Advice Pharma, Milan, Italy
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements

2. INTRODUCTION

First appearing in Wuhan, China, the coronavirus disease of 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
Given the rapid spread of this virus with consequences on an international scale, COVID-19 was declared a pandemic by the World Health Organization on March 11th 2020.
SARS-CoV-2, like other members of the Coronaviridae family, is an enveloped virus with nonsegmented, single stranded, positive-sense RNA genome[1, 2]. A number of SARS-related coronaviruses have been discovered in bats, and a working theory is that bats may have been the initial zoonotic host for SARS-CoV-2 given that its genome is 96.2% identical to a bat coronavirus[3].
Studies have demonstrated that SARS-CoV-2 as well as other coronaviruses can use the angiotensin-converting enzyme 2 (ACE2) protein for cell entry. ACE2 is a type I integral membrane protein which serves many important physiologic functions. It is highly expressed in lung alveolar cells, providing the main entry site for the virus into human hosts [3, 4]. After ligand binding, SARS-CoV-2 enters cells via receptor-mediated endocytosis in a manner akin to human immunodeficiency virus (HIV)[5]. ACE2 also serves a role in lung protection and therefore viral binding to this receptor deregulates a lung protective pathway, contributing to viral pathogenicity.
The infectivity of SARS-CoV-2 is greater than that of influenza, with an estimated R_0 value (the basic reproduction number, representing viral infectivity) of 2.28. Notably, the death rate associated with COVID-19 is also considerably higher compared with the most recent WHO estimate of seasonal influenza mortality rate of less than 0.1%, and may reach much higher rates in elderly patients, those with comorbidities, and absent efficient intensive care support.

2.1 COVID-19 and thrombotic events

There is emerging evidence that patients with SARS-CoV-2 are affected by increased coagulopathy, including in the most advanced forms, a fully blown disseminated intravascular coagulation, leading to multi organ failure (MOF).

Post-Morten observations from patients who died because of SARS-CoV-2 infection in Bergamo, Italy and other places (unpublished data) have revealed the presence of diffuse venous, arterial and microcirculatory thrombosis, not only restricted to the lung but also involving the kidneys, heart and gut.

Moreover, elevated D-dimers or low platelet count are independent predictors of morbidity and mortality among SARS-CoV-2 infected patients[6].

In a case series from China, increased D-dimer concentration at time of admission to hospital (>1 µg/mL) was associated with a risk of in-hospital mortality that was 18 times higher than among those with normal D-dimer concentrations[7].

The molecular mechanisms for coagulopathy among SARS-CoV-2 infected patients have not been identified yet. SARS-CoV-2 infects the host using the angiotensin converting enzyme 2 (ACE2) receptor, which is expressed in several organs, including the lung, heart, kidney, and intestine. ACE2 receptors are also expressed by endothelial cells. Whether vascular derangements in COVID-19 are due to endothelial cell involvement by the virus is currently unknown. Intriguingly, SARS-CoV-2 can directly infect engineered human blood vessel organoids in vitro. A recent case series demonstrated endothelial cell involvement across vascular beds of different organs in a series of patients with COVID-19[8].

Inflammation and haemostasis are tightly interrelated pathophysiologic processes that considerably affect each other. In this bidirectional relationship, inflammation leads to activation of the haemostatic system that in turn also considerably influences inflammatory activity. Inflammation shifts the haemostatic activity towards procoagulant state by the ability of proinflammatory mediators to activate coagulation system and to inhibit anticoagulant and fibrinolytic activities. Once the activation of haemostatic system occurs in inflammatory states, amplification of the haemostatic disorder canresult

in thrombosis and organ damage. In turn, uncontrolled activation of the haemostatic system can also amplify the initial inflammatory response thus causing additional organ injury. Such, the haemostatic system acts in concert with the inflammatory cascade creating an inflammation-haemostasis cycle in which each activated process promotes the other and the two systems function in a positive feedback loop.

A recent small study investigated sixteen patients with COVID-19 ARDS who received a complete coagulation profile at the admission in the intensive care unit[9]. Ten patients were followed in the subsequent 7 days, after increasing the dose of low molecular weight heparin, antithrombin levels correction, and clopidogrel in selected cases. the patients showed a pro-coagulant profile characterized by an increased clot strength (CS, median 55 hPa, 95% interquartile range 35-63), platelet contribution to CS (PCS, 43 hPa, interquartile range 24-45), fibrinogen contribution to CS (FCS, 12 hPa, interquartile range 6-13.5 elevated D-dimer levels (5.5 µg/mL, interquartile range 2.5-6.5), hyperfibrinogenemia (794 mg/dL, interquartile range 583-933). Fibrinogen levels were associated (R2=0.506, P=0.003) with interleukin-6 values (**Figure 1**).

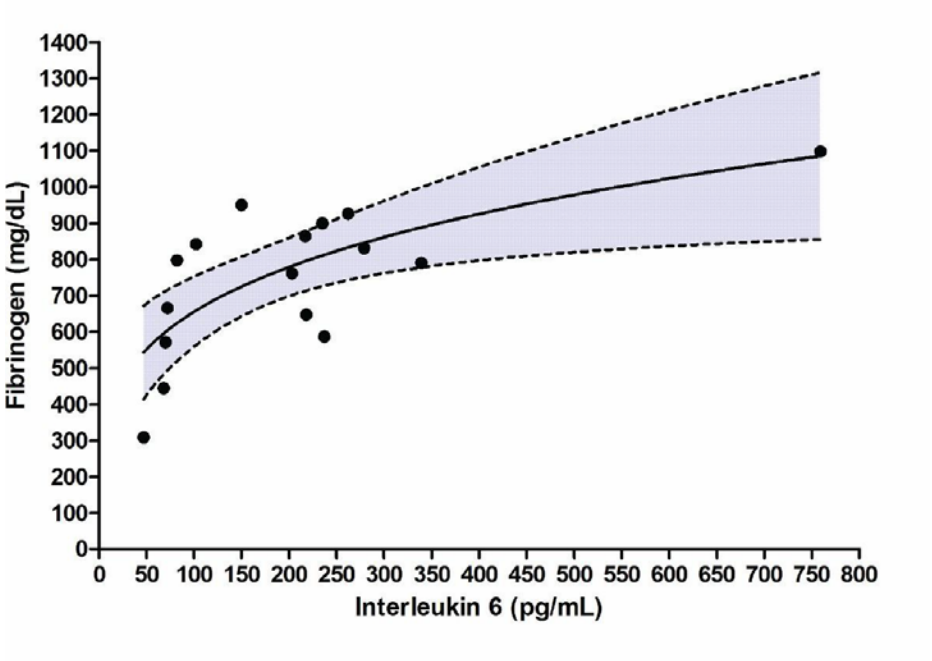

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Figure 1: Association between interleukin-6 values and fibrinogen levels. Logarithmic regression; grey area is 95% confidence interval.

After increasing the thromboprophylaxis, there was a significant (P=0.001) time-related decrease of fibrinogen levels, D-dimers (P=0.017), CS (P=0.013), PCS (P=0.035) and FCS (P=0.038) (**Figure 2**).

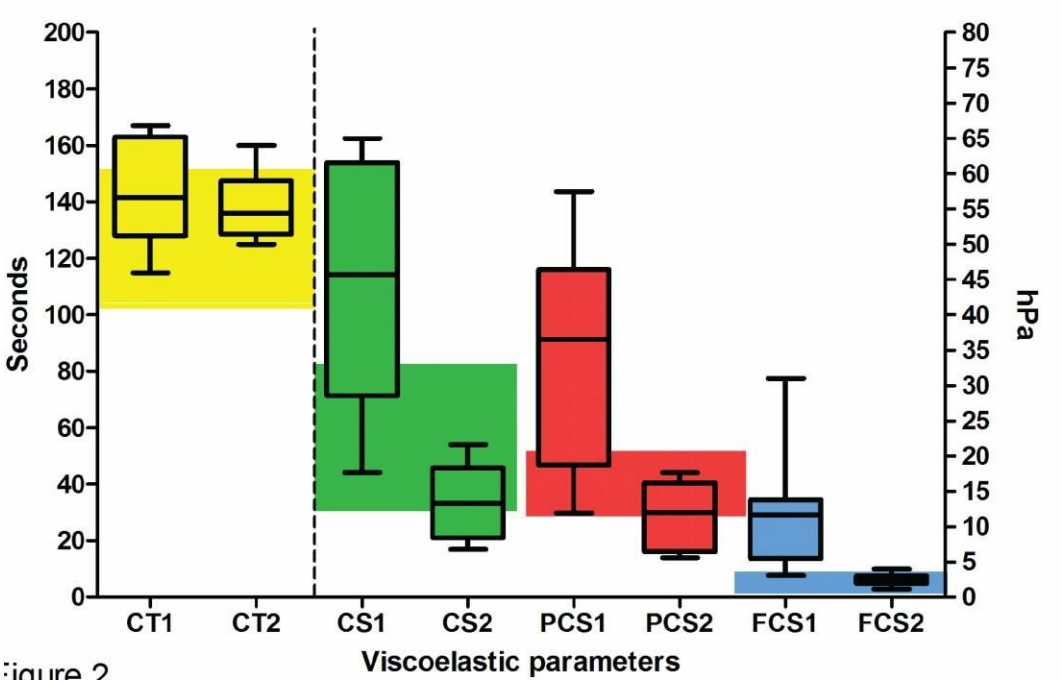


Figure 2: Baseline viscoelastic parameters. Boxes represent median and interquartile range, whiskers min to max values. CT: clotting time (left Y axis); CS: clot strength; FCS: fibrinogen contribution to clot strength; PCS: platelet contribution to clot strength (right Y axis).
Coloured areas are normal range. The numbers after the variables on the X-axis express baseline (1) and follow-up at 2 weeks (2). [9]

Another Italian study assessed whole blood from 24 patients admitted at the intensive care unit because of COVID-19 was collected and evaluated with thromboelastography by the TEG point-of-care device on a single occasion and six underwent repeated measurements on two consecutive days for a total of 30 observations. Plasma was evaluated for the other parameters of hemostasis. TEG parameters are consistent with a state of hypercoagulability as shown by decreased R and K values, and increased values of K angle and MA. Platelet count was normal or increased, prothrombin time and activated partial thromboplastin time were near(normal). Fibrinogen was increased and D-dimer was dramatically increased. Creactive protein was increased. Factor VIII and von Willebrand factor (n=11) were increased. Antithrombin (n=11) was marginally decreased and protein C (n=11) was increased[10]. The results of this cohort of patients with COVID-19 are not consistent with acute DIC, rather they support hypercoagulability together with a severe inflammatory state. These findings may explain the events of venous thromboembolism observed in some of these patients and support antithrombotic prophylaxis and treatment. Authors conclude that clinical trials are urgently needed to establish the type of drug, dosage and optimal duration of prophylaxis.

In Lille, France, among the 107 first consecutive confirmed COVID-19 patients admitted in ICU at Lille University Hospital from Feb 27 to March 31, Poissy *et al.* noticed an unexpected high number of PE during their stay in ICU, 22(20.6%) at the time of analysis, within a median time from ICU admission of 6 days (range 1 to 18 days)[11]. To determine whether this represents an increase in the expected incidence of PE over a similar time interval, the authors analyzed the files of 196 patients hospitalized in their institution during the same time interval in 2019. Despite a similar severity score at entrance in ICU, the frequency of PE in their COVID-19 series was twice higher than the frequency found in the control period, (20.6% vs 6.1%; absolute increase risk of 14.4%, 95%CI 6.1 to 22.8%). It was also twice higher than the 7.5% frequency of PE in the 40 Influenza ICU patients admitted between January 1 to December 31 2019 (3PE, absolute increase risk 13.1%, 95%CI 1.9 to 24.3%)[11].

Thrombin plays a central role in mediating clot forming as well as in mediating inflammation[12]. Therefore, we sought to assess the value of a direct factor X inhibitor, namely edoxaban as prophylactic measure to mitigate the risk of venous and arterial thrombotic complications and we will explore its effect on markers of inflammation as well as coagulation among SARS-CoV-2 patients at high riskfor developing COVID-19 -related morbidity and mortality.

2.2 COVID-19 and oral anticoagulation with edoxaban

Key messages

Currently there is no clinical evidence available that treatment with edoxaban should be discontinued in patients infected with the SARS-CoV-2 virus and who receive receiving antiviral or anti-malaria drugs.

In the edoxaban development program, patients with antiviral (i.e. HIV protease inhibitor) treatment or immunosuppression with cyclosporine were excluded from the clinical studies.

The recommended dose of edoxaban is 60 mg once daily (OD), reduced to 30 mg OD in patients with creatinine clearance (CrCl) 15–50 mL/min, body weight ≤60 kg or concomitant use of the following P-glycoprotein inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole (LIXIANA® European Summary of Product Characteristics, current version).

CYP4A4/5 metabolism

Cytochrome P450 isoenzymes play an insignificant role (<10%) in the metabolism of edoxaban (LIXIANA® European Summary of Product Characteristics), reducing the potential for drug-drug interactions with cytochrome P450 isoform inhibitors or inducers.

The use of chloroquine and hydroxychloroquine in the pivotal studies on edoxaban, ENGAGE AF-TIMI 48 and Hokusai-VTE was allowed, but data is limited. Specific drug-drug interaction studies between edoxaban and chloroquine or hydroxychloroquine have not been conducted. Chloroquine and hydroxychloroquine are both metabolized by cytochrome P450. Because Cytochrome P450 isoenzymes play an insignificant role (<10%) in the metabolism of edoxaban, clinically meaningful drug-drug interactions between chloroquine and hydroxychloroquine and edoxaban are rather unlikely. Both chloroquine and hydroxychloroquine, which are authorized for malaria and certain autoimmune diseases, have been used to treat patients with COVID-19 but their beneficial effects in this patient population are not established. Several observational studies in COVID-19 have reported that both drugs are associated with important side effects and in view of the emerging data, some Countries, including Switzerland, have suspended or stopped clinical trials investigating chloroquine and hydroxychloroquine in COVID-19 patients.

Tocilizumab is a humanised IgG1 monoclonal antibody against the human interleukin-6 (IL-6) receptor. The concomitant use of tocilizumab with edoxaban has not been studied, no data on potential interactions is currently available.

Strong P-glycoprotein inhibitors

P-glycoprotein (P-gp) is an efflux transporter primarily expressed in the luminal or apical membrane of epithelia of the small intestine, hepatocytes, renal proximal tubules, and blood–brain barrier, and plays a role in transporting drugs into and out of cells and helping to reduce cell exposure to potential toxins[13].

When administered together, drugs which inhibit or induce P-gp can alter the exposure of other drugs that are substrates for P-gp. Concomitant use of NOACs with strong P-gp inhibitors may increase systemic absorption, thereby increasing drug exposure and bleeding risk; while P-gp inducers may increase drug elimination, reduce exposure and result in insufficient anticoagulation and increased risk of thromboembolic events[14].

For the concomitant use of the strong P-glycoprotein inhibitors ciclosporine, dronedarone, erythromycin, or ketoconazole the recommended edoxaban dose is 30 mg OD (LIXIANA® European Summary of Product Characteristics, current version).

Other P-gp inhibitors (including HIV protease inhibitors)
HIV protease inhibitors include the following medicines, which are not Daiichi Sankyo products: amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir. For additional information on any of these molecules please consult the respective manufacturer.
The use of edoxaban with other P-gp inhibitors including HIV protease inhibitors has not been studied (LIXIANA® European Summary of Product Characteristics).

Lamivudine
Lamivudine is a substance part of nucleoside reverse transcriptase inhibitors drug class, commonly used for the treatment of HIV and Hepatitis B. The use of lamivudine in combination with edoxaban has not been studied and no data on potential interactions is currently available. The likelihood of metabolic substance interactions with lamivudine is small due to the small (5-10%) extent of hepatic metabolism and the low plasma protein binding.

Remdesivir
Remdesivir is an antiviral medicine that obtained recently a conditional marketing authorization from European Medicines Agency for the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen. The data regarding this intravenous nucleotide prodrug of an adenosine analog are limited, therefore potential for drug-drug interactions is unknown.
The use of remdesivir in combination with edoxaban has not been studied, no data on potential interactions is currently available.

Colchicine
Colchicine is a tricyclic alkaloid extracted from the flowering plants Colchicum autumnale (meadow saffron or autumn crocus) and Gloriosa superba (glory lily). Colchicine has been used since antiquity, with an extensive history of clinical experience in the treatment of many inflammatory diseases[15].
The principal mechanism of action of colchicine in gout is thought to be inhibition of cytoskeletal microtubule polymerization. Colchicine binds to b-tubulin in such a way that prohibits the formation of microtubules[15]. Downstream consequences of the inhibition of microtubule polymerization by colchicine include inhibition of neutrophil activation, degranulation and migration. Oral colchicine is approved outside Switzerland and including in the US for the treatment of acute gout flares in adult patients and the prophylaxis of gout flares in patients aged >16 years. It is also a classic treatment for acute pericarditis[16]. Moreover, in the recent ESC guidelines it is suggested that it may be administered for the prevention of post-pericardiotomy syndrome[16] and in a consensus document it is suggested that it may be used for prevention of atrial fibrillation recurrence after cardiac surgery or ablation procedures[17]. Beyond these, colchicine has been administered in numerous research protocols with various clinical settings (including stable coronary artery disease, acute myocardial infarction and stroke) showing a favourable safety profile and promising results[18-22]. In patients with elevated inflammatory markers, colchicine improves endothelial function[23].
SARS-CoV-2 entry in cells is dependent on the connection of viral proteins S with cellular receptors and activation of viral proteins by proteases of host-cells. Therefore, factors that may have an effect on clathrin-mediated endocytosis (a procedure that is – in part – regulated by microtubules remodeling) would potentially decelerate viral infection of cells. Therefore, Colchicine may exert anti-inflammatory as well as direct anti-viral effects among patients with SARS-CoV-2. Under this rational, multiple studies have been launched testing the value of colchicine in COVID-19 patients[24]. Yet, none will assess whether the use of colchicine accelerates SARS-CoV-2 clearance.

Key messages
Colchicine is a substrate of intestinal and hepatic cytochrome P450 3A4 (CYP3A4), which catalyzes demethylation of colchicine to inactive metabolites. Consistent with the current understanding of colchicine metabolism, certain drugs increase the potential for colchicine toxicity via modulation of

the efflux transporter P-glycoprotein (P-gp) and CYP3A4 activity. As such, during the duration of the trial, the concomitant use of erythromycin and clarithromycin is prohibited. Also the prescription of colchicine must be avoided with the concomitant consumption of grapefruit juice. If the creatinine clearance (CrCl) is between 15-30 ml/min the loading dosage will be 0.5 mg once daily while the maintenance dosage will remain unchanged.

3. STUDY OBJECTIVES

The aim of the CONVINCE study is therefore to assess the safety and efficacy of edoxaban and/or colchicine administration in SARS-CoV-2 infected patients who are managed outside the hospital with respect to the occurrence of fatalities, hospitalisation, major vascular thrombotic events or the SARS-CoV-2 clearance rate under RT PCR.

More specifically, the objectives of the study are to test the following hypotheses

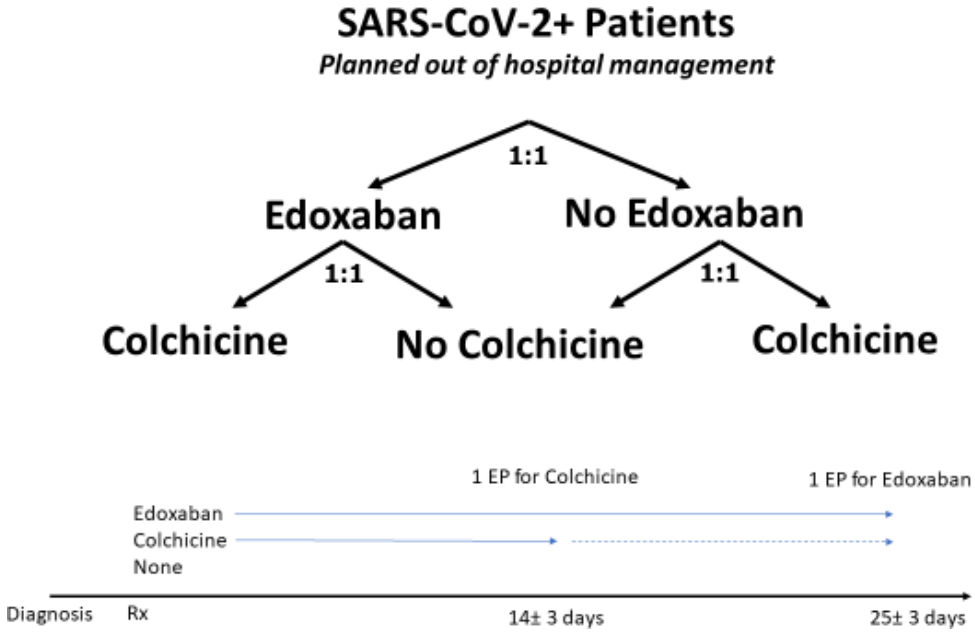
1) The edoxaban regimen is superior to no edoxaban treatment for occurrence of major vascular thrombotic events (MVTE), defined as the composite of asymptomatic proximal deep-vein thrombosis, symptomatic proximal or distal deep-vein thrombosis, symptomatic pulmonary embolism or thrombosis, myocardial infarction, ischemic stroke, non-CNS systemic embolism and all-cause death.

2) The colchicine regimen is superior to no colchicine treatment for the SARS-CoV-2 clearance rates under RT PCR or freedom from death or hospitalisation.

These hypotheses are tested independently.

4. STUDY DESIGN

An Investigator-initiated, open label, multi-center, randomized 2X2 factorial design clinical trial in SARS-CoV-2 positive patients managed outside the hospital.



5. REQUIREMENTS FOR PARTICIPATING SITES

Primary participating sites are hospitals or health care services with SARS-CoV-2 diagnostic facilities, typically but not limited to the emergency departments of academic or non-academic hospitals. The site is responsible for implementation of the randomized medication and for collection of follow-up information. Primary participating sites may rely on non-participating facilities for the execution of diagnostic examinations as long as non-participating facilities allow participating sites to collect relevant information and diagnostic images.

6. PATIENT SELECTION, RANDOMIZATION AND FOLLOW-UP

6.1 Inclusion criteria

Patient selection takes place at participating sites within 7 days from the SARS-CoV-2 diagnosis according to the following inclusion and exclusion criteria. Only patients ≥18 years old will be enrolled into the study.

6.1.1 Inclusion criteria

Patients ≥18 years old with symptoms compatible with active Coronavirus infection and laboratory confirmed SARS-CoV-2 infection (under RT PCR) who are managed at home or in nursery settings (out of hospital location).

6.2 Exclusion criteria

Patients are not eligible at any time if any of the following applies:

- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including Child-Pugh C cirrhosis with portal hypertension.
- Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial hemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Uncontrolled severe hypertension.
- Ongoing or planned treatment with parenteral or oral anticoagulants.
- Unilateral or bilateral above knee lower extremity amputation.
- Inability to take oral medication or otherwise unable or unwilling to undergo/perform study-specified procedures.
- Have received or will receive an experimental drug or used an experimental medical device within 30 days before the planned start of treatment.
- Pregnancy or breast-feeding or any plan to become pregnant during the study. Women (and men, for Colchicine group only) with child-bearing potential not using adequate birth control method note: as adequate method of birth control oral contraception is recommended. If oral contraception is not feasible, both partners should use adequate barrier birth control).
- Need for dual anti-platelet therapy consisting of aspirin and an oral P2Y12 inhibitor.
- Inflammatory bowel disease or chronic diarrhea or neuromuscular disease.
- Creatinine clearance (CrCl) <15 ml/min.
- Anticipated use of Hydroxychloroquine.
- Participation in any other clinical trial.
- Inability to understand the requirements of the study and to provide informed consent.

6.3 Informed consent

Eligible patients can be consented at any time within 7 days from SARS-CoV-2 diagnosis.
A written informed consent is then obtained at the randomization visit.

The informed consent in particular includes consent for the following:

- Randomization to edoxaban versus no treatment and colchicine versus no treatment
- Follow-up protocol
- Collection of clinical data
- Ascertainment of vital status via municipality registries
- Data collection in study database

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.
The participant must be informed that his/her medical records may be examined by authorised individuals other than their treating physician.
All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. Enough time needs to be given to the participant to decide whether to participate or not.
The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.
The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) at the same time as the participant sign, and it will be retained as part of the study records.

6.4 Randomization

Only patients ≥ 18 will be enrolled into the study, they can only be randomized only if all inclusion criteria (section 6.1) are met and if no exclusion criteria (section 6.2) apply. Patient can be only randomized in the presence of written informed consent. The randomization procedure is programmed into the eCRF, in random blocks of 4 to 8 stratified by clinical site and sex, to first edoxaban versus no treatment and second to colchicine versus no treatment in a 1:1:1:1 ratio.

After confirmation of selection criteria and presence of informed consent, the investigator triggers the randomization procedure, after which randomization to either edoxaban and/or colchicine is divulged. If the subject is randomized to edoxaban and/or colchicine, the Investigator takes the necessary measures so that the allocated regimen is implemented without any undue delay.

6.5 Treatment regimens

Patients are treated according to the randomized regimen(s) from the day of randomization until up to end of study visit at 25 (+/-3) days. After 25 (+/-3) post randomization, further therapy is at the discretion of treating physician.

6.5.1 Edoxaban

Edoxaban 60 mg q.d., or 30 mg q.d. per os in patients with CrCl = or <50 ml/min or body weight equal or less than 60 kg from randomization to end of study visit at day 25 (+/-3). Further treatment is at

discretion of the treating physician. If P-gp inhibitors such as ciclosporin, dronedarone, erythromycin, or ketoconazole need to be implemented, the recommended dose is 30 mg edoxaban once daily.

6.5.2 Colchicine

Colchicine at 0.5 mg per os twice daily for the first 3 days and then once daily from randomization to 14 (+/-3) day visit. If the creatinine clearance (CrCl) is between 15-30 ml/min the loading dosage will be 0.5 mg once daily while the maintenance dosage will remain unchanged.

If P-gp inhibitors and/or CYP3A4 inhibitors (such as erythromycin and clarithromycin) the prescription of colchicine will be interrupted. At 14 (+/-3) day visit, SARS-CoV-2 clearance rates under RT PCR are assessed as part of primary endpoint measure for the colchicine versus no colchicine treatment. In patients who have successfully cleared SARS-CoV-2, no further treatment with colchicine is foreseen by the protocol. Patients in whom SARS-CoV-2 clearance could not be demonstrated at 14 (+/-3) RT PCR continue the treatment until day 25 (+/-3) visit. Further treatment is at discretion of the treating physician.

6.5.3 Implementation of randomized study regimens

Study regimens are implemented by providing drug supply to all included patients. Commercially available packages will be labelled as investigational medicinal products and distributed to the clinical sites.
Patients will be queried on general drug adherence and pill count implemented during planned study visits.

6.5.4 Treatment in the event of new onset indication for anticoagulation

Patients with clinical indication to oral and or parenteral anticoagulation are excluded from participation. If a patient develops any new indication for anti-coagulation, (i.e. new onset atrial fibrillation with CHADS-VASC2 score >1, or detection of vascular thrombotic event), treatment with oral or parenteral anticoagulation must be started without any delay. If the patient was previously allocated to edoxaban, this treatment may continue as per protocol if clinically indicated as prophylactic or therapeutic measure of the new onset clinical condition. If the patient was not previously allocated to edoxaban, the choice of oral (NOAC or VKA) or parenteral anticoagulant regimen is at the discretion of the treating physician. In cases of new hospitalisation or bed rest, prophylactic anticoagulation regimen remains at discretion of the treating physician in the no edoxaban arm, whereas edoxaban treatment will continue as per protocol in the edoxaban group.
These treatment iterations will be analyzed as an integral “per protocol” part of implementation of randomized treatment regimen.

6.5.5 Treatment in the event of a bleeding or ischemic occurrence

- **BARC 2 bleeding**
  The randomized treatment regimen is adhered to as much as possible.

- **BARC 3 to 5 bleeding**
  Further antithrombotic treatment is at the discretion of the treating physician.

- **Stroke, myocardial infarction, confirmed deep vein or pulmonary thrombosis/embolism or systemic embolism in other districts**
  Further antithrombotic treatment is at the discretion of the treating physician.

- **Temporary discontinuation (e.g. Surgery or percutaneous catheter-based interventions)**
  The randomized trial regimen is resumed as soon as the indication of temporary discontinuation is resolved.

If the randomized treatment regimen is changed or discontinued, the follow-up continues unchanged.

6.5.6 Pregnancies

If a pregnancy occurs during the study medication intake, participants must immediately be withdrawn from the investigational medication. Pregnancies for patients must be followed up, also if a partner becomes pregnant during study medication intake.

6.6 Blood analyses and Biobank

Blood samplings are performed at the time of randomisation and during visits to outpatient clinic (local laboratory). Plasma (EDTA) and Serum will also be collected, processed and stored at -80°C in local biobanks. At the end of the trial, the samples from the biobank will be shipped to and analysed in a central core laboratory. Samples will be stored for a maximum of 5 years after study closure. Among others, the following biomarkers will be analysed:

- Thrombin anti-thrombin complex
- Factor XIa
- IL-6
- ADAMTS13
- Von Willenbrand factor
- Endothelin-1
- Asymmetric dimethyl arginine

The central core lab is located in Hospital Papa Giovanni XXIII, Department Immuno-Hematology and Transfusion Medicine Unit, Piazza OMS 1, 24127 Bergamo, Italy.

6.7 Follow-up

6.7.1 Scheduling of follow-up visit

In addition to the randomization visit, there are four scheduled follow-up visits, at 7 (+/-3) and 21 day (+/-3) (phone contact or video call if technically feasible) and at 14 (+/-3) and 25 (+/-3) day (visits to outpatient clinic).

6.7.2 Data collection

Patients are informed that data are collected at scheduled follow-ups as well as at unscheduled visits.

Collected data include medical history, any concomitant medications and any concomitant comorbidity and new or chronic symptom or sign. In particular, at each visit, the following information is collected:

- Major adverse organ or vascular events
  - Vital status
  - Potential stroke of any aetiology (ischemic, haemorrhagic and indeterminate)
  - Potential embolism or thrombosis in any organ or district, including legs, arms and lungs
- ANY clinically overt bleeding events
- Any new or chronic respiratory symptom or sign
- ANY new or chronic symptom or sign related to SARS-CoV-2 infection
- Body temperature
- EKG for QT segment measures and for detection of EKC changes associated to myo-pericarditis
- Compliance with randomized regimen(s)
- The following information will be collected during phone calls: medical history, medication regimen, (Serious) Adverse Event review.

6.7.3 Patient Withdrawal, Termination or Discontinuation of Trial

At any time during the study, the subject may withdraw their participation from the study. Every patient is encouraged to remain in the study until they have completed the protocol-required follow-up period. Patients who deviate from or discontinue the randomized regimen(s) after randomization continue to be followed up as per standard of care.

Clinical follow-up is only discontinued if the patient explicitly forbids the continuation of follow-up. This decision should be an independent decision that is documented in the patient study files. Survival status should be collected within legal and ethical boundaries for all subjects randomized who withdrew participation from the study. If follow-up is discontinued prematurely, the reason for discontinuation is documented. In case of discontinuation, the already collected data remain in the database unless the patient explicitly requests complete deletion of the records, which should be documented by the site. If the consent is revoked, the data and samples collected up to the time of withdrawal will be kept until the completion of the data analysis and will be anonymized/destroyed afterwards.

Decisions to discontinue the randomized study regimens or scheduled follow-up visit are considered modification of the informed consent.

Modifications of informed consent are recorded in the eCRF.

The eCRF distinguishes the following modifications in informed consent:

- Modification or discontinuation of the randomized treatment regimen
- Discontinuation of scheduled follow-up visit
- Discontinuation of replacing telephone contacts
- Disallowance of gathering clinical information from referring hospitals or general practitioner
- Disallowance of collecting vital status from municipal registry

Informed consent is only considered as withdrawn if a request to implement all of the above has been made.

6.7.4 Lost to follow-up

A subject would be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. If a subject is unable to return for a clinic visit or unable to be contacted by telephone, diligent attempts to contact the subject are made to obtain subject required information. All attempts are documented in the source documents. Only after failing to contact the subject at the final follow-up visit, the subject is considered lost to follow-up after last contact. It must be a high priority to obtain at least survival data on all subjects lost to follow-up. Survival status will be collected within legal and ethical boundaries for all subjects randomized. Vital status will be searched in public sources at the end of the follow-up period. If vital status is known at the last study visit, the subject will not be considered lost to follow-up.

6.7.5 Study Completion

The study completion will be reported to the ethics committee within 90 days or according local requirements. Any study interruption or even cancellation will be (including giving reasons) reported to the ethics committee within 15 days or according local requirements. Final report regarding the trial will be reported to the ethics committee within 1 year from the study completion or study interruption or according local requirements.

7. ENDPOINTS

7.1 Primary Endpoints

This study has 2 co-primary endpoints, one each randomization as follows:

Edoxaban vs. no active treatment

Major vascular thrombotic events (MVTE) at 25 (+/-3) days defined as a composite of:

- Asymptomatic proximal deep-vein thrombosis
- Symptomatic proximal or distal deep-vein thrombosis
- Symptomatic pulmonary embolism or thrombosis
- Myocardial infarction
- Ischemic stroke
- non-CNS systemic embolism
- Death

Colchicine vs no active treatment

The SARS-CoV-2 detection rates at day 14 (+/-3) under RT PCR or freedom from death or hospitalisation

7.2 Secondary Endpoints

The secondary endpoints of the study are the following:

1) Each component of the co-primary endpoints
2) Need for non-invasive or invasive ventilation
3) Need for oxygen therapy
4) Body Temperature kinetics
5) Need for analgesics including NSAIDs and/or paracetamol
6) Need for hospitalisation and total days in the hospital
7) Any combination of the above endpoints
8) Each component of the primary endpoint as well as pre-specified composite endpoints at the time all SAEs have come to a resolution
9) Impact of either intervention on coagulation and inflammatory biomarkers including IL-6, CRP, D-dimers, sCD40L, Fibrinogen, Factor X activity and Factor XIa
10) EKG analyses for QT segment measures and for detection of EKC changes associated to myo-pericarditis.
11) HsTroponin levels
12) Bleeding endpoints according to the Bleeding Academic Research Consortium (BARC) 2, 3 or 5 and ISTH major and clinically relevant non-major bleeding

8. STATISTICAL METHODS AND SAMPLE SIZE

8.1 General considerations

A general description of the statistical methods to be used to analyze the endpoints of the study drug is outlined below. A more detailed statistical analysis plan (SAP) is provided in a separate document. Statistical analysis is performed using STATA; the version used will be specified in the SAP. The SAP accommodates protocol amendments or unexpected issues in study execution or data that affect planned analyses, and provides more details on the analytic approaches, coding guidelines, censoring of time-to-event variables, and output tables and figures.

If not stated otherwise, all efficacy and the safety analyses are based on findings as confirmed by the Clinical Event Committee (CEC).

8.2 Analysis sets

Full analysis population (FAS) consists of all randomized subjects. Subjects are categorized according to the group to which they were assigned by the randomization process.

Per-protocol (PP) population consists of randomized patients who met the following criteria.

- No violation of inclusion and exclusion criteria
- Randomized treatment was implemented within 48 hours after randomization

On-treatment population consists of randomized patients in whom overall adherence to protocol mandated medications is of more than 80% or less than 120%.

Modified ITT population includes randomized subjects in whom at least 1 dose of study medication was administered and have an adequate assessment of MVTE (for the edoxaban versus no edoxaban arm) or an adequate assessment of SARS-CoV-2 infection rate under RT PCR (for colchicine versus no colchicine comparison).

An adequate assessment of MVTE is present if at least one of the following conditions is fulfilled:

- an adequate bilateral lower extremity venous ultrasonography was performed on Day 25 ± 3
- confirmed symptomatic lower extremity DVT up to Day 25 ± 3
- confirmed symptomatic PE up to Day 25 ± 3
- confirmed VTE related death up to Day 25 ± 3
- confirmed myocardial infarction up to Day 25 ± 3
- confirmed ischemic stroke up to Day 25 ± 3
- confirmed non-CNS systemic embolism up to Day 25 ± 3
- death has occurred before Day 25 ± 3

An adequate assessment of SARS-CoV-2 infection rate is present if follow-up RT-PCR is performed at Day 14± 3 or the patient died or was hospitalized.

8.3 Main analysis of the primary endpoints

Main analysis of the primary endpoints is performed in the mITT population.
Sensitivity analyses are performed in the ITT, PP and on-treatment populations. Follow-up is censored at the last date of known outcome status or at 28 days, whichever comes first.

Rates of primary endpoints are estimated as the cumulative incidence from the date of randomization to Day 14 ± 3 after randomization for the colchicine comparison and from the date of randomization to Day 25 ± 3 for edoxaban by the Kaplan-Meier methods.
The relative risk ratio (edoxaban/no edoxaban and colchicine versus no colchicine) with respect to the incidence rates of the primary efficacy endpoints will be estimated based on nonstratified estimators using Mantel-Haenszel weights and the corresponding non-stratified asymptotic 2-sided 95% confidence intervals.

8.4 Determination of sample size

A total of 204 patients per group will provide 80% power to assess the superiority of edoxaban as compared to no edoxaban on the composite MVTE or death endpoint at day 25 (+/-3) after randomization in the mITT population assuming an event rate of 8% and 2% in the no edoxaban and edoxaban group, respectively with an alpha error set at 5.0%.

A total of 167 patients per group will provide 80% power to assess the superiority of colchicine as compared to no colchicine on the SARS-CoV-2 detection rates or death or hospitalisation at day 14 (+/-3) after randomization in the mITT population assuming an event rate of 50% and 35% in the no colchicine and colchicine group, respectively, with an alpha error set at 5.0%.

8.5 Subgroup analyses

The following subgroups are pre-specified:

- Age ≥65 years vs. age <65 years
- Female vs. male gender
- High versus non-high risk
- Creatinine clearance equal or greater than 50 ml/min or < 50 ml/min or fulfilment of other dose reduction criteria for edoxaban
- Duration of COVID-19 symptoms to recruitment stratified by median value
- According to presence or absence of each high-risk criteria
- Allocation to edoxaban for colchicine randomisation and to colchicine for edoxaban randomisation.

High risk criteria include the following conditions:

1) Active malignancy
2) Prior myocardial infarction
3) History of heart failure
4) Diabetes mellitus
5) D-dimers above the upper limit of normal
6) Active smoking
7) Chronic obstructive pulmonary disease or other chronic lung diseases (e.g. pulmonary fibrosis)
8) Prior thrombo-embolic disorder
9) Other conditions which at discretion of the investigator put the patient at higher risk for COVID-19 related complications such as but not limited to severity of symptoms or hs-troponin elevation. This information will be recorded in the eCRF at the time of inclusion.

9. SAFETY REPORTING

9.1 Adverse Event (AE)/ Serious Adverse Event (SAE) - Definitions

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal

relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH E6 1.2)

A Serious Adverse Event (SAE) is classified as any untoward medical occurrence that:
- results in death,
- is life-threatening,
- requires in-patient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. (ICH E2A)

Both Investigator and Sponsor-investigator make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

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

Follow Up on SAEs:
SAEs will be followed up until resolution. Participants with ongoing SAEs (e.g. hospitalisation due to COVID-19 Symptoms) at study termination will be further followed up until SAE resolution.

9.2 Suspected Unexpected Serious Adverse Drug Reaction (SUSAR) - Definition

Unexpected Adverse Drug Reaction
An “unexpected” adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator’s Brochure for drugs that are not yet approved and Product Information for approved drugs, respectively). (ICH E2A)

Suspected Unexpected Serious Adverse Reaction (SUSAR)
The Sponsor-Investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

9.3 Reporting requirements

The investigator monitors the occurrence of Serious Adverse Events (SAEs) for each subject during the course of the study. For the purpose of this protocol, the reporting of SAEs begins directly after randomization in the corresponding page of the e-CRF. The Adverse Events occurred after the randomization will be documented by the investigator in a standardized manner.

Reporting of SAEs: All SAEs must be reported immediately and within a maximum of 24 hours of date of awareness to the Sponsor of the study.
SAEs resulting in death have to be reported by Sponsor to the Ethics Committee (EC) / Institutional Review Board (IRB) and competent authorities (CA) according local requirements.

The Sponsor will inform all Investigators participating in the clinical study of the occurrence of a SUSAR. All in the trial involved EC/IRB/ CA will be informed about SUSARs according the local requirements.

Reporting of Safety Signals: All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures, i.e. so called safety signals, must be reported to the Sponsor within 24 hours of date of awareness.

Pregnancies
Pregnancies of patients or partners of male patients will be reported within 24 hours to the Sponsor of date of awareness. Female patients will be immediately withdrawn from study medication and outcome of the pregnancy must be followed-up.

Health Hazards and Safety Amendments
Health hazards and Safety Amendments that require measures are reported to the Sponsor within a maximum of 24 h of date of awareness and reported according the local requirements to EC/IRB/CA.

Periodic safety reporting:
A yearly safety update-report is submitted by the Sponsor to the EC/ IRB/ CA per local requirements.

How to report to Sponsor
Reporting to Sponsor should take place by eCRF entry. Exceptionally, if eCRF is not available, events must be reported to convince@insel.ch. De-identified Source data must be provided as fast as possible to convince@insel.ch latest within 2 weeks of date of awareness.

Substantial Amendments
Any substantial amendments to the protocol, as well as associated documents, e.g. consent form changes, will be submitted to the EC/IRB/CA for written favourable opinion obtained prior to implementation according to local requirements.

9.4 Reporting to Authorization Holders

The Sponsor should report events considered related to edoxaban to the Marketing Authorisation Holder of edoxaban as required by national/local regulations, if applicable.

10. DATA SAFETY MONITORING BOARD

Endpoint-related and unrelated serious adverse events are periodically reviewed and analysed by an independent DSMB. Members of this board are not affiliated with any site enrolling patients into the trial, are not participating in the trial, and will declare any conflicts of interest should they arise. The composition, guiding policies, and operating procedures governing the DSMB are described in a separate charter.

11. RISK ANALYSIS

Edoxaban and as well as colchicine have been tested in multiple trials involving several thousands of patients and are both well tolerated medications.
The principal side effect of edoxaban is related to the bleeding risk. As with all anti-thrombotics, the risk is proportional to the dose used and duration of treatment. Considering that patients at high bleeding risk including those who experienced prior major bleeding as well as those in whom a dual anti-platelet therapy is needed are excluded form randomisation, the risk of assuming edoxaban at currently approved regimen for a maximum of 28 days is considered to be minimal.
The most commonly reported adverse events of colchicine were gastrointestinal in nature (diarrhoea, nausea and vomiting). These side effects are mainly dose related and occurred at very low rate (not higher than placebo) when the drug was employed at the low regimen used in the current trial in the context of post-infarction patients. Considering that patients with gastrointestinal symptoms are excluded from participation, the risk of observing important and frequent side effects related to this drug taken for a maximum of 28 days is considered to be minimal.
There is no published evidence on the possible drug-to drug interaction between edoxaban and colchicine. Yet, there are multiple case reports published in the literature describing the simultaneous administration of colchicine and oral or parenteral anticoagulant in patients with highly symptomatic deep vein thrombosis. Similarly, the European society of cardiology guidelines recommend the use of colchicine for the prevention of post-surgery atrial fibrillation, a context in which both oral direct factor X inhibitor (such as edoxaban) and colchicine are simultaneously administered.
Therefore, the risks associated with the separate or combined administration of edoxaban 60 / 30 mg and colchicine 0.5 mg for a maximum of 28 days is considered to be minimal.

12. MONITORING

The Sponsor will organize regular central as well as on-site monitoring visits, prior to the start and during the course of the study. The Investigators will provide access to the source data and documents and will be available to answer questions during monitoring visits.
The details of operating procedures for monitoring will be defined in a separate Clinical Monitoring Plan.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Compliance to Standards and Regulations

The protocol, informed consent form and other study-related documents will be submitted to the Ethics Committee (EC) / Institutional Review Board (IRB) and competent authorities (CA) and other regulatory bodies if required per local regulations.
The trial will only start at a clinical site after favourable opinion of the study has been obtained from all concerned bodies. Any additional requirements imposed by the authorities shall be implemented.

The study will be performed in accordance with the protocol and with the principles enunciated in the current version of the Declaration of Helsinki as well as the applicable international, national and local regulations.

13.2 Data Recording, Source Data Location List

Data will be encrypted for eCRF entry (no patient name or DOB) and the master subject list remains at site under the responsibility of the local Principle Investigator. All data entered into the electronic data capturing (EDC) system must be traceable to source documents available at the clinical site. In exceptional cases where data are recorded directly in the EDC (i.e. no other source documentation exists), this must be explicitly documented (e.g. in a note to file). In such a case, the corresponding electronic Case Report Form (CRF) should be printed out, signed, dated and filed with source document. For all data captured in the EDC, the location of the source should be documented on a specific Source Data Location List, which will be stored in the investigator site file at each studysite.

14. DATA MANAGEMENT AND QUALITY ASSESSMENT

14.1 Data management

14.1.1Data handling and record keeping

The CRFs in this trial are implemented electronically using a dedicated EDC system (ICE, Integrated Clinical Trial Environment, Advice Pharma) that fulfils the legal requirements for clinical trials. The EDC system is activated for the user only after successfully passing a formal test procedure. All data entered in the EDC are stored on a Linux server in a dedicated Oracle database.

14.1.2 Confidentiality, Data Protection

The server hosting the EDC system and the database is kept in a locked server-room. Only the system administrators have direct access to the server. A role concept with personal passwords (site investigator, statistician, monitor, administrator etc.) regulates permission for each user to use the system and database as he/she requires.
All data entered into the EDC are transferred to the database using Secure Sockets Layer (SSL) encryption. Each data point has attributes attached to it identifying the user who entered it with the exact time and date to ensure proper audit-trail. Retrospective alterations of data in the database are recorded by time, table, data field and altered value. A multi-level back-up system is implemented.

14.1.3 Archiving and Destruction

At interim and final analyses, data files will be extracted from the database into statistical packages to be analyzed. The status of the database at this time is recorded in special archive tables. The study database with all archive tables will be securely stored by Inselspital Bern. The sponsor also keeps the Trial Master File and interim and final reports both in electronic and in hard copy form for at least 10 years after trial completion. Site will archive the Investigator Site File and Source Data for at least 10 years after trial completion.

14.1.4 Electronic and Central Data Validation

Data is checked by the EDC system for completeness and plausibility. Furthermore, selected data points are cross-checked for plausibility with previously entered data for that participant. In addition, central data reviews will be performed on a regular basis to ensure completeness of the data collected and accuracy of the primary outcome data.

14.1.5 On-site Audits and Inspections

To ensure compliance with the Declaration of Helsinki and applicable national/local regulatory requirements, a member of the Sponsor’s or a designated CRO’s quality assurance unit, may arrange to

conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator agrees to cooperate with the Sponsor and/or its designee in the conduct of these audits and provide access to medical records and other relevant documentation, as required. The investigator/institution will be informed of the audit outcome.

Regulatory authorities worldwide may inspect the investigator during and after the study. The investigator should contact the sponsor immediately if this occurs, and must cooperate with the regulatory authority inspections as required.

15. ADJUDICATION OF EVENTS

The events are adjudicated by the clinical event committee (CEC) comprised of qualified physicians who are not investigators in the trial. The CEC is responsible for adjudicating all potential endpoint events as well as the reasons for hospitalisation. The composition, guiding policies, and operating procedures governing the CEC are described in a separate CEC Manual of Operations.

16. ORGANISATION

16.1 Sponsor

In this investigator-initiated trial, the Insel Gruppe AG will act as Sponsor (Freiburgstrasse, 3010, Bern, Switzerland) The co-Sponsor will be Azienda Socio-Sanitaria Territoriale of Lecco (Via dell'Eremo 9/11, 23900, Lecco, Italy). The Sponsor and co-Sponsor's responsibilities are described in chapter 22.

16.2 Executive Committee

The Executive Committee is responsible of the overall management of the study. Their names, roles and responsibilities are described in a separate Executive Steering Committee Charter.

16.3 Operational Committee

The operational committee is responsible for daily management of study execution in operational level under supervision of executive committee.

16.4 Steering Committee

The Steering Committee is comprised of the executive committee and national lead investigators.

16.5 National lead investigators

National lead investigators will be assigned by the Sponsor. During the regulatory submissions, they help to guide the other sites in their country, where required. In case of study management issues (e.g. protocol-related questions), national lead investigators support the sites and help them to solve any other problems that are particular to their clinic.

16.6 Data Management, Central Data Review and statistical analysis

Data management, central data review and statistical analysis will be conducted by the independent CRO, Advice Pharma in Milan, Italy (Via Giovanni Durando, 38/A, 20158 Milano MI, Italy).

17. DATA HANDLING AND RECORD KEEPING

17.1 Source Documentation (SD)

Regulations require that investigators maintain information in the patient's medical records that corroborate data collected in the electronic Case Report Form (eCRF). In order to comply with these regulatory requirements, at minimum, the following is a list of information that should be maintained and made available as required by monitors and/or regulatory inspectors (list is not exhaustive):

- Medical history/physical condition of the study patient before involvement in the study sufficient to verify protocol inclusion and exclusion criteria;
- Signed informed consent forms;
- Dated and signed notes on the day of entry into the study, protocol number, clinical site, patient number assigned and a statement that informed consent was obtained and that patient received a copy of the informed consent form;
- Notations on abnormal lab results;
- Serious adverse events reported and their resolution, including supporting documents such as discharge summaries, intervention reports, lab reports, ECGs, lab results;
- Notes regarding protocol-required and prescription medications taken during the study (including dose, start and stop dates);
- Study patient's condition upon completion of or withdrawal from the study.

17.2 Case Report Form Completion

All required data are accurately recorded by authorised personnel documented on the authorised signature log in the eCRF.

17.3 Record Retention

All eCRF information, study records, reports and source documents that support the eCRF must be retained in the files of the responsible investigator for a minimum 10 years following notification by the Sponsor or designee that all investigations have been completed and completed site close-out visit, in accordance with local, national and international regulations. This documentation must be accessible upon request by international regulatory authorities or the Sponsor (or designee). The Sponsor or designee must approve archiving or transfer of the documentation for relocation purpose of premises, in writing, prior to the actual file transfer. The investigator must notify the Sponsor, in writing, of transfer location, duration, and the procedure for accessing study documentation. The investigator must contact the Sponsor, or designee, before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

18. PUBLICATION POLICY

The Steering Committee and investigators are committed to the publication and widespread dissemination of the results of the study. Data from this study will not be withheld regardless of the findings.

The CONVINCE is an investigator-initiated and scientifically driven study nested within the Inselspital Institute and set up in collaboration with Daiichi Sankyo company. All public presentations and manuscript generation and submissions will be led under the auspices of the Coordinating Principal Investigators. However, this study represents a joint effort between investigators, Sponsor and collaborators, and as such, the parties agree that the recommendation of any party concerning manuscripts or text shall be taken into consideration in the preparation of final scientific documents for publication or presentation.

The final locked database will be housed at the data management centre, Advice Pharma, Milan. Advice Pharma will not publicly release data or study-related material, presentations, or manuscripts without the express permission of the Coordinating Principal Investigators. The Coordinating Principal Investigators will be listed as authors on all abstracts and publications, and as such must agree to their submission. The authors on the primary manuscript include the steering committee members and investigators according to the number of patients and quality of data. The publication and/or presentation of results from a single trial site are not allowed until publication and/or presentation of the multi-centre results. All single site data for public dissemination must be generated from the central database – local database projects are not permitted.

All proposed publications and presentations resulting from or relating to the study (whether from multicenter data or single site analysis) must be submitted to the Steering Committee for review and approval including the choice of authors prior to submission for publication or presentation.

19. FUNDING AND SUPPORT

The study will be supported by the company Daiichi-Sankyo (financial grant and support for the IMP edoxaban).
Applications for additional funding from national research supporting organizations will be submitted. Insel Gruppe AG, Bern University Hospital, Department of Cardiology will also financially support the trial.

20. INSURANCE

The Sponsor (Insel Gruppe AG) and the Co-Sponsor (ASST of Lecco) will provide an insurance for the trial's participants in accordance with the local law and regulations. A copy of the certificates are filed in each investigator site file and the trial master file.

21. INVESTIGATOR RESPONSIBILITIES

21.1 Investigator Responsibility/Performance

Prior to starting enrolment of patients, the investigator must read and understand this study protocol, and must sign and date the Protocol Signature page. The Investigator Site Agreement documents agreement to all conditions of the study protocol and agreement to conduct the study accordingly.

21.2 Required Documents

The following documents must be submitted to Sponsor, or designee prior to any patient enrolment:

- Signed Protocol Signature Page
- Recent signed and dated English Curriculum Vitae (CVs) of the Principal Investigator and co-investigators of the clinical site. These CVs should clearly show the investigator's and co-investigators' qualifications and experience.
- Certificate of adequate GCP training
- Copy of the written favourable EC/IRB/ CA opinion.
- Signed Clinical Site Agreement (CSA).
- Site Delegation Log with corresponding training logs.

21.3 Protocol Deviation

Investigator will document and explain any Protocol Deviation that occurred during the course of the study.

22. SPONSOR AND CO-SPONSOR RESPONSIBILITIES

22.1 Role of Sponsor (Insel Gruppe AG)

As Sponsor, Insel Gruppe AG has the overall responsibility for the conduct of the study, including assurance that the study satisfies international standards and the regulatory requirements of the relevant competent authorities.

General duties

Prior commencing the subject recruitment the sponsor shall submit any required application to all concerned regulatory bodies (CA) and Ethics Committee (EC/IRB) and ensure that respective written approvals are obtained and documented. Any amendment to the protocol, will be submitted to the concerned regulatory bodies in accordance with the applicable regulatory requirements and written approval obtained prior to implementation.

Selection of clinical investigators and sites

The Sponsor will select qualified investigators and facilities which have adequate study patient population to meet the requirements of the investigation.

Training of investigator and site personnel

The training of the investigator and appropriate clinical site personnel will be the responsibility of the Sponsor, or designee, and may be conducted during an investigator meeting, a site initiation visit, or other appropriate training sessions.

Documentation

The Sponsor will collect, store, guard and ensure completion by the relevant parties of the following documents (list is not exhaustive);

- All study relevant documents (protocol, Instruction for use, EC/IRB/ CA approval and comments, competent authority notification and comments, patient information and informed consent template, relevant correspondence, etc.)

- Signed and dated Case Report Forms
- Records of any Serious Adverse Events (SAEs) and CEC events reported to the Sponsor during the clinical investigation
- Any statistical analyses and underlying supporting data
- Final report of the clinical investigation

22.2 Confidentiality

All data and information collected during this study related to the participating subject will comply with the standards for protection of privacy based on applicable local/ national requirements for subject's confidentiality. All data used in the analysis and summary of this study will becoded (without specific study subjects' names, address, date of birth, etc). Access to study subject files will be limited to authorised personnel of the Sponsor, the investigator, and research staff. Authorised regulatory personnel have the right to inspect patient data.

22.3 Role of Co-Sponsor (ASST of Lecco)

As Co-sponsor, ASST of Lecco will provide the insurance for the trial's participants within the European Union in accordance with the applicable laws and regulation.
Also the Co-Sponsor will be in charge of shipping and analyzing in a central laboratory the samples stored in the local hospital biobank during the conduction of the trial.
Samples will be stored for a maximum of 5 years after study closure.
The role of the Co-sponsor is defined more in detail in a separate document.

APPENDIX I - Summary of follow up visits

Day 0: SARS-COV-2 diagnosis	**V1:**	**V2**	**V3**	**V4**	**V5**
	Within 7 days	*7±3 days post randomization*	*14±3 days post randomization*	*21±3 days post randomization*	*25±3 days post randomization*
Type of contact	Visit and Letter*	Phone	Visit and Letter*	Phone	Visit and Letter*
Inclusion/ exclusion criteria	X				
Informed consent	X				
Physical examination	X		X		X
Medical history	X	X	X	X	X
Randomization	X				
Electrocardiogram (12 lead ECG)	X**		X**		X**
Medication regimen	X	X	X	X	X
(Serious) Adverse Event review	X	X	X	X	X
Bilateral lower extremity venous ultrasonography					X
RT-PCR for SARS-COV-2			X		X
Blood sampling for local laboratory assessment	X***(*)		X***		X***
Blood sampling for plasma and serum biobanking	X		X		X

*) A letter with details of randomized regimen is sent to the patient and to the treating physician to ensure the implementation of randomized regimen and to inform him/her on results of SARS-COV-2 (repeat) testing.
**) Only in the centers where this is a part of usual clinical practice
***) Troponin and other biomarkers according to the local practice
***(*)) Human chorionic gonadotrophin (HCG) urine pregnancy test for all child-bearing women

APPENDIX II - Definitions

BLEEDING

All potential bleeding events will be primarily adjudicated according to Bleeding Academic Research Consortium (BARC) classification.[25]

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional. May include episodes leading to self-discontinuation of medical therapy by the patient, without consulting a health care professional.
Type 2	Any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that does not fit the criteria for Types 3, 4, or 5 but does meet at least one of the following criteria: Requiring non-surgical, medical intervention by a health care professional Leading to hospitalization of increased level of care Prompting evaluation
Type 3a	Overt bleeding plus hemoglobin drop of 3 to <5** g/dL (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding
Type 3b	Overt bleeding plus hemoglobin drop ≥5** g/dL (provided hemoglobin drop is related to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental / nasal / skin / hemorrhoid) Bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal) Subcategories: confirmed by autopsy or imaging or LP Intra-ocular bleed compromising vision
Type 4	CABG-related bleeding Perioperative intracranial bleeding within 48 hours Reoperation following closure of sternotomy for the purpose of controlling bleeding Transfusion of ≥ 5 units of whole blood or packed red blood cells within 48 hour period* Chest tube output ≥ 2 L within a 24 hour period
Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation, but clinically suspicious
Type 5b	Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

Obs: Platelet transfusions should be recorded and reported, but are not included in these definitions until further information is obtained about the relationship to outcomes. * Corrected for transfusion (1 U packed red blood cells or 1 U whole blood_1g/dL hemoglobin). † Cell saver products will not be counted.

ISTH Bleeding Criteria

ISTH Bleeding Criteria
Major bleeding • Clinically overt bleeding that is associated with: o A fall in hemoglobin of 2 g/dL or more, or o A transfusion of 2 or more units of packed red blood cells or whole blood, or o A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or o A fatal outcome
Non-major clinically relevant bleeding • Overt bleeding event not meeting the criteria for a major bleeding event but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study drug treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life. Examples include: o Epistaxis if it lasts for more than 5 minutes, if it is repetitive (i.e., 2 or more episodes of true bleeding, i.e., no spots on a handkerchief, within 24 hours), or leads to an intervention (packing, electrocautery, etc.) o Gingival bleeding if it occurs spontaneously (i.e., unrelated to tooth brushing or eating), or if it lasts for more than 5 minutes o Hematuria if it is macroscopic, and either spontaneous or lasts for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract o Macroscopic GI hemorrhage: at least 1 episode of melena or hematemesis, if clinically apparent o Rectal blood loss, if more than a few spots o Hemoptysis, if more than a few speckles in the sputum, or o Intramuscular hematoma o Subcutaneous hematoma if the size is larger than 25 cm^2 or larger than 100 cm^2 if provoked o Multiple source bleeding events
Minimal • All other overt bleeding episodes not meeting the criteria for major or clinically relevant non-major bleeding.

THROMBOEMBOLISM

Symptomatic Deep Vein Thrombosis (DVT)

Symptomatic proximal vein thrombosis (of the leg) will be confirmed if there are typical symptoms of DVT associated with

- non-compressible vein segment on ultrasonography or
- an intra-luminal filling defect on venography, CT venography or MRI venography,
- located in the inferior vena cava (IVC), the iliac vein, the common femoral vein, the femoral or the popliteal vein.

Asymptomatic DVT

Asymptomatic proximal DVT is a thrombus that is detected during imaging testing performed for study screening purposes. A thrombus detected in the inferior vena cava (IVC) or iliac veins on a (staging) abdominal or pelvic CT will be considered diagnostic. Because of potential flow artefacts and layering of contrast, a suspected thrombus detected in the common femoral vein or more distal veins can only be considered if confirmatory compression ultrasound (CUS) or (CT) contrast venography diagnostic criteria are also met. Criteria will be:

- An intraluminal filling defect on (staging) CT scan or MR venography in the IVC or iliac veins.
- A non-compressible venous segment in the popliteal vein or above on ultrasonography or a filing defect
- on venography or CTV in the inferior vena cava (IVC), the iliac vein, the common femoral vein, the femoral or the popliteal vein.

Symptomatic PE

Symptomatic PE will be confirmed if there are typical symptoms of PE associated with

- an intra-luminal filling defect in (sub) segmental or more proximal branches on spiral computed tomography scan (CT) or computerized tomographic pulmonary angiography (CTPA).
- a considerable perfusion defect (~ 75% of a segment) with a local normal ventilation result (high probability) during perfusion-ventilation lung scan (PLS, VLS or V/Q scan).
- an intraluminal filling defect or a sudden cut-off of vessels (~more than 2.5 mm in diameter) on a catheter guided pulmonary angiogram.

In case of an inconclusive CTPA, inconclusive V/Q scan (including perfusion scan only) or inconclusive angiography demonstration of DVT in the lower extremities e.g. by compression ultrasound or venography will be required.

Asymptomatic PE

Asymptomatic PE is a clot that is detected during imaging testing performed for other reasons and not for suspicion of PE. This incidental finding will only be considered diagnostic if the clot is in a segmental or more proximal artery. Clots in sub-segmental or more peripheral arteries detected during staging in an asymptomatic subject will not be classified as PE (due to risk of a false positive result). Criterion will be an intraluminal filling defect in segmental or more proximal branches on spiral CT or MR scan.

Recurrent venous thromboembolism (VTE)

Recurrent VTE is either:

- symptomatic confirmed (recurrent) DVT or (recurrent) PE.
- unsuspected (new) proximal DVT of the legs or unsuspected (new) PE located in segmental or more proximal arteries:
    - Unsuspected DVT or PE are thrombi that are detected during imaging testing performed for other reasons and not for suspicion of DVT or PE.

- fatal PE (confirmed at autopsy).

Symptomatic confirmed (recurrent) DVT or (recurrent) PE
Confirmation of (recurrent) symptomatic DVT requires symptoms of DVT and the following criteria:

- In the absence of previous DVT investigations at baseline:
  - A non-compressible venous segment on ultrasonography or
  - An intraluminal filling defect on venography. CT –scan or MR venography located in the deep veins of the leg or IVC.
- If there were previous DVT investigations at baseline:
  - Abnormal CUS where compression had been normal or, if previously non-compressible, a substantial increase (4 mm) in diameter of the thrombus during full compression, or
  - An extension of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of non-visualization of veins in the presence of a sudden cut-off on venography CT-scan or MR- venography.

Confirmation of (recurrent) symptomatic PE requires symptoms of PE and one of the following findings:

- A (new) intraluminal filling defect in (sub) segmental or more proximal branches on spiral CT scan.
- A (new) intraluminal filling defect or an extension of an existing defect or a new sudden cut-off of vessels on the pulmonary angiogram.
- A (new) considerable perfusion defect (~ 75% of a segment) with a local normal ventilation result (high-probability) on ventilation/perfusion lung scintigraphy (V/Qscan).
- An inconclusive lung scan accompanied by documentation of (new) DVT in the lower extremities e.g., by compression ultrasound or venography.

Diagnosis of fatal PE is based on one or more of the following:

- Objective diagnostic testing.
- Autopsy.
- Death which cannot be attributed to a documented cause and for which PE/DVT cannot be ruled out.

Asymptomatic (new) DVT or (new) PE
Asymptomatic DVT is only considered an outcome if located in popliteal or more proximal veins. For the 2 scenarios when previous imaging was normal or when previous objective imaging was abnormal asymptomatic DVT will be considered an outcome if it meets criteria as defined in below table.

Previous objective imaging normal Previous objective imaging abnormal
An intraluminal filling defect on (staging) CT scan or MR venography in the IVC or iliac veins.
Previous objective imaging abnormal
An extension of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of non-visualization of the iliac IVC in the presence of a sudden cut-off on staging CT-scan (or MR- venography).

Asymptomatic PE will be considered an outcome if it is a (new) intraluminal filling defect in segmental or more proximal branches on spiral CT or MR scan.

DEATH

Death will be classified in 5 categories with respect to cause.
Thromboembolism, cardiovascular, bleeding, Pulmonary other known cause.
In general, all deaths will be assumed to be due to thromboembolism or pulmonary in nature unless another cause is obvious.

- VTE death is defined as death due to a documented PE (either an objective test prior to death of the subject or PE detected during autopsy) or unexplained death i.e. death without a clear alternate cause and not a primary consequence of subject's underlying pulmonary disease
- Pulmonary deaths**:** Death in which the mode of death can be attributed to the direct effects of SARS-COV-2 pneumonitis or reinfection. (e.g. Acute Respiratory Distress Syndrome, pneumonia with sepsis) or death in a subject with progressive respiratory disease who had a (gradual) decline in general condition or a complication (e.g. infection) or in whom palliative treatment only was decided
- Cardiovascular death: is defined as death due to documented cardiovascular cause : acute myocardial infarction, stroke, congestive heart failure, arrhythmia, cardiac surgery, systemic embolic, other cardiovascular cause
- Bleeding: BARC 5a or b
    - 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinical suspicious
    - 5b: definite fatal bleeding; overt bleeding or autopsy or imaging confirmation
- Other known cause: include those caused primarily by infection (non-pulmonary), accident, renal failure, or other non-cardiovascular organ system failure, trauma, non-cardiac surgery, suicide.

HOSPITALISATION

All-cause hospitalisation is defined as admission to an inpatient unit or ward in the hospital for ≥24 h, including an emergency department stay. Hospitalis ations planned for pre-existing conditions are excluded unless there is worsening of the baseline condition.

Hospitalisation is further subclassified as:

- Hospitalisation for worsening COVID-19 with the need for oxygen therapy, non-invasive mechanical ventilation, or invasive mechanical ventilation.
- Hospitalisation for thrombo-embolic disease
- Hospitalisation for bleeding ('bleeding related')
- Cardiovascular hospitalization: such as for coronary artery disease, acute myocardial infarction, hypertension, cardiac arrhythmias, cardiomegaly, pericardial effusion, atherosclerosis, stroke, or peripheral vascular disease without qualifying thrombo-embolic disease
- Other.

MYOCARDIAL INFARCTION

For the primary analysis, MI endpoint will be defined based on the third universal definition of myocardial infarction with the exception of periprocedural MI after PCI, which will be defined according to the SCAI definition. [26, 27]

For secondary analyses, PCI-related MI according to the Third Universal MI definition (type 4a) will be also adjudicated.

1. Spontaneous MI (>48 hours after intervention, MI type 1)

Symptoms suggestive of ischemia/infarction in association with ECG, cardiac biomarker or pathologic evidence of infarction as follows:[26]:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin T or I) with at least one value above the 99th percentile upper reference limit and with at least one of the following:
- Symptoms of ischemia
- New or presumed new significant ST segment-T wave (ST-T) changes or new LBBB
- Development of new Q waves in the ECG
  Evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

Spontaneous MI typically occurs after the periprocedural period and may be secondary to late stent complications or progression of native disease (e.g., non-culprit lesion plaque rupture). Performance of ECG and angiography supports adjudication to either a *target* or *non-target vessel or lesion* in most cases.

Type 2 MI

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy/bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3 MI

Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

Type 4a MI (NOT USED for primary analysis; see definition below)

Type 4 MI is defined by elevation of cTn values (>5 x URL) occurring within 48h of the procedure in patients with normal baseline values (≤URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling.
In addition, at least one of the following is required:

- symptoms suggestive of myocardial ischaemia
- new ischaemic ECG changes
- angiographic findings consistent with a procedural complication
- imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality

Type 4b MI
Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of evidence of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the URL.

Type 4c MI

A spontaneous MI where a restenosis is the only angiographic explanation

Type 5 MI
Coronary artery bypass grafting (CABG) related MI is defined by elevation of troponin values (>10 x URL) occurring within 48h of the procedure in patients with normal baseline cTn values (≤URL).

In addition, at least one of the following is required:

- new pathological Q waves or new LBBB
- angiographic documented new graft or new native coronary artery occlusion
- imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Periprocedural MI after PCI (within 48 hours after PCI)

Periprocedural MI is defined based on the SCAI definitions as follows:[27]

1) In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, *OR* in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB. .
2) In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
3) In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above *plus* new ST-segment elevation or depression *plus* signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

STROKE

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by central nervous system (CNS) vascular injury as a result of hemorrhage or infarction.

CNS includes brain, spinal cord and retina.

Classification:

Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by CNS infarction. Evidence of infarction is defined as"Pathological, imaging, or other objective evidence of acute cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or

In absence of the above (i.e. imaging or autopsy unavailable), clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury is based on symptoms persisting ≥24 hours or until death, and other etiologies excluded.

Note, Hemorrhagic infarction, defined as a parenchymal hemorrhage after CNS infarction, is considered an ischemic stroke

Cerebral Hemorrhage

Hemorrhages in the CNS are classified as stroke if they are nontraumatic, caused by a vascular event, and result in injury to the CNS. In contrast, traumatic hemorrhages will not be characterized as stroke. Subdural hematoma will not be classified as a stroke. The diagnoses included in this section are intracerebral hemorrhage (intraparenchymal and intraventricular) and subarachnoid hemorrhage (both aneurysmal and nonaneurysmal).

Stroke caused by intracerebral hemorrhage

Rapidly developing clinical signs of neurological dysfunction (focal or global) attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

Stroke caused by subarachnoid hemorrhage

Rapidly developing signs of neurological dysfunction (focal or global) and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma. Hemorrhages may be further classified according to location (example, supratentorial, subtentorial, etc.)

Stroke not otherwise specified

An episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥24 hours or until death, but without sufficient evidence to be classified as one of the above.

NON-CNS SYSTEMIC EMBOLISM

Non-CNS systemic embolism is defined as abrupt vascular insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms. In the presence of atherosclerotic peripheral artery disease (PAD), diagnosis of embolism to the lower extremities required angiographic demonstration of acute arterial occlusion.

APPENDIX III - Abbreviations and Acronyms

ACE2	Angiotensin converting enzyme2
ARC	Academic Research Consortium
ASA	Acetylsalicylic acid
BARC	Bleeding Academic Research Consortium
CABG	Coronary Artery Bypass Surgery
CAD	Coronary Artery Disease
COVID-19	Coronavirus disease of 2019
CNS	Central nervous system
CRP	C-reactive protein
CRA	Clinical Research Associate
CrCl	Creatinine clearance
CT	Clotting time
(e)CRF	(electronic)Case Report Form
DAPT	Dual AntiPlatelet Therapy
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
EC	Ethics Committee
ECG/EKG	Electrocardiography
ESC	European Society of Cardiology
HS	High sensitive
IRB	Institutional Review Board
IFU	Instruction For Use
IRB	Institutional Review Board
ISTH	International Society of Thrombosis and Hemostasis
MOF	Multiorgan failure
MVTE	Major vascular thrombotic events
MCB	Major or clinically relevant non-major bleeding
MI	Myocardial Infarction
NOAC	New Oral Anticoagulant
OAC	Oral Anticoagulant
PAD	Peripheral Artery Disease
PE	Pulmonary embolism
PO	Per os
PCI	Percutaneous Coronary Intervention
RT PCR	Reverse transcriptase-polymerase chain reaction
SAE	Serious Adverse Event
SAPT	Single AntiPlatelet Therapy
SARS-CoV-2	Coronavirus responsible for COVID-19
SD	Source Documentation
TIA	Transient Ischaemic Attack
UFH	UnFractionated Heparin
ULN	Upper Limit of Normal

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