FREEDOM COVID Anticoagulation Strategy Randomized Trial

Protocol Number:	V1.6 10AUG2020
Protocol Version #:	1.6 EU
Protocol Date:	August 10, 2020
EudraCT Number:	2020-005763-31
NCT Number:	NCT04512079
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Investigator Initiated Sponsor's Agreement to Protocol Version 1.6 EU, August 10, 2020

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Signature of Authorized Personnel: _____

Date of Approval: _____
DD-MM-YYYY

SYNOPSIS

Objectives	1. To determine the effectiveness of enoxaparin and apixaban in patients hospitalized (but not yet intubated) with confirmed COVID-19 2. To determine the safety of enoxaparin and apixaban in patients hospitalized (but not yet intubated) with confirmed COVID-19
Study design	Prospective, multi-center, open label, randomized controlled comparative safety and effectiveness trial
Study Period	The duration of the study is approximately 18 months, which includes ~15 months to enroll all patients plus 3-month follow-up for all enrolled patients.
Target population (Inclusion and Exclusion Criteria)	***Inclusion Criteria*** 1. Hospitalization within the prior 24 hours for either confirmed (based on PCR or antigen positive test for SARS-CoV-2) or suspected COVID-19 based on 3 criteria (all 3 must be present for suspected cases): a. Fever >38 degrees Celsius b. O2 saturation ≤94 c. Abnormal laboratory marker (at least 1) i. d-dimer ≥1.0 µg /mL ii. CRP >2 mg/L iii. Ferritin >300 µg /L iv. Lymphopenia <1500 cells /m^3 2. Patient or legal guardian provides written informed consent ***Exclusion Criteria*** 1. Age <18 years 2. Mechanical ventilation on admission or high likelihood for the need for invasive mechanical ventilation within 24 hours of admission 3. Anticipated duration of hospital stay ≤72 hours 4. Treatment with therapeutic dose UFH or LMWH, vitamin K antagonists, or NOACs within seven days 5. Active bleeding 6. Risk factors for bleeding, including: a. intracranial surgery or stroke within 3 months b. history of intracerebral arteriovenous malformation c. cerebral aneurysm or mass lesions of the central nervous system d. intracranial malignancy e. history of intracranial bleeding f. history of bleeding diatheses (e.g., hemophilia) g. history of gastrointestinal bleeding within previous 3 months

	h. thrombolysis within the previous 7 days i. presence of an epidural or spinal catheter j. recent major surgery <14 days k. uncontrolled hypertension (sBP > 200 mmHg or dBP > 120 mmHg) l. other physician-perceived contraindications to anticoagulation m. Platelet count <50 x10^9/L, INR >2.0, or baseline aPTT >50 seconds n. Hemoglobin <80 g/L (to minimize the likelihood of requiring red blood cell transfusion if potential bleeding were to occur) o. current treatment with antithrombotics or antiplatelet agents including but not limited to ticagrelor, prasugrel, and aspirin> 100mg, or non-steroidal anti-inflammatory drugs (e.g. ibuprofen, naproxyn, etc.) due to increased risk of bleeding, unless such agents can be permanently discontinued (aspirin <= 100mg and clopidogrel <=75mg is permitted) 7. Acute or subacute bacterial endocarditis 8. History of heparin induced thrombocytopenia (HIT) or other heparin allergy including hypersensitivity 9. Patients with non-COVID-19 related clinical condition for which life expectancy is <6 months 10. Pregnancy (women of childbearing potential are required to have a negative pregnancy test prior to enrollment) 11. Active enrollment in other trials related to anticoagulation 12. Patients has end stage kidney disease (ESKD) on chronic dialysis 13. Patient is a member of a vulnerable population: In the judgment of the investigator the patient is unable to give Informed Consent for reasons of severe chronic incapacity, immaturity, adverse personal circumstances or lack of autonomy. This may include: Individuals with mental disability, persons in nursing homes, children, impoverished persons, persons in emergency situations, homeless persons, nomads, refugees, and those incapable of giving informed consent. Vulnerable populations also may include members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the Sponsor, members of the armed forces, and persons kept in detention. Note: Patients who are unable to give informed consent because of their acute illness may enter the trial if consent is provided by a legally authorized representative.

Comparison arms & Treatment (1:1:1 randomization)	1. Prophylactic enoxaparin (40 mg SC QD; 30 mg SC QD for CrCl <30 mL /min) 2. Full-dose enoxaparin (1 mg/kg SC Q12h; 1 mg/kg SC QD for CrCl <30 mL /min) 3. Apixaban (5 mg Q12h; 2.5 mg Q12h for patients with at least two of three of age ≥80 years, weight ≤60 kg or s. creatinine ≥1.5 mg/dL)
Primary endpoints	● **Effectiveness –** The primary effectiveness outcome endpoint is the time to first event rate within 30 days of randomization of the composite of all-cause mortality, intubation requiring mechanical ventilation, systemic thromboembolism (including pulmonary emboli) confirmed by imaging or requiring surgical intervention OR ischemic stroke confirmed by imaging ● **Safety** – The primary safety outcome endpoint is the in-hospital rate of BARC 3 or 5 bleeding (binary)
Secondary endpoints (each assessed at 30 days and 90 days after randomization)	1. Myocardial infarction (according to the 4th universal definition, types 1,2, and 3) 2. Deep vein thrombosis with confirmation on imaging 3. Intubation and mechanical ventilation 4. All-cause death 5. Cause specific death 6. Stroke confirmed by imaging or autopsy (all, ischemic and hemorrhagic) 7. Pulmonary emboli confirmed by imaging or autopsy 8. Systemic thromboembolism confirmed by imaging or requiring surgical intervention 9. Organ support-free days 10. Total ICU days 11. ICU-free days 12. Need for non-invasive mechanical ventilation or high flow nasal cannula 13. Ventilator-free days (days alive free of mechanical ventilator support) 14. Total hospital days 15. Hospital-free days (days alive out of hospital assessed through 90 days post randomization) 16. BARC 2, 3 or 5 bleeding 17. Laboratory confirmed Heparin induced thrombocytopenia (HIT)
Sample size	The study is designed to enroll approximately 1200 patients in each of the three arms for a total of approximately 3600 patients

Duration of Treatment	From randomization through duration of hospitalization (until hospital discharge)
Participant Duration	Through 90 days after randomization

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TABLE OF CHANGES

Rev.	Section	Change	Reason	Page
1	Exclusion Criteria	additional exclusion criteria of antithrombotic agents including antiplatelet agents and NSAIDS	Due to increased risk of bleeding	12-13
2	Exclusion	FDA exemption/permission to include low dose aspirin and clopidogrel (<=100mg and <=75mg respectively)	Due to frequency patient population with coronary artery disease and use for primary prevention on these medications, with otherwise low bleeding risk profiles	12-13
3	Exclusion Criteria	Anticipated duration of hospital stay <72 hours	Due to concerns that patients may be discharged within a short period of time and not receive a course of clinically effective anticoagulation	12-13
4	Subgroup Analysis	1) Severity of COVID-19 infection at baseline 2) Duration of anticoagulation therapy during hospitalization	To better understand the effect of anticoagulation in key subgroups (by severity of disease at baseline and by duration of anticoagulation)	25
5	Interim Analysis	Added section of Interim analysis	To increase trial safety monitoring	
1.6_EU		1. Sponsor's address details added 2. DM address details added 3. Information regarding study duration 4. Adjustments in terms of ECs requirements	To comply with European regulation requirements	

LIST OF ABBREVIATIONS

Ensure all abbreviations used within the protocol are listed here

AE	Adverse Event
aPTT	activated partial thromboplastin time
AR	Adverse Reaction
CCC	Clinical Coordinating Centre
CrCl	Creatinine Clearance
CRO	Clinical Research Organization
CTA	Clinical Trial Application
dBP	diastolic Blood Pressure
DCC	Data Coordinating Centre
DIC	Disseminated Intravascular Coagulation
DOAC	Direct oral anticoagulant
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
EAC	Events Adjudication Committee
EC	Ethics Committee
EDC	Electronic Data Capture
ESKD	End Stage Kidney Disease
FDA	Food and Drug Administration
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HIT	Heparin-Induced Thrombocytopenia
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IL-6	Interlukin-6
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
LAR	Legally Acceptable Representative
LMWH	Low-Molecular Weight Heparin
PE	Pulmonary Embolus
REB	Regulatory Ethics Board
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
sBP	systolic Blood Pressure
SpO_2	Oxygen Saturation
SSC	Scientific and Standardization Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
UFH	Unfractionated Heparin
VTE	Venous Thromboembolism
WHO	World Health Organization

OBJECTIVES

1. To determine the effectiveness of LMWH and novel oral anticoagulants (NOACs) in patients hospitalized with confirmed COVID-19
2. To determine the safety of LMWH and NOACs in patients hospitalized with confirmed COVID-19

BACKGROUND

Coronavirus Disease (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has led to unprecedented morbidity and mortality in the modern era. To date, nearly 13 million people have contracted COVID-19, leading to more than 550,000 deaths worldwide. (1) As the number of affected individuals continues to climb, effective strategies for treatment and prevention of the disease are of paramount importance. SARS-CoV-2 is understood to directly invade cells via the human angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed predominantly in the lungs but also throughout the cardiovascular system (2). Thus, while acute respiratory distress syndrome remains a feared complication, new thromboembolic disease has emerged as a common and potentially catastrophic manifestation of COVID-19. (3-6)

Reports from China (7) and the Netherlands (8) have cited 25% and 31% rates of venous or arterial thrombosis respectively, in some cases despite thromboprophylaxis. Helms et. al observed 64 relevant thrombotic complications among 150 patients referred to the intensive care unit for ARDS in France. Of the 99 patients who underwent computed tomography angiography, pulmonary emboli were observed in 25%. (9) Autopsy studies have further corroborated these observations by demonstrating a high incidence of macro and microthrombi in multiple organs. (10-12) In one study of 12 autopsies performed in Hamburg, Germany, 7 were found to have major thromboembolism including deep vein thrombosis or pulmonary emboli, and six of the 9 men in the cohort were found to have thrombosis of the prostatic venous plexus.(10) Similarly, in another study of 11 autopsies performed in Austria, all patients were found to have segmental or subsegmental pulmonary artery thrombosis.(11) In all cases, thrombi appeared to have formed in situ and ante-mortem.(12)

Perturbations in laboratory markers of coagulation were noted early on among patients who were hospitalized with COVID-19 with reports demonstrating an association between elevated d-dimer and increased risk of mortality.(13,14) Several pathologic mechanisms including endothelial dysfunction with increased levels of von Willebrand factor, systemic inflammation, hypoxemia, as well as elevated levels of antiphospholipid antibody, among others, have been implicated to account for laboratory abnormalities and clinical observations.(5) These factors likely contribute to a distinct “COVID-19 related coagulopathy” which results in increased thrombosis.(4)

Accordingly, observational analyses have suggested potential benefit for in-hospital use of anticoagulation. Yet, due to a lack of rigorous evidence for optimal anticoagulation regimens, practice patterns among hospitalized patients with COVID-19 vary significantly. Specifically, the choice of anticoagulant, dosing, and duration of treatment are not well understood. A preliminary analysis of approximately 2700 patients admitted to the Mount Sinai Health System (MSHS) in New York, demonstrated an association between in-hospital administration of therapeutic AC and improved survival compared to no or prophylactic dose AC.(3) A subsequent analysis under review of a larger 4400 patient cohort with longer follow up demonstrated similar associations with reduction in the risk of mortality and risk of intubation. Further analyses suggest more pronounced benefit with therapeutic as opposed to prophylactic doses. Bleeding rates were generally low overall, but higher among patients on therapeutic anticoagulation. Finally, though exploratory in nature, a potential signal for benefit was observed for patients on novel oral anticoagulant therapy (primarily apixaban) at therapeutic doses compared to low molecular weight heparin. Ultimately, randomized controlled trials are needed to elucidate the optimal anticoagulation regimen to improve outcomes in patients hospitalized with COVID-19.

PATIENT ELIGIBILITY

This trial will be conducted in compliance with the protocol and GCP. Any questions about eligibility criteria must be addressed prior to patient registration. All patients must be enrolled within 24 hours of admission.

Inclusion Criteria

1. Hospitalization within the prior 24 hours for either confirmed (based on PCR or antigen positive test for SARS-CoV-2) or suspected COVID-19 based on 3 criteria (all 3 must be present for suspected cases):
    - Fever > 38 degrees Celsius
    - O2 saturation ≤94%
    - Abnormal laboratory marker (at least 1)
        a. d-dimer ≥1.0 µg/mL
        b. CRP >2 mg/L
        c. Ferritin >300 µg/L
        d. Lymphopenia <1500 cells/m^3
2. Patient or legal guardian provides written informed consent

Exclusion Criteria

1. Age<18 years
2. Mechanical ventilation on admission or high likelihood for the need for invasive mechanical ventilation within 24 hours of admission
3. Anticipated duration of hospital stay $\leq$72 hours
4. Treatment with therapeutic dose UFH or LMWH, vitamin K antagonists, or NOACs within seven days
5. Active bleeding
6. Risk factors for bleeding, including:
    a. intracranial surgery or stroke within 3 months
    b. history of intracerebral arteriovenous malformation
    c. cerebral aneurysm or mass lesions of the central nervous system
    d. intracranial malignancy
    e. history of intracranial bleeding
    f. history of bleeding diathesis (e.g., hemophilia)
    g. history of gastrointestinal bleeding within previous 3 months
    h. thrombolysis within the previous 7 days
    i. presence of an epidural or spinal catheter
    j. recent major surgery <14 days
    k. uncontrolled hypertension (sBP >200 mmHg or dBP >120 mmHg)
    l. other physician-perceived contraindications to anticoagulation
    m. Platelet count <50 x10^9/L, INR >2.0, or baseline aPTT >50 seconds
    n. Hemoglobin <80 g/L (to minimize the likelihood of requiring red blood cell transfusion if potential bleeding were to occur)

o. current treatment with antithrombotics or antiplatelet agents including but not limited to ticagrelor, prasugrel, and aspirin> 100mg, or non-steroidal anti-inflammatory drugs (e.g. ibuprofen, naproxyn, etc.) due to increased risk of bleeding, unless such agents can be permanently discontinued (aspirin <= 100mg and clopidogrel <=75mg is permitted)

7. Acute or subacute bacterial endocarditis
8. History of heparin induced thrombocytopenia (HIT) or other heparin allergy including hypersensitivity
9. Patients with non-COVID-19 related clinical condition for which life expectancy <6 months
10. Pregnancy (women of childbearing potential are required to have a negative pregnancy test prior to enrollment)
11. Active enrollment in other trials related to anticoagulation
12. Patients with ESKD on dialysis
13. Patient is a member of a vulnerable population. In the judgment of the investigator the patient is unable to give Informed Consent for reasons of severe chronic incapacity, immaturity, adverse personal circumstances or lack of autonomy. This may include: Individuals with mental disability, persons in nursing homes, children, impoverished persons, persons in emergency situations, homeless persons, nomads, refugees, and those incapable of giving informed consent. Vulnerable populations also may include members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the Sponsor, members of the armed forces, and persons kept in detention. Determination of incapacity will be documented in the clinical record along with the individual who made the capacity assessment. Note: Patients who are unable to give informed consent because of their acute illness may enter the trial if consent is provided by a legally authorized representative.

Patient Consent

Consent forms will be provided in the languages appropriate for each country in which the study will be conducted with a copy of the IRB/EC approval and approved consent form sent to the Clinical Coordinating Center in New York. The subject/LAR must sign consent prior to registration or may provide consent as per FDA guidance document Coronavirus (COVID-19) Update: FDA Issues Guidance for Conducting Clinical Trials or REB/IRB recommendations.

Patients admitted to the hospital that have confirmed SARS-CoV-2 on the basis of a positive PCR or antigen test or strongly suspected to have SARS-CoV-2 according to enrollment criteria will be assessed for eligibility. Screening will include a review of inclusion and exclusion criteria. Study staff will discuss with the treating clinical team a potential subject's suitability to be approached for the trial. Information about the study will be presented to potential subjects (or legally authorized representative, which can include a substitute decision-maker in cases of incapacity). In the event an incapacitated individual regains capacity during their participation in the trial, they will be re-consented.

Given the potential for viral transmission and the nature of the studied intervention, consent will be obtained as per the IRB/EC recommendations or FDA Guidance.

Patient Registration

The randomization and registration process will be provided to the sites at site start-up phase.

STUDY PLAN

Study Schedule

- PCR testing for SARS-CoV2 must be performed in the emergency department or within 24 hours of hospital admission, unless the patient is admitted with a positive PCR or antigen test for COVID-19 as an outpatient within 7 days.

- Anticoagulation study drug will be administered as soon as possible, but no later than 12 hours after randomization and until hospital discharge. Patients will be followed in-person during the hospitalization and then through telephone/remote contact for 90-days post-randomization.

- Patients who have received 1-2 doses of prophylactic unfractionated heparin or enoxaparin prior to randomization (which must occur within 24 hours of admission) are still eligible for participation.

- The following laboratory assessments are mandatory at baseline (within 24 hours of admission) (see Table below). Thereafter laboratory assessments should be performed as per standard of clinical care.

TABLE 1. Schedule of assessments

Investigations	**Pre-Treatment (Baseline)***	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 30**	**Day 90**	**Discharge**	**Worst Value during hospital admission until discharge**
Windows		+/- 3 days					+/- 3 days	+/- 7 days		
PCR testing for SARS-CoV2	x									
Informed Consent	x									
Randomization	x									
Medical History	x									
Concomitant Medications	x						x			
Weight	x									
Vitals documented (SpO2 and FiO2, heart rate, blood pressure, respiratory rate, temperature)	x	x	x		x		x			

Hematology Bloodwork (WBC, Neutrophil count-excluding bands, bands count, lymphocyte count, monocyte count, hemoglobin platelet count, International Normalized Ratio, aPTT, Fibrinogen)	x									x
Metabolic bloodwork (serum creatinine, serum albumin, total bilirubin, AST/SGOT, ALT/SGPT)	x									x
Cardiovascular markers (Troponin, BNP, NT-pro BNP)	x									x
D-dimer	x									x
Other Inflammatory Markers (Ferritin, CRP, Procalcitonin)	x									x
Anticoagulant and Antiplalet Administration	x	x	x	x	x	x	x	x	X	
All SAEs and AEs related to the study IMP (ARs)	x	X								

*mandatory

INTERVENTION

Study participants will be randomized in a 1:1:1 fashion to 1 of 3 arms:

1. Prophylactic enoxaparin (40 mg SC QD; 30 mg SC QD for CrCl <30 mL/min)
2. Full-dose enoxaparin (1 mg/kg SC Q12h; 1 mg/kg SC QD for CrCl <30 mL/min)
3. Apixaban (5 mg PO BID; 2.5 mg Q12h for patients with at least two of three of age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL)

Important note: Patients randomized with suspected COVID-19 who are deemed not to be positive after the return of the first PCR test (preferred) or antigen test will stop randomization and be treated per local standard of care. Such patients will not be included in the final 3600 patient totals but will be followed during their in-hospital course and their final diagnosis and safety outcomes reported. Such patients will be replaced to include 3600 total patients with eventually confirmed COVID-19, representing the final intention-to-treat cohort.

OUTCOME MEASURES

Primary effectiveness outcome

The primary effectiveness outcome endpoint is the time to first event rate within 30 days of randomization of the composite of all-cause mortality, intubation requiring mechanical ventilation, systemic thromboembolism (including pulmonary emboli) confirmed by imaging or requiring surgical intervention OR ischemic stroke confirmed by imaging

The primary safety outcome

The primary safety outcome endpoint is the in-hospital rate of BARC 3 or 5 bleeding (binary).

Secondary outcomes (each assessed at 30 and 90 days after randomization)

1. Myocardial infarction (according to the 4th universal definition, types 1,2, and 3)
2. Deep vein thrombosis with confirmation on imaging
3. Intubation and mechanical ventilation
4. All-cause death
5. Cause specific death
6. Stroke confirmed by imaging or autopsy (all, ischemic and hemorrhagic)
7. Pulmonary emboli confirmed by imaging or autopsy
8. Systemic thromboembolism confirmed by imaging or requiring surgical intervention
9. Organ support-free days
10. Total ICU days
11. ICU-free days
12. Need for non-invasive mechanical ventilation or high flow nasal cannula
13. Ventilator-free days (days alive free of mechanical ventilator support)
14. Total Hospital Days
15. Hospital-free days (days alive out of hospital assessed through 90 days post randomization)
16. BARC 2, 3 or 5 bleeding
17. Laboratory confirmed Heparin induced thrombocytopenia (HIT)

CONCOMITANT MEDICATIONS

Concomitant medications including approved and experimental COVID-19 treatments and anti-platelet agents will be collected at baseline and through 90 days.

Drug Interactions

Non-study drug anticoagulants and antiplatelet agents including glycoprotein IIb/IIIa antagonists, aspirin, platelet inhibitors, vitamin K antagonists, other direct factor Xa and IIa inhibitors and fibrinolytic therapy should not be used after enrollment because of increased risk of bleeding, unless the treating physicians consider the potential benefits to be greater than the potential risks. Notwithstanding this statement, low-dose heparin flushes to keep intravenous lines patent and short-term anticoagulation (e.g. unfractionated heparin for procedures) may be used as clinically indicated.

ANTICOAGULATION

Enoxaparin

Enoxaparin is a low molecular weight heparin (LMWH). It should be administered within this trial only per the study doses, which are adjusted for renal insufficiency.

Unfractionated heparin (UFH)
Since all patients will be receiving at a minimum prophylactic dose of anticoagulation, UFH should in general not be used within this trial. However, UFH may be used to flush intravenous lines, during dialysis or other procedures as clinically indicated.

Apixaban
Apixaban is a direct oral anticoagulant. It should be administered within this trial only per the study doses, which are adjusted for renal insufficiency, age and body weight.

Dose Adjustments

Daily drug administration including name of drug, dose, and route of administration will be recorded in the source documents and captured into an eCRF.

Premature Withdrawal/ Discontinuation Criteria
Treating physicians may choose to discontinue therapy at their discretion. A premature discontinuation of treatment will be defined as an interruption in study drug for >24 hours. Temporary, shorter interruptions, for example to safely facilitate invasive procedures, are not considered interruptions or discontinuations in therapy provided the interruption does not exceed 24 hours. Reasons for treatment discontinuation may include but is not limited to:

- Heparin induced thrombocytopenia or other heparin allergy/hypersensitivity
- Thrombocytopenia if platelet count <50 $x10^9$/L
- Major Bleeding
- Coagulopathy associated with an elevated INR (e.g. >2.0) or hypofibrinogemia
- Following invasive procedures where heparin is deemed unsafe to re-institute
- Patients requiring systemic fibrinolytic therapy
- Treating physician discretion

RANDOMIZATION
All patients presenting at study centers with confirmed or suspected COVID-19 will be screened for inclusion. Eligible patients who provide informed consent can be enrolled. Randomization will be performed through a web-based randomization system. Patients will be randomized in a 1:1:1 ratio across the three treatment arms. Randomization will be stratified by center, admission type (ward vs ICU) and age (<65 years vs >= 65 years). Permuted block randomization with randomly defined blocks will be used to provide treatment distribution in equal proportions.

In-hospital study drug changes

After the patient is randomized, he/she must receive only the allocated study drug regimen throughout the hospital duration, until the time of discharge, without change. Exceptions: If the patient experiences a primary endpoint event requiring a change in anticoagulation regimen (e.g. an arterial or venous thrombosis necessitating full-dose anticoagulation, or a stroke or intubation), or another indication for full-dose anticoagulation (e.g. new onset atrial fibrillation), the in-hospital anticoagulation regimen may be changed as clinically appropriate. Similarly, if the patient experiences a major complication on the assigned regimen (e.g. a major bleed), the assigned regimen may be changed as clinically appropriate. The reasons for any such changes will be documented in the case report form.

Post-discharge anticoagulant and antiplatelet agent use.

There is currently is no strong rationale to discharge COVID-19 patients who did not experience an in-hospital thrombotic complication on an anticoagulant agent (either a heparin, NOAC or vitamin K antagonist); as such patients will be exposed to the hemorrhagic risks of these agents with little chance of benefit. Thus, for the current protocol:

1. The use of an anticoagulant agent (either a heparin, NOAC or vitamin K antagonist, whether the study assigned mediaction or a different medication) is not allowed at discharge unless the patient has a recognized clinical indication for the use of one of these agents (e.g. thromboembolic disease, atrial fibrillation, etc.). Absent such an indication, the routine use of an anticoagulant for the sole purpose of thromboprophylaxis in the COVID-19 patient enrolled in this protocol who did not experience an adverse thromboembolic event or other event requiring anticoagulation will be considered a protocol violation.

2. The protocol also recommends that the COVID-19 patient enrolled in this study who did not experience an adverse thromboembolic event not be discharged on an antiplatelet agent for the sole purpose of thromboprophylaxis (absent a recognized clinical indication for the use of one of these agents – e.g. coronary artery or cerebrovascular disease). However, at site discretion if there is a strong desire to discharge the uncomplicated patient on some prophylaxis, either aspirin $\leq$100 mg per day or clopidogrel $\leq$75 per day (but not both, and not other antiplatelet or anticoagulant agents) is permitted and will not be considered a protocol violation. The decision to use an antiplatelet agent should not vary according to the randomization arm.

The outcomes of patients discharged on either an antithrombotic agent or an antiplatelet agent compared to no such agents will be examined in subgroup and other analyses.

SAFETY AND REPORTING REQUIREMENTS

A) FOR EUROPEAN COUNTRIES

Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences, which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product, which is related to, any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalization or prolongation of existing hospitalization • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardize the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorization, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

Operational definitions

The following adverse event definitions are in compliance with Good Clinical Practice; Consolidated Guidance (ICH E2 & E6).

Adverse Event (AE) is defined as any untoward medical occurrence in a patient who was treated with a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease, whether or not related to the medicinal (investigational) product.

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

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

The following events should not be reported as (S)AEs but recorded separately:
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition.
- Any admission to hospital/other department or other institution for general care where there was no deterioration in condition.
-Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

According to the CT-3 Guideline, 'Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol'.
During the study, out of range (abnormal) laboratory value(s) should be captured in eCRF as an Adverse Event(s) (AR/SAE - depending whether meet the definition), only if clinically significant .

Recording and reporting of SAEs and SUSARs

All SAEs and SUSARs occurring from the time of written informed consent, as well as SARs and SUSARs occurring from the first dose of investigational medicine product until end of the trial must be recorded on the dedicated Event Form in electronic Case Report Form (eCRF) within 24 hours of the research staff becoming aware of the event. Assessment of seriousness and causality for trials involving IMPs must be made by the PI or another authorized doctor. If an authorized doctor from the reporting site is unavailable, initial reports without causality assessment should be submitted to the Sponsor by a healthcare professional within 24 hours of becoming aware of the SAE, but must be followed up by medical assessment as soon as possible thereafter.

For each SAEs and SUSARs the following information will be collected:
- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action(s) taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug), in the opinion of the investigator.

Any change of condition or other follow-up information should be provided to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All SAEs that will occur either in EU or outside EU country (where the study will be conducted) and assigned by the PI or delegate (or following central review) and as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the applicable Regulatory Bodies in accordance with European and national regulations and requirements.
Details concerning the safety reporting process will be described in the Safety Management Plan prepared for the study.

Responsibilities

This section defines and summarize the responsibilities for reporting and reviewing toxicity and safety information arising from the trial.

Principal Investigator (PI, at each study site):
- Checking for ARs when participants attend for treatment/follow-up and recording in the appropriate Form(s) in the eCRF in a timely manner. All Events to be collected during the study should be recorded since Informed Consent Form is signed.
- Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness (if requested by Sponsor) using the Reference Safety Information approved for the trial.
- Ensuring that all SAEs and SARs (including SUSARs) are recorded in eCRF within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that ARs/SAEs/SARs/SUSARs are recorded and reported to the Sponsor in line with the requirements of the protocol.
- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
- Immediate review of all SUSARs.
- Reporting of suspected adverse reaction(s) related to the medicinal product(s) other than IMP to the Competent Authority or appropriate Marketing Authorization Holder in accordance with national regulations and requirements, if applicable.
- Cooperation in preparing the clinical sections of the Development Safety Update Report (DSUR), if applicable.

Sponsor:
- Central data collection and verification of ARs, SAEs, SARs and SUSARs according to the trial protocol.
- Reporting safety information to the independent oversight committees identified for the trial (Data Safety Monitoring Board) according to the established procedures.
- Expedited reporting of SUSARs to the applicable Regulatory Bodies in accordance with the European and national regulations and requirements and within required timelines.
- Notifying Investigators of SUSARs that occur within the trial.
- Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
- Preparing standard tables and other relevant information for the DSUR in collaboration with the PIs and ensuring timely submission to the CA and EC, if applicable.

Notification of deaths

All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the IMP, or an unrelated event. Events, which lead to death, will be reported according to the procedure of Serious Adverse Events reporting, as these events fulfill the SAE definition.

Pregnancy reporting

All pregnancies within the trial (either the trial participant or the participant's partner) should be reported to the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification. Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/fetus. If the outcome meets the serious criteria, this would be considered an SAE. Pregnancy will be monitored till delivery, and potential influence of IMP on pregnancy and child born to a pregnant trial subject, or to the partner of a male trial subject will be described and reported.

Overdose

In case of improper administration / overdose of IMP this situation will be reported to the Sponsor. This information will be placed in protocol deviation log, and will be considered in project report.
If an serious adverse event is associated with the overdose, this event will be handled according to the SAE reporting procedure, and the overdose will be fully described in the report form.

Reporting urgent safety measures

If any urgent safety measures are taken, it should be reported to the Sponsor. This event will be reported to the appropriate Regulatory Bodies together with the circumstances giving rise to those measures in accordance with national requirements.

The type and duration of the follow-up of subjects after adverse events

All patients, who are enrolled to the trial, will be observed for 90 days after randomization. If any adverse event which could be related with IMP or SAE occur, patient will be observed as long, as the event is resolved or a final outcome has been reached.

Development safety update reports

Sponsor will prepare and submit Development Safety Update Report(s) (DSUR(s)) to the CA and EC in accordance with the national regulations and requirements, if applicable. ICH guideline E2F on development safety update report should be followed for preparation of report(s) as far as applicable.

B) FOR COUNTRIES OUTSIDE EU

Adverse Event (ONLY study drug related AEs will be reported - ARs)

As an open label trial of anticoagulation, adverse events captured in this trial are those that are **plausibly related** to the investigational agent. Adverse events **plausibly related** to anticoagulant strategy include (but are not limited to) major bleeding and HIT.

Serious Adverse Events

All Serious Adverse Events (SAEs) will be reported (whether related to the study IMP or not) in this study.

Adverse Event Documentation

IMP-related AEs (ARs) must be recorded in the eCRFs. Documentation must be supported by an entry in the subject's file.

All SAEs must be recorded in eCRF.

SAEs believed to be **plausibly related** to the study drug will include (but are not limited to):

- Major bleeding
- Laboratory confirmed heparin-induced thrombocytopenia

As per ICH guidelines, a **Serious Adverse Event** is any AE occurring at any dose that**:**

- Results in death
- Is life-threatening
- Requires prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly or birth defect

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event that hypothetically might have caused death if it were more severe.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Important medical event: Any adverse event may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition.
Any death (regardless of cause) that occurs from the time of administration of the first dose of study therapy until 28 days after the final administration of the study drug, and any death occurring after this time that is judged at least possibly related to prior treatment with the study drug, will be promptly reported

Reporting Serious Adverse Events

All serious adverse events (SAE) defined as per ICH guidelines (see above) must be recorded on case report forms. Such events must be reported by using the SAE form and must be submitted to Mount Sinai Heart. **All** SAEs should be reported within 24 hours of becoming aware of the event.

Serious Adverse Event Reporting Instructions
All serious adverse events must be reported as follows:
Within 24 hours: Report initial information (on trial specific SAE report form) by fax and e-mail to: FREEDOM.COVID@mssm.edu

Mount Sinai Heart
1 Gustave Levy Place
Box 1030
New York, NY 10029
Phone: 212-241-7911
Fax: 212-423-9488

The initial information should always contain:

- Name of Reporter/Investigator,
- Subject Identification,
- Adverse Event Term,
- Study Drug Dose and Start/Stop Dates

Procedure for Expedited Reporting

Responsibility for Reporting Serious Adverse Events to Regulatory Agency

Mount Sinai Heart will provide expedited reports of SAEs to the regulatory authorities according to applicable guidelines and regulations (including the 7-day notification for death and life-threatening events), i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

Responsibility for Reporting Serious Adverse Events to Sponsor

Mount Sinai Heart will be responsible for submitting SAE reports (Initial and/or Follow-up reports) received from the sites, to the Sponsor within 24hrs after receipt of the SAE form at Mount Sinai Heart.

Reporting Serious Adverse Events to Local Research Ethics Boards

Mount Sinai Heart will notify all Investigators on this study of all Serious Adverse Events that are reportable to regulatory authorities in the United States. This includes all serious events that are unexpected and related to protocol treatment. Investigators must notify their Research Ethics Boards (IRBs) and file the report with their Investigator Site File. Documentation that serious adverse events (SAEs) have been reported to IRBs must be kept on file at Mount Sinai Heart. Documentation can be any of the following:

1. letter from the IRB acknowledging receipt
2. stamp from the IRB, signed and dated by IRB chair, acknowledging receipt
3. letter demonstrating the SAE was sent to the board

All expedited serious adverse events occurring within a center should also be reported to local IRBs/ECs as per country-specific requirements.

DATA SAFETY AND MONITORING PLAN

Safety Monitoring

All investigators must report all serious adverse events to the Data and Clinical Coordinating Center and their individual Institutional Review Boards (IRBs)/Research Ethics Boards or Committees (REBs) in compliance with their institutional policies, local regulations and study specific process documents (if applicable).

A Data Safety and Monitoring Board (DSMB) is in place for this study. In addition to ad hoc communications with the DSMB members on an as needed basis, the study statisticians will provide summary data, clinical events, and SAEs to the board members for review at formal DSMB meetings.

The DSMB will have the prerogative to halt enrollment or temporarily or permanently stop the study should evidence arise, in their judgement, that study participants are at increased risk of specific events (e.g., bleeding events and heparin-induced thrombocytopenia). However, the final decision with regard to the study continuation always lays with the study Sponsor. Data on these particular SAEs will be provided to the DSMB at the scheduled meeting as well as at any time at their request.

DSMB responsibilities and workflow will be described in details in the charter.

Data Monitoring

The DCC will employ a risk-based approach to monitoring for this study. This will be accomplished

via centralized or remote monitoring of data via the EDC with a focus on safety,study endpoints, data completion and data outliers. Clinical centers will provide de-identified source documentation to the DCC for remote monitoring. The DCC will generate performance metrics to analyze site characteristics such as recruitment rates and timeliness of data entry. This will allow the DCC to identify trends across sites and to address low-performing sites appropriately.

All study data will be entered in a dedicated Electronic Data Capture system. Study personnel requiring access will have their own Login/Password. Access to clinical study information will be based on individuals' roles and responsibilities. The EDC supports efficient data collection and management and facilitates rapid data closure. A strong advantage of web-based design is that the DCC has immediate and ongoing access to the data from all clinical centers so that queries can be generated and distributed to the sites in real-time and the frequency of missing data and data entry errors can be reduced. The EDC will be used for the centralized monitoring planned for this study.

Study Management and Governance

Executive Committee and Steering Committee

The Executive Committee will consist of the Principal Investigators, as well as representatives from the CCC, DCC and eCRF. The Executive Committee is responsible for the execution of the trial according to the study protocol. A Steering Committee will be responsible for providing clinical and methodological guidance, including overall study design, execution, analysis, and publication of the main study results. The Steering Committee will oversee the management of the clinical trial sites and will also act as the Publication Committee. While the study is ongoing, the Committee will approve any protocol amendment that may become necessary and is responsible for maintaining the scientific integrity of the study.

Clinical Coordinating Center

The Clinical Coordinating Center (CCC) will be directed by Mount Sinai Heart and Dr. Valentin Fuster.

Data Coordinating Center

The Data Coordinating Center (DCC) is a collaboration between the International Center for Health Outcomes and Innovation Research *(InCHOIR),* Department of Population Health Science & Policy, Icahn School of Medicine at Mount Sinai (under the direction of Professors Annetine Gelijns and Emilia Bagiella) and the Cardiovascular Research Foundation (under the direction of Dr. Ori Ben-Yehuda).

Data and Safety Monitoring Board (DSMB)

To meet the study's ethical responsibility to its study participants, an independent data safety monitoring board (DSMB) will monitor results during the study. The board consists of physicians and a biostatistician who have no formal involvement or conflict of interest with the subjects, the drug manufacturers, the investigators, the DCC or the clinical sites. The DSMB will review interim summary results of the accumulating data from the Event Adjudication Committee periodically as described in the DSMB charter. These data include adverse events (e.g., bleeding and other primary outcome events) and mortality. The DSMB will act in a senior advisory capacity to the DCC and the study Steering Committee. They will communicate their findings directly to the DCC. The DSMB will be unblinded but will prepare their interim reports in a form that will keep the DCC and Steering Committee blinded unless a strong recommendation is made by the DSMB to revise the study protocol that requires the study leadership be unblinded to consider the recommendation. The clinical centers will have no contact with the members of DSMB and no voting member of the committee may participate in the study as an investigator. The DSMB will approve the DSMB charter outlining responsibilities and will operate under its rules.

Event Adjudication Committee

The scope of the Event Adjudication Committee (EAC) is to review source documents and to adjudicate clinical events and Serious Adverse Events according to the charter. The individuals who will serve on the committee will be appointed by the DCC. The EAC will meet as needed to adjudicate adverse events and outcomes data for each subject enrolled.

Clinical Sites and Investigators

The roles and responsibilities of the Investigators and Clinical Sites include, but are not limited to (a) assuring that the trial is conducted according to the Protocol and MOP; (b) identifying, recruiting, and enrolling subjects; (c) obtaining informed consent from each subject and protecting their rights; (d) collecting and entering study data into the EDC, and following subjects through study completion; (e) collecting and filing source documentation; (f) assuring regular IRB/REB/EC review; and (g) maintaining communication with the DCC.

ANALYTICAL PLAN

General considerations

The primary objective of this trial is to determine the effectiveness and safety of different anticoagulation regimens in patients hospitalized with confirmed COVID-19.

The primary efficacy outcome endpoint is time to first event rate within 30 days of randomization of the composite of all-cause mortality, intubation requiring mechanical ventilation, systemic thromboembolism (including pulmonary emboli) confirmed by imaging or requiring surgical intervention OR ischemic stroke confirmed by imaging. The primary safety endpoint is the in-hospital occurrence of BARC 3 or 5 bleeding. Secondary outcomes of this study will be assessed at 30 and 90 days after randomization and include: a) all-cause mortality; b) CV death; c) Intubation and mechanical ventilation; d) all Myocardial infarction (according to the 4th universal definition, types 1, 2,or 3); e) pulmonary emboli confirmed by imaging or autopsy; f) stroke (all, ischemic and hemorrhagic) confirmed by imaging or autopsy; g) Systemic thromboembolism confirmed by imaging or requiring surgical intervention; h) Deep vein thrombosis with confirmation on imaging; i) Organ support-free days; j) ICU-free days; k) Need for non-invasive mechanical ventilation or high flow nasal cannula; l) Ventilator-free days (days alive free of mechanical ventilator support); m) Hospital-free days (days alive out of hospital assessed through 90 days post randomization); n) BARC 2, 3 or 5 bleeding; o) Laboratory confirmed Heparin induced thrombocytopenia (HIT).

The statistical analysis plan of the trial will follow the following close test procedure plan that will control the type I error:

Level 1: We will first assess whether the full-dose enoxaparin and apixaban arms combined is superior to prophylactic enoxaparin with respect to the primary effectiveness outcome. If the null hypothesis is rejected in this test, then we will proceed to the next level. If level 1 is passed, then we will also test the individual therapeutic regimen against the prophylactic dose as an exploratory analysis.

Level 2: The non-inferiority of apixaban compared to full-dose enoxaparin will be tested for the primary effectiveness outcome. If the non-inferiority analysis passes the acceptance criterion we will proceed to the next level.

Level 3: The superiority of apixaban compared to full-dose enoxaparin will be tested on the primary safety outcome of BARC 3 or 5 bleeding. If the null hypothesis is rejected in this test, we will proceed to the next level.

Level 4: If superiority of apixaban is established with respect to safety in level 3, then therapeutic full dose of apixaban will be tested against therapeutic full dose enoxaparin for superiority of effectiveness.

Power and sample size

The sample size for the trial is based on obtaining at least 80% power for the level 2 non-inferiority comparison of apixaban vs. full dose enoxaparin. The sample size is based on the composite primary endpoint, which assumes an event rate of 20.0% in each of the enoxaparin and the apixaban arms. A randomized sample size of 1200 eligible patients in each arm with 30-day data would provide 80% power for establishing non-inferiority. The test statistic for this computation uses a relative non-inferiority margin of 20% (4% absolute difference) at one-sided α=0.025 using a log-rank test.

Therefore, the study is designed to enroll 1200 patients in each of the three arms for a total of 3600 patients. This sample size will also provide 80% power to determine superiority of apixaban vs. full dose enoxaparin on the safety end point of BARC 3 or 5 bleeding assuming that the proportion of patients with bleeding will be 5.6% in the full dose enoxaparin group and 3.2% in the apixaban group using a test for two independent proportion at the two-sided alpha=0.05.
Power for all study endpoints is summarized in the table below:

TABLE 2. Study endpoints

Hierarchy	Primary Comparison	Outcome	NI Margin	Superiority Margin	Power	Total Sample size in analysis
Level 1	Therapeutic enoxaparin + Therapeutic apixaban **is superior to** Prophylactic LMWH	Primary effectiveness outcome	N/A	20% minimum assuming 25% event in reference group	>95%	3600 (2:1 comparison)
Level 2	Therapeutic apixaban is **non-inferior to** therapeutic enoxaparin	Primary effectiveness Outcome	20% relative margin on assumed 20% event rate in reference group	N/A	80%	2400 (1:1 comparison)
Level 3	Therapeutic apixaban **is superior to** therapeutic enoxaparin	Primary safety outcome BARC 3 or 5 bleeding	N/A	42.8% relative reduction from 5.6% in LMWH arm	80%	2400 (1:1 comparison)

Level 4	Therapeutic apixaban **is superior to** therapeutic enoxaparin	Primary effectiveness Outcome	N/A	20% minimum improvement assuming 20% event rate in reference group	>85%	3600 (1:1comparison)
	All pairwise comparisons	Secondary endpoints – continuous measures	N/A	0.15 standard deviations	> 90%	3600 (1:1 :1 comparison)
	All pairwise comparisons	Categorical	N/A	Minimum. OR = 0.64 for any outcome with prevalence of 0.1 in reference group	85%	3600 (1:1:1 comparison)

Interim Analysis

The objectives of interim monitoring are to (1) monitor for safety, (2) track participant accrual rates, and (3) monitor the primary and secondary outcomes for early evidence of efficacy, harm or futility. To accomplish this, summaries of data quality, accrual, adherence, distribution of baseline factors, safety, study endpoints and other analyses as requested will be prepared for review by the DSMB.

A single interim analysis and one final analysis are planned for this trial, for a total of two analyses. The interim analysis will be conducted when half of the total number of patients will have reached the primary effectiveness endpoint of the composite of all-cause mortality, intubation requiring mechanical ventilation or systemic thromboembolism by 30 days post randomization. This interim analysis will evaluate the level 1 superiority hypothesis of the combined therapeutic AC therapies (apixaban and enoxaparin) vs the prophylactic enoxaparin arm. We will use an alpha-spending O'Brien-Fleming sequential procedure as a guideline for decision-making. At the interim analysis the value of the test statistic will be compared with the alpha spending function critical value. The p-values for the interim monitoring analysis and the final analysis are, 0.0031, and 0.05, respectively.

Stopping Rules

Should the interim analysis provide strong evidence of early efficacy of the full-dose therapeutic regimen(s), the DSMB may recommend closing the prophylactic arm of the trial. A futility boundary for the level 1 hypothesis is not considered in this trial as an early termination for futility in level 1 would prevent full ascertainment of the bleeding events.

A decision to stop the trial for safety reasons will be based on the result of the interim analysis as well as other supporting evidence that any arm of the trial poses unacceptable risk to patients. Should the safety data suggest that the rate of primary endpoint events is significantly higher in one group than the others at the interim analysis, additional analyses and sub-group analyses will be conducted to supplement this information including investigation of all adverse events and other ad-hoc pertinent analyses as discussed and agreed upon with the DSMB.

Patients with suspected COVID-19 who are deemed not to be positive after the return of the first PCR (preferred) or antigen test will be terminated and will be replaced to keep the total of 3600 patients with confirmed COVID-19.

Analysis Plan
The primary analysis will be an intent-to-treat analysis that will include all randomized study participants regardless of treatment actually received or follow-up schedule. All hypothesis testing will be conducted using two-sided tests at a α=0.05.

Patient Disposition
A CONSORT flow diagram will summarize the numbers of patients randomized, who received each treatment (with details), and completed follow up. The number and reasons for patients lost to follow-up will be presented as well as patients who were not treated according to the arm to which they were randomized. The number of patients who were initially randomized but subsequently had a negative PCR or antigen test and were thus "de-randomized" and treated per local standard of care (not included in the final 3600 patients) will also be reported.

Univariate Analysis
All baseline characteristics and outcome measures will be described in a univariate analysis. For continuous variables means and standard deviations will be calculated. For discrete and dichotomous variables, contingency tables will be used.

Analysis of the Primary Effectiveness Endpoint
The primary effectiveness outcome endpoint is time to first event rate within 30 days of randomization of the composite of all-cause mortality, intubation requiring mechanical ventilation, systemic thromboembolism (including pulmonary emboli) confirmed by imaging or requiring surgical intervention OR ischemic stroke confirmed by imaging. The patient will be deemed to have experienced the endpoint when the first of the components occurs. Otherwise, the patient will be censored for analysis on the last date known alive and event free. Overall time to first event will be defined as the number of days between randomization and the occurrence of an event. Time to first event will be estimated using Kaplan-Meier curves. The endpoint test on the event rate difference will be performed as a one-sided non-inferiority test at alpha = 0.025, using the non-inferiority margin of a relative 20%. The test will be performed by computing the two-sided 95% confidence limit for the event risk ratio. The acceptance criterion is that the upper confidence limit be ≤1.2.

Analysis of Primary Safety Endpoint
The primary safety endpoint of In-hospital BARC 3 or 5 bleeding will be tested using a test for two independent proportions. Rates of bleeding between groups will be compared using Poisson regression.

Analysis of Secondary Endpoints
All-cause mortality, CV death, Intubation and mechanical ventilation, all myocardial infarction (according to the 4th universal definition, types 1, 2, or 3), pulmonary emboli confirmed by imaging or autopsy, all stroke (and separately ischemic and hemorrhagic stroke) confirmed by imaging or autopsy, systemic thromboembolism confirmed by imaging or requiring surgical intervention and deep vein thrombosis with confirmation on imaging will be analyzed will be analyzed at 30 and 90 days after randomization in time to first event analysis using the log-rank test in superiority

analyses of apixaban vs. full dose enoxaparin vs. prophylactic enoxaparin statistic in the manner of the primary outcome. Competing risks analysis with death as a competing risk using the methods of Gray and Fine will be used to calculate cause-specific cumulative incidence. Organ support-free days, ICU-free days and hospital-free days (days alive out of hospital assessed through 90 days post randomization) will be analyzed using the Mann-Whitney test. Patients who die will be assigned the worst ranks in order according to their time of death. Need for non-invasive mechanical ventilation or high flow nasal cannula, ventilator-free days (days alive free of mechanical ventilator support), , BARC 2, 3 or 5 bleeding , laboratory confirmed Heparin induced thrombocytopenia (HIT) will be analyzed using a test for two independent proportions.

All tests will be conducted using a two-sided alpha level at 0.05 and no adjustment for the alpha level will be performed for the analysis of the secondary endpoints.

Missing Data

Given the short follow-up time for the assessment of the primary outcome and the nature of the primary outcome events (most of which will occur during the initial hospitalization), we anticipate that we will be able to assess the primary outcome on all patients with minimal drop-out. Patients who drop-out, withdraw or are lost to follow-up at the time of the assessment will be censored in time to event analyses as of the time they were last assessed. Missing data will not be imputed in the analyses of the secondary endpoints.

Planned Subgroup Analysis

Exploratory subgroup analyses will be conducted only with respect to the primary outcome. Treatment effect in each subgroup will be presented along with the p value for the interaction term in the model. Forest plots will be used to illustrate the estimated treatment hazard ratio and the corresponding 95% confidence interval. The intent of the subgroup analysis is to determine whether there might be heterogeneity of treatment effects based on subgroup. There will be no adjustment made for multiple testing since this is meant to ascertain potential treatment heterogeneity rather than to test specific hypotheses about each subgroup.

We will conduct exploratory subgroup analyses based on the following strata:

3) Age
4) Sex
5) Body Mass Index
6) History of Diabetes Mellitus
7) Geography
8) Renal function
9) Baseline biomarkers
10) History of Hypertension
11) History of Heart Failure
12) History of lung disease
13) Tobacco history
14) Baseline WBC
15) Baseline Hemoglobin
16) CHA2DS2-VASc Score
17) Severity of COVID-19 infection at baseline
18) Duration of anticoagulation therapy during hospitalization

Additional subgroup analyses will be conducted on variables of interest as long as the prevalence of the condition is at least 15% in the sample.

PUBLICATION POLICES AND DISCLOSURE OF DATA

ETHICS

Ethics Board Approval

All study sites are required to obtain local ethics approval of the protocol and consent form by the respective IRB/EC prior to commencement of the clinical trial at each site and Regulatory Bodies approval in accordance with European and national regulations and requirements.

Continuing approval: Annual (or as required by the REB/IRB/EC) re-approval may be required for as long as subjects are being followed on protocol. It will be investigator's responsibility to apply for and obtain the re-approval.

Amendment: All protocol amendments will be confirmed in writing and submitted, as appropriate, for review by the REB/IRB/EC and Regulatory Authorities. Amendments will be reviewed and approved by applicable Regulatory Authorities prior to central implementation of the amendment, and by REB/IRBs/ECs prior to local implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial subjects or when the change(s) involves only logistical or administrative aspects of the trial.

RECORD ACCESS AND MAINTENANCE OF STUDY RECORDS

Documentation of Subject's Participation

A statement acknowledging the participation of a subject in this clinical trial must be documented in the subject's medical records along with the signed ICF.

Regulatory Requirements

Subject Confidentiality and Access to Source Data/Documents

Any research information obtained about the subject in this study will be kept confidential. A subject will not be identified by name, only by his/her initials. The subject's name or any identifying information will not appear in any reports published as a result of this study.

However, information obtained from an individual subject's participation in the study may be disclosed with his/her consent to the health care providers for the purpose of obtaining appropriate medical care.

A subject's name will not be given to anyone except the researchers conducting the study, who have pledged an oath of confidentiality. All identifying information will be kept behind locked doors, under the supervision of the study Principal Investigator and will not be transferred outside of the hospital.

A subject may take away his/her permission to collect, use and share information about him/her at any time. If this situation occurs, the subject will not be able to remain in the study. No new information that identifies the subject will be gathered after that date. However, the information about the subject that has already been gathered and transferred may still be used and given to others as described above in order to preserve the scientific integrity and quality of the study.

Confidentiality of the Study

Data generated as a result of this study will be available for inspection on request by local health authority auditors, the Sponsor's Study Monitors and other personnel (as appropriate) and by the IRB/EC and Regulatory Authorities. The Investigator shall permit sponsor, authorized agents of the sponsor and regulatory agency employees to enter and inspect any site where the study intervention or records pertaining to the study intervention are held, and to inspect all source documents, unless there are entry

restrictions into the hospital sites due to the pandemic. The protocol and other study documents contain confidential information and should not be shared or distributed without the prior written permission of sponsor.

Registration of Clinical Trial

Prior to the first subject being registered/enrolled into this study, the Sponsor will be responsible for ensuring that the clinical trial is registered appropriately to remain eligible for publication in any major peer-reviewed journal, adhering to the guidelines put forth by the International Committee of Medical Journal Editors (ICMJE).

DATA REPORTING

Maintenance of Study Records

To enable evaluations and/or audits from Regulatory Authorities, or the Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eCRFs and hospital records), all original signed informed consent forms, source documents, and detailed records of treatment disposition. The Investigator should retain these records for 25 years after study close-out as required by FDA regulations.

QUALITY ASSURANCE AND QUALITY CONTROL

As per the ICH Guidelines of Good Clinical Practice, the sponsor will be responsible for implementing and maintaining quality assurance and quality control systems.

ADMINISTRATIVE PROCEDURES

Amendments to this Protocols

Modifications of this protocol is only possible by approved protocol amendments authorized by the Sponsor. Where required, all protocol amendments will be approved by the IRB/EC/country specific Regulatory Authority prior to implementation. The Investigator must not implement any deviation from, or change to the protocol, except where it is necessary to eliminate an immediate hazard to trial subject or when the change(s) involves only logistical or administrative aspects of the trial.

Protocol Deviations and Violations

All violations or deviations are to be reported to the site's IRB/EC (as per IRB/EC guidelines) for each sub-study, as applicable. All IRB/EC correspondence is to be forwarded to Mount Sinai Heart.

Premature Discontinuation of the Study

The Sponsor reserves the right to discontinue any trial for any reason but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigators must contact all participating subjects immediately after notification. Follow-up for subjects will be assured and, where required by the applicable regulatory requirement(s), the relevant Regulatory Authority (ies) will be informed.

The IRB/EC will be informed promptly and provided with a detailed written explanation for the termination or suspension.

As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

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