A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic and Additional Strategies in Hospitalized Adults with COVID-19

Short Title: ACTIV-4 ACUTE (AC-INPT)

ClinicalTrials.gov Number: NCT04505774

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Protocol Revision History:

Version Number	Status/Summary of Revisions Made	Version Date
1.0	Appendix 1 outlined possible example scenarios for adaptive design. Arms A and B included.	August 21, 2020
1.1	• Section 5.1 Inclusion Criteria: Broadened type of SARSCoV2 tests, in accordance with NIH recommendations • Appendix 1: Revised to reflect the master protocol current state of arms • Appendix 1.1: Adds arm C • Appendix 1.2: Adds arm D • Appendix 2: Neuroimaging detailed criteria for hemorrhagic stroke conversion removed to be refined in the event charter • Appendix 2: The method of calculation of ventilator-free days was removed from the description of the primary endpoint, where it is not relevant. The definition will appear in a manual. • Appendices 1 and 3: New exclusion for Arm A for patients who require ICU level of care at screening, based on DSMB review and NHLBI Determination, as of Dec 19. 2020 • New exclusion for Arm B for patients who do not require ICU level of care at screening, based on DSMB review and NHLBI Determination, as of Jan 21. 2021 • Appendix 3: Added recommendation to enroll patients with elevated d-dimer • Appendices 3, 4: Clarified quality of life assessment on schedule of assessments • Appendix 5: Clarification on blood collection window • Appendix 7 Added for arm C • Section 13.3.2: Added investigator *"designee"* to consent process • Appendix 8: Added for arm D	February 01, 2021
1.2	• Added additional study personnel to contacts section • Study duration changed to approximately 2 years • Added potential follow-up after one year • Added Quality of Life and Functional Status assessment and recording of hospital readmissions in the master protocol study follow-up (Section 7) • Exclusion criteria updated to include breastfeeding • Added secondary outcomes • Section 1.1: Added background information for additional treatments. • Appendix 1: Revised to refer to the Manual of Operations for the current state of arms and to the statistical analysis plan for the current analytic plan. Removed appendices 1.1-1.3. • Appendices 3, 4 and 8: Retired	September 14, 2021

	• Appendix 9: Added for arm E • Appendix 10: Added for arm F	
1.2	• Appendix 1: Added definition of domain to clarify the difference between domain and arms • Appendix 9: Added clinical use of crizanlizumab as an exclusion	October 19, 2021

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Statement of Compliance

In the United States this study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") and the General Data Protection Regulations (GDPR) will be applied only to the extent that it is compatible with FDA and DHHS regulations.

Outside of the United States this study will be conducted according to local legal and regulatory requirements and regulations, ICH guidelines, and GDPR guidelines as applicable.

The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations (if applicable), and ICH E6(R2) GCP guidelines.

Version Date: Oct 19. 2021

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Signature of Principal Investigator Date

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Printed Name of Principal Investigator

_____

Name of Facility

_____

Location of Facility (City, Country)

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List of Abbreviations

AE	Adverse Event/Adverse Experience
ARDS	Acute Respiratory Distress Syndrome
ASA	Acetylsalicylic Acid/Aspirin
AT	Arterial Thrombosis
BMI	Body mass index
CFR	Code of Federal Regulations
CNS	Central Nervous System
CrCl	Creatinine Clearance
COVID-19	Coronavirus Disease
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DIC	Disseminated Intravascular Coagulation
DKA	Diabetic Ketoacidosis
DSMB	Data and Safety Monitoring Board
DVT	Deep Vein Thrombosis
ECMO	Extracorporeal Membrane Oxygenation
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
FFR	Federal Financial Report
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GI	Gastrointestinal
HFNO	High-flow Nasal Oxygen
HIPAA	Health Insurance Portability and Accountability Act
HIT	Heparin Induced Thrombocytopenia
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IRB	Institutional Review Board

ISM	Independent Safety Monitor
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent to Treat
IV	Invasive Ventilation
JAK	Janus kinase inhibitors
KDIGO	Kidney Disease Improving Global Outcomes
LAR	Legally Authorized Representative
MI	Myocardial Infarction
MOP	Manual of Procedures/Operations
N	Number (typically refers to participants)
NIH	National Institutes of Health
NIV	Non-invasive ventilation
OHRP	Office for Human Research Protections
OHSR	Office of Human Participants Research
OSFD	Organ Support Free Days
PE	Pulmonary Embolism
PI	Principal Investigator
POCUS	Point of Care Ultra Sound
PTT	Partial Thromboplastin Time
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SCD	Sickle cell disease
SGLT2i	Sodium-glucose transport protein 2 inhibitor
SOC	Standard of Care
SOP	Standard Operating Procedure
US	United States
VTE	Venous thromboembolism
VWF	Von Willebrand Factor
WHO	World Health Organization

Master Protocol Summary

Title	A Multicenter, Adaptive, Randomized, Open Label Controlled Platform Trial of the Safety and Efficacy of Antithrombotic and Additional Strategies in Hospitalized Adults with COVID-19
Short Title	ACTIV-4 ACUTE
Brief Summary	This is a randomized, open label, adaptive platform trial to compare the effectiveness of antithrombotic and additional treatment strategies for prevention of adverse outcomes in COVID-19 positive inpatients
Objectives	**1.** To determine the most effective antithrombotic and additional treatment strategies for increasing the number of days free of organ support and reducing death. **2.** To determine the most effective antithrombotic and additional treatment strategies on the composite endpoint of death, pulmonary embolism (PE), myocardial infarction (MI), ischemic stroke, or other systemic arterial thrombosis (AT). **3**. To assess the safety of antithrombotic and additional treatment strategies. **4.** To compare the effect of antithrombotic and additional treatment strategies on the endpoint of all-cause mortality in the study population. Assessment of efficacy and safety will yield information of the risk/benefit of different treatment strategies in the study population. It will also yield information on outcomes specific to under-represented minority populations, specifically African- and Hispanic-descent persons.
Methodology	Adaptive Randomized Platform Trial

Endpoints	Primary Endpoint: 21 Day Organ Support Free Days, which is defined as the number of days that a patient is alive and free of organ support through the first 21 days after trial entry. Organ Support is defined as receipt of invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, or ECMO support, with death at any time (including beyond 21 days) during the index hospitalization assigned -1 days. Secondary Endpoints: • Categorization of the primary endpoint into a three-level ordinal outcome (Death, invasive mechanical ventilation without death, neither invasive mechanical ventilation nor death) • Categorization of the primary endpoint into a three-level ordinal outcome (Death, organ support (any respiratory or cardiovascular) without death, neither organ support nor death) (for moderate illness severity at enrollment) • Days free of death and respiratory and cardiovascular organ support and renal replacement therapy (RRT) during Index Hospitalization through Day 28. • Composite endpoint of death, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke at hospital discharge or 28 days, whichever occurs first. Other Secondary Endpoints: Acute kidney injury. Individual endpoints comprising the primary and secondary endpoint components; death during hospitalization, WHO clinical scale and 90 day mortality Safety Endpoints: Intervention specific
Study Duration	Approximately 2 years
Participant Duration	Hospital duration with periodic contact post-discharge, including at 90 days, and potentially at approximately 1 year and thereafter
Duration of assigned treatment strategy	During hospitalization (unless otherwise specified in description of arm)
Population	Adult patients hospitalized for COVID-19
Study Sites	Approximately 400 sites
Number of participants	The sample size is described in each arm-specific appendix.
Description of Study Agents	This platform trial allows for multiple therapies to be investigated in this trial over time. The trial is governed by a Master Protocol that describes the trial design, endpoint collection, primary endpoint, and inclusion/exclusion criteria. Different therapies, referred to as arms, are detailed in arm-specific appendices. These arm-specific appendices work in a modular fashion as arms are removed and added to the platform trial.
Key Procedures	Observation during hospitalization, contact at 90 days post-enrollment, and collection of standard of care laboratory results. Ancillary biobanking will be completed in consenting patients at capable centers.

Statistical Analysis	Inferences in this trial are based on a Bayesian statistical model, which considers the variation in outcomes by site, disease state, time, and arm of the trial. The specific analyses for each arm, including interim analysis schedule, are specified in each arm-specific appendix, and associated statistical analysis plan

1 Introduction, Background Information and Scientific Rationale

1.1 Background Information, Significance and Relevant Literature

The severe acute respiratory syndrome coronavirus 2, which causes the highly contagious coronavirus disease 2019 (COVID-19), has resulted in a global pandemic.

The clinical spectrum of COVID-19 infection is broad, encompassing asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure and death. The risk of thrombotic complications is increased, even as compared to other viral respiratory illnesses, such as influenza (1-4). A pro-inflammatory cytokine response as well as induction of procoagulant factors associated with COVID-19 has been proposed to contribute to thrombosis as well as plaque rupture through local inflammation (5). Patients with COVID-19 are at increased risk for arterial and vein thromboembolism(6), with high rates observed despite thromboprophylaxis (7). Autopsy reports have noted micro and macro vascular thrombosis across multiple organ beds consistent with an early hypercoagulable state (8).

Notably, in COVID-19, data in the U.K. and U.S. document that infection and outcomes of infection are worse in African and Hispanic descent persons than in other groups. The reasons for this are uncertain.

Viral Infection and Thrombosis

A large body of literature links inflammation and coagulation; altered hemostasis is a known complication of respiratory viral infections (9-11). Procoagulant markers are severely elevated in viral infections. Specifically, proinflammatory cytokines in viral infections upregulate expression of tissue factor, markers of thrombin generation, platelet activation, and down-regulate natural anticoagulant proteins C and S (11).

Studies have demonstrated significant risk of deep venous thrombosis (DVT), pulmonary embolism (PE), and myocardial infarction (MI) associated with viral respiratory infections (10,12). In a series of patients with fatal influenza H1N1, 75% had pulmonary thrombi on autopsy (a rate considerably higher than reported on autopsy studies among the general intensive care unit population (13). Incidence ratio for acute myocardial infarction in the context of Influenza A is over 10 (14). Severe acute respiratory syndrome coronavirus-1 (SARS CoV-1) and influenza have been associated with disseminated intravascular coagulation (DIC), endothelial damage, DVT, PE, and large artery ischemic stroke (11,15). Obi et al. found that patients with Influenza H1N1 and acute respiratory distress syndrome (ARDS) had a 23.3-fold higher risk for pulmonary embolism, and a 17.9-fold increased risk for deep vein thrombosis (16). Compared to those treated with systemic anticoagulation, those without treatment were 33 times more likely to suffer a VTE (16).

Thrombosis, both microvascular and macrovascular, is a prominent feature in multiple organs at autopsy in fatal cases of COVID-19 (8). Thrombosis may thus contribute to respiratory failure, renal failure, and hepatic injury in COVID-19. The number of megakaryocytes in tissues is higher than in other forms of ARDS, and thrombi are platelet-rich based on specific staining. Thrombotic stroke

has been reported in young COVID-19 patients with no cardiovascular risk factors (17). Both arterial and venous thrombotic events have been seen in increasing numbers of hospitalized patients infected with COVID-19. The incidence of thrombosis has ranged from 10 to 30% in hospitalized patients; however, this varies by type of thrombosis captured (arterial or vein) and severity of illness (ICU level care, requiring mechanical ventilation, etc.).

D-dimer, a biomarker of fibrin formation and degradation, is elevated in conditions associated with thrombosis, and has been strongly associated with increased mortality among patients with COVID-19 (1, 2, 3, 6, 7). In a retrospective analysis of 191 patients with COVID-19, Zhou et al. found that non-survivors were more likely to have D-dimer levels > 1 ug/mL than survivors (81% v 24%) (5). Similarly, in a study of 183 patients, Tang et al. noted that non-survivors had significantly higher D-dimer values on admission than survivors (2.12 v 0.61 ug/mL, P < 0.001) (6). In a retrospective study, patients with COVID-19 and D-dimer values > 6-fold upper limit of normal had lower 28-day mortality when treated with prophylactic anticoagulation compared with no anticoagulation (32.8% v 52.4%, p=0.017) (8). Data suggest a strong association between D-dimer and the outcomes of ICU intubation and all-cause mortality, and the association between D-dimer and (1) mortality, (2) critical illness, (3) acute kidney injury, and (4) thrombotic risk is increased at a D-dimer between 1X to 2X the upper limit of normal. Thrombosis is also increased in those with elevated inflammation indexed by C-reactive protein level (20). Preliminary data suggest that platelet activity is increased in COVID-19(18) and that biomarkers of platelet activity correlate with the incidence of death or thrombosis in hospitalized patients with COVID-19. Platelet-fibrin thrombi have been observed in alveolar capillaries, where they may affect gas exchange (8), and in the renal peri-tubular capillaries, where they may contribute to acute tubular necrosis and renal dysfunction. Consistently, autopsy findings demonstrate an increase in the number of circulating megakaryocytes outside the bone marrow and lung. Finally, thrombotic events have been noted – even among patients treated with full dose anticoagulation.

There may be racial and ethnic differences in response to COVID 19 infection. It is hypothesized that antithrombotic interventions being tested will benefit all patients, including those who are disproportionately affected. (21–25, 26).

The ACTIV-4 ACUTE investigators postulate that strategies designed to reduce the need for organ support, including antithrombotic, anti-inflammatory and other therapies that offer other mechanisms for organ protection, will improve clinical outcomes in COVID-19 patients. This protocol intends to define the optimal regimen in an adaptive randomized trial of patients hospitalized with COVID-19 at risk for adverse clinical outcomes. The primary outcome will be the number of days free of organ support within 21 days after randomization. This primary outcome was selected because it is pragmatic and yet objective and clinically relevant. Organ support free days is defined by days in which patient is not on invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, or ECMO support (see Appendix 2), with death assigned the value of –1 days.

Additional treatment strategies

Data from the multiplatform randomized controlled trial (mpRCT) demonstrated that (1) therapeutic dose anticoagulation with heparin was not beneficial in improving clinical outcomes compared to standard of care prophylactic dose heparin in severely ill (ICU level of care) patients, and (2) therapeutic dose anticoagulation with heparin was beneficial in improving organ support free days compared to standard of care prophylactic dose heparin in moderately ill (hospitalized and not requiring organ support) patients. (27, 28) However, there remains significant residual risk for adverse clinical outcomes and excess mortality for severely ill as well as moderately ill patients.

Antithrombotic regimens that are shown to be efficacious will be combined in clinical practice with other agents to treat COVID-19 hospitalized patients. This adaptive platform trial will test other promising agents when added to proven therapies, such as heparin. The rationale and risks for each agent will be included in the arm-specific appendix.

1.1.1 Adaptive Design

This platform trial will have multiple arms, which may be dropped or added as the platform trial progresses. Sample size will be flexible: the trial will be stopped for efficacy or futility based on pre-determined statistical thresholds as defined in the arm-specific appendices. Each arm will have an adaptive component for determinations of futility or success.

1.2 Potential Risks & Benefits

See arm-specific Appendices for details

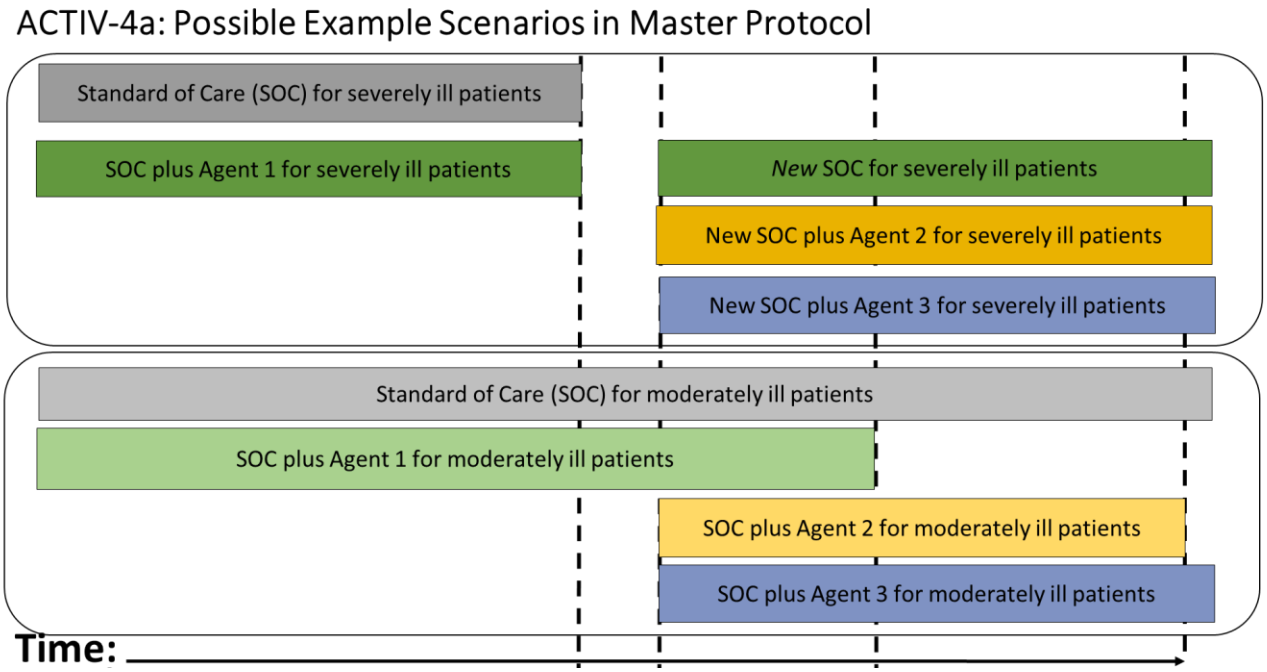
2 Study Design

2.1 Overall Study Design

This trial design is built as a process – with the possibility of multiple interventions being investigated simultaneously or in series. The trial is designed to be flexible, and these flexible aspects are planned as part of the protocol. This trial may incorporate a flexible number of interventions, and the number of interventions may evolve as the science evolves. Intervention arms will be added or dropped based on criteria defined in arm-specific appendices. Co-enrollment in other trials is permitted as long as the other trial does not test agents with that present a safety concern or scientific contraindication. Arm-specific appendices will address concerns about co-enrollment.

2.2 Randomization

Randomization assignments are at the participant level and are assigned at baseline. Randomization will be stratified by enrolling site and may also be stratified by severity of illness and/or other arm-specific criteria. In general, allocation will be equally distributed across arms for which the participant is eligible, but may be altered with future arm-specific appendices. If a participant is eligible for multiple arms, they would be equally randomized (1:1) to all eligible arms.



3 Objectives and Purpose

The overarching objective of this adaptive platform design is to iteratively learn which treatment strategies, including but not limited to antithrombotic strategies, are best for reducing the primary, secondary, and safety outcomes. Additional alternative strategy(-ies) will be compared to the current standard of care arm, which may trigger new standard of care designated arms as appropriate based on interim analysis results and evolving literature. This process will continue until no new strategies replace the standard of care or potential options for additional interventions are exhausted.

4 Study Design and Endpoints

4.1 Description of Study Design

This trial design is built as a process – with the possibility of multiple interventions being investigated. It is an open label randomized trial of patients hospitalized for COVID-19 who are assigned to different treatment regimens.

4.2 Study Endpoints

4.2.1 Primary Study Endpoint

21 Day Organ-Support free-days. The primary endpoint is the number of days that a patient is alive and free of organ support through 21 days after trial entry. Organ support is defined by receipt of invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, or ECMO support. If the patient dies at any time during the index hospital stay through 90 days, they are assigned the worst possible score of –1.

4.2.2 Secondary Endpoints

- Categorization of the primary endpoint into a three-level ordinal outcome (Death, invasive mechanical ventilation without death, neither invasive mechanical ventilation nor death)
- Categorization of the primary endpoint into a three-level ordinal outcome (Death, organ support (any respiratory or cardiovascular) without death, neither organ support nor death) (for moderate illness severity at enrollment)
- Days free of death and respiratory and cardiovascular organ support and renal replacement therapy (RRT) during Index Hospitalization through Day 28. If the patient dies at any time during the index hospital stay through 90 days, they are assigned the worst possible score of –1.
- A composite endpoint of death, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke during hospitalization or at 28 days after enrollment (whichever is earlier) – "major thrombotic events or death"
- 28 Day Hospital free days (non-ICU level patients)
- 28 Day Ventilator-Free Days (ICU level patients)
- 28 Day Vasopressor-Free Days (ICU level patients)
- 28 Day Renal Replacement Free Days
- Hospital readmission within 28 days
- Acute kidney injury
- Deep vein thrombosis
- Pulmonary embolism
- Systemic arterial thrombosis or embolism
- Myocardial infarction
- Ischemic stroke
- Renal replacement therapy
- Use of extracorporeal membrane oxygenation (ECMO) support
- Mechanical circuit (dialysis or ECMO) thrombosis
- WHO ordinal scale (peak scale over 28 days, scale at 14 days, and proportion with improvement by at least 2 categories compared to enrollment, at 28 days)
- All-cause mortality at 28 days
- All-cause mortality during initial hospitalization (includes death after 28 days)
- All-cause mortality at 90 days

4.2.3 Additional Study Endpoints

- Individual endpoints of the thrombotic events composite endpoint
- Length of Hospital stay
- Exploratory endpoints
  - Cardiac injury (e.g., troponin)
  - Trajectories of biomarkers related to COVID-19
  - Hospital readmission within 90 days
  - All-cause mortality at 1 year

See arm-specific Appendices for additional tertiary endpoints of interest specific to arm.

4.2.4 Safety Endpoints

Safety Endpoints: Intervention specific

5 Study Enrollment

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- ≥ 18 years of age
- Hospitalized for COVID-19*
- Enrolled within 72 hours of hospital admittance or 72 hours of positive COVID test
- Expected to require hospitalization for > 72 hours
- See arm-specific Appendices for additional criteria and details

*It is strongly recommended to confirm SARSCoV2 with a positive PCR or other commercial or public health assay prior to randomization. At centers where there is a delay in confirming the diagnosis, a sufficiently high clinical suspicion is sufficient to proceed with randomization as long as confirmation is expected within 24 hours.

5.2 Exclusion Criteria

- Imminent death
- Requirement for chronic mechanical ventilation via tracheostomy prior to hospitalization
- Pregnancy and breastfeeding
- See arm-specific appendices for additional criteria and details.

5.3 Vulnerable Subjects

Critically ill patients with COVID-19 may not have capacity to provide consent. This trial will include participants who have no capacity to consent only if their legal proxy is able to consent on their behalf. It has become increasingly apparent that individuals with COVID-19 are at risk for adverse outcomes. Patients without the capacity to consent for themselves will have a potential for direct benefit by being part of the trial.

Capacity assessment will be conducted by the treating physician or an independent medical provider with appropriate expertise based on the standard clinical assessment of capacity and communicated to the study team. Surrogate consent will be provided by the subject's Legally Authorized Representative as defined by local policies and state/country regulations.

Consent will be obtained from the LAR before any study related procedures begin. Participants' capacity will be monitored throughout the study by working with the treatment team. Once the participant regains the capacity to consent, they will be informed of their participation in the study and will have an opportunity to withdraw from further participation in the study. The enrollment of patients without capacity is important because critically ill patients, especially those who are not ambulatory, are at higher risk of developing adverse outcomes.

5.4 Strategies for Recruitment and Retention

Listings of patients admitted to the participating sites with COVID-19 may be reviewed for eligibility by the study team, to identify and recruit potential participants, until study enrollment goals have been met. The study team should communicate with the inpatient care team. All treating physicians will be informed of the study and will have the option to advise of any conditions that would preclude any individual patient being approached.

5.5 Duration of Study Participation

Duration of study participation is 90 days from enrollment, and potential follow-up at approximately one year and thereafter.

5.6 Total Number of Participants

The total sample size for the platform trial is not pre-determined. The sample size for each arm will be set in the arm-specific appendix and will incorporate an adaptive design. There will be interim monitoring to allow early stopping for futility, efficacy, or safety. If one strategy proves to be efficacious, then this strategy may become the reference arm for comparison(s) with new experimental treatment(s). New arms can be introduced according to scientific and public health needs. Some arms may not relate solely to antithrombotic therapy.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. Discontinuation of a study agent, regardless of the reason, e.g. patient or physician request, or adverse event, does not constitute study withdrawal. Patient data will still be collected as planned and analyzed as intent to treat unless the participant withdraws consent for continued follow-up. An investigator may terminate participation in the study if any situation occurs such that continued participation in the study would not be in the best interest of the participant

5.8 Premature Termination or Suspension of Study

All deaths and DSMB-specified severe adverse events within the study period will be reviewed by the DSMB. The decision to stop or suspend the study, or an arm of the study, will be made by the DSMB after considering the totality of the data and the benefit-risk of continuing the study.

This study, or an arm of the study, may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants in a strategy, such as excess mortality and/or major bleeding (this will be determined by the oversight data safety monitoring plan)
- Demonstration of efficacy or lack thereof that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent and Procedural Intervention

6.1 Study Agents

Each arm in this platform trial will include different treatment strategies. Information about the treatment strategies for a given arm can be found in the arm-specific appendices.

6.2 Duration of Therapy

Once participants are randomized to a treatment strategy (arm), they will remain on treatment for the duration specified by the relevant appendix. However, if a participant randomized to one arm develops an indication for a different strategy (e.g., thrombotic event, worsening clinical status), the participant will be treated based on institutional guidelines with any measures required by local clinical judgment.

7 Study Procedures and Schedule

7.1 Study Schedule

Activity	Screening/ Enrollment	Hospital Duration	28 days and/or hospital discharge***	90-days post randomization and longer term follow-up
Eligibility				
Consent	X			
Demographic and Medical History	X			
Assessment of Inclusion/Exclusion criteria	X			
Self-reported race/ethnicity and gender	X			
Study Drug Administration				
Randomization	X			
Study treatment	X	X		
Study Procedures				
Height	X			
Weight	X			
Vital signs	X			
Concomitant medications	X	X		
WHO ordinal assessment	X	X	X	X
Quality of Life and Functional Status#	X			X
Outcomes Assessment#		X	X	X
SOC Laboratory Assessments				
Chemistry panel	X	X	X	
Hematology panel	X	X		
D-dimer*	X			
Blood Group**	X			

See arm-specific appendices for additional measures

*D-dimer is strongly recommended for measurement in all participants as close to the time of randomization as feasible.

**Blood group will come from hospital record or self-report if available. Biospecimens see appendix 4.

***Assessments indicated in the table above will be ascertained at discharge, or at 28 days, whichever comes first. Participants must be followed for vital status until discharged from the hospital or another care facility (if transferred on organ support) up to 90 days. To maximize retention, participants will be contacted intermittently post-discharge and that contact will be recorded in the EDC.
#Participants may be assessed for functional status and quality of life that reflects baseline status pre-COVID illness and functional and vital status and quality of life at 90 days and longer-term follow-up (Instruments detailed in the manual of operations). Participants may be contacted in the future, including after this study is over to collect information about their health status (e.g. quality of life, functional and vital status) and ascertain their interest in other studies about COVID-19.

Laboratory Procedures/Evaluations
See arm-specific appendices.

All analyses will be performed on SOC labs and procedures done for usual care. The standard operating procedures for samples to be collected for research purposes are included as Appendix 5. All research samples will be timed with clinical lab draws to limit provider exposure. Collection of research samples as outlined in Appendix 5 is strongly encouraged where safe and feasible.

7.1.1 Visit 1 and Hospitalization Visits (see arm-specific appendices for details)

Visit 1 (Screening and Randomization)

1. Informed consent obtained
2. Assessment of inclusion/exclusion criteria assessed
3. Screening, consisting of reviewing participant medical history and information in their chart such as height, weight, vital signs, and normal clinically performed laboratory assessments, including pregnancy test for all women of childbearing age.
4. If confirmed eligible, following randomization, initiation of treatment with the assigned strategy

Hospitalization Visits

1. Recording of specifics of study treatment and adherence according to assigned arm
2. Laboratory assessments as part of standard of care
3. Daily WHO ordinal assessment
4. Ongoing daily outcomes and safety assessment

7.1.2 28 days and/or Date of Hospital Discharge

1. Recording of outcomes and safety assessments as reported by participant or observed by investigator
2. WHO Ordinal Assessment
3. Recording of vital status and ascertainment of events
4. Recording of participant's adherence to treatment strategy, if patient is in hospital

These assessments will be ascertained at discharge, or at 28 days, whichever comes first. Participants must be followed for vital status until discharged from the hospital or another care facility (if transferred on organ support) up to 90 days.

7.1.3 90 days post-randomization

1. Recording of vital status
2. May include quality of life and functional status assessment

3. May include recording of hospital readmissions

7.1.4 Potential one year post-randomization follow up

1. Recording of vital status
2. May include quality of life and functional status assessment
3. May include recording of hospital readmissions

Participants may be contacted by a research contact and/or by the participating hospital study team periodically for longer term follow-up to collect information about their health status (e.g. quality of life, functional and vital status) and ascertain their interest in other studies about COVID-19. To maximize retention, participants will be contacted intermittently (e.g. once or twice post-discharge). Discharge visits must be completed.

7.2 Concomitant Medications, Treatments, and Procedures

Concomitant medications taken during study participation will be recorded on the case report forms (CRFs). Concomitant medications to be recorded are:

- Antithrombotics (e.g., aspirin, heparin, and other agents)
- Any treatments used for the treatment of COVID-19 infection (e.g., remdesivir, systemic steroids, IL-6 inhibitor such as tocilizumab, Janus kinase (JAK) inhibitors, convalescent plasma)
- Others specified in arm-specific appendices

7.3 Expedited Critical and Major Event Reporting

All efficacy and safety outcome events will be assessed and documented in the participants' study records. The ACTIV-4 Platform will have a uniform policy for reporting adverse events to ensure that all events are assessed quickly and are submitted to the DSMB, IRB(s), and other groups as needed (e.g., FDA), following each group's reporting guidelines and timelines. Events meeting the independent DSMB-specified criteria will be reported immediately and within the time frames specified by the DSMB.

Sites are required to follow their local reporting guidelines.

7.4 Data and Safety Monitoring Plan and Study Halting Rules

The ACTIV-4 Platform will have a uniform Data and Safety Monitoring Plan, encompassing all research carried out within the Platform.

8 Statistical Considerations

8.1 Statistical and Analytical Plans (SAP)

There will be a formal Statistical Analysis Plan (SAP) and each arm added to the trial will have its own arm-specific SAP. This will include the primary analysis, the primary comparison, futility and success rules, and interim analysis schedule. The SAP will be created prior to the first interim analysis for the study and each arm-specific SAP will be created before the first interim analysis for that arm.

8.2 Statistical Modeling for the Primary Analysis

Inferences in this trial are based on a Bayesian statistical model for the ordinal primary outcome, organ-support free-days (OSFD). There is a single Bayesian model for the primary outcome across

each arm and subpopulation. The Bayesian model is an ordinal cumulative logistic regression model described below.

Let $Y_i = \{-1, 0, 1, \ldots, 21\}$ denote the ordinal outcome (OSFD) for patient i. The probability of patient i observing y OSFD or less is denoted as $\pi_{iy} = \Pr(Y_i \leq y)$. The parameters in the model are structured so that a value > 0 implies treatment benefit, and hence an odds-ratio > 1 implies treatment benefit. In this section we describe the generic model for the study, but arm-specific appendices may vary in its modeling assumptions. The generic primary analysis model is formulated as follows:

$$\log\left(\frac{\pi_{iy}}{1-\pi_{iy}}\right) = \alpha_{y,s} - \left[\nu_{Site,s} + \lambda_{Time,s} + \theta_{a,s} + \beta_{Age,s} + \beta_{Sex,s}\right]$$

1. The "subtype" variable, *s*, corresponds to the two patient subgroups defined by disease severity:
    a. subtype = 1 is non-ICU level care
    b. subtype = 2 is ICU-level care
2. The "site" variable is the clinical site within the trial. These will be site effects estimated separately within the non-ICU and ICU level of case disease states.
3. The "time" variable is an indicator of the month of enrollment in the trial, numbered decreasing from the first enrollment to the last enrollment for the analysis. The time effects will be estimated separately within the non-ICU and ICU level of case disease states.
4. The "arm" the patient is randomized to is labeled as *a*. The effects of arm are modeled by the disease state.
5. The "age" variable is a categorical classification of age as ≤ 39, 40-49, 50-59, 60-69, 70-79, and 80+. The age effects will be estimated separately within the non-ICU and ICU level of case disease states.
6. The "sex" variable is sex at birth. The sex effects will be estimated separately within the non-ICU and ICU level of case disease states.

If additional covariates (e.g. race and ethnicity) are added to the model they will by default, unless otherwise specified, vary by disease state.

If patients are randomized simultaneously to multiple arms the primary analysis will adjust using a covariate for each other randomized agent assigned. In addition, some interactions between randomized arms may be included.

The $\alpha_{y,subtype}$ parameters are the baseline rates of the ordinal outcome, which are modeled

separately by disease subtype.

8.3 Model Priors

The treatment effects for arm *a*, within disease subtype *s* are modeled with the θ_s parameters. The β parameters model any covariate effects included in the model. The λ parameters model the

effect of time within the pandemic.

The ordinal endpoint rates are modeled using an inverse Dirichlet model where the individual probabilities for the 23 outcomes are based on 1 patient's weight on equally likely outcomes.

$$logit(\alpha_{y,s}) \sim Dirichlet(1 * P), where\ \mathrm{P} \propto 1$$

The site effects, ν_{Site}, are modeled using a hierarchical model where site is nested within the country of the site:

$$\nu_{Site,s} \sim N(\mu_{country,s}, \tau^2_{country,s}), site = 2, \ldots, N_{Site}$$

$$\mu_{country,s} \sim N(0,1);\ \tau^2_{country,s} \sim IG(0.25,0.1), s = 1,2$$

A referent site, expected to be the largest enrolling site, will be set such that $\nu_{Site} \equiv 0$. The hyper-parameters of the site hierarchical model are separate by disease state *s*.

The effect of time (*T*) is modeled using a second-order normal dynamic linear model separately by disease state, *s*. The most recent two time periods are modeled as the referent time epochs with the time parameters set to 0. The preceding time epochs are modeled as a normal dynamic linear model as:

$$\lambda_1 = \lambda_2 \equiv 0$$

$$\lambda_3 \sim N(0,0.15^2)$$

$$\lambda_T - 2\lambda_{T-1} + \lambda_{T-2} \sim N(0,\tau^2_{Time}), T \geq 4$$

The treatment effect parameters are set against a control arm, which will be labeled in the arm-specific appendix. The treatment effect for the control arm, labeled as arm *a* = 1, will be set to 0 for each of the disease states:

$$\theta_{1,S} \equiv 0.$$

The effect of each treatment arm introduced will typically be modeled hierarchically across disease subtypes. The modeling of the treatment arms will be specified in appendices.

Any additional covariates included in the model will have independent N(0,1) priors unless otherwise specified.

8.4 Assessing Effectiveness

The treatment effect parameters, θ, represent the log-odds ratio, of the treatment, for the cumulative logistic for the ordinal model. In this parametrization an odds ratio > 1, or a log-odds ratio > 0, signifies improved outcomes relative to the referent control treatment. The odds-ratio parameter $\exp(\theta)$, labeled OR, will be used to summarize the treatment effect relative to control or $\exp(\theta_{a_1} - \theta_{a_2})$ for the odds-ratio between arms a_1 and a_2. The posterior mean, median, standard deviation, and 95% credible intervals for the odds-ratio will be used to summarize relative treatment effects.

The posterior probability that an arm, a_1, is superior to another arm, say, a_2, is:

$$\Pr(\theta_{a_1} > \theta_{a_2}).$$

This probability will be used for triggers of superiority of one arm to another arm.

The posterior probability that an arm, a_1, is superior to another arm, say, a_2, by a specified difference on the odds-ratio scale is:

$$\Pr(\exp(\theta_{a_1}) > \exp(\theta_{a_2}) + \delta).$$

This probability will typically be used for futility. If the probability is small that a treatment has benefit above a control of some specified amount (δ), the arm may be dropped for futility.

8.5 Analysis Datasets

The intention-to-treat (ITT) analysis dataset will be the source of data for primary analyses. This will include all randomized participants regardless of actual receipt or compliance with therapy. The safety analysis set will consist of all participants who received at least one dose of study medication. The per protocol analysis will be conducted based on adherence to assigned treatment; this dataset will support sensitivity analyses to complement the primary ITT analyses.

The ITT group for an arm consists of the participants that were randomized in the platform that were eligible to be randomized to that arm. This may vary from the platform ITT population, which consists of all participants randomized.

Participants who are randomized to receive one strategy may in fact be treated with another strategy based on health status and provider discretion. Exploratory analyses will estimate the causal effect of the treatment for these participants using marginal structural modelling techniques. These techniques use inverse probability weighting methods that are based on patient-level covariates to create comparable groups for the analysis.

8.5.1 Safety Analyses

Monitoring for safety will be conducted continuously. For each arm-specific appendix potential adverse events of importance will be identified. A Bayesian monitoring rule will be used to summarize the adverse event rates across all arms for the adverse events of importance within each arm-specific appendix. A Bayesian prior distribution of a beta (0.1, 0.9) will be used to model the likelihood of each adverse event of importance. For each adverse event of importance , the

posterior mean event rates, the posterior mean of the difference between each arm, and the 95% credible intervals for the risk-difference and odds-ratio will be summarized.

8.5.2 Adherence and Retention Analyses

The primary analysis is by intention to treat. Per protocol analysis will be conducted based on adherence to assigned treatment. For any scheduled follow-up post hospital discharge every effort will be made to recontact participants who are unreachable. Due to the short trial participation timeline, excellent patient retention is anticipated.

8.5.3 Baseline Descriptive Statistics

All variables will be summarized using mean, median, standard deviation, and range (for continuous variables) and frequency (for categorical variables). Treatment groups will be compared with respect to baseline characteristics to verify randomization balance.

8.5.4 Planned Interim Analysis

An independent data safety and monitoring board (DSMB) will review all interim analyses prepared by an unblinded statistical analysis committee.

8.5.5 Safety Review

Monitoring for safety will be conducted continuously. The DSMB will be monitoring safety for each arm-specific appendix. The DSMB monitoring plan includes guidance on stopping specific arms for safety concerns.

8.5.6 Tabulation of Individual Response Data

The composite outcome evaluated will be tabulated and broken down by component (e.g., death, pulmonary embolus, myocardial infarction, etc.). Note that some participants may experience more than one component of the primary endpoint.

8.5.7 Exploratory Analyses

Exploratory analyses will be conducted in a subset of participants on whom additional clinical and basic science assays are performed. These will be descriptive and hypothesis-generating.

8.6 Sample Size

Sample size for the platform trial is not pre-determined. The platform trial will run as long as there is a need and there are investigational arms enrolling. The sample size for each arm will be specified in the arm-specific appendix. Interim analyses for each arm will take place in the platform trial and detailed in the arm-specific appendix. Conclusions of futility or superiority may be drawn specific to a patient subtype. Effort will be taken to conduct all interim analyses at the same time in the platform trial since there is a single Bayesian model of the efficacy of all arms conducted. If one strategy proves to be efficacious, then this strategy may become the reference arm for comparison(s) with new experimental treatment(s). New arms can be introduced according to scientific and public health needs.

9 Measures to Minimize Bias

9.1 Enrollment/Randomization

9.1.1 Enrollment

1. Patients hospitalized for COVID-19 are screened daily within the eligibility time window for inclusion/exclusion criteria. Any patient who meets all inclusion criteria and no exclusion criteria will be approached for enrollment.

2. Patients remain in the intention-to-treat group if they receive another treatment strategy after randomization.

9.1.2 Randomization

Randomization assignments are performed for participants at baseline. Randomization will be equal across all arms a patient is eligible. Randomization stratification will be done by site, and disease subtype (ICU and non-ICU level care) and/or other arm-specific criteria.

10 Source Documents and Access to Source Data/Documents

The ACTIV-4 Platform will have uniform policies describing what source documents are, how to make corrections, and who can access them.

11 Quality Assurance and Quality Control

The ACTIV-4 Platform will have uniform policies for quality assurance at the data entry level and site monitoring.

12 Ethics/Protection of Human Subjects

12.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

12.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3 Informed Consent Process

12.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant, and written documentation of informed consent is required prior to starting intervention/administering study product.

A written consent will be sought from every participant via a face to face consenting process or remotely by using an e-consent option as per IRB approved method.

12.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Informed consent will be obtained following institutional COVID policy to protect study staff.

An extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator or designee will explain the research study to the participant and answer any questions that may arise. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be provided to participants. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Participants who have no capacity to consent for themselves will have a surrogate consenting process via legally authorized representative.

12.4 Posting of Clinical Trial Consent Form

The informed consent form will be posted on the Federal website after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

12.5 Participant and Data Confidentiality

The ACTIV-4 Platform will have uniform policies for protecting the privacy of participants and maintaining confidentiality. These policies will adhere to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

13 Data Handling and Record Keeping

13.1 Data Collection and Management Responsibilities

The ACTIV-4 Platform will have uniform policies for data management.

13.2 Study Records Retention

The ACTIV-4 Platform will have uniform policies for records retention.

13.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

13.4 Publication and Data Sharing Policy

The ACTIV-4 Platform will have uniform policies for publications and data sharing.

14 Study Finances

14.1 Funding Source

National Institutes of Health. Agent specific information listed in Appendices as applicable.

14.2 Costs to the Participant

Participant health insurance may be billed for the costs of medical care during this study since these expenses would have happened even if the participant were not in the study. If the participant's insurance does not cover these costs or the participant does not have insurance, these costs will be participant's responsibility.

15 Conflict of Interest Policy

The ACTIV-4 Platform will have uniform policies for identifying and disclosing potential conflicts of interest.

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Summary of Appendices:

Appendix #	Description	Arm
1	Master Protocol State of Arms	N/A
2	Definition and Determination of Outcomes	N/A
3 (Retired)	Therapeutic-dose Anticoagulation (Arm A)	A
4 (Retired)	Prophylactic Dose Anticoagulation (Arm B)	B
5	ACTIV-4 Blood Sampling – proposed samples and times for sites participating in mechanistic studies and biorepository	N/A
6	Additional data inclusion from other trials merged under ACTIV-4 platform	N/A
7	Anticoagulation plus P2Y12 inhibitor for ICU Level of Care (Severe) Cohort	C
8 (Retired)	Anticoagulation plus P2Y12 inhibitor for non-ICU Level of Care (Moderate) Cohort	D
9	Crizanlizumab	E
10	SGLT2 Inhibitor	F

Appendix 1: Master Protocol State of Arms

This appendix will be updated as arms for each protocol version appear below.

- Version 21AUG2020 1AB: Outlined possible example scenarios for adaptive design. Arms A and B included.
- Version 01FEB 2021: Adds Arms C and D (Appendices 7 and 8), implements suspension of Arm A in participants with ICU level of care (severe cohort) at the time of randomization due to futility, and suspension of Arm B for non-ICU level of care participants (moderate illness) at the time of randomization, due to superiority of Arm A.
- Version 19OCT2021: Refers to the Manual of Operations for the current state of arms and to the statistical analysis plan for the current analytic plan based on the current state of arms. Appendix 1.1 and 1.2 were retired. Appendix 1.3 was moved to the statistical analysis plan. Removed inactive appendices 3, 4, 8. The standard of care arm does not have its own appendix.

Each study agent is tested in a domain. Within the domain a participant is randomized to study arms in which they receive or not receive that active agent. The Manual of Operations (MOO) describes the current state of arms. The MOO will be updated when any arm is added or removed, when assignment to a treatment is limited to a subset of potential participants based on interim analyses. When a new study test agent is added, the protocol will be amended to add the relevant appendix. If any arm or a subset of potential participants is stopped, the trial will continue with randomization to the remaining arms and/or the other subsets as long as the DSMB has indicated that there is no safety concern.

Please refer to the Statistical Analysis Plan for the most current version of the analysis plan, taking into account the current state of arms.

All participants will receive standard of care, which includes anticoagulation as clinically indicated, taking into account the illness severity and any available data on effective interventions at the time of enrollment. Standard of care, also referred to as usual care will change over time and is determined locally by sites, taking into account what treatments are available in each region. ACTIV-4a previously tested intensity of heparin anticoagulation; recommended doses for standard of care may be found in the manual of operations.

Appendix 2: Definition and Determination of Outcomes

A2.1 Approach to ascertainment and verification of outcomes

Outcomes are assessed locally and will not be centrally adjudicated in this pragmatic trial platform, except as specified in the arm-specific appendix. Outcomes should be assessed by a local investigator or other qualified study team member who is blinded to treatment assignment, using the definitions below.

A2.2 Outcome definitions

21 Day Organ-Support Free-Days (OSFD)

Defined as the number of days that a patient is alive and free of organ support through 21 days after trial entry. Organ support is defined by receipt of invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, ECMO support. If the patient dies at any time (through 90 days) during the index hospital stay, they are assigned the worst possible score of –1.

- Non-invasive mechanical ventilation is defined as BIPAP or CPAP when used for acute respiratory support (the use of BIPAP or CPAP at night or when sleeping for sleep apnea is not considered organ support).
- High Flow Nasal Cannula Oxygen is defined as delivery of oxygen through a system that typically delivers oxygen at 20 to 60 liters per with a titratable FiO2.
- Invasive mechanical ventilation is defined as positive pressure ventilation through endotracheal tube or tracheostomy.
- Vasopressor support includes infusion of any vasopressor or inotropic medication.
- Any patient dying in the acute hospital stay (up to day 90) are assigned 21 Day Organ-Support Free Days of –1.
- If there is intervening time in which a patient is free of organ support but goes back on organ support the intervening time does not count toward the organ support free days endpoint. Only time before organ support and after the last use of organ support are counted as “free days.”
- If a patient was discharged alive without mechanical ventilation prior to Day 21, the patient is assumed to be free of organ support after hospital discharge for the remainder of the 21 days.
- If a patient was discharged alive on mechanical ventilation prior to Day 21, a call to the discharge facility is needed to confirm ventilation status on Day 21 and the last day on mechanical ventilation.

Primary Endpoint

Days free of organ support within 21 days after randomization. Organ support free days (OSFD) is defined as days in which patient is not on invasive or non-invasive mechanical ventilation, high flow nasal oxygen, or vasopressor therapy or ECMO support. If the patient dies at any time (including beyond 21 days) during the index hospital stay, they are assigned the worst possible score of –1.

To be specific about which organ support was affected, secondary outcomes include: ventilator free days, vasopressor free day, and additionally renal replacement therapy free days.

Justification for use of OSFD:

- Pragmatic
- Can be calculated from WHO ordinal scores
- Incorporates clinically important need for organ support but also duration of organ support
- No additional data collection is necessary to calculate secondary outcomes of ventilator free days, renal replacement free days, and vasopressor free days to understand which organ support was most impacted
- Incorporates mortality as the worst possible outcome

Secondary Endpoints

Days free of organ support or RRT during index hospitalization
Defined as the number of days that a patient is alive and free of cardiovascular and respiratory organ support and free of renal replacement therapy, during the index hospitalization through 28 days after trial entry. Organ support is defined by receipt of invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, ECMO support. If the patient dies at any time (through 90 days) during the index hospital stay, they are assigned the worst possible score of –1.

Deep vein thrombosis
Deep vein thrombosis will be diagnosed by venous ultrasound or point-of-care ultrasound (POCUS) or other imaging modality and documented in a note, and performed for clinical indications. A positive ultrasound test is defined by a noncompressible or partially noncompressible venous segment and should be reported. Thrombosis may involve the cerebral venous sinus or any venous bed, including the upper extremities. Routine screening for deep vein thrombosis is not recommended. If deep vein thrombosis is diagnosed and treated without imaging due to imaging availability concerns or risk of exposure to SARS CoV-2, this will be classified as probable deep vein thrombosis. Later imaging is preferable in these cases when possible.

Pulmonary embolism
Pulmonary embolism will be confirmed by chest CT with PE protocol, pulmonary angiography or ventilation-perfusion scan. Events may also be defined without this imaging by the care team, as evidenced by, for example, “clot in transit” on echocardiogram. If PE is diagnosed and treated without imaging due to imaging availability concerns or risk of exposure to SARS CoV-2, this will be classified as probable PE. Later imaging is preferable in these cases when possible.

Stroke/ Peripheral Arterial Systemic Thromboembolism
Stroke or systemic embolism as diagnosed by imaging (i.e., head CT, lower extremity CT angiogram) or deemed “highly-likely” by the provider based on physical examination (i.e., acute hemiplegia thought to be due to stroke, acute distal lower extremity hypoperfusion). Systemic thromboembolism may involve the retinal artery, spinal cord or other vascular beds. Classification of ischemic vs. other etiologies is based on neuroimaging. Venous sinus thrombosis will be included in the category of vascular occlusion/ischemic stroke on the venous side. Primary CNS hemorrhage: intracerebral hemorrhage, subarachnoid hemorrhage, subdural hematoma, and rarely epidural hematoma or spinal hematoma. Secondary hemorrhagic stroke: blood associated with an ischemic infarct.

ICU Level of care disease state (severe illness)

Defined as receipt of cardiovascular or respiratory organ support as defined in the 21-day organ support free days. ICU level of care is defined as being on invasive or non-invasive mechanical ventilation, high flow nasal oxygen, or vasopressor therapy or ECMO support.

Myocardial infarction
Myocardial infarction is defined according to the universal definition of MI, which excludes myocardial injury e.g., isolated elevation of cardiac troponin. MI must include rise and fall of cardiac troponin above the 99th percentile with at least one of the following: symptoms of acute ischemia, ECG changes consistent with ischemia, new/presumed new wall-motion abnormalities or other imaging evidence of MI, abnormal coronary angiography (e.g. identification of a coronary thrombus).

Acute Kidney Injury
Acute kidney injury after enrollment is defined by KDIGO criteria for Acute Kidney Injury in the setting of not meeting these criteria upon enrollment:

Modified Stages:

- Stage 2: Serum Cr 2.0–2.9 times baseline
- Stage 3: Serum Cr ≥ 3.0 times baseline, OR Increase in serum creatinine to ≥ 4.0mg/dl, OR Initiation of renal replacement therapy

Renal Replacement Therapy (RRT)
This refers to initiation of RRT during the index hospitalization, such as hemodialysis, peritoneal dialysis or continuous venovenous hemofiltration.

WHO ordinal scale for clinical improvement (https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf)

Patient State	Score	Descriptor
Uninfected	0	No clinical or virological evidence of infection
Ambulatory	1	No limitation of activities
	2	Symptomatic: Limitation of activities
Hospitalized: Mild disease	3	Hospitalized; no oxygen therapy
	4	Hospitalized; oxygen by mask or nasal prongs
Hospitalized: Severe disease	5	Non-invasive ventilation or high-flow oxygen
	6	Intubation & Mechanical ventilation
	7	Ventilation and additional organ support – pressors, RRT, ECMO
Death	8	Death

Appendix 3: Therapeutic-dose Anticoagulation (Arm A) - RETIRED

Appendix 4: Prophylactic Dose Anticoagulation (Arm B) - RETIRED

Appendix 5: ACTIV-4 Blood Sampling – proposed samples and times for sites participating in mechanistic studies and biorepository

The goal of the Mechanistic Studies Center and the Biorepository/Central Lab is to add significant value to the clinical trials by collecting high-quality blood samples for studies aimed at elucidating underlying disease mechanisms and insights into how the therapy modifies these underlying disease processes. The plan is to identify biomarkers of pathological mechanisms, predict outcomes, direct therapy, and/or identify higher-risk patient subpopulations.

A5.1 Inpatient sampling

Blood collection times for inpatients:

- Days 0 (time of enrollment), 3, 7 and 14. Samples should be obtained within 24 hours after the assigned time point (example: the day 3 sample should be obtained within 72-96 hours after randomization)
- Samples should be coordinated with clinical lab blood draws when possible.

Standard samples to be collected & volumes at each time point:

- Citrate plasma
  - Two 4.5 mL Citrate tubes (BD # 369714)
- EDTA plasma
  - One 10 mL EDTA tube (BD# 366643)
- Serum
  - One 5.0 mL Serum tube (BD # 367814)

Note 1: *We anticipate that some sites may not be able to collect & process all the samples and time points listed above. We plan to work with those sites to identify more limited time points and/or discard samples that could be collected, processed and sent to the biorepository.*

Note 2: *We anticipate that some high-functioning sites may, in addition to the sample collections noted above, also participate in enhanced collections & studies, which may include:*

- Additional blood collection tubes such as:
  - HTI SCAT-144 plasma
  - Paxgene RNA whole blood
  - Cell Prep Tube (CPT)
- Whole blood assays:
  - Viscoelastic assays (thromboelastography or thromboelastometry)
  - Platelet aggregometry
  - Whole blood genomics

A5.2 Sample processing

A detailed Manual of Operations (MOP) will provide instructions to clinical lab and research personnel regarding sample processing including centrifugation, processing, freezing, storing, & shipping samples. Also, the following will be provided: training materials; sample processing kits with prelabeled transport and/or storage vials; sample tracking software; shipping materials.

A5.3 Biorepository/Central Lab

The Biorepository will archive biosamples from the clinical sites, and distribute them to the labs doing ACTIV-4 approved mechanistic studies and other research. If ACTIV-4 biosamples cannot be shipped to the Biorepository for some reason, the information will be captured and used to form a "Virtual Biorepository", so that those samples can contribute to the mechanistic studies as well.

Appendix 6: Additional data inclusion from other trials merged under ACTIV-4 platform

There are several clinical trials that have been testing safety and efficacy of Arm A and B regimens. Data collected in these trials will be included in the data analysis under this protocol provided that the subjects consented for the data to be shared or a waiver of consent and authorization had been granted by the reviewing IRB. The data will be labeled with subject ID and only include dates which are necessary to assess safety and efficacy endpoint events. All other private health information (PHI) will be removed. The data will be stored at the study coordinating center, University of Pittsburgh, in HIPAA compliant electronic system and only coordinating center staff will have access to the data. The statistical analysis plan will account for this additional data.

Appendix 7: Background and Rationale for Arm C: P2Y12 inhibitor for ICU Level of Care (Severe) Cohort

A7.1 Background and Rationale for Arm C

Analysis of therapeutic vs prophylactic dose anticoagulation in severely ill patients demonstrated that therapeutic dose anticoagulation was not superior, and there was a trend toward harm. Therefore prophylactic dose anticoagulation is considered standard of care for severely ill patients. The number of days with organ support or death over the first 21 days of the index hospitalization remained high despite standard of care treatment, and bleeding risk was < 2%. Therefore, additional antithrombotic and additional treatment strategies should be tested.

Autopsy and clinical data highlight the potential role of platelets and their precursors in the pathogenesis of COVID-19.[1-3] Platelets are shed into circulation by megakaryocytes, and during this process, megakaryocytes distribute their transcriptome into platelets. Once in the circulation, platelets can respond to local and systemic conditions and induce monocyte, macrophage and endothelial cell activation.[4-6] Prior to COVID-19, it was described that platelet-viral interactions alter the platelet transcriptome and induce a proinflammatory immune mediated platelet phenotype.[7] Consistently, platelets isolated from COVID-19 patients are hyperreactive and have an altered transcriptomic signature compared to disease-free controls.[3] Biomarkers of platelet activity are elevated in COVID-19 and are associated with thrombosis and all-cause mortality even after multivariable adjustment. These data suggest that platelets are activated in COVID-19 and represent a therapeutic target for improved clinical outcomes.

A7.2. Eligibility Criteria for Arm C

Note that to be eligible for randomization in a specific comparison during this adaptive trial patients are required to meet eligibility criteria for at least the standard of care arm and one comparator arm.

A7.2.1 Inclusion Criteria for Arm C

Same as the Master Protocol.

A7.2.2 Exclusion Criteria for Arm C

In addition to the exclusion criteria noted in the master protocol, arm-specific exclusion criteria are as follows:

- Moderate illness severity – non-ICU level of care at the time of randomization (not receiving HFNO, NIV, IV, vasopressors or inotropes, or ECMO)
- Contraindication to P2Y12 inhibitor, including but not limited to
    - known bleeding within the last 30 days requiring emergency room presentation or hospitalization
    - known hypersensitivity to all P2Y12 inhibitors
    - known history of an inherited or active acquired bleeding disorder
    - history of intracranial hemorrhage at any time
- Platelet count < 50 x 10^9/L
- Hemoglobin < 8 g/dL
- Requirement for ASA >162mg per day that it cannot be stopped safely
- Requirement for P2Y12 inhibitor that cannot be stopped safely

A7.3 Study Agents

Arm C consists of the combination of standard of care treatment, plus an antiplatelet agent in the P2Y12 inhibitor family.

A7.3.1. Standard of Care Treatment

Please refer to the manual of operations for recommended standard of care treatment.

A7.3.2. P2Y12 Inhibitor

The table shows the preferred dosing for P2Y12 inhibitor treatment. Ticagrelor is the preferred P2Y12 inhibitor, but any of the following strategies are acceptable.

Age	Weight	Ticagrelor#	Prasugrel*	Clopidogrel
<75 years	<60 kg	no load; 60 mg BID	no load, 5 mg daily	300 mg load**, then 75 mg daily
	≥60 kg		30 mg load**, 10 mg daily	
≥75 years	<60 kg	no load; 60 mg BID	not recommended	300 mg load**, then 75 mg daily
	≥60 kg		no load, 5 mg daily	

The preferred P2Y12 inhibitor is ticagrelor, which has a rapid onset of action without the need for a loading dose, unless there is a concern about drug-drug interactions (see Manual of Operations). The 60 mg twice daily dose is recommended; *If ticagrelor 60 mg is not available, 90 mg dose, may be used.* If ticagrelor is not available or is not preferred locally, prasugrel or clopidogrel may be used, preferably with a loading dose, taking into account relevant drug-drug interactions (see Manual of Operations).

if a participant will be continued on aspirin in addition the assigned P2Y12 inhibitor, aspirin dose must be ≤100 mg when administered with ticagrelor

* Prasugrel is NOT permitted in anyone with a prior stroke or TIA

**The loading dose is preferred because the average time to therapeutic effect with clopidogrel is 5 days without a loading dose, and for prasugrel is 3 days without a loading dose. A loading dose is not required.

The first dose should be administered as soon as possible after randomization.

A7.3.3. Participants previously taking aspirin before randomization

Participants taking aspirin before randomization are permitted to continue or stop aspirin therapy at the discretion of the treating physician. If a patient is randomized to Arm C and chronic ASA is continued per MD judgment, the recommended dose is 80-100 mg daily; the dose MUST be ≤100 mg daily when administered with ticagrelor.

A7.4 Duration of treatment

It is recommended that participants be given prophylactic-dose anticoagulation and a P2Y12 inhibitor daily for at least 14 days or until hospital discharge, whichever comes first. Treatment may

continue beyond 14 days at the discretion of the most responsible physician. At the time of treatment discontinuation, standard of care antithrombotic prophylaxis should be administered.

A7.5 Discontinuation of study intervention

Anticoagulation and/or P2Y12 inhibitor should be discontinued if there is clinical bleeding or another complication sufficient to warrant cessation in the opinion of the treating clinician. Major bleeding, including death due to bleeding, is an SAE. Assigned treatment may be resumed if deemed appropriate by the treating clinician.

Occurrence of HIT must result in the cessation of UFH or LMWH without recommencement regardless of treatment assignment. Use of an acceptable alternative agent is required in this instance as clinically indicated. Occurrence of HIT is an SAE. If HIT occurs, the P2Y12 inhibitor may be continued, at the discretion of the treating physician, taking into account the platelet count.

Study interventions can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient. Temporary cessation – for the shortest period of time possible – such as to allow surgical or other procedures is not a protocol deviation.

Temporary or permanent cessation of study intervention for bleeding is not a protocol deviation.

A7.6 Study Schedule

Activity	**Screening/ Enrollment**	**Hospital Duration**	**28 days and/or hospital discharge+**	**90 days post randomization and long term follow-up++**
Eligibility				
Consent	X			
Demographic and Medical History	X			
Assessment of Inclusion/Exclusion criteria	X			
Self-reported race/ethnicity and sex	X			
Pregnancy Test, for women of childbearing potential	X			
Study Drug Administration				
Randomization	X			
Study treatment	X	X¥		
Study Procedures				
Height	X			
Weight	X			
Vital signs	X	X		
Concomitant medications	X	X		
WHO ordinal assessment	X	X	X	X

Quality of Life and Functional Status[#]	X			X
Outcomes assessment		X	X	X
SOC Laboratory Assessments				
Chemistry panel	X	X	X	
CBC with platelet count	X	X	X	
Blood Group*	X			
PT, PTT if known	X	X		
Anticoagulation Monitoring (ex, PTT/ Antifactor Xa level)**	X	X (site-specific)		
D-dimer***	X	X	X	
Troponin****	X	X	X	
Coagulation and inflammatory markers*****	X	X	X	
Optional Biorepository	X	X		
BNP or NT-proBNP *****	X	X	X	

*Blood group taken from hospital record or self report if that is not available.
** Frequency and mode (Anti-factor Xa/PTT) of testing will be based on site routine. Anti-factor Xa monitoring is preferred over PTT
*** Baseline D-dimer is recommended. All values collected should be recorded.
****Strongly recommended as part of routine care, all values collected should be recorded
*****Optional, listed in case report form
[¥]or 14 days, whichever is earlier
[#]Participants may be assessed for functional status and quality of life that reflects baseline status pre-COVID illness and functional status and quality of life at 90 days, when contacted to ascertain vital status. (Instruments detailed in the manual of operations).
[+]Assessments indicated in the table above will be ascertained at discharge, or at 28 days, whichever comes first. Participants must be followed for vital status until discharged from the hospital or another care facility (if transferred on organ support) up to 90 days. To maximize retention, participants will be contacted intermittently post-discharge and that contact will be recorded in the EDC
[++]Participants may be contacted to ascertain vital status.

A7.7 Potential Risks & Benefits

A7.7.1 Known Potential Risks

Participants are monitored as per standard of care to minimize the risk of bleeding or developing clots. The standard of care plus P2Y12 inhibitor group will receive both anticoagulation and antiplatelet therapy and thus may be at higher risk of bleeding.

A7.7.2 Known Potential Benefits

Accruing data suggest that platelets are hyperactive in the setting of COVID-19. The platelet transcriptome isolated from hospitalized patients with COVID-19 is more pro-inflammatory than the platelet transcriptome from matched controls without COVID-19. Additionally, biomarkers of platelet activity are correlated with incident thrombosis and all-cause mortality. This arm seeks to test the hypothesis that there is a benefit of antiplatelet therapy in addition to standard of care for decreasing adverse events, including macro and micro-thrombosis. This potential benefit is hypothesized to offset an increase in bleeding risk. All participants will be closely monitored by the study team and any changes in antiplatelet therapy will be discussed with the treating physicians

and/or clinical team. There is a potential direct benefit of identifying thrombus or bleeding more rapidly based on close study monitoring. This trial will contribute to the body of generalizable knowledge about the antiplatelet strategy to minimize the risk of thrombus and adverse events in patients with COVID-19.

A7.8 Event Adjudication

A subset of thrombotic events will be centrally adjudicated, with the proportion adjusted as needed based on agreement between the site and the event committee.

A7.9 Safety Analyses

The safety events of importance for the standard of care plus P2Y12 inhibitor are serious thrombotic events and bleeding. The rates of serious thrombotic events and mortality will be monitored. The rates of serious thrombotic events will be compared to the standard of care arm, as well as to any additional arms added to the platform trial subsequently. For serious thrombotic events the DSMB will review the number of events, the event rates, and the posterior mean and 95% credible intervals for the event rates, difference between arms, and odds-ratios between arms will be summarized.

Major bleeding is a safety event of importance for this arm. The rates of ISTH major bleeding, ICH and fatal bleeds, and mortality will be monitored. The rates of bleeding will be compared to the control arm (standard of care, no P2Y12 inhibitor) as well as to additional arms. For ISTH major bleeding, ICH and fatal bleeds, and all-cause mortality the DSMB will review the number of events, the event rates, and the posterior mean and 95% credible intervals for the event rates, difference between arms, and odds-ratios between arms will be summarized.

A7.10 Statistical Analyses

The primary Bayesian statistical model (see Statistical Analysis Plan) will be used for modeling this arm in comparing to other arms. The Statistical Analysis Plan presents the interim analysis schedule and adaptive decision rules.

A7.11 References

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2. Barrett TJ, Lee A, Xia Y, et al. Biomarkers of Platelet Activity and Vascular Health Associate with Thrombosis and Mortality in Patients with COVID-19. *Circ Res.* 2020.
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8. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest

Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 suppl):e227S-277S.
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Appendix 8: Anticoagulation, Plus P2Y12 Inhibitor (Arm D) for non-ICU Level of Care (Moderate) Cohort – RETIRED

Appendix 9: Standard of Care Plus Crizanlizumab (Arm E)

A9.1 Background and Rationale for Arm E

Microvascular inflammation and thrombosis play a central role in the pathophysiology of COVID-19 and its clinical sequela, and growing data implicate endothelial damage as a major component in COVID-19 disease[1]. Release of both P-selectin and Von Willebrand Factor (VWF) from endothelial granules occurs in the setting of endothelial cell activation and has been related to severity of disease in COVID-19[2-4]. P-selectin mediates leukocyte rolling and anchors VWF to the vessel wall, where VWF then interacts with platelets. Thus, P-selectin may play a role in leukocytes and platelet adherence to endothelial cells and obstruction of the lung microvasculature, which appears common in severe COVID-19 disease. As resting endothelial cells and platelets do not express P-selectin, the interaction between P-selectin expressed on the cell surface and its ligand may be an initial step in vascular inflammation and thrombosis following endothelial injury or activation. P-selectin on the surface of platelets also plays a role in platelet adherence and thrombosis.

Crizanlizumab is an IgG2 kappa humanized monoclonal antibody that binds to P-selectin with high affinity, blocking the interaction between P-selectin and its ligand. The SUSTAIN clinical trial showed that crizanlizumab reduced vaso-occlusive events in patients with sickle cell disease (SCD), a process that involves endothelial release of P-selectin and vaso-occlusion[5]. Crizanlizumab was well tolerated and is FDA approved to reduce the frequency of vaso-occlusive crisis in patients 16 and older with SCD.

Crizanlizumab was tested in a randomized controlled pilot trial in patients with COVID-19 (NCT04435184). In 42 patients who were randomized, received drug, and had evaluable data for follow-up, crizanlizumab resulted in a substantial and sustained reduction in soluble P-selectin. Crizanlizumab also appeared to be related to biochemical changes in markers of thrombosis suggestive of induction of fibrinolysis. No safety signals emerged.

Pharmacology: Crizanlizumab is administered 5.0 mg/kg intravenously over 30 min in patients with SCD. Crizanlizumab is 100% bioavailable. The median time to reach maximum concentration is 1.6 h. The volume of distribution is 4.3 L after a single dose in healthy volunteers. The half-life is 10.6 d. The route of elimination is not through the liver or kidneys.

Safety: Crizanlizumab is generally well-tolerated. In a randomized, double-blind, placebo-controlled trial (SUSTAIN) of 198 patients, serious adverse events were reported in 55 patients, including 17 patients in the placebo group, 21 in the low dose crizanlizumab group, and 17 in the high dose crizanlizumab group. The serious adverse events that occurred in ≥2 patients in either active treatment group and at a higher frequency than in the placebo group were pyrexia and influenza. A total of 5 patients died during the trial, including 2 patients in the high-dose crizanlizumab group (1 patient from the acute chest syndrome, and 1 from endocarditis and sepsis), 1 in the low-dose crizanlizumab group (from the acute chest syndrome, aspiration, respiratory failure, and progressive vascular congestion), and 2 in the placebo group (1 from right ventricular failure, and 1 from vaso-occlusive crisis, ischemic stroke, coma, sepsis, and venous thrombosis of the right lower limb). Three, single-occurrence adverse events considered to be both serious and

life-threatening, but that did not result in death included: sepsis (in the placebo group), anemia (in the low-dose crizanlizumab group), and intracranial hemorrhage (in the low-dose crizanlizumab group). The patient with intracranial hemorrhage was being treated with ketorolac at the time of the event, which is associated with an increased risk of hemorrhagic stroke. No other clinically significant bleeding events were observed in the trial. Adverse events that occurred in ≥10% of patients in either active-treatment group were headache, back pain, nausea, arthralgia, pain in upper and lower limbs, urinary tract infection, upper respiratory tract infection, pyrexia, diarrhea, musculoskeletal pain, pruritus, vomiting, and chest pain[5]. Adverse events that occurred in ≥10% of patients in either active treatment group and at a frequency that was at least twice as high as that in the placebo group were arthralgia, diarrhea, pruritus, vomiting, and chest pain[5].

Infusion-related reactions: Administration of monoclonal antibodies can be associated with infusion-related reactions (IRR). In the SUSTAIN trial of crizanlizumab to prevent vaso-occlusive events in patients with SCD, IRRs were more frequent in the 5 mg/kg arm (23 patients, 34.8%) than placebo arm (13 patients, 21.0%). However, only 1 event, nausea, was reported in at least 10% of patients: 10.6% vs. 1.6% patients in 5 mg/kg vs. placebo arm, respectively. Except for nausea, none of the events were reported with an absolute difference of more than 5% in the crizanlizumab 5 mg/kg arm vs. placebo. A review of potential IRR events revealed few cases supportive of typical IRRs. None of these AEs were suggestive of severe allergic or anaphylactic reactions. Most patients continued their treatments without need for premedication[5].

A9.2 Eligibility Criteria for Arm E

A9.2.1 Inclusion Criteria for Arm E

Inclusion criteria contained in the master protocol in addition to the following:

Moderate illness severity – defined as non-ICU level of care at the time of randomization (not receiving high flow nasal oxygen (HFNO), non-invasive ventilation (NIV), invasive ventilation (IV), vasopressors or inotropes, or extracorporeal membrane oxygenation (ECMO)
OR
Severe illness severity – defined as ICU level of care at the time of randomization (receiving HFNO, NIV, IV, vasopressors or inotropes, or ECMO)

For moderate illness severity, participants are required to meet one or more of the following risk criteria:

1. Age ≥ 65 years *or*
2. *≥2 of the following:*
    - O_2 supplementation > 2 liters per minute
    - BMI ≥ 35
    - GFR ≤ 60
    - History of Type 2 diabetes
    - History of heart failure (regardless of ejection fraction)
    - D dimer ≥ 2x the site's upper limit of normal (ULN)
    - Troponin ≥ 2x the site's ULN
    - BNP≥100 pg/mL or NT-proBNP≥300 pg/mL
    - CRP ≥50 mg/L

A9.2.2 Exclusion Criteria for Arm E

- Exclusion criteria contained in the master protocol, and

- Any condition that, in the opinion of the investigator, precludes the use of crizanlizumab such as uncontrolled bleeding or severe anemia (hemoglobin<4 g/dL)
- Open label treatment with crizanlizumab within the past three months

A9.3 Study Agent

Arm E consists of the combination of standard of care plus crizanlizumab. Please refer to the manual of operations for recommended standard of care, including standard of care antithrombotic therapy for moderate and severe illness severity, respectively.

A9.3.1. Crizanlizumab

Crizanlizumab is a monoclonal IgG2 kappa humanized antibody to P-selectin. In patients randomized to receive crizanlizumab, the drug will be administered intravenously as a fixed-dose, one-time infusion of 5.0mg/kg over 30 minutes.

In the pivotal SUSTAIN trial[5] of crizanlizumab for the prevention of vaso-occlusive events in patients with SCD, there were a total of 198 patients, of which 67 patients received high-dose crizanlizumab at a dose of 5mg/kg administered every 2 weeks, 66 patients received low-dose crizanlizumab at a dose of 2.5mg/kg administered every two weeks, and 65 patients received placebo. High-dose crizanlizumab was found to be effective in this trial. The FDA has subsequently approved the use of crizanlizumab 5.0 mg/kg every two weeks to prevent vaso-occlusive disease in patients with SCD.

In a randomized controlled pilot trial of crizanlizumab in COVID-19 (NCT04435184), patients were randomly assigned in a 1:1 ratio to receive double-blind treatment with one intravenous dose of crizanlizumab 5.0 mg/kg or placebo as a single dose. A total of 54 patients fulfilled study entry criteria, and were randomized to receive crizanlizumab (n = 27) or placebo (n = 27). In total, 25 patients received crizanlizumab, and 25 patients received placebo, and the primary endpoint was available in 22 patients in the crizanlizumab group and 20 in the placebo group. Crizanlizumab infused as a single intravenous dose of 5.0 mg/kg was associated with 89% (95% Confidence Interval: 93% to 80%) reduction in P-selectin levels relative to baseline by day 3 or before discharge.

Pharmacology: Crizanlizumab is administered intravenously and is 100% bioavailable. The median time to reach maximum serum concentration (Tmax) was 1.6 hours at steady-state following an intravenous administration of 5 mg/kg over 30 minutes in SCD patients. Distribution is typical of endogenous human antibodies within the vascular and extracellular spaces. The volume of distribution at steady state (Vz) was 4.3 L after a single 5 mg/kg intravenous infusion in healthy volunteers. Antibodies are predominately eliminated via proteolysis by lysosomal enzymes into small peptides and amino acids. In healthy volunteers, the mean terminal elimination half-life (T1/2) was 10.6 days, and the mean clearance was 11.7 mL/hr at a dose level of 5 mg/kg. In patients with SCD, the mean apparent T1/2 during dosing interval was 7.6 days, and the estimated clearance was 17.2 mL/hr. There was no indication of accelerated clearance or time-dependent change in the PK properties of crizanlizumab following repeated administration. No dedicated studies have been conducted to evaluate specific pathways of crizanlizumab excretion or to investigate the pharmacokinetics PK of crizanlizumab in patients with renal or hepatic impairment since antibodies are not metabolized by cytochrome P450 enzymes, and the kidneys or liver are not a major organ for antibody metabolism or excretion.

Interactions between crizanlizumab and other medicinal products have not been investigated in dedicated studies. Monoclonal antibodies are not metabolized by cytochrome P450 (CYP450) enzymes. Therefore, medicinal products that are inhibitors or inducers of CYP450 are not expected to affect the PK of crizanlizumab. Concomitant medications, including Hydroxyurea/Hydroxycarbamide, did not affect crizanlizumab PK in patients with SCD in clinical studies.

Based on the data generated to date, crizanlizumab does not have a clinically relevant effect on the QT interval. The relationship between crizanlizumab exposure and changes in QTc from baseline (ΔQTc) was assessed using a linear mixed-effects model in pooled data from 66 healthy subjects for whom at least 1 valid time-matched PK-ECG measurement was available. The model estimated mean ΔQTc at steady-state Cmax observed in SCD patients was 0.23 ms (90% CI: -0.72, 1.20 ms). This effect is not clinically relevant since the upper 90% CI is well below the regulatory threshold of change in QTc interval of 10 ms.

Storage: Crizanlizumab must be stored at a temperature between 2°C to 8°C (36°F to 46°F) in the original carton. Crizanlizumab must be stored separately from ordinary hospital stocks and must be stored in a securely locked area accessible only to authorized trial personnel until dispensed. The temperature must be monitored and documented on the appropriate form for the entire time that the investigational product is at the trial site. If the storage temperature deviates from the permitted range, crizanlizumab must not be administered, and the Site Investigator or responsible person should contact the DCC for further instructions.

Administration: The pharmacist or designated personnel will prepare individual doses of crizanlizumab for subjects on a milligram per kilogram basis (at a dose of 5 mg/kg) in a 100 mL infusion bag according to the guidance in the prescribing information for crizanlizumab. Crizanlizumab will be administered over 30 minutes by intravenous infusion as soon as possible after randomization.

A9.3.3 Participants receiving additional monoclonal antibody treatment(s)

Co-administration or prior administration of a monoclonal antibody as part of standard of care or as part of another investigational treatment is permitted. However, efforts should be made to avoid intravenous monoclonal antibody therapy in the 36 hours prior to and 36 hours after crizanlizumab infusion unless it is felt to be medically necessary.

A9.3.4 Participants who become pregnant within 90 days of study treatment

Sexually active men and women of childbearing potential must use highly effective form(s) of birth control (contraception) for at least 15 weeks (105 days) after crizanlizumab infusion. Pregnancy status in female participants of childbearing potential and partners of sexually active male participants will be obtained at the 90-day follow-up assessment. If pregnancy is reported, site investigators will report a serious adverse event and obtain verbal consent from participants to obtain contact information for the participant's treating physician/obstetrician for further follow up. If consent is obtained, the study team may provide details to the treating physician/obstetrician (including DOB) to help identify the patient of interest. Novartis safety team may contact treating physicians to obtain further information on pregnancy outcomes using a study assigned participant ID that will be provided to both parties (Novartis and treating physician.) Participant direct identifiers will not be provided to the drug supplier, Novartis.

A9.4 Duration of treatment

Crizanlizumab is administered as a single, one-time infusion, and duration of action is known to extend up to one month in studies of patients with SCD.

A9.5 Discontinuation of study intervention

Discontinuation during study infusion is based on unexpected or other adverse events during infusion. The overall duration of infusion is less than 30 minutes. If study drug is discontinued due to an unexpected or adverse event during infusion, re-initiation will not be allowed.

A9.6 Study Schedule

Activity	Screening/ Enrollment	Hospital Duration	28 days or hospital discharge+	90 days post randomization and long term follow-up++
Eligibility				
Consent	X			
Demographic and Medical History	X			
Assessment of Inclusion/Exclusion criteria	X			
Self-reported race/ethnicity and sex	X			
Pregnancy Test, for women of childbearing potential	X			
Study Drug Administration				
Randomization	X			
Study treatment (infusion)	X	X		
Study Procedures				
Height	X			
Weight	X			
Vital signs	X	X		
Concomitant medications	X	X		
WHO ordinal assessment	X	X	X	X
Quality of Life and Functional Status#	X			X
Outcomes assessment		X	X	X
Pregnancy Outcomes				X
SOC Laboratory Assessments				
Chemistry panel	X	X	X	
CBC with platelet count	X	X	X	
Blood Group*	X			
PT, PTT if known	X	X		
D-dimer***	X	X	X	
Troponin****	X	X	X	
Coagulation and inflammatory markers*****	X	X	X	
Optional Biorepository	X	X		

BNP or NT-proBNP*****	X	X	X	

*Blood group taken from hospital record or self-report if that is not available.
** Frequency and mode (Anti-factor Xa/PTT) of testing will be based on site routine. Anti-factor Xa monitoring is preferred over PTT
*** Baseline D-dimer is recommended. All values collected should be recorded.
****Strongly recommended as part of routine care, all values collected should be recorded
*****Optional, listed in case report form
#Participants may be assessed for functional status and quality of life that reflects baseline status pre-COVID illness and functional status and quality of life at 90 days when contacted to ascertain vital status. (Instruments detailed in the manual of operations).
+Assessments indicated in the table above will be ascertained at discharge or 28 days, whichever comes first. Participants must be followed for vital status until discharged from the hospital or another care facility (if transferred on organ support) for up to 90 days. To maximize retention, participants will be contacted intermittently post-discharge and that contact will be recorded in the EDC
++Participants will be contacted to ascertain pregnancy and vital status. Pregnancy tests will not be administered.

A9.7 Potential Risks & Benefits

A9.7.1 Known and Potential Risks

Participants are monitored as per standard of care to minimize the risk of bleeding or developing clots. The crizanlizumab group may receive anticoagulants or additional antithrombotic therapies as part of standard care and thus could be at higher risk of bleeding.

Administration of monoclonal antibodies can be associated with infusion-related reactions (IRR). In the SUSTAIN trial of crizanlizumab to prevent vaso-occlusive events in patients with SCD, IRRs were more frequent in the 5 mg/kg arm (23 patients, 34.8%) than placebo arm (13 patients, 21.0%). However, only 1 event, nausea, was reported in at least 10% of patients: 10.6% vs. 1.6% patients in 5 mg/kg vs. placebo arm, respectively. Except for nausea, none of the events were reported with an absolute difference of more than 5% in the crizanlizumab 5 mg/kg arm vs. placebo. A review of potential IRR events revealed few cases supportive of typical IRRs. None of these AEs were suggestive of severe allergic or anaphylactic reactions. Most patients continued their treatments without need for premedication[5].

Interactions between crizanlizumab and other medicinal products have not been investigated in dedicated studies. Monoclonal antibodies are not metabolized by cytochrome P450 (CYP450) enzymes. Therefore, medicinal products that are inhibitors or inducers of CYP450 are not expected to affect the PK of crizanlizumab. Concomitant medications, including Hydroxyurea/Hydroxycarbamide, did not affect crizanlizumab PK in patients with SCD in clinical studies.

Based on the data generated to date, crizanlizumab does not have a clinically relevant effect on the QT interval. The relationship between crizanlizumab exposure and changes in QTc from baseline (ΔQTc) was assessed using a linear mixed-effect model in pooled data from 66 healthy subjects for whom at least 1 valid time-matched PK-ECG measurement was available. The model estimated mean ΔQTc at steady-state Cmax observed in SCD patients was 0.23 ms (90% CI: -0.72, 1.20 ms). This effect is not clinically relevant since the upper 90% CI is well below the regulatory threshold of change in QTc interval of 10 ms.

There is no evidence that crizanlizumab causes a reduction in circulating platelets or has a pro-aggregant effect in vivo. In pooled data from SUSTAIN and the single-arm CSEG101A2202 trial, 111 patients with SCD received the 5mg/kg dose of crizanlizumab, of which 15 patients (13.5%) had any thrombocytopenia, and 3 patients (2.7%) had Grade 3 or 4 thrombocytopenia. These rates of thrombocytopenia were similar to that of SCD patients given placebo. Among 28 healthy volunteers dosed with 5mg/kg of crizanlizumab, one patient had thrombocytopenia.

Crizanlizumab can cause lab testing artifacts in automated platelet counts. Platelet counts in blood drawn from patients can show false low platelet levels due to platelet clumping in the test tube. To mitigate the potential for this laboratory test interference, it is recommended to run the respective test as soon as possible (within 4 hours of blood collection) or use citrate tubes. When needed, platelet counts can be estimated via a peripheral blood smear.

P-selectin plays a role in the initial recruitment of leukocytes to the site of injury during inflammation. Therefore, crizanlizumab could potentially be associated with an increased risk for infections. In the SUSTAIN trial, urinary tract infection occurred in 9 (14%) of patients allocated to the high dose crizanlizumab group, 7 (11%) patients allocated to the low dose crizanlizumab group, and 7 (11%) patients allocated to placebo. Upper respiratory tract infection rates were similar across groups, occurring in 7 (11%) of patients allocated to the high dose crizanlizumab group, 7 (11%) patients allocated to the low dose crizanlizumab group, and 6 (10%) patients allocated to placebo. In pooled data from SUSTAIN and the single-arm CSEG101A2202 trial, a total of 111 patients received the 5mg/kg dose of crizanlizumab, of which 13 (11.7%) had upper respiratory tract infection. Lower respiratory tract infection occurred in 1 (0.9%) patient. Among healthy controls in a Phase I study to the PK/PD of crizanlizumab, viral upper respiratory tract infection occurred in 3 subjects (10.7%) who received crizanlizumab at a higher dose of 7.5 mg/kg. In summary, no increased frequency or severity of infections has been observed in clinical studies with crizanlizumab to date.

A9.7.2 Known Potential Benefits

A substantial and growing body of evidence suggests that endothelial injury is widespread and may link inflammation and thrombosis in severe COVID-19 disease. Endothelial granules contain VWF and P-selectin, which are released by exocytosis in response to endothelial injury. Following release, P-selectin is displayed on the surface of endothelial cells and serves to anchor VWF multimers to the cell surface. These mechanisms may contribute to the micro and macro thrombotic complications common in severe disease.

This arm seeks to test the hypothesis that the P-selectin inhibitor crizanlizumab, in addition to standard of care, would decrease adverse outcomes, including death, organ support free days, and micro and macro thrombosis. There is a potential benefit of identifying thrombus or bleeding more rapidly based on close study monitoring. This trial will contribute to the body of generalizable knowledge about this therapy and the role of P-selectin in COVID-19 disease.

A9.8 Event Adjudication

A subset of thrombotic events will be centrally adjudicated, with the proportion adjusted as needed based on agreement between the site and the event committee.

A9.9 Safety Analyses

The rate of infusion-related SAEs will be monitored. The rates of ISTH major bleeding, ICH and fatal bleeds, major thrombotic events, and mortality will be monitored in comparison to the standard of care arm as well as to any additional arms added to the platform trial. The DSMB will review the number of events, the event rates, and the posterior mean and 95% credible intervals for the event rates, difference between arms, and odds-ratios between arms will be summarized.

A9.10 Statistical Analyses

This arm will be compared to the Crizanlizumab standard of care arm. Patients eligible for Crizanlizumab will be randomized to either Crizanlizumab or no Crizanlizumab. These same patients may be randomized to other therapies within this master protocol. The comparison will be between those randomized to Crizanlizumab vs those randomized to no Crizanlizumab.

The primary Bayesian statistical model (see Statistical Analysis Plan) will be used for modeling the effect of Crizanlizumab in comparison to no Crizanlizumab with the following exceptions:

1. The model will contain a main effect for each other therapy that was randomized for each patient.
2. Site will not be included in the primary analysis model, but instead the country for the site will be included.

The Statistical Analysis Plan presents the interim analysis schedule and adaptive decision rules.

The primary analysis for Crizanlizumab will be restricted to only patients in the intent-to-treat for Crizanlizumab. This group are those patients that have been randomized to potentially receive Crizanlizumab. No patients that were not randomized to yes/no for Crizanlizumab will be used in the primary analysis for Crizanlizumab.

A9.11 Safety Reporting

The following safety information should be reported:

- Serious Adverse Events (SAEs), excluding study endpoints, in patients exposed to crizanlizumab should be reported within 14 calendar days of becoming aware of it, including those which may have been the reason for the patient to discontinue infusion.
- Any other relevant safety information listed below in patients exposed to crizanlizumab should be reported within 14 calendar days of becoming aware of it:
    - overdose (with or without clinical symptoms),
    - intentional drug misuse/abuse (with or without clinical symptoms),
    - medication errors (including maladministration, dispensing or prescribing errors, with or without clinical symptoms),
    - suspected drug-drug or drug-food interaction (with or without clinical symptoms)
    - Pregnancy within 90 days of receiving crizanlizumab

A9.12 References

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Appendix 10: Standard of care plus SGLT2 inhibitor

A10.1 Background and Rationale for Arm F

Patients who are hospitalized with coronavirus disease 2019 (Covid-19) remain at high risk for multi-organ failure and death. Given the dearth of efficacious therapies that reduce the risk of major clinical events, there is a large unmet need for additional treatment options.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors provide organ protection and reduce cardiovascular and kidney events in large trials of predominantly ambulatory patients with type 2 diabetes, cardiovascular and/or kidney disease (1-3). Although the mechanisms underlying these benefits remain a subject of investigation, prior studies have shown that SGLT2 inhibitors favorably affect a number of pathways that are dysregulated in the setting of acute illness (including Covid-19) such as inhibition of glycolysis (a pathway that can be used by respiratory pathogens) and stimulation of lipolysis, reduction in oxidative stress and inflammation, as well as improved endothelial function and oxygen carrying capacity, and protection against capillary leak (4-11). These effects may help prevent multi-organ damage and improve recovery in Covid-19.

A previous large trial of SGLT2 inhibitor dapagliflozin in patients with chronic kidney disease demonstrated significant reduction in all-cause death, driven predominantly via lower rates of non-cardiovascular (and specifically infection-related) death (12). Large observational studies have also suggested lower risk of major clinical events in patients hospitalized with Covid-19 that were on background SGLT2 inhibitor therapy (13).

The effectiveness and safety of SGLT2 inhibitor dapagliflozin was investigated in the Dapagliflozin in Respiratory Failure in Patients with Covid-19 (DARE-19) which randomized 1250 patients with cardiometabolic risk factors hospitalized with Covid-19 across 7 countries and 95 sites to either dapagliflozin 10 mg daily or placebo for 30 days (14). Treatment was continued in case of patients' clinical status deterioration requirining ICU level care, and regardless of hospital discharge. Fewer patients treated with dapagliflozin experienced the composite endpoint of respiratory, cardiovascular or kidney failure, or death from any cause at 30 days (HR 0.80, 95% CI 0.58-1.10); although this was not statistically significant, the trial only accrued 156 of the initially planned 380 events (due to a large decline in event rates during the course of the trial) and therefore did not have sufficient power for this endpoint. Importantly, the results were directionally favorable to dapagliflozin across each component of this composite outcome, including death from any cause (HR 0.77, 95% CI 0.52 – 1.16).

Dapagliflozin was well tolerated, with fewer serious adverse events than placebo.

Dapagliflozin is considered as the preferred SGLT2 inhibitor for this arm of the trial, given the following considerations: 1) it is the only agent in the class for which the efficacy and safety data from randomized controlled trials in patients hospitalized with Covid-19 is available 2) it has a well established safety profile across various patient populations and 3) extensive clinical experience and broad availability in more than 90 countries. However, because the potential benefits of SGLT2i are expected to represent a class effect, other SGLT2 inhibitors (such as empagliflozin) can be used if dapagliflozin is not available at the participating hospital site.

Pharmacology: Dapagliflozin is a highly selective SGLT2 inhibitor that is administered at the dose of 10 mg once daily, via enteral route. Dapagliflozin is 78% bioavailable. The median time to reach

maximum concentration is 2 h. The half-life is 12.9 h. The route of elimination is via kidneys and GI tract.

Empagliflozin is a highly selective SGLT2 inhibitor that is administered at the dose of 10 mg once daily, via oral route. The median time to reach maximum concentration is 1.5 h. The half-life is 12.4 h. The route of elimination is via kidneys and GI tract.

Safety: Dapagliflozin has been used extensively in clinical practice (predominantly for management of Type 2 diabetes and heart failure) since its approval (in European Union) in 2011, has been evaluated in tens of thousands of patients in clinical trials across Type 2 diabetes, heart failure and chronic kidney disease, and prescribed to millions of patients (with marketing authorization in more than 90 countries).

The safety of dapagliflozin in patients hospitalized with Covid-19 was specifically evaluated in the DARE-19 Trial, where it was well tolerated. Specifically, fewer patients treated with dapagliflozin as compared with placebo experienced serious adverse events (including fatal SAEs), adverse events leading to discontinuation of study medication, and adverse events of acute kidney injury. Due to potential concerns regarding the risk of diabetic ketoacidosis in patients treated with dapagliflozin, a proactive surveillance program was used in the DARE-19 trial, with mandatory daily monitoring of acid-base status among those with Type 2 diabetes (15). Only 2 cases of DKA were observed in patients treated with dapagliflozin (versus 0 with placebo). Both of these occurred in patients with Type 2 diabetes, were non-severe, and resolved rapidly after discontinuation of study medication.

A10.2. Eligibility Criteria for Arm F

A10.2.1 Inclusion Criteria for Arm F

Inclusion criteria contained in the master protocol in addition to the following:

Moderate illness severity – defined as non-ICU level of care at the time of randomization (not receiving high flow nasal oxygen (HFNO), non-invasive ventilation (NIV), invasive ventilation (IV), vasopressors or inotropes, or extracorporeal membrane oxygenation (ECMO))
OR
Severe illness severity – defined as ICU level of care at the time of randomization (receiving HFNO, NIV, IV, vasopressors or inotropes, or ECMO)

For moderate illness severity, participants are required to meet one or more of the following risk criteria:

1. Age ≥ 65 years *or*
2. ≥*2 of the following:*
    - O_2 supplementation > 2 liters per minute
    - BMI ≥ 35
    - GFR ≤ 60
    - History of Type 2 diabetes
    - History of heart failure (regardless of ejection fraction)
    - D dimer ≥ 2x the site's upper limit of normal (ULN)
    - Troponin ≥ 2x the site's ULN
    - BNP≥100 pg/mL or NT-proBNP≥300 pg/mL
    - CRP ≥50 mg/L

A10.2.2 Exclusion Criteria for Arm F

In addition to the exclusion criteria noted in the master protocol, arm-specific exclusion criteria are as follows:

- Known hypersensitivity to any SGLT2 inhibitors
- Type 1 diabetes
- History of diabetic ketoacidosis
- eGFR <20 and/or requirement for renal replacement therapy
- Open label treatment with any SGLT2 inhibitor

A10.3 Study Agents

Arm F consists of the combination of standard of care plus an SGLT2 inhibitor (dapagliflozin preferred). Please refer to the manual of operations for recommended standard of care, including standard of care antithrombotic therapy for moderate and severe illness severity, respectively.

A10.3.2. SGLT2 inhibitors

Dapagliflozin (preferred SGLT2 inhibitor for this arm) is a highly selective sodium glucose cotransporter 2 (SGLT2) inhibitor. In patients randomized to receive SGLT2 inhibitors, dapagliflozin (or empagliflozin) will be administered orally at 10 mg once daily. If patient requires intubation and mechanical ventilation, or cannot receive oral medications for another reason, the tablet can be crushed and flushed down the feeding tube.

In the international, multi-center, double-blind, placebo-controlled DARE-19 trial of dapagliflozin for prevention of organ failure or death in patients hospitalized with Covid-19, fewer patients treated with dapagliflozin experienced the composite endpoint of respiratory, cardiovascular or kidney failure, or death from any cause ((HR 0.80, 95% CI 0.58-1.10); although this was not statistically significant due to fewer accrued events than originally anticipated. The results were directionally favorable to dapagliflozin as compared with placebo for each component of this composite outcome (respiratory, cardiovascular, kidney decompensation, and death from any cause). Dapagliflozin was well tolerated, with fewer serious adverse events than placebo.

Dapagliflozin is considered as the preferred SGLT2 inhibitor for this arm of the trial, given the following considerations: 1) it is the only agent in the class for which the efficacy and safety data from randomized controlled trials in patients hospitalized with Covid-19 is available 2) it has a well established safety profile across various patient populations and 3) extensive clinical experience and broad availability in more than 90 countries. However, because the potential benefits of SGLT2i are expected to represent a class effect, other SGLT2 inhibitors (such as empagliflozin) can be used if dapagliflozin is not available at the participating hospital site.

Pharmacology: The main action of SGLT2 inhibitors is enhanced excretion of glucose and sodium via inhibition of sodium glucose cotransporter 2 in the proximal tubule. Dapagliflozin is administered enterally, and is 78% bioavailable. The median time to reach maximum serum concentration (Tmax) is 2 hours. The mean terminal elimination half-life (T1/2) is 12.9 hours. Dapagliflozin is predominantly excreted via kidneys (75%) and GI tract (21%). Empagliflozin is a highly selective SGLT2 inhibitor that is administered at the dose of 10 mg once daily, via enteral route. The median time to reach maximum concentration is 1.5 h. The half-life is 12.4 h. The route of elimination is via kidneys (54%) and GI tract (41%).

There are no meaningful drug-drug interactions reported with dapagliflozin (or empagliflozin), with exception of enhanced glucose-lowering when co-administered with insulin or insulin secretagogues.

Storage: SGLT2 inhibitors will be stored per local pharmacy policies and procedures.

Administration: Dapagliflozin (or empagliflozin) will be administered orally (or via feeding tube, if applicable) at the dose of 10 mg daily. The first dose should be administered as soon as possible after randomization.

A10.3.3 Participants receiving additional Covid-19 therapies

Co-administration or prior administration of other Covid-19 therapies (other than an SGLT2 inhibitor) as part of standard of care or as part of another investigational therapy is permitted.

A10.4 Participants who become pregnant within 90 days of study treatment

Sexually active women of childbearing potential must use highly effective form(s) of birth control (contraception) until the treatment with an SGLT2 inhibitor has been completed. If a participant reports being pregnant during the 28 day treatment period the SGLT2 inhibitor will be permanently discontinued.

A10.5 Duration of treatment

Treatment with dapagliflozin (or empagliflozin/another SGLT2 inhibitor) will be continued through Day 28.

A10.6 Discontinuation of study intervention

At any time, patients are free to discontinue treatment or withdraw from the study, without prejudice to further treatment. A patient that decides to discontinue treatment will always be asked about the reason(s).

Discontinuation from investigational product is not the same as complete withdrawal from the study. It is essential to collect data for all patients throughout the study. For that reason, a patient who discontinues treatment should optimally continue to follow up study assessments up to and including day of discharge (or Day 28). Alternatively, if the patient does not agree to this approach, modified follow-up should be arranged (eg, less frequent assessments, one contact at Day 30, or other means). Patients who agree to some kind of modified follow up are still participating in the study.
If a patient for some reason cannot be reached during the study, every attempt should be made to retrieve as much information regarding this patient as possible. The site should continuously try to reach the patient, the patient's family, or pre-identified contact person and search for information regarding the patient's status in applicable sources to protect the validity of data. These attempts should be documented.

A10.7 Study Schedule

Activity	Screening/ Enrollment	Hospital Duration	28 days or hospital discharge[+]	90 days post randomization and long term follow-up[++]
Eligibility				
Consent	X			
Demographic and Medical History	X			
Assessment of Inclusion/Exclusion criteria	X			
Self-reported race/ethnicity and sex	X			
Pregnancy Test, for women of childbearing potential	X			
Study Drug Administration				
Randomization	X			
Study treatment	X	X	X	
Study Procedures				
Height	X			
Weight	X			
Vital signs	X	X		
Concomitant medications	X	X		
WHO ordinal assessment	X	X	X	X
Quality of Life and Functional Status[#]	X			X
Outcomes assessment		X	X	X
SOC Laboratory Assessments				
Chemistry panel	X	X	X[^]	
CBC with platelet count	X	X	X	
Blood Group*	X			
PT, PTT if known	X	X		
D-dimer***	X	X	X	
Troponin****	X	X	X	
Coagulation and inflammatory markers*****	X	X	X	
Optional Biorepository	X	X		
BNP or NT-proBNP *****	X	X	X	

^Chemistry panel (e.g. creatinine, acid-base) is strongly recommended to be measured at days 1,3,7,14, and at hospital discharge. Monitoring of acid-base balance in patients with T2DM during hospitalization represents a standard of care in most institutions; if there is a clinical concern for DKA due to acid base status, this should be further investigated (see A10.8.1).
*Blood group taken from hospital record or self-report if that is not available.
** Frequency and mode (Anti-factor Xa/PTT) of testing will be based on site routine. Anti-factor Xa monitoring is preferred over PTT
*** Baseline D-dimer is recommended. All values collected should be recorded.
****Strongly recommended as part of routine care, all values collected should be recorded
*****Optional, listed in case report form

[#]Participants may be assessed for functional status and quality of life that reflects baseline status pre-COVID illness and functional status and quality of life at 90 days when contacted to ascertain vital status. (Instruments detailed in the manual of operations).
[+]Assessments indicated in the table above will be ascertained at discharge or 28 days, whichever comes first. Participants must be followed for vital status until discharged from the hospital or another care facility (if transferred on organ support) for up to 90 days. To maximize retention, participants will be contacted intermittently post-discharge, and that contact will be recorded in the EDC. For participants discharged prior to Day 28, this will include information about treatment adherence, to be collected as close to 30 days post-randomization as possible.
[++]Participants will be contacted to ascertain vital status.

A10.8 Potential Risks & Benefits

A10.8.1 Known and Potential Risks

The standard of care plus SGLT2 inhibitor group may receive anticoagulants and/or antiplatelet or additional antithrombotic therapies agents as part of standard care. SGLT2 inhibitors are not known to have any impact on bleeding or thrombosis.

The safety profiles of dapagliflozin (and empagliflozin) are already well established from prior clinical studies in various clinical settings. These studies have demonstrated that SGLT2 inhibitors are generally safe and well tolerated.

Dapagliflozin and empagliflozin, as inhibitors of SGLT2, increase urinary glucose excretion, which is commonly believed to increase the risk of urinary tract infections. Urinary tract infections have been reported in dapagliflozin-treated patients in a slightly higher proportion than in placebo-treated patients in some global Phase III studies, although the rates of urinary tract infections (and serious urinary tract infections) observed in large clinical trials of dapagliflozin and other SGLT2i have been similar to placebo (16, 2). Increased urinary glucose excretion may also lead to an increased risk of developing genital infections. Genital infections are considered common side effects (in ≥1/100 to <1/10 patients), but the risk of these events is considered to be low due to the brief duration of treatment planned in this trial.

Dapagliflozin and empagliflozin modestly reduce blood pressure and may reduce blood volume from their diuretic effects, which could be a potential concern in patients with Covid-19. A pooled analysis of patients with T2DM and HF in the dapagliflozin development program, showed no increase of volume depletion events (17). In DARE-19 trial, there was no indication of increased risk for volume depletion and the number of acute kidney injury events was lower with dapagliflozin as compared with placebo.

Neither dapagliflozin nor empagliflozin have been shown to induce hypoglycemia in non-diabetic patients. In clinical pharmacology studies of dapagliflozin, healthy subjects have been treated with single oral doses of up to 500 mg and multiple oral doses of 100 mg up to 14 days without any hypoglycemic events. However, in patients with T2DM and on insulin or sulfonylurea medication, there is an increased risk of hypoglycemia. Patients with T2DM will be monitored in the hospital as part of standard of care, which includes blood glucose monitoring.

There have been reports of ketoacidosis, including DKA, in patients with T2DM taking dapagliflozin and other SGLT2 inhibitors. Diabetic ketoacidosis (which may occur without substantial elevation of blood glucose values – i.e. euglycemic diabetic ketoacidosis) is considered a rare (in ≥1/10000 to <1/1000 patients) adverse drug reaction for dapagliflozin in patients with T2DM (15). Patients treated with dapagliflozin who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise, and shortness of breath, should be assessed

for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, interruption of dapagliflozin (and other SGLT2 inhibitor) therapy should be considered, and the patient should be evaluated promptly. Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (eg, type 1 diabetes, history of pancreatitis, or pancreatic surgery), insulin dose reduction, reduced caloric intake, or increased insulin requirements caused by infections, illness or surgery and alcohol use.

In DARE-19 trial, only two cases of DKA were reported in patients treated with dapagliflozin (versus 0 with placebo), both in patients with Type 2 diabetes; both were non-severe, and resolved quickly after discontinuation of study medication.

Appropriate measures are in place to monitor and minimize potential risks to participating patients, including the use of an DSMB that will continuously evaluate safety data. Patients with type 1 diabetes mellitus and patients with a history of DKA are excluded from this study. Monitoring of acid-base balance in patients with T2DM during hospitalization represents a standard of care in most institutions. Should there be an abnormal increase in anion gap and/or reduced bicarbonate levels, measurement of blood levels of ketones, lactate, and analysis of pH should be performed, and treatment with SGLT2 inhibitors should be temporarily discontinued, if DKA is suspected.

A diagnosis of DKA should only be made in a clinical setting consistent with DKA (based on patient history, symptoms, and physical exam) and in the absence of more likely alternative diagnoses and causes of acidosis (such as lactic acidosis). The following biochemical data should support diagnosis:

- Ketonemia ≥3.0 mmol/L and/or significant ketonuria (more than 2+ on standard urine sticks) in the absence of elevated lactate (lactate should be <2 mmol/L to be considered a potential DKA) and
- At least one of the following criteria suggesting high anion gap metabolic acidosis:
  - (a) Arterial or Venous pH ≤7.3
  - (b) Serum bicarbonate ≤18 mEq/L
  - (c) Anion gap [Na – (Cl + HCO3)] >10

If a diagnosis of DKA is confirmed, treatment with SGLT2 inhibitors should be permanently discontinued.

A10.8.2 Known Potential Benefits

Preliminary data from DARE-19 trial strongly suggest that use of SGLT2 inhibitors in patients hospitalized with Covid-19 may reduce the risk of organ failure or death from any cause via a number of pathophysiologic pathways, including favorable effects on endothelial function, oxidative stress, inflammation, oxygen-carrying capacity and tissue hypoxia, as well as through inhibition of glycolysis and lipogenesis.

This arm seeks to test the hypothesis that the SGLT2 inhibitors dapagliflozin or empagliflozin, on top of standard of care therapy, would decrease adverse events, including death and organ support free days. This trial will contribute to the body of generalizable knowledge about SGLT2 inhibitor therapy and the role of organ protection through SGLT2 inhibition in Covid-19 disease to minimize the risk of adverse events in patients hospitalized with Covid-19.

All patients in the study are expected to be treated optimally according to background local standard of care therapy, including treatments to control co-morbidities. SGLT2 inhibitors dapagliflozin or empagliflozin will be administered in addition to these treatments.
These patients are hospitalized and will receive close medical attention, irrespective of treatment allocation.

A10.9Event Adjudication

A subset of thrombotic events will be centrally adjudicated, with the proportion adjusted as needed based on agreement between the site and the event committee.

A10.10 Safety Analyses

The rate of SAEs (including DKA) will be monitored. The DSMB will review the number of events, the event rates, and the posterior mean and 95% credible intervals for the event rates, difference between arms, and odds-ratios between arms will be summarized.

A10.11 Statistical Analyses

This arm will be compared to the SGLT2 inhibitor standard of care arm. Patients eligible for SGLT2 inhibitor will be randomized to either an SGLT2 inhibitor or no SGLT2 inhibitor. These same patients may be randomized to other therapies within this master protocol. The comparison will be between those randomized to SGLT2 inhibitor vs those randomized to no SGLT2 inhibitor.

The primary Bayesian statistical model (see Statistical Analysis Plan) will be used for modeling the effect of SGLT2 inhibitor in comparison to no SGLT2 inhibitor with the following exceptions:

1. The model will contain a main effect for each other therapy that was randomized for each patient.
2. Site will not be included in the primary analysis model, but instead the country for the site will be included.

The Statistical Analysis Plan presents the interim analysis schedule and adaptive decision rules.

The primary analysis for SGLT2 inhibitor will be restricted to only patients in the intent-to-treat for SGLT2 inhibitor. This group are those patients that have been randomized to potentially receive an SGLT2 inhibitor. No patients that were not randomized to yes/no for SGLT2 inhibitor will be used in the primary analysis for SGLT2 inhibitor.

A10.12 Safety Reporting

Safety reporting will be the same as outlined in the Master Protocol. In addition, serious adverse events of DKA will be collected.

A10.13 References

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