Assessing Safety, Hospitalization and Efficacy of rNAPc2 in COVID-19 (ASPEN-COVID-19)

Subtitle: A Phase 2b Adaptive Study that Assesses the Efficacy in D-dimer Reduction and Safety of rNAPc2 Regimens versus Heparin in Hospitalized COVID-19 Patients

Protocol Number: NAPc-201/301

Principal Investigator: Marc Bonaca, MD, MPH

Sponsor: ARCA biopharma, Inc.

Version Number: 6.0

07 July 2021

Summary of Changes:

Affected Section(s)	Summary of Revisions Made	Rationale
Protocol V2.00 31Aug2020		
Synopsis, Section 4	• Sequential Phase 2/3 design with Phase 3 powered for standalone analysis • 2nd dose level of rNAPc2 added to Phase 2b • Manage distribution of subjects to prophylactic vs therapeutic dose heparin in Phase 2b • Local clinical laboratory assessments, research samples adjusted • Day 15 visit removed	• Enable unblinding, in depth analysis and possible amendments to Phase 3 portion of the protocol • Assess dose-response for safety and biomarker effects in target population; inform dose selection for Phase 3 • Facilitate assessment of heparin regimens vs rNAPc2 • Safety • Operational Considerations
Section 3	• Clarify Phase 2b objective & endpoints	• Clarity
Sectionssections 4.1, 6.3	• Separate stratification for remdesivir and for other therapies with demonstrated efficacy in COVID-19	• Distribute concurrent treatments among treatment groups
Section 5	• Exclusion criteria: platelet count, eGFR, bilirubin cutoffs added	• Safety
Section 6	• Recommended low molecular weight heparin (LMWH) specified	• Reduce variability
Section 9	• Statistical detail provided	• Clarity
Protocol V3.00 16Sep2020		
All	• Minor administrative updates	• Administrative/improve clarity
Section 1.2	• Updated schema to reflect all protocol v2.00 changes • Moved schedule of activities (SoA) to section 8.1.1	• Administrative/improve clarity
Section 3	• Separated phase 2b and phase 3 safety objectives in the table	• Administrative/improve clarity
Section 6.3	• Updated blinding information (participants and CEC will be blinded)	• Consistency throughout protocol

Section 8.1.1	• SoA moved here and updated	• Consistency with protocol v2.00 changes and improve clarity
Section 8.1.2	• Section added	• Clarify laboratory samples and values from SoA
Section 8.1.3	• Section added	• Elaborate on SoA
Section 8.2	• Clarification around clinical events and efficacy outcomes	• Administrative/improve clarity
Section 10.1.5	• Section added	• Clarify study committees
• **Protocol V4.00 28Oct2020**		
Throughout	• Changed "coagulation and inflammatory biomarkers" to "biomarkers associated with outcomes including those related to coagulation and inflammation"	• Clarity
Throughout	• Administrative updates	• Consistency and clarity
4.1 & 9.4.2	• Stratification changed from "ongoing treatment with remdesivir and other agents with demonstrated efficacy in patients with COVID-19" to "participant's local laboratory D-dimer level at screening"	• Removed as agents with demonstrated efficacy have become standard of care. D-dimer reflects disease severity
4.3 & 6.3	• Removed clinical sites will be designated as prophylactic or therapeutic	• Reflects evolution of standard of care
5.1	• Inclusion criterion 7 • Exclusion criterion 2 • Exclusion criterion 3	• Align language with intent
6.2.4	• Storage of prepared syringes of rNAPc2 updated.	• Clarity
6.3	• Site-based randomization	• Clarity
8.1.1 & 8.1.3	• Schedule of Activities (SoA) and visit descriptions updated to reflect daily clinical assessments	• Clarity
8.1.2	• Record local laboratory values for troponin, brain natriuretic peptide (BNP) and NT-proBNP	• Capture cardiac biomarkers
8.1.3	• Demographics moved to Screening visit; sex, childbearing potential, and race added	• Capture demographics for all screened participants

8.2	• Section re-arranged	• Clarity & consistency
9.4.3	• Analysis method for proportion of participants alive and out of the hospital at 30 days post-randomization added	• Clarity
9.4.6	• Alpha level for final analysis added	• Clarity
9.4.8	• Executive Committee (EC) Chair or representative will be a member of the Unblinded Review Committee (URC)	• Consistent with Data Safety Monitoring Committee charter
10.1.5	• DSMC unscheduled meetings and real-time notification for severe safety events	• Safety
• **Protocol V5.00 01Feb2021**		
Throughout	• Revision of primary efficacy endpoint to change in D-dimer from baseline to Day 8 or day of discharge, if discharge prior to Day 8	• Change based on additional clinical information for duration of hospitalization in COVID-19 patients.
Throughout	• Revision of primary safety endpoint to major or non-major clinically relevant bleeding within 8 days of randomization	• Changed to facilitate a more accurate assessment of bleeding events between rNAPc2 and heparin
5.3 & 8.1.2	• Revised to require negative pregnancy test for women of childbearing potential and clarification of effective contraception during the study	• Health Regulatory agency feedback
8.1	• Visits and central lab assessments revised to align with endpoints: add Day 2; change Day 8 to Day 8 or day of discharge, if discharge prior to Day 8; remove Day 10	• Changed based on additional clinical information for duration of hospitalization in COVID-19 patients
6.1.2	• Add clarification for standard of care thromboprophylaxis when fewer than 3 doses of rNAPc2 are prescribed (if patient is discharged prior to Day 5).	• Safety
6.5	• Clarification to prohibited concomitant medication use during	• Safety

	trial and concurrently with study drug administration.	
8.4.5	• Clarify AE/SAE reporting requirements, especially as related to expedited reporting	• Safety
Throughout	• Administrative updates throughout, including incorporation of appendices	• Clarity and consistency
• **Protocol V6.00 07Jul2021**		
Throughout	• Administrative updates	• Consistency and clarity
4.3	• Justification for dose	• Justification was expanded for clarity and to include additional detail from prior investigations
5.0	• Inclusion/Exclusion criteria clarifications	• In agreement with regulatory agency requests, some inclusion/exclusion criteria were revised to include additional details/clarification while preserving the intention of each modified criterion
5.1 & 5.3	• Added language requiring male patients to avoid partner pregnancy and sperm donation	• In agreement with regulatory agency request
8.1.2	• Removed central laboratory assessment of AST, ALT and bilirubin	• Remove duplication of laboratory assessments in line with standard of care site COVID-19 practices
8.5	• Removed Unanticipated Problem Section and Unanticipated Problem Reporting Section	• These sections did not inform clinical trial execution for ASPEN-COVID-19
9.0	• Increase to study sample size • Addition of an interim efficacy analysis and removal of Unblinded Review Committee • Clarification that primary endpoint analysis will evaluate proportional changes in D-dimer at Day 8; to be detailed in the statistical analysis plan	• Given the evolution of COVID-19 management since the start of ASPEN-COVID-19, the original rNAPc2 sample size and treatment effect assumptions were updated in order to increase experience in a diversity of COVID-19 patients. Changes in COVID-19 management that were considered include 1) evolving evidence for standard of care, 2) widespread use of several COVID-19 therapies of proven

		benefit, and 3) changes in background therapy.

Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
2.00	28Aug2020	Design adjustments prior to study initiation	Incorporate feedback
3.00	16Sep2020	Administrative adjustments prior to study initiation	Ensure consistency and clarity throughout the protocol
4.00	28Oct2020	Adjustments prior to study initiation	Incorporate feedback
5.00	01Feb2021	Update to endpoints and revision of laboratory assessments; Clarification on requirements for women of child-bearing potential and safety reporting	Scientific revision of endpoints; safety clarifications
6.00	07Jul2021	Clarification of some inclusion/exclusion based on regulatory agency review; increase of study sample size	Given the evolution of COVID-19 management since the start of ASPEN-COVID-19, the original rNAPc2 sample size and treatment effect assumptions were updated in order to increase experience in a diversity of COVID-19 patients

Protocol Approval Signature:

The signatory has reviewed and agrees to the content of the final clinical study protocol as presented.

Name:	Marc Bonaca, MD, MPH	Date
Role:	Study Principal Investigator	

Name:	Michael Bristow, MD, PhD	Date
Role:	Sponsor Representative	

Site Principal Investigator Signature:

The signatory has read the content of the final clinical study protocol and agrees to conduct the study as presented.

Signature: _____ Date: _____

Name: _____

Affiliation: _____

1 TABLE OF CONTENTS

STATEMENT OF COMPLIANCE

This study will be conducted in compliance with Good Clinical Practice (GCP) and applicable regulatory requirements.

STUDY ADMINISTRATION

Principal Investigator	Sponsor representatives
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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:

Assessing Safety, Hospitalization and Efficacy of rNAPc2 in COVID-19 (ASPEN-COVID-19)

Study Description:

This protocol describes sequential randomized, multicenter, active comparator studies evaluating the hypothesis that rNAPc2, a novel, potent and highly selective tissue factor inhibitor with anticoagulant, anti-inflammatory and potential antiviral properties, shortens time to recovery compared to heparin in hospitalized patients with COVID-19 and elevated D-dimer levels. The study utilizes a PROBE (Prospective Randomized Open-label, Blinded End-point) design. Study participants and Clinical Endpoint Committee (CEC) members assessing the clinical endpoints will be blinded to treatment assignment. The protocol comprises sequential Phase 2b and Phase 3 studies. Analysis of Phase 2b data could lead to study discontinuation, adjustment of eligibility criteria or sample size, and will inform the rNAPc2 dose regimen to be studied in Phase 3.

Objectives:

Phase 2b: The primary safety and efficacy objectives are to identify an rNAPc2 dosing regimen with an acceptable bleeding profile and which reduces D-dimer levels compared to standard of care (SoC) heparin regimens. Secondary and exploratory objectives are to compare the treatment groups in terms of biomarkers associated with outcomes including those related to coagulation and inflammation, as well as clinical and functional outcomes that will also be assessed during Phase 3.

Phase 3: The primary safety and efficacy objectives are to assess major or

non-major clinically relevant bleeding and whether rNAPc2 reduces time to recovery relative to heparin. Secondary and exploratory objectives are to compare the treatment groups in terms of a composite of thrombotic events and all-cause mortality; thrombotic events; all-cause mortality; biomarkers associated with outcomes including those related to coagulation and inflammation; health resource utilization; and post-COVID-19 functional status.

Endpoints:

Phase 2b

Primary efficacy endpoint: change in D-dimer level from Baseline to Day 8, or day of discharge if prior to Day 8.

Primary safety endpoint: major or non-major clinically relevant bleeding within eight (8) days of randomization as compared to heparin.

Secondary and exploratory efficacy endpoints: change in D-dimer level from baseline to 24h post-dose (Day 2) and Day 3, change in biomarkers associated with outcomes including those related to coagulation and inflammation from baseline through Day 8; other clinical and functional outcomes, including time to recovery as measured by the 8-point Adaptive COVID-19 Treatment Trial (ACTT) scale.

Secondary safety endpoints: major or non-major clinically relevant bleeding with rNAPc2 vs. heparin, bleeding with higher vs. lower dose rNAPc2 through Day 30, and other adverse events (AEs).

Phase 3

Primary efficacy endpoint: time to recovery within thirty (30) days of randomization using the ACTT ordinal scale.

Primary safety endpoint: major or non-major clinically relevant bleeding within eight (8) days of randomization as compared to heparin.

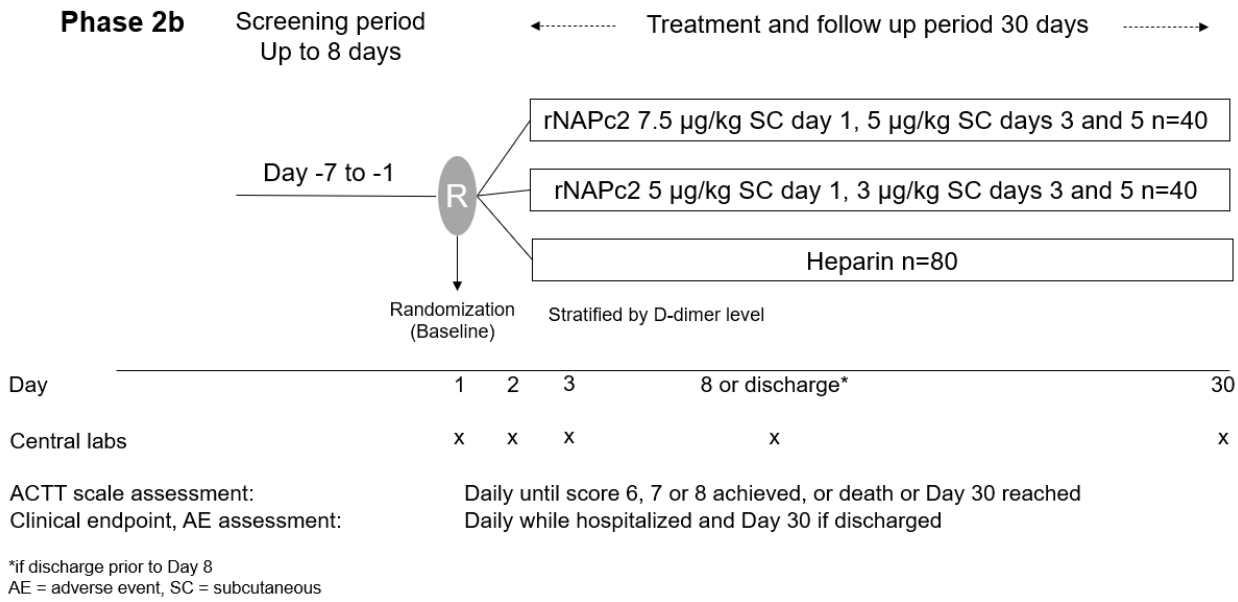
Secondary and exploratory efficacy endpoints: time to first occurrence of a composite of thrombotic events and all-cause mortality within thirty (30) days of randomization; time to first occurrence of thrombotic events within 30 days of randomization; time to all-cause mortality within thirty (30) days of randomization; change in biomarkers associated with outcomes including those related to coagulation and inflammation from Baseline through Day 8; proportion alive and out of hospital at thirty (30) days post-randomization; days in intensive care unit, on ventilator, vasopressors, renal replacement therapy, and circulatory support; Post-COVID Functional Status (PCFS) score at discharge and Day 30.

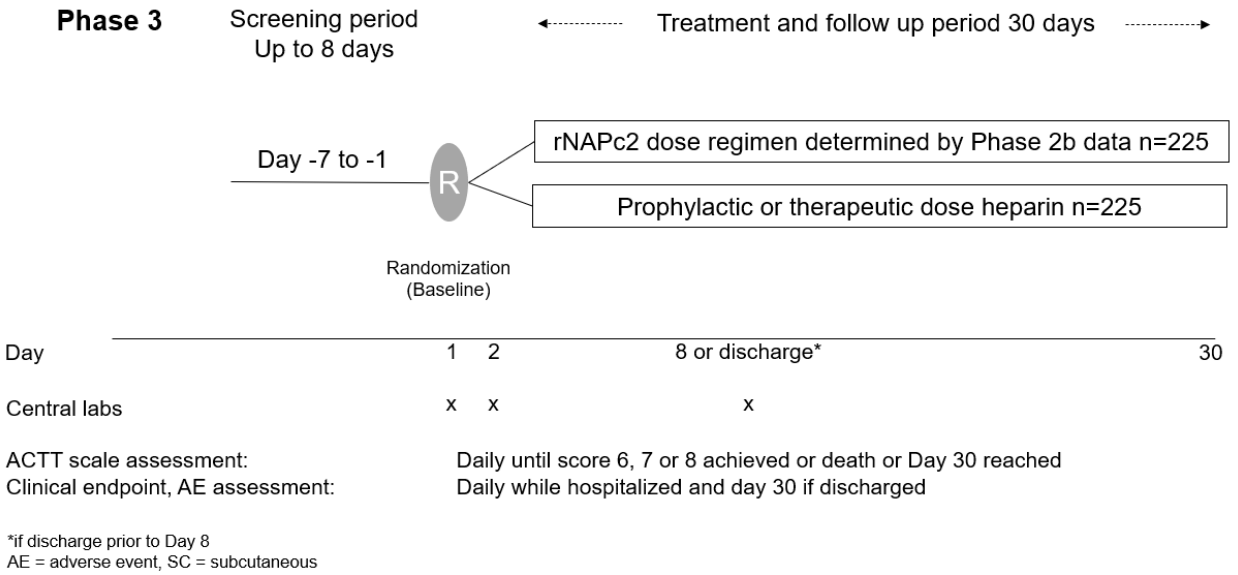
Secondary safety endpoints: major or non-major clinically relevant bleeding with rNAPc2 or heparin, and other AEs.

Study Population:	Phase 2b: Approximately 160 men or women enrolled at approximately 20 sites, 18 to 90 years of age with COVID-19 documented by a validated test such as polymerase chain reaction (PCR) within one (1) week of hospitalization or screening and D-dimer above the upper limit of normal. Phase 3: Approximately 450 additional participants (same criteria as listed for Phase 2b) at up to approximately 80 sites.
Phase:	2b/3
Description of Sites/Facilities Enrolling Participants:	Approximately 80 global clinical sites (in total between Phases 2b and 3) will be selected based on prior performance in randomized clinical trials and access to patients with COVID-19.
Description of Study Intervention:	Phase 2b: Participants will be randomly assigned 1:1:2 to receive rNAPc2 at 1 of 2 dose regimens, or a heparin regimen per site SoC (prophylactic or therapeutic). The higher rNAPc2 dose regimen will include a 7.5 µg/kg subcutaneous (SC) loading dose on Day 1 followed by 5µg/kg SC on Days 3 and 5; the lower dose regimen will be administered as a 5 µg/kg SC loading dose on Day 1 followed by 3µg/kg SC on Days 3 and 5. Prophylactic or therapeutic doses of low molecular weight heparin (LMWH) or unfractionated heparin (UFH) will be administered according to local SoC in the control group. Participants will be stratified by local laboratory D-dimer level at screening. Phase 3: Participants will be randomly assigned to receive rNAPc2 at a dose regimen selected based on Phase 2b data or to heparin (1:1).
Participant Duration:	Up to 40 days

1.2 SCHEMA

Figure 1. Schematic of study design: Phase 2b (Study NAPc-201) in upper panel. Phase 3 (Study NAPc-301) in lower panel





2 INTRODUCTION

2.1 STUDY RATIONALE

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been declared a pandemic by the World Health Organization and is responsible for significant morbidity and mortality worldwide.[1] Mortality is predominantly related to progressive pneumonia and acute respiratory distress syndrome which may progress to thrombotic events and multi-organ failure. Pathologic examination of pulmonary vasculature from patients with COVID-19 pneumonia has demonstrated vessel wall edema and immune cell infiltration, small vessel and capillary thrombosis, and infarction.[2,3] The underlying pathophysiology of COVID-19 is incompletely understood but appears to involve a severe inflammatory response and coagulopathy promoting venous and arterial thrombosis despite conventional anticoagulation.[4] Supporting this is the observed association between elevated D-dimer levels and mortality.[5] The prevalence and clinical impact of COVID-19-associated coagulopathy highlight the need for novel antithrombotic therapies.

One such novel therapy is rNAPc2, an 85 amino acid recombinant peptide with anticoagulant, anti-inflammatory, and potential antiviral effects originally cloned from the saliva of canine hookworm *Anclyostoma caninum*.[6] rNAPc2 is a potent inhibitor of the tissue factor (TF)-activated factor VII (fVIIa) complex that initiates the extrinsic coagulation pathway (Figure 2) and activates members of the protease activated receptor (PAR) family that plays a role in inflammatory disorders such as sepsis.[7,8,9] TF appears to be the major activator of the coagulation cascade during viral infection,[10] providing a mechanistic rationale for rNAPc2 in COVID-19. Preclinical evidence supporting examination of rNAPc2 includes its effect on D-dimer levels, which predict adverse COVID-19 outcomes including death.[11] rNAPc2 reduced D-dimer response to Ebola virus infection in non-human primates by approximately 70% compared with placebo.[12]

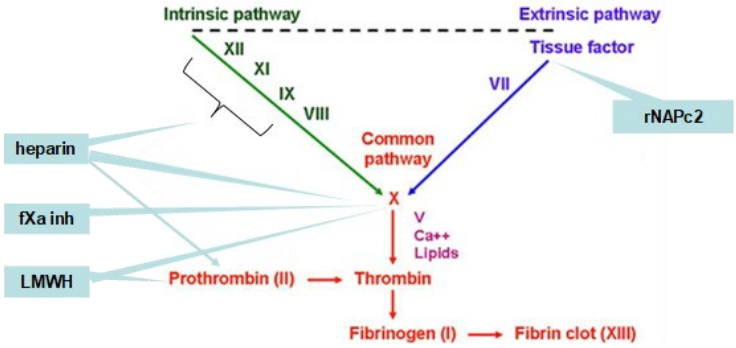


Figure 2. rNAPc2 is an upstream inhibitor of the extrinsic pathway

TF also plays a central role in inflammatory signaling and dysregulated immunity related to viral infections.[13,14] Because of rNAPc2's mechanism of action as a TF inhibitor, it was evaluated as a potential therapeutic agent to counteract haemorrhagic viral infections in which disseminated intravascular coagulation was a key pathophysiologic element. rNAPc2 showed evidence of survival benefit against lethal Ebola and Marburg virus challenges in non-human primates,[12] attenuated inflammatory biomarker response and, in Ebola, reduced viral load.[12]

TF also enhances viral dissemination.[15] In experimental models, rNAPc2 has been shown to reduce vascular dissemination of viruses that incorporate host TF into their envelopes,[16] a characteristic which may be beneficial in COVID-19. Taken together, the anticoagulant, anti-inflammatory, and potential antiviral effects of rNAPc2 support its evaluation for treatment of patients with COVID-19.

rNAPc2 was originally in development for the prevention of thrombotic complications following orthopedic surgery, percutaneous coronary intervention (PCI) and non-ST elevation acute coronary

syndrome (NSTE-ACS).[17,18,19] During this cardiovascular development program, rNAPc2 was tested in multiple Phase 1 and 2 clinical trials involving more than 700 human participants. Due to commercial factors unrelated to safety or efficacy, cardiovascular development of rNAPc2 did not proceed to pivotal studies. Availability of safety data in several patient populations including those with acute illness, in conjunction with immediate availability of investigational product for human use, enables immediate initiation of a pivotal study in patients with COVID-19.

2.2 BACKGROUND

rNAPc2 is a novel, potent (K_i =10 pM), highly selective TF inhibitor with anticoagulant, anti-inflammatory, and potential antiviral properties.

Mechanism of action

rNAPc2 inhibits the quaternary complex of TF/activated factor X (fXa) /fVIIa that catalyzes thrombin formation, by a unique mechanism requiring initial binding of rNAPc2 to zymogen or fXa before formation of the final quaternary inhibitory complex (Figure 3). The TF/fXa/fVIIa complex also activates the pro-inflammatory protease activated receptors PAR1 and PAR2; inhibition of this signaling is the likely basis for the anti-inflammatory effects of rNAPc2 in humans.[20,21] Cell derived TF incorporated into virus envelope substantially promotes infectivity[15] and is inhibited by rNAPc2 through the same mechanism of forming an inhibitory quarternary complex which is presumably why rNAPc2 reduced viral load in Ebola-infected monkeys and Herpes simplex virus 1 (HSV1)-infected mice.[12,16]

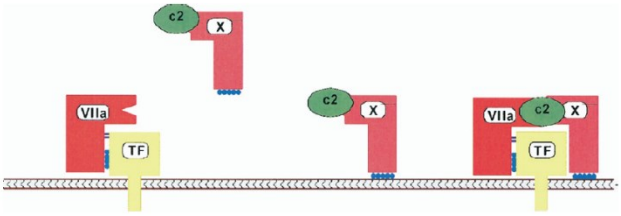


Figure 3. rNAPc2 mechanism of action: 1) rNAPc2 binds tightly to zymogen factor X; 2) docking of the rNAPc2-fX complex to TF/fVIIa assembled on a procoagulant phospholipid surface; and 3) presentation of the reactive loop of rNAPc2 to the active site of fVIIa, resulting in a tightly bound quarternary inhibitory complex. c2 rNAPc2; TF tissue factor; VIIa fVIIa; X factor X[19]

Clinical data with rNAPc2

Pharmacokinetics: Systemic exposure to rNAPc2 increased with increasing doses from 1.5 to 5.0 µg/kg SC with no significant differences in T_{max} among doses. The mean $t_{1/2}$ values ranged from 47.0 to 64.1 hours following the first dose on Day 1 and from 70.8 to 78.9 hours following the third dose on Day 5 and are independent of route of administration (intravenous [IV] or SC). The prolonged $t_{1/2}$ in humans has been determined to be a result of stoichiometric binding of rNAPc2 to fX in plasma.[22] SC bioavailability, estimated in the dog and cynomolgus monkey, was in excess of 95% and rNAPc2 was undetected in urine.

There have been six Phase 1 and 3 Phase 2 trials of rNAPc2 that enrolled 800 participants. A total of 704 participants have received rNAPc2 via IV (N=235) and SC (N=469) administration. In these trials, there were 174 participants who received a single dose of rNAPc2 and 530 participants who received multiple doses of rNAPc2. Early phase clinical studies with rNAPc2 are summarized (Table 1).

Table 1: Summary of Previous Clinical Trials of rNAPc2

Study	Description	Dose	N Total (N on drug)	Finding
CVS/A-0101	Phase 1 SAD in HS	3-7.5 µg/kg IV Single dose	28 (20)	Well tolerated
CVS/A-9704	Phase 1 SAD in DIC	0.7 – 5 µg/kg SC Single dose	13 (10)	Well tolerated
CVS/G-9704	Phase 1 SAD in HS	0.3-5 µg/kg SC Single dose	29 (20)	Well tolerated
CVS/A-9801	Phase 1 Coadministered with fVIIa in HS	3.5 µg/kg SC Single dose	6 (6)	fVIIa normalized rNAPc2 PT elevations
CVS/C-9802	Phase1 MAD in HS	1.5-5 µg/kg SC Multiple dose	18 (12)	Drug accumulation with multiple dosing rNAPc2 antibodies observed in 3 pts
CVS/MC-9803	Phase 2 in knee replacement	1.5-5 µg/kg SC Multiple dose	293 (293)	Dose-related increase in major bleeds No drug neutralizing antibodies observed
CVS/NL-9901	Phase 2 in elective PCI	3.5-10 µg/kg SC Single dose	154 (124)	Dose-related increase in minor bleeds
NUVO-0201 ANTHEM/TIMI-32	Phase 2 in NSTE-ACS	1.5-10 µg/kg IV Multiple dose*	255 (215)	Trend for less ischemia 13% of pts had rNAPc2 antibodies
NAP-0601	Phase 1 in colon cancer	2.5-10µg/kg SC Multiple dose	4 (4)	Stopped for poor recruitment (40 planned)

DIC disseminated intravascular coagulation, fVIIa activated factor VII, HS healthy subjects, IV intravenous, MAD multiple ascending dose, nAb neutralizing antibody, NSTE-ACS non-ST elevation-acute coronary syndrome, PCI percutaneous coronary intervention, PT prothrombin time, SAD single ascending dose, SC subcutaneous.
*183 pts had single dose of rNAPc2, and 32 pts had multiple doses of rNAPc2. Source: rNAPc2 IB

Pharmacodynamic effect: rNAPc2 prolonged prothrombin time (PT) in a dose-dependent manner (Figure 4).

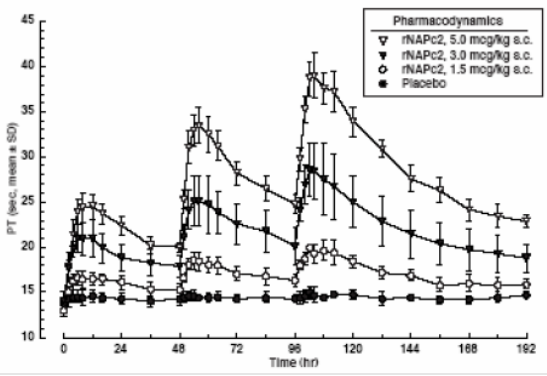


Figure 4. PT versus time from study CVS/C-9802, multiple ascending dose administration in healthy subjects. Mean ± standard deviation, N=4 or 6 per dose group (***IB***)

Efficacy: The initial clinical development program for rNAPc2 explored its utility as an anticoagulant, focusing on clinical settings associated with increased risk for arterial and venous thrombosis (Table 1). In a dose-escalation trial of 154 patients undergoing elective PCI randomized to placebo or 4 doses of rNAPc2, systemic thrombin generation, assessed by prothrombin fragment 1.2, was suppressed in all rNAPc2 dose groups to levels below baseline values.[18] rNAPc2 was also assessed in a sequential dose-ranging study in patients undergoing total knee replacement.[17] The mean rate of deep vein thrombosis (DVT) among patients receiving three regimens of rNAPc2 within 6-12 hours post-operatively was 21.5%. Administration of rNAPc2 (3.0 µg/kg) within 1 hour after surgery reduced the rate of DVT to 12.2% (95% CI 5.7%-21.8%). In comparison, rates of DVT after knee replacement among patients treated with LMWH range from 8%-36%.[23,24,25] In 203 patients presenting with NSTE-ACS treated with early coronary angiography, rNAPc2 (7.5 ug/kg) suppressed prothrombin fragment 1.2 generation (Figure 5) and reduced ischemia by 50% compared with placebo.[19]

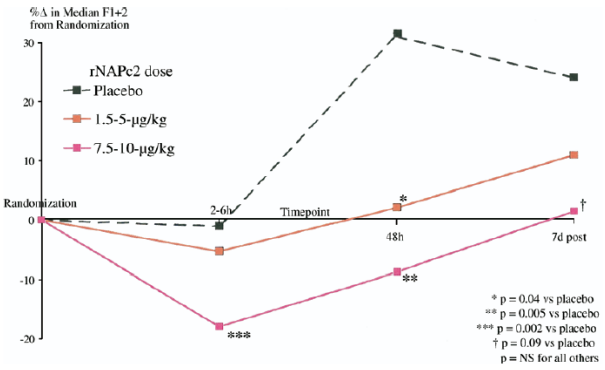


Figure 5. Prothrombin fragment 1.2 (F1.2), a marker of new thrombin generation, was reduced significantly at 2 to 6 and 48 h with 7.5 µg/kg rNAPc2 compared with placebo. Lower-dose rNAPc2 (1 to 5 µg/kg) blunted the increase in F1.2 seen at 48 h in the placebo group (JACC 2007;49:2398

Safety: Among patients undergoing knee replacement surgery, no dose-related increase in minor bleeding was observed. Major bleeding events were observed in 0, 3.4%, and 10.6% of patients receiving 1.5, 3.0, and 5.0 µg/kg SC at 6-12 hours postoperatively, respectively.[17] None of the major bleeds were considered serious. In 203 patients presenting with NSTE-ACS treated with early coronary angiography, rNAPc2 at 7 increasing IV doses from 1.5 µg/kg to 10 µ/kg or placebo most of whom who were also receiving heparin and aspirin plus clopidogrel did not significantly increase major bleeding vs. placebo (3.7% vs. 2.5%; p=NS) despite increasing the international normalized ratio in a dose-related fashion.[19] Among patients undergoing elective PCI, the frequency of minor bleeding in the 3.5 and 5.0 µg/kg dose groups was comparable to placebo, increasing to 11% and 31% in the 7.5 and 10 µg/kg SC dose groups, respectively.[18] Occurrence of major bleeding was not dose-dependent in this population which was also receiving a variety of antiplatelet and other anticoagulant therapies. Following rNAPc2 administration, infusion of rfVIIa normalized PT in healthy subjects, suggesting rfVIIa may be useful in transiently reversing the anticoagulant effects of rNAPc2.[26] In Phase 1 and 2 studies anti-rNAPc2 antibody formation was observed in 33 of 324 (10%) treated participants, without any neutralizing antibody formation or associated AEs (refer to the Investigator Brochure).

Preclinical studies with rNAPc2

In rhesus monkeys infected with Ebola, a virus that induces overexpression of TF in primate monocytes and macrophages, treatment with rNAPc2 lowered D-dimer levels ($p<0.0001$) compared with placebo and improved survival ($p=0.0184$) (Figure 6). Interleukin-6 (IL-6) elevation appeared less frequent in the rNAPc2-treated monkeys and viral load was decreased.[12]

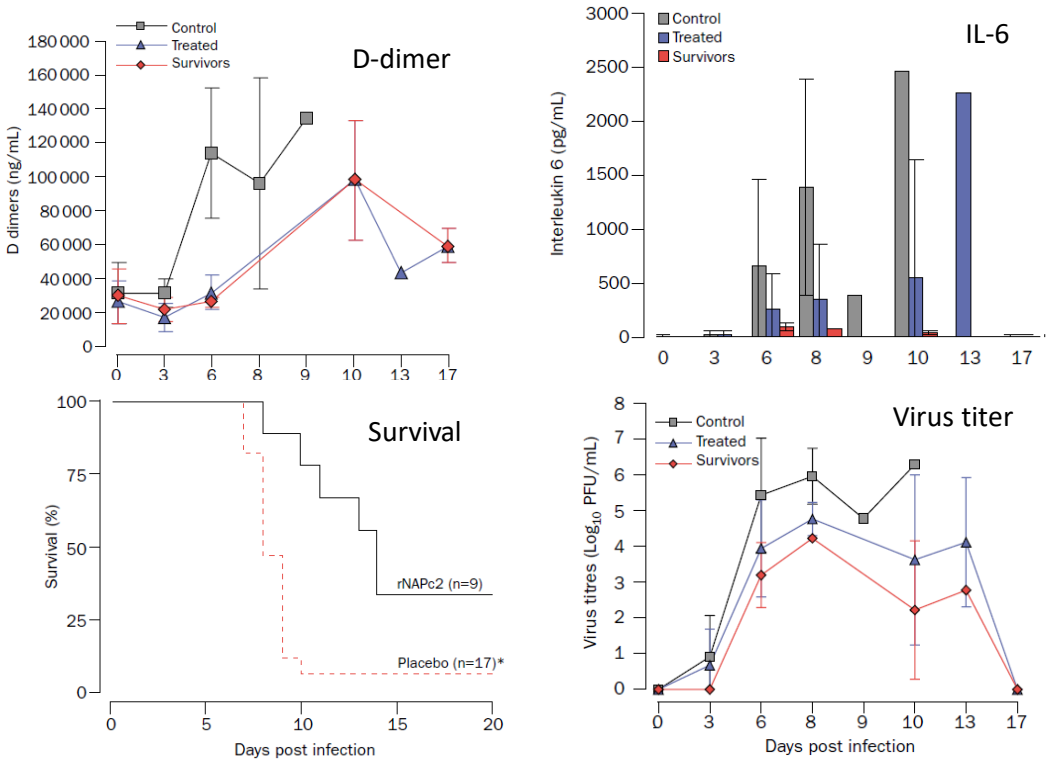


Figure 6. Effect of rNAPc2 treatment on D-dimer, survival, interleukin-6 (IL-6) and virus titer in non-human primates (rhesus macaque). rNAPc2 ("treated") n=9, placebo ("control, n=3 investigated contemporaneously with rNAPc2 and 4 historical controls, total N = 7), rNAPc2 treated survivors ("Survivors", a subset of Treated, N = 3). For survival analysis, the placebo group was supplemented with 7 additional historical controls for a total N of 14.

Prior data have shown that host cell-derived TF on viral envelopes enhances cell infection *in vitro*.[15] Antiviral effects of rNAPc2 were evaluated in BALB/c mice inoculated with HSV1 which has TF as a constituent of its envelope. The viral load, quantified by plaque forming assay, in different organ systems including brain, liver, heart, and lung, was significantly reduced ($p<0.05$) when mice were concurrently treated with rNAPc2 compared with HSV1 alone.[16]

Taken together, these clinical and preclinical data suggest that rNAPc2 may have potential advantages over marketed anticoagulants for which COVID-19 trials are planned or underway.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Due to the anticoagulant action of rNAPc2, there is a risk of bleeding. Dose-related increased bleeding, with associated anemia in some cases, was observed in Phase 2 studies of patients undergoing knee replacement and in patients undergoing elective PCI who were concurrently receiving a variety of anti-platelet and other anti-thrombotic therapies.[17,18] A potential risk with rNAPc2 is fever which was observed in a study of patients undergoing knee replacement in whom fever was attributed to inflammation associated with the surgery (refer to the Investigator Brochure). Other potential risks include generic risks with biologic drugs: formation of neutralizing antibodies and allergic reactions including anaphylaxis. If any signs or symptoms of serious hypersensitivity reactions occur after rNAPc2

administration, discontinue further treatment with rNAPc2, treat according to the standard of care, and monitor until signs and symptoms resolve. This includes patients who may present with a hypersensitivity to the investigational medication components.

2.3.2 KNOWN POTENTIAL BENEFITS

rNAPc2 has no established clinical benefits. Participants enrolled in the proposed study will have COVID-19 with elevated D-dimer, which predicts a higher risk of thrombosis and death.[5] Potential benefits with rNAPc2 include reduced risk of thrombosis during COVID-19 and shorter time to recovery due anti-thrombotic effects, as well as reduced inflammation and viral load.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risk/benefit profile for the proposed study is expected to be favorable as eligibility criteria are designed to select a population at increased risk of thrombosis and death and rNAPc2 doses are selected to reduce bleeding risk while retaining anti-thrombotic efficacy.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Phase 2b- Safety		
The Phase 2b safety objective is to identify an rNAPc2 dosing regimen with an acceptable bleeding profile compared to SoC heparin regimens	Primary safety endpoint: major or non-major clinically relevant bleeding (Section 8.3 Safety and Other Assessments) within eight (8) days of randomization as compared to heparin Secondary safety endpoints are: • major or non-major clinically relevant bleeding with rNAPc2 vs. heparin • bleeding with higher vs. lower dose rNAPc2 through Day 30 • Other AEs	Both rNAPc2 and heparin cause bleeding
Phase 3 – Safety		
The Phase 3 safety objective is to assess tolerability of rNAPc2 compared with heparin	Primary safety endpoint: major or non-major clinically relevant bleeding within eight (8) days of randomization as compared to heparin (Section 8.3 Safety and Other Assessments) Secondary safety endpoints are: • major or non-major clinically relevant bleeding with rNAPc2 vs. heparin through Day 30	Both rNAPc2 and heparin cause bleeding

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	• Other AEs	
Phase 2b – Primary efficacy		
The primary efficacy objective is to identify a rNAPc2 dosing regimen which reduces D-dimer levels compared to SoC heparin regimens	Primary efficacy endpoint: change in D-dimer level from baseline to Day 8, or day of discharge if prior to Day 8	D-dimer reflects the rNAPc2 mechanism of action and predicts survival in patients with COVID-19
Phase 2b – Secondary and exploratory		
Secondary objectives are to compare the rNAPc2 and heparin groups in terms of biomarkers associated with outcomes including those related to coagulation and inflammation Exploratory objectives are to compare the treatment groups in terms of clinical and functional outcomes that will also be assessed during Phase 3	Secondary efficacy endpoints: • change in D-dimer level from baseline to 24 hours post-dose (Day 2) and Day 3 • change in biomarkers associated with outcomes including those related to coagulation and inflammation from baseline through Day 8 Exploratory efficacy endpoints: • clinical and functional outcomes (including time to recovery as measured by the ACTT ordinal scale)	Inflammatory biomarkers reflect rNAPc2 mechanism of action and inflammation is believed to play a pathophysiologic role in COVID-19. Time-to-event outcomes from the overall study will determine the definitive efficacy of rNAPc2. Functional assessments will determine the effect of rNAPc2 on functional recovery.
Phase 3 – Primary efficacy		
The primary objective is to assess whether rNAPc2 reduces time to recovery relative to heparin	Primary efficacy endpoint: time to recovery within thirty (30) days of randomization using the ACTT ordinal scale	Time to recovery is a clinically meaningful outcome for patients.
Phase 3 – Secondary and exploratory		
Secondary objectives are to compare the treatment groups in terms of a composite of thrombotic events and all-cause mortality; thrombotic events; and all-cause mortality. Exploratory objectives are to compare the treatment groups in terms of: • Biomarkers associated with outcomes including those	Secondary efficacy endpoints: • time to first occurrence of a composite of thrombotic events and all-cause mortality within thirty (30) days of randomization • time to first occurrence of thrombotic events within thirty (30) days of randomization • time to all-cause mortality within thirty (30) days of randomization Exploratory endpoints are: • change in biomarkers associated with outcomes including those	rNAPc2 anticoagulant activity may reduce arterial and venous thromboembolic events in patients with COVID-19. Healthcare resource utilization is a meaningful outcome to patients and the health system, as is functional recovery.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
related to coagulation and inflammation • Health resource utilization • Post-COVID-19 functional status	related to coagulation and inflammation from baseline through Day 8 • proportion alive and out of hospital at thirty (30) days post-randomization • days in intensive care unit, on ventilator, vasopressors, renal replacement therapy, and circulatory support, e.g. extracorporeal membrane oxygenation • PCFS scale score at discharge and Day 30	

4 STUDY DESIGN

4.1 OVERALL DESIGN

Hypothesis: rNAPc2, a novel, potent and highly selective tissue factor inhibitor with anticoagulant, anti-inflammatory and potential antiviral properties, shortens time to recovery in hospitalized patients with COVID-19.

This protocol describes sequential Phase 2b/3 randomized, active comparator, multicenter superiority studies comparing rNAPc2 to heparin in hospitalized patients with COVID-19 and elevated D-dimer level. The study utilizes a PROBE (Prospective Randomized Open-Label, Blinded End-point) design [27,28]. Study participants and Clinical Endpoint Committee (CEC) members assessing the clinical endpoints will be blinded to treatment assignment. Randomization will be stratified by the participant's local laboratory D-dimer level at screening (> or ≤ 2X the assay's upper limit of normal (ULN)).

The primary objective of the Phase 2b study is to identify a rNAPc2 dosing regimen with an acceptable bleeding profile and which reduces D-dimer levels compared to SoC heparin regimens. The primary safety endpoint is major or non-major clinically relevant bleeding within 8 days of randomization and the primary efficacy endpoint is change in D-dimer level from Baseline to Day 8, or day of discharge if prior to Day 8. Secondary and exploratory objectives and endpoints are detailed in Section 3 OBJECTIVES AND ENDPOINTS.

During Phase 2b, an interim efficacy analysis will be conducted when 120 participants have completed Day 8 assessments, or Day of Discharge assessments if the participant is discharged prior to Day 8. To account for early recovery, deaths, and lab errors which may lead to lack of Day 8 D-dimer in approximately 20% of patients, 120 participants will provide for approximately 100 participants to be evaluated in the interim efficacy analysis. The interim efficacy analysis will test for futility based on the primary study hypothesis. Additionally, at the interim efficacy analysis, the Data Safety Monitoring Committee will be empowered to adjust sample size as pre-specified in the Phase 2b interim analysis

plan. While this review is taking place, the study will continue to enroll. Upon completion of Phase 2b, the database will be locked for analysis of clinical and biomarker data.

The primary objective of the Phase 3 trial is to test the hypothesis that the rNAPc2 dose regimen identified in Phase 2b reduces time to recovery relative to heparin. The Phase 3 primary efficacy endpoint is time to recovery within 30 days of randomization using the ACTT ordinal scale. The primary safety endpoint is major and non-major clinically relevant bleeding within 8 days of randomization. Secondary and exploratory objectives and endpoints are detailed in Section 3 OBJECTIVES AND ENDPOINTS. Although the Phase 3 primary endpoint is being measured in the Phase 2b study as a secondary endpoint, the primary analysis of Phase 3 will not include the Phase 2b data.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Accumulating data linking COVID-19 to thrombotic events has shifted equipoise away from inclusion of a placebo group. Consequently, rNAPc2 will be compared to heparin administered according to local SoC. Clinical pathways for anticoagulation of hospitalized patients with COVID-19 vary from institution to institution reflecting the current state of clinical uncertainty. To avoid potential confusion and error due to deviation from these pathways, heparin-allocated participants will receive regimens according to local institutional practice. As many hospitalized patients with COVID-19 participate in trials of antiviral and other therapies, concurrent participation in interventional trials that do not include anti-thrombotic or anti-platelet therapy is permitted. Based on data that D-dimer levels are related to patient outcomes in hospitalized COVID-19 patients,[5] randomization will be stratified by local laboratory D-dimer level at screening.

4.3 JUSTIFICATION FOR DOSE

Dose selection is based on data from three (3) Phase 2 dose-ranging studies which collectively enrolled more than 700 patients with acute coronary syndrome, undergoing knee replacement surgery, or after PCI. Based on the extensive pharmacokinetic (PK) data from the previous trials of rNAPc2 showing a consistently long half-life that increased with repeat dosing and produced escalating dose levels after both the 2nd (Day 3) and 3rd (Day 5) doses, a loading dose is used for both rNAPc2 regimens. The rationale is that with rNAPc2's long half-life, steady state is not reached within the 8 days of the ASPEN-COVID-19 efficacy follow-up period, as areas under the curve (AUCs) increase following each dose during that interval. As COVID-19 patients ill enough to be hospitalized are at immediate risk for the conditions that lead to micro- or macrovascular thromboses, the therapeutic goal is rapid attainment of rNAPc2 plasma levels approximating those achieved at steady state, thus the decision was made to start the regimen with a loading dose.

Pharmacokinetic and pharmacodynamic studies following single doses of rNAPc2 demonstrated a dose dependent increase in international normalized ratio (INR) ranging from 1.5 at 3.0 μg/kg to 1.75 at 5.0 μg/kg and 2.1 at 7.5 μg/kg. Based on these data, an initial dose of 5 μg/kg followed by 3.0 μg/kg on Days 3 and 5 (where the long T 1/2 produces greater levels than for the initial dose) was estimated to be equivalent to prophylactic dose heparin. A dose of 7.5 μg/kg followed by 5 μg/kg on days 3 and 5 was estimated to correlate with a higher intensity of anticoagulation approximating therapeutic heparin.

In Phase 2b, 2 rNAPc2 dose regimens will be evaluated:

- Higher dose: loading dose of 7.5 μg/kg SC on Day 1 followed by 5 μg/kg SC on Days 3 and 5

- Lower dose: loading dose of 5 μg/kg SC on Day 1 followed by 3 μg/kg SC on Days 3 and 5.

The dose regimen for Phase 3 will be selected based on Phase 2b data.

The active comparator will be heparin at either prophylactic or therapeutic doses per SoC. SoC may evolve to reflect emerging data from COVID-19 anti-thrombotic trials and clinical experience.

4.4 END OF STUDY DEFINITION

Participants will complete their study participation after their final or Day 30 contact. The end of the study is defined as completion of the last enrolled participant's final visit or contact.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Patients must meet *all* of the following inclusion criteria to be eligible for randomization in this study:

1. Age ≥ 18 years and ≤ 90 years at the Screening assessment
2. Weight ≥ 50 kg at randomization
3. Hospitalized with a diagnosis of COVID-19 and in need of inpatient medical care
4. Positive for SARS-CoV-2 on nasopharyngeal, oropharyngeal or other tissue/body fluid samples by PCR or validated other test of ongoing infection (not an antibody test for prior exposure), within seven (7) days of hospitalization or screening assessment
5. D-dimer level > upper limit of normal at screening (local lab; initial value as collected at the time of hospital admission, prior to initiation of heparin treatment preferred)
6. Provided electronic or written informed consent, either personally or through a legally authorized representative (LAR)
7. Must agree not to participate in a concurrent interventional study involving anticoagulation or anti-platelet therapy
8. Female patients of reproductive or childbearing potential must be willing to use an effective method of contraception for the duration of the study (see section 5.3.1), and male patients must be willing to use an effective method of contraception to avoid partner pregnancy and abstain from sperm donation for at least 90 days after last dose.

5.2 EXCLUSION CRITERIA

Patients who meet any of the following exclusion criteria are not eligible for randomization in this study:

1. High bleeding risk, e.g. major surgery within prior 1 month, history of a major bleed while receiving anticoagulation, recent hemorrhagic stroke, current or planned (during current hospitalization) dual anti-platelet therapy, platelet count <25,000/μL, current therapeutic anticoagulation for a medical indication other than COVID, e.g. atrial fibrillation, known thrombosis, hereditary or acquired coagulopathy treated with therapeutic anticoagulation. Patients receiving prophylactic anticoagulation are eligible if they are willing to discontinue current anticoagulation.
2. Sustained systolic blood pressure < 90 mmHg considered to be clinically significant

3. Persistent eGFR <20 ml/min/1.73m^2
4. Known severe liver disease (e.g. bilirubin >3.5 mg/dL (60 umol/L))
5. Life expectancy estimated to be < 72 hours based on current clinical condition
6. Anticipated hospital discharge or transfer within 5 days based on current clinical condition
7. Known anti-phospholipid syndrome
8. Unable to receive heparin, e.g. history of heparin-induced thrombocytopenia and thrombosis (HITT)
9. Participation in any interventional clinical study with an investigational product within seven (7) days of the Screening assessment or within 5 half-lives of the investigational agent, whichever is longer

5.3 PARTICIPANTS OF CHILD-BEARING POTENTIAL

There are no studies of rNAPc2 in pregnant women. Therefore, a urine pregnancy test will be required prior to study drug initiation (Baseline/Day 1 visit) for all female participants of child-bearing potential. A female who is surgically sterile or post-menopausal for at least 12 months is not considered to be of childbearing potential. Female participants of child-bearing potential must be willing to use a highly effective method of contraception for the duration of the study, otherwise they will be excluded from study participation.

Male patients must be willing to use effective method of contraception to avoid partner pregnancy and abstain from sperm donation for at least 90 days after last dose.

5.3.1 CONTRACEPTION METHODS

Examples of effective contraception methods include the following:

- Contraceptive pill or transdermal patch (established at least 30d prior to screening)
- Single barrier plus spermicide
- Intrauterine device
- Implants for contraception
- Injections for contraception (with prolonged release)
- Hormonal vaginal device
- Sterilization, surgical tubal ligation
- Sole sexual partner consisting of surgically sterilized male partner with appropriate post-surgical documentation of the absence of spermatozoa in the ejaculate
- Same sex partner

5.4 SCREEN FAILURES

The study will screen and enroll hospitalized patients with documented COVID-19, in the US and other countries with high rates of COVID-19. Each potential participant will be assigned a screening identification number. Only patients who test positive for SARS-CoV-2 will be randomized.

Ineligible individuals may be rescreened. At the time of rescreening, a new informed consent must be obtained, and a new screening number will be assigned.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The target sample size for Phase 2b is approximately 160 participants, with an additional approximately 450 planned during Phase 3. Eligibility criteria are broad to facilitate enrollment, the primary requirement being elevated D-dimer. In published data, 68% of patients hospitalized with COVID-19 had D-dimer > 0.5 ng/mL.[32]

Enrolled participants are anticipated to reflect the epidemiology of COVID-19. In May 2020, 46%, 30% and 24% of hospitalized patients with COVID-19 in the US were >65, 50-64 and <50 years of age, respectively. Race/ethnicity was reported as 37% Non-Hispanic White, 40% Non-Hispanic Black and 14% Hispanic. Concomitant medical conditions included hypertension 59%, CV disease 35%, metabolic disease 42%, obesity 50% and renal disease 16%.[29]

We anticipate enrolling at approximately 20 sites in Phase 2b and 80 clinical sites in Phase 3, selected for experience providing high quality clinical trial data and for the prevalence and ability to recruit the target population. Sites will be selected in geographic areas with high rates of COVID-19 in the US and abroad. Because of the rapid timeline, regulatory approval and drug importation time will be considered during site selection.

Adherence is facilitated by planned administration of all study medication in-hospital. Retention should be facilitated due to the short duration of follow up and limited number of study-related activities. Follow up for clinical outcomes and AEs may be conducted remotely.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

rNAPc2 is a non-glycosylated, single-chain, 85 amino acid peptide manufactured according to Good Manufacturing Practices using fermentation in yeast and subsequent purification. Heparin will be provided by hospitals according to their local policies and investigator-determined SoC.

6.1.2 DOSING AND ADMINISTRATION

Participants will be randomized to either rNAPc2 or heparin. In Phase 2b, rNAPc2-allocated participants will be assigned to receive either the higher dose (7.5 µg/kg SC on Day 1, and 5 µg/kg SC on Days 3 and 5) or lower dose regimen (5 µg/kg SC on Day 1, and 3 µg/kg SC on Days 3 and 5). For Phase 3, a single dose regimen will be selected based on Phase 2b data. Participants who are discharged after 1 rNAPc2 dose may receive SoC thromboprophylaxis, if clinically indicated, 48 hours after receipt of rNAPc2. Those discharged after 2 or more rNAPc2 doses may receive SoC thromboprophylaxis, if clinically indicated, 72 hours after receipt of second rNAPc2 dose. Hospitalized rNAPc2 allocated participants may receive SoC

thromboprophylaxis, if clinically indicated, starting on Day 8, after the D-dimer and other Day 8 central laboratory measurements are drawn.

Example of rNAPc2 dose calculation: a patient weighing 80 kg randomized to the higher dose would receive 0.6 mg SC (0.6 ml at 1 mg/ml) on Day 1 and 0.4 mg SC (0.4 ml) on Days 3 and 5. As each vial contains 0.5 ml, the Day 1 dose would require 2 vials, Day 3 would require 1 vial and Day 5 would require 1 vial, with the excess volume discarded on each day. This is an example; each participant's weight-based dose should be calculated based on their individual weight at baseline. Weight-based dosing is capped at 115 kg, so participants with higher body weight will receive the dose for weight of 115 kg.

Participants randomized to heparin will be treated with LMWH or UFH per local SoC.[30] Enoxaparin and dalteparin are the preferred LMWH.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

rNAPc2 study drug will be shipped from the drug depot using dry ice, and with a temperature-monitoring device (TempTale or equivalent). This device will record the temperature maintained during shipment.

At the time of or immediately after study initiation, and as needed thereafter, study drug will be shipped to the site. The site will be responsible for confirming the supplies received match the shipping record. Each time a participant is enrolled, the carton and vial number used must be documented. A Study Drug Accountability Form is to be completed for every participant being treated with the study drug. All accountability logs must be available to authorized Sponsor representatives (auditors) for inspection.

Each site will initially be supplied with adequate quantities of rNAPc2 to ensure study medication supply for timely randomization. Study drug will be tracked through a Drug Accountability system.

If the study drug is lost or damaged or is exposed to a temperature which is outside of the required study drug storage range the Sponsor should be notified immediately. The final decision regarding whether a site will be re-supplied with study drug, or if further action is required, will be determined by the Sponsor.

After a participant has been treated, the drug vial with the remainder of the study drug must be retained until the study coordinator or designee obtains approval from the Coordinating Center or Sponsor to return or destroy the drug. Following completion of drug accountability and confirmation by the site monitor (Clinical Research Associate [CRA]), the vials can be destroyed in accordance with all local, state, and federal laws and in accordance with the destruction policies at the participating site. Documentation of destruction must be provided to the Sponsor. A copy of the documentation of destruction should be kept with the sites' pharmacy documentation.

At the end of the study and following final drug accountability, any unused vials should be destroyed in accordance with all local, state, and federal laws and in accordance with destruction policies at the participating site. Documentation of destruction must be provided to the Sponsor. If the participating site does not have properly documented or appropriate destruction policies in place, the used and unused study drug should be returned to the distribution depot, after verification of drug accountability.

The Coordinating Center will assess the adequacy of the policies and procedures and collect necessary documentation.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

rNAPc2 is supplied in labelled glass vials as a frozen, sterile, clear, colorless solution (1 mg/mL) in 65 mM sodium phosphate/80 mM NaCl, pH 7.0. Each 2 mL vial is filled to a volume of 0.5 mL and contains 0.5 mg of active rNAPc2. Vials contain no preservative and are designed for single use only.

Vials will be supplied in labeled cartons (1 vial per carton), and each vial will be labelled with a unique vial number identifier, together with the study number, the lot number, expiration date, and Sponsor information.

6.2.3 PRODUCT STORAGE AND STABILITY

All study medication must be stored in a secure location under controlled -20^{o}C frozen conditions (acceptable temperature range is between -30^{o}C and -10^{o}C). Records of the storage conditions must be maintained throughout the study by continuous temperature recording systems, regularly maintained temperature alarm systems, or by visual inspection of a calibrated thermometer. The temperature, date, and time must be recorded daily and initialed by the appropriate study-site personnel.

The rNAPc2 study drug contains no antibacterial preservatives and should be thawed immediately before use. Vials should be thawed at room temperature and should not be heated or shaken. Vials may be gently swirled and inverted to promote thawing and mixing. After thawing, if necessary, vials can be stored at ambient temperature (15^{o}C - 25^{o}C, with excursions up to 30^{o}C) for up to twenty-four (24) hours, or under refrigerated conditions (2 - 8^{o}C) for up to 3 months. Exposure or storage at elevated ambient temperature (> 25^{o}C) should be limited to < 2 hrs.

6.2.4 PREPARATION

After vial thawing, the appropriate volume of rNAPc2 drug product, based on the calculated dose for a patient, should be drawn from the vial into a polypropylene syringe for SC injection. Vials of drug product should be used for preparing one dose for one participant only. rNAPc2 in polypropylene syringes may be stored at refrigerated conditions (2 - 8^{o}C) for up to 24 hours, or at room temperature for up to 4 hours. The product should be allowed to equilibrate to ambient temperature before administration.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Intervention Allocation
Site-based randomization will be implemented in this study. Participants will be randomly assigned to treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the Sponsor. The randomization will be balanced by using randomly permuted blocks for each site and the D-dimer level stratification. After confirming eligibility, the requestor will obtain the participant's randomization assignment.

Blinding
To minimize the potential for bias, data that may potentially unblind the intervention assignment will be handled with special care to maintain the integrity of blinding for the participant and the CEC. This includes discouraging speculation and avoiding verbal disclosure to the participant and redacting the

data in question from medical records reviewed by the CEC. Study site investigators assessing potential clinical efficacy and safety events should be blinded to treatment allocation, if possible. Neither the study site, Sponsor, CEC, nor study participants will have access to the central laboratory results during the conduct of the trial with the exception of clinical safety alerts.

The investigator will not be provided with randomization codes. The study site will know the treatment assignment, however; participants should not be made aware of their treatment assignment.

6.4 STUDY INTERVENTION COMPLIANCE

Both rNAPc2 and heparin should be administered and documented in-hospital by hospital staff. Dates, doses and mode of administration will be recorded in the electronic Case Report Form (eCRF).

6.5 CONCOMITANT THERAPY

Use of the following prohibited concomitant therapy is excluded at any time during the study:

- Treatment with an investigational drug or device, defined as one not approved for any indication in the US, Europe or Japan. If treatment with an investigational drug or device is initiated, study medication should be discontinued. Follow up procedures continue as shown on the Schedule of Activities (SoA).

If the patient requires the following therapies for medical indications, rNAPc2 should be not be concomitantly administered:

- Dual antiplatelet therapy, e.g., aspirin + ticagrelor, clopidogrel, or prasugrel
- Systemic anticoagulation, e.g., warfarin, factor Xa inhibitors, direct thrombin inhibitors

Appropriate investigator discretion based upon the prior therapy should apply for washout timelines of these therapies in advance of rNAPc2 administration. As per standard pharmacokinetic studies, a delay of 4 to 5 half-lives should be allowed to washout most drugs.

6.5.1 MANAGEMENT OF BLEEDING EVENTS

rNAPc2 is expected to be dosed in-hospital on Days 1, 3 and 5; half-life of rNAPc2 following the day 5 dose is approximately 72 hours. Heparin is expected to be dosed in-hospital; half-life of LMWH is approximately 4½ hours, half-life of UFH is approximately 1 hour. If serious bleeding occurs in-hospital the following routine measures should be considered:

- Delay the next study drug administration or discontinue treatment if indicated.
- Consider the usual treatment measures for bleeding events, including fluid replacement and hemodynamic support, blood transfusion, and fresh frozen plasma, if physical examination and laboratory testing suggest benefit could be obtained.

If rescue management is required, participant should remain blinded to treatment assignment if possible. For uncontrolled major bleeding in a patient receiving rNAPc2 for whom usual treatment measures have been ineffective, recombinant activated clotting factor VII (rfVIIa) may be administered.[26] In a Phase 1 study in healthy volunteers, administration of rfVIIa 4 hours after rNAPc2 normalized PT, which was correlated with the activation of the coagulation cascade as measured using

biochemical markers of factor X and factor IX activation. This study suggests that rfVIIa may be useful in transiently reversing the anticoagulant effects of rNAPc2. However, the effect of rfVIIa in an actively bleeding patient who has received rNAPc2 is currently unknown (refer to the Investigator Brochure).

If the participant is not hospitalized, a serious bleeding event should be referred for evaluation at the appropriate facility such as an urgent care center or emergency department depending on the severity of the bleeding.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

A participant's study medication must be discontinued if:

- The participant withdraws consent to receive study medication
- The investigator believes that for safety reasons or tolerability reasons (e.g. AE) it is in the best interest of the participant to discontinue study medication
- The participant develops any condition, which in the investigator's judgment requires long-term therapeutic anticoagulation or fibrinolysis
- The participant initiates treatment with an investigational drug or device, defined as one not approved for any indication in the US, Europe or Japan
- The participant becomes pregnant.

If a participant discontinues study medication for any reason before the end of the study, study assessments should continue in accordance with the SoA to ascertain full safety and efficacy information.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. Data collected in the database and research samples collected up to the date of withdrawal remain part of the study. If the participant wishes to have their data removed and/or samples destroyed, they must make a written request to the investigator at their clinical site. The intention is to follow all randomized participants for safety and vital status even if they desire to withdraw from study participation.

If a participant withdraws from the study, the reason for withdrawal will be recorded on the eCRF and the final visit will be completed at that time. If obtaining vital status via direct contact with the participant is not possible, vital status may be obtained at study end through the participant's physician, medical claims or public information according to local guidelines and as allowed by local regulations.

In Phase 2b, participants who sign the informed consent form (ICF) and are randomized but do not receive the study intervention may be replaced. Participants who sign the ICF, are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced. Phase 3 is event driven, so replacement of participants is not an issue.

7.3 LOST TO FOLLOW-UP

All randomized participants will be followed for outcomes until Day 30 whether study medication has been continued or discontinued. Only if a participant withdraws consent for all follow-up (active and passive) will they be considered to have withdrawn consent. If a participant cannot be contacted or has requested no contact, site staff will ascertain clinical endpoint events through the patient's physician or electronic medical record. A participant will be considered lost to follow-up if he or she is unable to be reached by the study site staff and no information from external sources (e.g. treating physicians, electronic medical record, family, registries) can be obtained. Only participants for whom no information can be ascertained, will be considered lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 STUDY PROCEDURES

8.1.1 SCHEDULE OF ACTIVITIES

Table 2a. Schedule of Activities (SoA)

Activity	Screen Day -7 to 1	Baseline Day 1	Day 2 (24h post-dose ±2h)	Day 3±1d	Day 5±1d	Day 8±1d	Day of Hospital Discharge	Day 30±3d
Informed consent	x							
Assess eligibility	x	x						
Randomize		x						
Medical history (COVID-19, cardiovascular, medical/ surgical history) [b]		x						
Concomitant medication[b]		x	x	x	x	x	x	x[d]
Baseline demographics[b]	x							
Focused physical examination, vital signs, weight, height[b]		x						
Study medication [c]		rNAPc2 7.5 µg/kg SC on **Day 1** and 5µg/kg SC on **Days 3 and 5** **or** rNAPc2 5 µg/kg SC on **Day 1** and 3 µg/kg SC on **Days 3 and 5** **or** heparin per SoC						
Local laboratory values	x[a]	Record values of interest performed in the hospital clinical laboratory until hospital discharge or day 30 visit (whichever is first). In the case where a lab test is measured multiple times per day, the first scheduled values as well as any additional values that represent a clinically significant change should be reported.						
Assess need for inpatient medical services & complete ACTT			Daily until discharged to outpatient status or death or Day 30 reached					
Clinical & adverse events[g]	x	x	x	x	x	x	x	x[d]
Post-COVID functional status (PCFS) scale							x[h]	x[d]
Vital status								x[d]
Healthcare utilization							x	x[d]
Central Laboratory assessments (see Table 2b)		x	x	x[e]		x[f]	x[f]	x[e]

[a] Local lab D-dimer drawn during hospitalization and prior to randomization will be used for eligibility and randomization stratification
[b] May be obtained/extracted from medical record to minimize staff exposure to COVID-19
[c] rNAPc2 must be dosed on Days 1, 3 and 5; only one rNAPc2 dose regimen is anticipated in Phase 3; Participants randomized to receive heparin will have doses administered per standard of care (SoC)

[d] Participants who are discharged prior to Day 30 may have these activities performed remotely
[e] For phase 2b only
[f] If participant is discharged prior to Day 8, central laboratory assessments should be performed at hospital discharge
[g] Participants will be assessed at minimum daily, while hospitalized, for the occurrence of any clinical and adverse events (See Section 8.2 Efficacy Assessments and Section 8.4 Adverse Events and Serious Adverse Events) by the clinical care team as a part of standard of care. The clinical care team should inform the study team of any potential events. Additionally, the study team is expected to assess for the occurrence of potential events during scheduled study visits.
[h] If hospital discharge occurs before Day 30, the PCFS should be performed the day after hospital discharge (up to 3 days after discharge allowed). A retrospective assessment of PCFS pre-COVID-19, which reflects functional status during the month preceding COVID-19 infection, should be performed after current PCFS assessment at hospital discharge.

Following hospital discharge, study activities may be performed remotely except for central laboratory blood collection.

8.1.2 LABORATORY SAMPLES AND VALUES

Participants will have laboratory samples collected and analyzed both locally and centrally in accordance with the SoA.

Local Laboratory Values

Laboratory tests of interest listed below, obtained via the local laboratory that are used to assess eligibility*, or are collected during the participant's enrollment until hospital discharge or Day 30 visit (whichever is first) should be reported via the eCRF. In the case of D-dimer, initial value (eligibility) is preferred as collected at the time of hospital admission, prior to initiation of heparin treatment. In the case where a lab test is measured multiple times per day, the first scheduled values as well as any additional values that represent a clinically significant change should be reported.

- Hemoglobin
- D-dimer*
- White blood cell count (WBC)
- Platelet count*
- Estimated glomerular filtration rate (eGFR)*
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Total bilirubin
- Prothrombin time (PT)
- Partial thromboplastin time (PTT)
- Troponin
- Brain natriuretic peptide (BNP)

Central Laboratory Sample(s)

Central laboratory samples should be collected and shipped to the central laboratory as described in the Laboratory Manual. The following table outlines the samples that will be collected and analyzed via the central laboratory.

Table 2b. Central Laboratory Blood Collection

Day 1[a]	Day 2 (24h post-dose)	Day 3 Phase 2b only	Day 8[b], or Day of Hospital Discharge (if prior to Day 8)	Day 30 Phase 2b only
Samples for clinical laboratory tests				
IL-6, hsCRP			IL-6, hsCRP	
D-dimer, PT, PTT, factor Xa tissue factor, antiphospholipid antibody	D-dimer, PT, PTT	D-dimer, PT, PTT	D-dimer, PT, PTT, factor Xa tissue factor, antiphospholipid antibody	antiphospholipid antibody
ADA for rNAPc2 subjects **(Phase 2b only)**	PK sample for rNAPc2 subjects **(Phase 2b only)**		PK sample for rNAPc2 subjects **(Phase 2b only)**	ADA for rNAPc2 subjects
Samples for future research use[c]				
Future use serum and plasma aliquots and buffy coat			Future use serum and plasma aliquots	

[a] Baseline Central Laboratory sample should be collected before administration of study medication (rNAPc2 or heparin). A sample up to 1-hour post-administration is acceptable.
[b] For rNAPc2-allocated participants, Day 8 Central Laboratory samples should be collected before that day's dose of SoC thromboprophylaxis, if prescribed.
[c] Note, samples for future research use should only be collected for those participants that consent for optional sample banking for future research.
ADA = anti-drug antibodies, hsCRP = high sensitivity C-reactive protein, IL-6 = interleukin-6, PT = prothrombin time, PTT = partial thromboplastin time

The central laboratory will extract deoxyribonucleic acid (DNA) from buffy coat of participants consenting to genetic research, aliquot, store and batch ship DNA and future use serum and plasma samples to biobank, if applicable.

Central laboratory results will not be provided to clinical sites but will be reviewed by the Data Safety Monitoring Committee.

For females of child-bearing potential, a negative urine pregnancy test is required prior to initiation of study drug treatment at the Baseline/Day 1 visit, and additionally as required by local regulatory requirements.

8.1.3 VISIT DESCRIPTION

Screening Visit (Day -7 to 1)

The screening visit may occur up to 7 days prior to the Baseline visit. The Screening and Baseline Visit may be performed on the same day, if appropriate.

The following procedures will occur during the screening visit:

- Informed consent
    - Informed consent must be obtained prior to any other research procedures.

- Assess eligibility
- Local laboratory values, as applicable
- Baseline demographics
    - Age
    - Sex
    - Childbearing Potential
    - Ethnicity
    - Race
- Adverse events assessment
    - Assess for the occurrence of any serious adverse events and report via the eCRF as appropriate. See Section 8.4 Adverse Events and Serious Adverse Events for more information about adverse events.

Baseline Visit (Day 1)

The Baseline visit will be considered Day 1 and may be performed on the same day as the Screening Visit, if appropriate.

The following procedures will occur during the Baseline visit:

- Assess eligibility
- Medical history (may be obtained/extracted from the medical record to minimize staff exposure to COVID-19)
    - COVID-19 symptoms
    - Cardiovascular history
    - Medical/surgical history
- Concomitant medication (may be obtained/extracted from the medical record to minimize staff exposure to COVID-19)
- Focused physical examination
- Vital signs
    - Height
    - Weight
    - Temperature
    - Blood pressure
    - Respiratory rate
    - Heart rate
    - Oxygen saturation
- Local laboratory values, if applicable
- Central laboratory samples
    - The baseline samples should be collected before administration of study medication (rNAPc2 or heparin). A sample up to 1-hour post-administration is acceptable.
    - For females of child-bearing potential a negative urine pregnancy test is required prior to initiation of study drug

    - An additional central laboratory sample must be collected 24h after the first dose of study drug (±2hours)
- Randomization
- Study medication administration
- Clinical events and adverse events assessment
    - Assess for the occurrence of any adverse events and report via the eCRF as appropriate. See Section 8.4 Adverse Events and Serious Adverse Events for more information about adverse events.
    - Assess for the occurrence of any clinical event that suggests the possibility that an efficacy outcome event has occurred. See Section 8.2 Efficacy Assessments for more information about clinical events of interest.

Day 2 (24 hours post dose +/- 2 hours)

The following procedures will occur during the Day 2 visit:

- Central laboratory samples must be collected 24h after the first dose of study drug (+/- 2hours)
- Concomitant medication (may be obtained/extracted from the medical record to minimize staff exposure to COVID-19)
- Assess need for inpatient medical services and complete ACTT
    - The need for inpatient medical services should be assessed daily after randomization until the participant is discharged from the hospital, deceased, or Day 30 visit is reached.
    - Documentation pertaining to this assessment must be provided to the CEC as outlined in the Site Manual.
- Clinical events and adverse events assessment
    - Assess for the occurrence of any adverse events and report via the eCRF as appropriate. See Section 8.4 Adverse Events and Serious Adverse Events for more information about adverse events.
    - Assess for the occurrence of any clinical event that suggests the possibility that an efficacy outcome event has occurred. See Section 8.2 Efficacy Assessments for more information about clinical events of interest.

Day 3 Visit (+/- 1 Day)

The following procedures will occur during the Day 3 visit:

- Concomitant medication (may be obtained/extracted from the medical record to minimize staff exposure to COVID-19)
- Study medication administration
    - If an rNAPc2-allocated participant is discharged from the hospital before receiving the Day 3 dose, the dose(s) should be recorded in the electronic Case Report Form (eCRF) as not administered.
- Local laboratory values, if applicable

- Assess need for inpatient medical services and complete ACTT
    - The need for inpatient medical services should be assessed daily after randomization until the participant is discharged from the hospital, deceased, or Day 30 visit is reached.
    - Documentation pertaining to this assessment must be provided to the CEC as outlined in the Site Manual.
- Clinical events and adverse events assessment
    - Assess for the occurrence of any adverse events and report via the eCRF as appropriate. See Section 8.4 Adverse Events and Serious Adverse Events for more information about adverse events.
    - Assess for the occurrence of any clinical event that suggests the possibility that an efficacy outcome event has occurred. See Section 8.2 Efficacy Assessments for more information about clinical events of interest.
- Central laboratory samples (Phase 2b only)

Day 5 Visit (+/- 1 Day)

The following procedures will occur during the Day 5 visit:

- Concomitant medication (may be obtained/extracted from the medical record to minimize staff exposure to COVID-19)
- Study medication administration
    - If an rNAPc2-allocated participant is discharged from the hospital before receiving the Day 5 dose, the dose(s) should be recorded in the electronic Case Report Form (eCRF) as not administered.
- Local laboratory values, if applicable
- Assess the need for inpatient medical services and complete ACTT
    - The need for inpatient medical services should be assessed daily after randomization until the participant is discharged from the hospital, deceased, or Day 30 visit is reached.
    - Documentation pertaining to this assessment must be provided to the CEC as outlined in the Site Manual.
- Clinical events and adverse events assessment
    - Assess for the occurrence of any adverse events and report via the eCRF as appropriate. See Section 8.4 Adverse Events and Serious Adverse Events for more information about adverse events.
    - Assess for the occurrence of any clinical event that suggests the possibility that an efficacy outcome event has occurred. See Section 8.2 Efficacy Assessments for more information about clinical events of interest.

Day 8 Visit (+/- 1 Day)

The following procedures will occur during the Day 8 visit:

- Concomitant medication (may be obtained/extracted from the medical record to minimize staff exposure to COVID-19)
- Study medication administration, if randomized to heparin and still hospitalized
- Local laboratory values, if applicable
- Assess need for inpatient medical services and complete ACTT
    - The need for inpatient medical services should be assessed daily after randomization until the participant is discharged from the hospital, deceased, or Day 30 visit is reached.
    - Documentation pertaining to this assessment must be provided to the CEC as outlined in the Site Manual.
- Clinical events and adverse events assessment
    - Assess for the occurrence of any adverse events and report via the eCRF as appropriate. See Section 8.4 Adverse Events and Serious Adverse Events for more information about adverse events.
    - Assess for the occurrence of any clinical event that suggests the possibility that an efficacy outcome event has occurred. See Section 8.2 Efficacy Assessments for more information about clinical events of interest.
- Central laboratory samples, if not already collected at Day of Hospital Discharge

Day of Hospital Discharge

The following procedures will occur on the Day of Hospital Discharge:

- Concomitant medication (may be obtained/extracted from the medical record to minimize staff exposure to COVID-19)
- Study medication administration, if applicable
- Local laboratory values, if applicable
- Assess need for inpatient medical services and complete ACTT
    - The need for inpatient medical services should be assessed daily after randomization until the participant is discharged from the hospital, deceased, or Day 30 visit is reached.
    - Documentation pertaining to this assessment must be provided to the CEC as outlined in the Site Manual.
- Clinical events and adverse events assessment
    - Assess for the occurrence of any adverse events and report via the eCRF as appropriate. See Section 8.4 Adverse Events and Serious Adverse Events for more information about adverse events.
    - Assess for the occurrence of any clinical event that suggests the possibility that an efficacy outcome event has occurred. See Section 8.2 Efficacy Assessments for more information about clinical events of interest.
- Post-COVID functional status (PCFS) scale
    - If hospital discharge occurs before Day 30, PCFS assessment should be performed the day after hospital discharge (up to 3 days after discharge allowed).
    - PCFS scale may be performed remotely e.g. by telephone.

  - A retrospective assessment of PCFS pre-COVID-19, which reflects functional status during the month preceding COVID-19 infection, should be performed after current PCFS assessment at hospital discharge.
- Healthcare Resource Utilization Assessment
- Central laboratory samples, if Day of Hospital Discharge is prior to Day 8

Day 30 Visit (+/- 3 Days)

The following procedures will occur at the Day 30 visit:

- Visit procedures other than central lab assessment may be performed remotely for participants who have already been discharged from the hospital
- Concomitant medication (may be obtained/extracted from the medical record to minimize staff exposure to COVID-19)
- Study medication administration, if randomized to heparin and still hospitalized
- Local laboratory values, if applicable
- Assess need for inpatient medical services and complete ACTT
  - The need for inpatient medical services should be assessed daily after randomization until the participant is discharged from the hospital, deceased, or Day 30 visit is reached.
  - Documentation pertaining to this assessment must be provided to the CEC as outlined in the Site Manual.
- Clinical events and adverse events assessment
  - Assess for the occurrence of any adverse events and report via the eCRF as appropriate. See Section 8.4 Adverse Events and Serious Adverse Events for more information about adverse events.
  - Assess for the occurrence of any clinical event that suggests the possibility that an efficacy outcome event has occurred. See Section 8.2 Efficacy Assessments for more information about clinical events of interest.
- Post-COVID functional status (PCFS) scale
  - PCFS scale may be performed remotely e.g. by telephone.
  - For patients discharged on Day 30, a retrospective assessment of PCFS pre-COVID-19, which reflects functional status during the month preceding COVID-19 infection, should be performed after current PCFS assessment.
  - PCFS scale assessments should be omitted if the patient remains hospitalized through Day 30 as the instrument is intended to assess outpatient recovery.
- Vital Status (alive or deceased)
- Healthcare Resource Utilization Assessment
- Central laboratory samples (Phase 2b only)

8.2 EFFICACY ASSESSMENTS

Efficacy assessments include clinical outcomes, functional outcomes, and biomarker laboratory values. Refer to Section 3 OBJECTIVES AND ENDPOINTS for detailed information on study objectives and endpoints.

Adjudication of clinical outcomes will be performed centrally by the CEC operating under the CEC charter through review of redacted medical records. If the patient received care in a different health system, the clinical site will be responsible for obtaining medical records for review by the CEC and for archiving those records. Adjudication results will be recorded in the adjudication eCRF.

Clinical and functional outcomes will be assessed and documented by study site staff at the timepoints outlined in the SoA. Assessment may occur via telephone/web contact, review of the eCRF, electronic medical records (EMR), claims databases, Social Security Death Index, or other source documents. Study site staff should provide all information/documentation necessary for evaluation of the efficacy endpoints.

Clinical outcomes: Clinical outcomes of interest as efficacy endpoints include:

- Venous thromboembolic event (VTE)
- Myocardial infarction (MI)
- Stroke (ischemic, hemorrhagic, unknown etiology)
- Acute limb ischemia (ALI)
- Other arterial and venous thromboembolic events
- All-cause mortality (and cause of death if known)
- COVID digit
- Time to recovery (as measured by the ACTT ordinal scale)
- Re-hospitalization to an acute care facility*

Any event that suggests the possibility that a clinical outcome has occurred (including acute coronary syndrome and transient ischemic attack) should be recorded in the eCRF and will be assessed by the CEC (*with the exception of re-hospitalization which will be investigator-reported). The Coordinating Center will also review serious adverse events (SAEs) to identify potential clinical thrombotic events. COVID-19 has been associated with emboli in a variety of locations, including internal organs (e.g. mesenteric artery, renal artery). These should all be included in the event of “systemic embolization.” Unusual locations for VTE have also been reported in association with COVID-19 such as thrombosis of the cerebral veins or sinuses, gonadal or splanchnic veins. These should be recorded in the eCRF as VTE.

Functional outcomes:

- PCFS

Biomarker laboratory values:

- Biomarkers associated with outcomes including those related to coagulation and inflammation (e.g., D-dimer, PT, PTT, Tissue Factor, factor Xa, antiphospholipid antibodies, IL-6, hsCRP).

ACTT ordinal scale: Study-site personnel will record ACTT information on the eCRF. Additionally, source documentation will be reviewed by the CEC which will adjudicate the ACTT and record the results in the

adjudication eCRF. The CEC will leverage the committee structure and collective experience to align on consistent criteria to distinguish between scores 5 and 6.

1. Death
2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7. Not hospitalized, limitation on activities and/or requiring home oxygen
8. Not hospitalized, no limitations on activities

Post-COVID-19 Functional Status Scale: The PCFS[31] will be used to evaluate patient-reported functional status at hospital discharge, and 30-days post-randomization (if the patient has been discharged) (Figure 7). Retrospective assessment of pre-COVID-19 functional status will also be recorded. Instructions for using the scale are provided in Section 10.4.

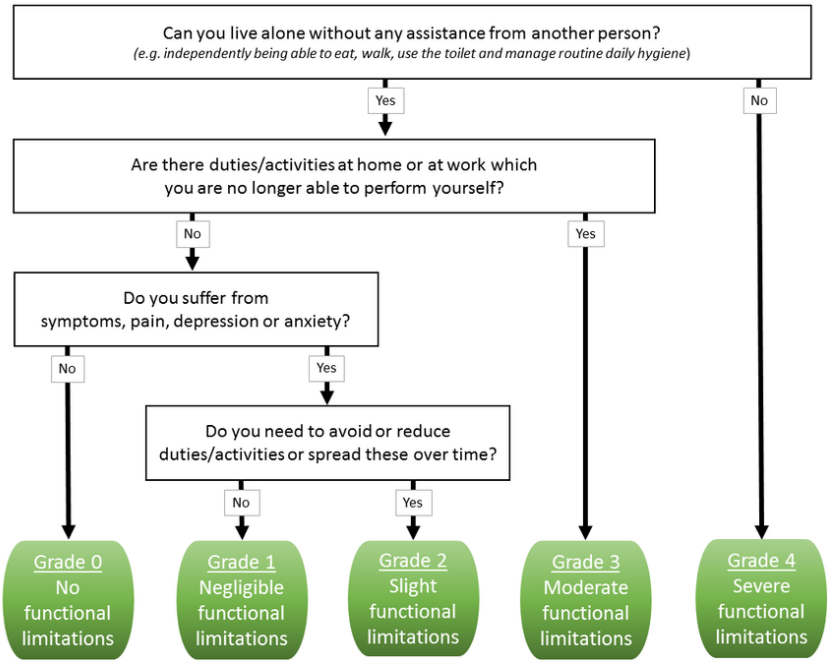


Figure 7. Post-COVID Functional Status Scale

8.3 SAFETY AND OTHER ASSESSMENTS

Safety assessments will include monitoring of serious and non-serious AEs and study endpoints. Efficacy and safety endpoints, including all bleeding events, will not be considered as AEs or SAEs (see Section 8.4 Adverse Events and Serious Adverse Events). Safety evaluations will be assessed by the investigator per the SoA via EMR review, telephone or web contact with the participant or their health care provider.

Safety Events:
Bleeding events are considered safety endpoints for the study.

The study will classify bleeding events as major, non-major clinically relevant or non-major non-clinically relevant. Safety endpoints for this study include major, critical site and fatal bleeding and non-major clinically relevant bleeding using modified International Society on Thrombosis and Haemostasis (ISTH) bleeding criteria. All bleeding events will be assessed, classified and reported by the investigator in the eCRF. Major bleeding events will be adjudicated by the CEC.

An ISTH major bleeding event is defined as overt bleeding that is associated with:

- A fall in hemoglobin of 2 g/dL (1.24 mmol/L) or more, or
- A transfusion of 2 or more units of packed red blood cells or whole blood, or
- A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- A fatal outcome.

Non-major clinically relevant bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled visit or telephone call with a healthcare provider or temporary or permanent cessation of study treatment or associated with discomfort for the participant such as pain or impairment of activities of daily life.

Bleeding events not meeting the definition of major or non-major clinically relevant bleeding will be classified as non-major, non-clinically relevant.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS

An AE is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

COVID-19 Related Events

The following are considered COVID-19-related symptoms:

World Health Organization-specified COVID-19 symptoms[32]	
Most Common Symptoms	Fever, dry cough, tiredness
Less Common Symptoms	aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell, a rash on skin, or discoloration of fingers or toes
Serious Symptoms	difficulty breathing or shortness of breath, chest pain or pressure, loss of speech or movement

Other COVID-19 related events include: adult respiratory distress syndrome (ARDS), and disseminated intravascular coagulation (DIC).

Symptoms and events that are known to be associated with COVID-19 will be reported by the investigator in the eCRF when they meet criteria as AEs or SAEs. Safety evaluations will be assessed by the investigator per the SoA via EMR review, telephone or web contact with the participant or their health care provider.

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.4.3 CLASSIFICATION OF AN ADVERSE EVENT

8.4.3.1 SEVERITY OF EVENT

The investigator will classify AE severity according to the following scale.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."

8.4.3.2 RELATIONSHIP TO STUDY INTERVENTION

The investigator will assess the relationship of AEs to study intervention using the categories below.

- **Related** – The AE is known to occur with the study intervention or there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).
- **Not Related** – There is not evidence to suggest a causal relationship with study intervention or an alternate etiology has been established.

8.4.3.3 EXPECTEDNESS

For rNAPc2, expectedness of an AE will be determined by whether it is listed in the Investigator Brochure, section on Risks, Side Effects and Precautions.

8.4.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Adverse Events and SAEs will be identified as per the SoA. All AEs will be collected from the time of randomization until the participant completes their Day 30 visit or final contact.

All SAEs from the time of consent until the participant completes their Day 30 visit or final contact, whichever is longer, must be reported. All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Follow up may be conducted by EMR review or communication with the participant's health care provider.

8.4.5 SERIOUS ADVERSE EVENT REPORTING

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within twenty-four (24) hours of their knowledge of the event.

Regulatory Reporting Requirements for Serious Adverse Events
The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor or delegate will also report all suspected unexpected serious adverse reactions (SUSARs) to clinical site investigators. The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

To protect the integrity of the study, thromboembolic and bleeding endpoints will **not** be unblinded for reporting to Health Authorities or investigators as safety reports unless otherwise requested by Health Authorities or IEC/IRB.

After study completion, these events will be included in the final analysis which will be unblinded and submitted to Health Authorities with the study report.

Expedited Reporting Requirements
The Sponsor will promptly evaluate all SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs, ECs, and applicable health authorities based on applicable legislation. Certain events are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting, as noted below in Table 3:

Table 3: Reporting of Suspected Unexpected Serious Advers Reactions (SUSARs; Unless Otherwise Requested by Health Authorities or Ethics Committees)

Event type	Expedited report to health authorities and investigators	Unblinded to health authorities	Unblinded to investigators
Study endpoint events, including bleeding endpoints	N	N	N
Non-endpoint SAEs determined to be related to study drug	Y	Y	N
Non-endpoint SAEs determined to un-related to study-drug (e.g., COVID-19 related events)	N	N	N

Data Safety Monitoring Committee oversight is described in Section 10.1.6 Safety Oversight.

8.4.6 REPORTING EVENTS TO PARTICIPANTS

After study completion, a summary of study results will be provided to clinical sites for transmission to study participants.

8.4.7 EVENTS OF SPECIAL INTEREST

Safety events of interest that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without participant/patient exposure to the sponsor study drug, e.g. administration to the wrong patient)

Special reporting situations should be recorded in the eCRF and source documents. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

8.4.8 REPORTING OF PREGNANCY

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within twenty-four (24) hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported on the SAE page of the eCRF. Participants who become pregnant should permanently discontinue treatment with rNAPc2. Management of heparin-allocated participants should be deferred to the participant's treating physician for thrombotic risk assessment.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

During Phase 2b, the null hypothesis for the primary endpoint is that treatment with rNAPc2 and heparin will similarly reduce D-dimer at Day 8; the alternative hypothesis is that rNAPc2 is superior to heparin in reducing D-dimer.

During Phase 3, the null hypothesis for the primary endpoint is that time to recovery within 30 days of randomization is similar for treatment with rNAPc2 and heparin; the alternative hypothesis is that rNAPc2 is superior to heparin by promoting shorter time to recovery.

9.2 SAMPLE SIZE DETERMINATION

During Phase 2b, approximately 160 participants will be enrolled and randomized 1:1:2 to rNAPc2 dose regimen 1, rNAPc2 dose regimen 2, and heparin standard of care, respectively. Assuming approximately 20% of participants may not be evaluable for any reason, 160 randomized participants will provide for approximately 130 evaluable participants. At a sample size of 160 or greater, the study will have adequate power across a range of effect sizes. This sample size was selected to ensure inferences for the primary endpoint analysis will be robust, given certain potential confounding factors such as missing data (random or non-random), heterogeneous application of heparin (low molecular weight and unfractionated; prophylactic and therapeutic), effects of subject-level covariates (e.g., cormorbidities), and effects of site-level covariates (e.g., country).

Power, Primary Endpoint							
			Effect Size (Proportional Reduction)				
	Enrolled Subjects	*Evaluable* Subjects	*20%*	*25%*	*30%*	*35%*	*40%*
Sample Size	80	64	55.8%	67.4%	75.6%	81.0%	84.5%
	100	80	60.5%	72.7%	80.1%	84.9%	87.8%
	110	88	63.6%	76.2%	80.7%	86.6%	89.2%
	120	96	65.2%	78.0%	82.8%	86.9%	91.0%
	130	104	68.2%	79.3%	84.8%	88.7%	91.7%
	140	112	68.9%	80.7%	86.6%	89.3%	92.5%
	160	128	71.3%	83.1%	88.3%	91.3%	94.1%
	180	144	74.9%	84.5%	89.5%	92.5%	94.6%
	200	160	77.2%	86.5%	91.0%	93.8%	95.8%

*Significance via $\alpha = 0.05$
†Simulated with 20% Missing Data
‡Percentages as Averages Across Other Simulation Conditions

During Phase 3, 450 patients yielding 360 recovery events randomized 1:1 into the two treatment groups have approximately 80% power with 5%, two-sided type 1 error assuming median recovery times of 11 and 15 days for the rNAPc2 and heparin groups, respectively (i.e., treatment hazard ratio (HR)=1.36). As described in Section 9.4.6 Planned Interim Analyses, at the second Phase 3 interim analysis (67% of the initial target number of events), if conditional power, based on the estimated interim hazard ratio, falls within 30% and 80%, the sample size and target number of events will be increased to target 90% conditional power for the final analysis.

9.3 POPULATIONS FOR ANALYSES

Randomized participants consist of all screened participants with randomization assignment, regardless of whether or not study intervention was administered. Participants treated without being randomized or treated before randomization will not be considered as randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately, and they will not be included in the safety population.

The efficacy analysis population will be the intent-to-treat (ITT) population, consisting of all randomized participants as defined above. Participants in the ITT population will be analyzed according to the treatment group allocated by randomization.

An additional efficacy analysis population for sensitivity analyses of the primary efficacy endpoints will be the modified intent-to-treat (mITT) population, consisting of the subset of the ITT population that received at least one dose of study drug. Participants in the mITT population will be analyzed according to the treatment group allocated by randomization.

A per protocol population will include all participants who are randomized and receive all three doses of study drug post-randomization. Participants will be analyzed according to the treatment actually received.

The safety analysis population will be the safety population, consisting of the randomized population who received at least one dose or part of a dose of study treatment. Participants will be analyzed according to the treatment received (rNAPc2 or heparin).

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The statistical analyses described in this section will be performed as further detailed in a separate statistical analysis plan. The statistical analysis plan will supersede the protocol in the event of any differences between the two documents in the plans for data analysis, and the protocol will be amended if appropriate. The statistical analysis plan will be included as an appendix in the clinical study report for this protocol.

Descriptive statistics for continuous variables will include the number of participants, mean and standard deviation, median, first and third quartiles, and minimum and maximum values. Descriptive statistics for categorical variables will contain count and percentage.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Phase 2b: Primary efficacy endpoint is change in D-dimer level from Baseline to Day 8, or day of discharge if prior to Day 8. The change in D-dimer will be calculated using proportional change in D-dimer level from the level at baseline to the level at either Day 8 or discharge if discharge occurs before Day 8. A Wilcoxon rank sum test will be performed to compare baseline and Day 8 (or early discharge) D-dimer levels within each treatment group. A second Wilcoxon rank sum test will be used to compare proportional change from baseline to Day 8 (or early discharge) between treatment groups. The primary analysis will involve a comparison of the pooled rNAPc2 treatment groups against the heparin treatment group. Secondary and sensitivity analyses of the primary endpoint will be conducted as described in the statistical analysis plan.

Because the optimal dose rNAPc2 is unknown and its determination is a key objective of the Phase 2b study, the assumption that both doses will be effective and thus can be pooled for statistical analysis may not be correct. Therefore, a series of secondary analyses will be conducted, consisting of analysis for dose response, effectiveness in a single dose group, effectiveness that is related to the extent of baseline D-dimer elevation, and the subgroup analyses described in Section 9.4.7 SubGroup Analyses.

Missingness within the data is to be expected. Subject profile, mortality, or early discharge give rise to the possibility that nonrandom attrition may bias the point estimate for the treatment effect for the primary endpoint. Therefore, missingness will be handled by multiple imputation during a sensitivity analysis as described in the Statistical Analysis Plan (SAP).

Phase 3: The primary efficacy endpoint is time to recovery by Day 30, with day 1 being the date of randomization. Recovery is defined as the first day a participant meets criteria for category 6, 7 or 8 of the ACTT ordinal scale. The analysis of the primary efficacy endpoint will be a comparison of the two treatment groups by a stratified log-rank test, where stratification is according to local laboratory screening D-dimer level > or ≤ 2X local laboratory ULN. Cumulative incidence by treatment group will be

summarized by Kaplan-Meier estimates. Additionally, a treatment hazard ratio and corresponding 95% confidence interval will be estimated by a Cox proportional hazard model stratified by local laboratory D-dimer level at screening.

In the analysis of the primary efficacy endpoint, participants who die within 30 days of randomization will be censored at Day 30. In addition, participants surviving to Day 30 who have not met the criteria for recovery by the time of their last ACTT scale assessment on or prior to Day 30 will be censored on the day of their last assessment. There will be no censoring prior to Day 30 due to study treatment discontinuation, initiation of non-study treatment, or intermittently missed ACTT scale assessments.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Phase 2b: Proportional change in D-dimer level from Baseline to 24 hours post-dose (Day 2) and Day 3 and change in the additional biomarkers associated with outcomes, including those related to coagulation and inflammation from baseline through Day 8, will be analyzed by the same methods as described for the primary efficacy endpoint. Time-to-event outcomes will be analyzed by the same methods as described for Phase 3.

Phase 3: Time to first occurrence of a composite of thrombotic events and all-cause mortality within 30 days of randomization and time to all-cause mortality within 30 days of randomization will be analyzed by the same methods as described for the primary efficacy endpoint, with the exception that deaths will be counted as an event. Events included in these analyses will be those as adjudicated by the CEC. Participants without an adjudicated event by Day 30 will be censored on the study day of last contact or Day 30, whichever is earlier. Similar to the primary endpoint, there will be no censoring prior to Day 30 due to study treatment discontinuation or initiation of non-study treatment. The analysis method for the proportion of participants alive and out of the hospital at 30 days post-randomization will be specified in the Statistical Analysis Plan (SAP) which will also include a multiplicity plan for alpha allocation within the secondary endpoints.

Change in the biomarkers associated with outcomes including those related to coagulation and inflammation will be analyzed by the same methods as described for Phase 2b.

Days in intensive care unit, on ventilator, vasopressors, renal replacement therapy, and circulatory support will be summarized with descriptive statistics.

9.4.4 SAFETY ANALYSES

Incidence rates of AEs including adjudicated bleeding events, all, serious, fatal, severe and treatment-related AEs reported throughout the conduct of the study will be tabulated by preferred term and system organ class.

Changes in laboratory values and vital signs will be summarized with descriptive statistics. The incidence of concomitant medications will also be summarized.

Drop in hemoglobin level as reported per local laboratory data will be used as an indicator of potential bleeding risk.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline demographic information and patient characteristics including, but not limited to, gender, race, age, COVID-19 symptoms, ACTT ordinal scale category, study entry D-dimer median value , remdesivir or other antiviral therapy, concomitant medications, vital signs, and laboratory parameters will be summarized by treatment group for the ITT population.

9.4.6 PLANNED INTERIM ANALYSES

Additional details of the planned interim analyses will be provided in interim analysis plans, 1 plan each for Phase 2b and Phase 3, respectively.

Phase 2b: An interim efficacy analysis will be conducted when 120 participants have completed Day 8 assessments or Day of Discharge assessments if the participant is discharged prior to Day 8. To account for early recovery, deaths, and lab errors which may lead to lack of Day 8 D-dimer in approximately 20% of patients, 120 participants will provide for approximately 100 participants to be evaluated in the interim efficacy analysis. The interim efficacy analysis will test for futility based on the primary study hypothesis. Additionally, at the interim efficacy analysis, the Data Safety Monitoring Committee will be empowered to adjust sample size as pre-specified in the Phase 2b interim analysis plan. An interim safety analysis will occur after approximately one third of the total target enrollment (i.e., 30-40 participants) completes the Day 8 assessments. Outcomes of the interim analyses may include changes to dose regimens, or other adjustments related to safety or trial logistics. No spending of type 1 error will occur during the interim analysis.

Phase 3: Interim analyses on time to recovery will occur when approximately 33% and 67% of the initial target number of events (i.e., 120 and 240) have occurred. The following is an outline of the interim analysis plan:

- Both interim analyses will include a non-binding assessment for futility; no formal boundary will be used in the first interim analysis, while the second will use a boundary corresponding to 10% conditional power.
- Both interim analyses will have a specified boundary for unequivocal efficacy corresponding to a p-value of 0.0001, 1-sided solely for the purposes of a sample size re-estimation at the second interim analysis; the study will not be stopped for unequivocal efficacy even if this boundary is crossed at one of the interim analyses.
- The interim analysis at 67% of the initial target number of recovery events will include a "promising zone" analysis of conditional power, whereby sample size may be increased by up to 150 additional participants (e.g., 600 total participants) and 120 additional events (i.e., 480 total events) to target 90% conditional power for the final analysis if conditional power, based on the estimated interim HR, is within 30% and 80%.

In addition to the unblinded interim analyses described above, given that the Phase 3 is event-driven and participants are followed for the primary endpoint for a fixed period of time (30 days), the event rate will be monitored in a blinded fashion throughout the study. If the blinded (noncomparative) event rate indicates that less than 360 primary events are unlikely to be observed among 450 randomized participants – or the upsized number of events and participants based on the conditional power analysis

at the second interim analysis described above – the number of randomized participants will be increased to ensure the target number of events is achieved.

The alpha level for the final analysis will be 0.05 − 0.0001, or 0.0499.

9.4.7 SUBGROUP ANALYSES

For the primary efficacy endpoint for each Phase, the treatment effects across the following subgroup factors will be examined:

- D-dimer
- Gender
- Age group (<65, ≥65 years)
- Race/ethnicity
- Planned or ongoing therapy with an agent with demonstrated efficacy in patients with COVID-19 (yes, no)
- Baseline ACTT ordinal scale category
- Background antiplatelet therapy at baseline

For the Phase 2b primary efficacy endpoint, possible heterogeneity in the treatment effect for subgroups within each factor will be assessed by including the factor and the interaction between the factor and treatment in the analysis of covariance (ANCOVA) model.

Additionally, the heterogeneous application of heparin dichotomized by therapeutic vs. prophylactic uses, as well as the different standards of use across site, pose the need for sensitivity analyses to determine the degree to which the primary endpoint finding generalizes across sites.

Similarly, for the Phase 3 primary efficacy endpoint, possible heterogeneity in the treatment effect for subgroups within each factor will be assessed by including the factor and the interaction between the factor and treatment in the Cox proportional hazards model.

9.4.8 PHASE 2B TO 3 TRANSITION

At the end of the Phase 2b study, data will be analyzed, and a dose and comparator arm will be identified. The Phase 3 study will then resume once appropriate regulatory authority communications have been conducted and concluded.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Each participant or their Legally Authorized Representative (LAR) must provide electronic or written informed consent according to local requirements after the nature of the study has been fully explained.

A LAR is defined by the US Department of Health and Human Services as “any individual person, judicial body or other body of individuals who are legally authorized under state and federal law to consent to research participation on behalf of a designated person.” The LAR may be a parent, grandparent, or caregiver who has the legal authority to grant consent on behalf of another who has been invited to participate in research.

The ICF must be signed before performance of any study-related activity. The ICF and any other written information provided to participants must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The consent should be in accordance with principles that originated in the Declaration of Helsinki, current International Conference on Harmonisation (ICH) and GCP guidelines, applicable regulatory requirements, and sponsor policy.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain (in a language the participant understands) to potential participants or their LAR the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Participants will be told that refusal to take part in the study will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF, the participant or LAR is authorizing such access, which includes permission to obtain information about his or her survival status.

The participant or LAR will be given sufficient time to read the electronic ICF and the opportunity to ask questions. Once the participant or LAR understands all aspects of the ICF, consent should be appropriately recorded by means of the participant’s or LAR’s signature. After having obtained the consent, the participant will receive a signed/dated copy for their records.

If the participant or LAR is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant [or LAR] is obtained.

The ICF and any other written information provided to participants will be revised whenever important new information becomes available that may be relevant to their consent, or there is an amendment to the protocol that necessitates a change to the content of the patient information and/or ICF. The investigator will inform the participant or their LAR of changes in a timely manner and will ask the participant or their LAR to confirm his/her participation in the study by signing the revised ICF. Any revised written ICF and written information must receive the IEC/IRB`s approval/favorable opinion in advance of use.

Informed consent for study participation includes collection and storage of plasma and serum samples for future research on sequelae of COVID-19. Separate consent will be requested for collection and analysis of Deoxyribonucleic acid (DNA) for future research on genetics of COVID-19 sequelae and

response to treatment. Participants may join the study without agreeing to collection and analysis of DNA.

10.1.2 STUDY CLOSURE

The sponsor may temporarily or permanently stop the study for any reason. If the study is prematurely terminated or suspended, the sponsor will notify clinical site investigators who must promptly inform their IEC/IRB and study participants. The sponsor will provide instructions for interim or closeout procedures.

10.1.3 CONFIDENTIALITY AND PRIVACY

The electronic enrollment log at each clinical site which links participant identifiers to their screening identification number will be treated as confidential and filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by identification number.

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential. The informed consent obtained from the participant (or his or her LAR) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other study-related entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Plasma, serum and samples for DNA extraction will be processed and stored at the clinical sites for batch shipping to the study biobank, consistent with local regulatory requirements. The site investigator will maintain full traceability of collected biological sample shipment or disposal (where appropriate) and documentation of receipt of arrival. The sample receiver keeps full traceability of samples arrival, storage and use until used or disposed of or until further shipment.

Withdrawal of informed consent for biological samples

If a patient withdraws consent for the use of biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, the sponsor is not obliged to

destroy the results of this research. When the site investigator receives notification of withdrawal of consent to the use of collected biological samples, he/she should:

- document this notification in the participant's record
- Ensure that biological samples from that participant, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented
- If the participant's samples have been shipped to the study biobank, ensure the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed documentation returned to the study site for archiving
- Ensures that the participant and sponsor are informed of the sample disposal.

For additional information on participant discontinuation or withdrawal, see Section 7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL.

10.1.5 TRIAL COMMITTEES

Executive Committee

The Executive Committee (EC) consists of members of the academic leadership of the study and the sponsor. Ad hoc members may be appointed as necessary. The EC has overall responsibility for the design, conduct and reporting of the study. The EC will monitor overall safety during the study and will receive any recommendations from the DSMC regarding possible additional analyses or modifications to the study and decide whether to accept them. The EC will oversee the implementation of any modifications to the study and publication of the results.

Clinical Endpoint Committee

A CEC, comprised of physicians blinded to treatment assignment, will review source documentation and centrally adjudicate clinical and functional outcomes for the trial. The CEC will be responsible for adjudicator training, endpoint definitions and classification procedures for suspected thrombotic events and quality control procedures as described in the CEC charter.

Data Safety Monitoring Committee

A DSMC will be appointed by and provide its input to the EC to monitor safety and evidence of effectiveness and to recommend modifications to the adaptive trial design. Modifications to eligibility criteria could include enrollment in Phase 3 of participants 16-17 years of age, based on safety data with weight-based dosing of rNAPc2 in the target population. For safety, ISTH major bleeding, SAEs and all-cause mortality will be monitored monthly by the DSMC Chairperson and at scheduled interim analyses by the full committee (Section 9.4.6 Planned Interim Analyses). Based on monthly reviews, the DSMC Chairperson may call additional undscheduled meetings at anytime during the study. In addition, the study team may advise the DSMC chair of severe safety events (e.g. fatal bleeding) in a blinded fashion in real time, enabling the chair to work with the DSMC statistician and committee as needed to ensure the safety of study participants. The DMSC will operate under the rules of a charter that will be reviewed at the organizational meeting of the DSMC and approved by the principal investigator and Sponsor.

10.1.6 SAFETY OVERSIGHT

A DSMC will be appointed by and provide its input to the EC to monitor safety and evidence of effectiveness and to recommend modifications to the trial design.

10.1.7 CLINICAL MONITORING

The Sponsor or designee will review eCRF data for accuracy and completeness via centralized, remote, and/or on-site monitoring methods described in the Monitoring Plan. Representatives of the sponsor may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees. Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites and review of protocol procedures with the investigator and study-site personnel before the study. Guidelines for eCRF completion will be provided and reviewed with participating study-site personnel before the start of the study. The Sponsor, or designee will review eCRF data for accuracy and completeness via centralized, remote, and/or on-site monitoring methods; any discrepancies will be resolved with the investigator or designee, as appropriate.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Study data will be recorded into the electronic data capture system. The data system includes password protection and internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from source documents.

10.1.9.2 STUDY RECORDS RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least two (2) years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least two (2) years have elapsed since the formal discontinuation of clinical

development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor. If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.1.10 PROTOCOL DEVIATIONS

Protocol deviations will be identified manually and programmatically prior to unblinding. However, as the primary analysis is ITT, protocol deviations will not imply exclusion from analysis. A summary of major protocol deviations will be given by frequency tables showing the number of participants with major protocol deviations overall and by deviation.

10.1.11 PUBLICATION AND DATA SHARING POLICY

All information, including but not limited to information regarding rNAPc2 or the sponsor's operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of rNAPc2, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study. The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study-site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event

that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information.

For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

10.1.12 CONFLICT OF INTEREST POLICY

The Sponsor will register and disclose the existence and results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study.

10.2 ACRONYMS

ACTT	Adaptive COVID-19 Treatment Trial
ADA	Anti-drug antibodies
AE	Adverse event
ALI	Acute limb ischemia
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
CEC	Clinical endpoint committee
CRA	Clinical Research Associate
DIC	Disseminated intravascular coagulation
DSMC	Data Safety Monitoring Committee
DNA	Deoxyribonucleic acid
DVT	Deep vein thrombosis
EC	Executive Committee
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMR	Electronic medical record
fVIIa	Activated factor VII
fXa	Activated factor X
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HITT	Heparin-induced thrombocytopenia and thrombosis

HR	Hazard ratio
HS	Healthy subjects
hsCRP	High sensitivity C reactive protein
HSV1	Herpes simplex virus 1
ICF	Informed consent form
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IL-6	Interleukin-6
IND	Investigational New Drug Application
IEC/IRB	Independent Ethics Committee/Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intention-To-Treat
IV	Intravenous
LAR	Legally authorized representative
LMWH	Low molecular weight heparin
MAD	Multiple ascending dose
mITT	Modified intention-to-treat
NSTE-ACS	Non-ST elevation acute coronary syndrome
PAR	Protease activated receptor
PCI	Percutaneous coronary intervention
PCR	Polymerase chain reaction
PCFS	Post COVID-19 Functional Status
PK	Pharmacokinetic
PT	Prothrombin time
PTT	Partial thromboplastin time
rfVIIa	Recombinant activated factor VII
rNAPc2	Recombinant nematode anticoagulant protein c2
SAD	Single ascending dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SoA	Schedule of Activities
SoC	Standard of care
SUSAR	Suspected unexpected serious adverse reactions
TF	Tissue factor
UFH	Unfractionated heparin
ULN	Upper limit of normal
UP	Unanticipated Problem
VTE	Venous thromboembolic event
WBC	White blood cell count

10.3 HEPARIN GUIDANCE

Population	Guidance
VTE prophylaxis in non-ICU hospitalized COVID-19 patients	1. A universal strategy of routine thromboprophylaxis with standard-dose UFH or LMWH should be used after careful assessment of bleed risk, with LMWH as the preferred agent. Intermediate dose LMWH may also be considered. 2. VTE prophylaxis recommendations should be modified based on extremes of body weight, severe thrombocytopenia (i.e. platelet counts of 50 000 × 109 per liter or 25 000 × 109 per liter) or deteriorating renal function.
VTE prophylaxis in sick ICU hospitalized COVID-19 patients	1. Routine thromboprophylaxis with prophylactic-dose UFH or LMWH should be used after careful assessment of bleed risk. Intermediate-dose LMWH (50% of respondents) can also be considered in high risk patients. Patients with obesity as defined by actual body weight or BMI should be considered for a 50% increase in the dose of thromboprophylaxis. Treatment-dose heparin should not be considered for primary prevention until the results of randomized controlled trials are available. 2. Multi-modal thromboprophylaxis with mechanical methods (i.e. intermittent pneumonic compression devices) should be considered.

Perioperative and Critical Care Thrombosis and Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis.[30]

10.4 POST-COVID FUNCTIONAL STATUS SCALE

The post-COVID-19 functional status (PCFS) scale[31] focuses on relevant aspects of daily life during follow-up after the infection. The scale is intended to help users becoming aware of current functional limitations in COVID-19 patients, whether or not as a result of the specific infection, and to objectively determine this degree of disability. This will aid in demarcating effective and ineffective COVID-19 therapies on functional outcomes in an experimental setting, as well as pave the road for value-based healthcare.

General description of each scale grade

- Grade 0 reflects the absence of any functional limitation.
- Grades 1 and 2 correspond to a condition for which usual duties/activities could be carried out, defined as any activity that patients undertake on a monthly basis or more frequently, either at home or at work/study. Importantly, this includes sports and social activities. Specifically, *Grade 1* is reserved for patients with some symptoms, which however do not prohibit or limit doing any usual activities. Grade 2 is reserved for patients who are able to independently perform all usual activities

but at a lower intensity, sometimes combined with mild limitations in participation in usual social roles.

- Grade 3 accounts for moderate functional limitations that force patients to structurally modify usual activities, reflecting the inability to perform certain activities which, therefore, need to be taken over by others. Those patients may require assistance in instrumental activities of daily living, e.g. managing basic household chores, community mobility, shopping for groceries or necessities, or participation in usual social roles is restricted.
- Grade 4 describes those patients with severe functional limitations who require assistance with activities of daily living (ADL), not necessarily administered by a certified nurse. It should be indicated that assistance with some ADL activities, e.g. using the toilet, managing routine daily hygiene and functional mobility, is essential. Participation in usual social roles is likely restricted.

Timing

The PCFS is intended to be assessed 1) at the time of discharge from the hospital and 2) in the first weeks after discharge to monitor direct recovery. Providing a pre-COVID-19 reference value will allow to measure the change in status. To measure this pre-COVID-19 functional status, the functional status assessment should refer to the status 1 month prior to the infection. Assessment of the pre-COVID-19 functional status should be performed after assessment of the current functional status.

General Instructions

Characteristics of the PCFS scale

The scale is ordinal, has 6 steps ranging from 0 (no symptoms) to 5 (death, D), and covers the entire range of functional outcomes by focusing on limitations in usual duties/activities either at home or at work/study, as well as changes in lifestyle.

Procedure

The post-COVID-19 functional status scale can be assessed by either medical experts or trained interviewers during a short, structured interview. For any type of data collection, raters are encouraged to base their assessments on the *ability* of the patient to perform the activity rather than whether the patient actually performs the activity currently. This prevents overestimation of the severity of symptoms in patients who have chosen to abandon or who simply never performed certain activities**.**

Information should be ideally obtained primarily from the patient and/or a close friend or caregiver (proxy) who is familiar with the daily routine of the patient. If the patient lacks insight into some questions or if responses are inconsistent, it may be helpful to interview a caregiver or relative independently. Limitations or symptoms may vary over time, *the measurement concerns the average situation of the past week (except for when assessed at discharge, in that case it concerns the situation of the day of discharge).* The standardized questions cover 5 sections corresponding to the separate levels of disability, see below table.. However, it is encouraged to ask questions beyond those stated to ensure that the patient has grasped the meaning of the question and to further clarify their responses. Additionally, it is recommended to adapt the interviewing strategy according to the patient's status and his/her answers. Open questions can be a great way to start the interview, during which some key information will be obtained useful to score the patients. Later, more targeted or even closed questions can help to make a clear distinction between adjacent grades. The corresponding PCFS scale grade is provided in the column besides each specific response. In case two grades seem to be appropriate, the

patient will be assigned to the highest grade with the most limitations.

Question	PCFS scale grade if the answer is 'YES'
1. SURVIVAL	
1.1 Has the patient died after the COVID-19 diagnosis?	D
2. CONSTANT CARE Explanation: meaning someone else needs to be available at all times. Care may be provided by either trained or an untrained caregiver. The patient will usually be bedridden and may be incontinent.	
2.1 Do you require constant care?	4
2. BASIC ACTIVITIES OF DAILY LIVING Explanation: assistance includes physical assistance, verbal instruction, or supervision by another person. It may be considered essential when there is a need for physical help (by another person) with an activity or for supervision, or the patient needs prompting or reminding to do a task. The need for supervision for safety reasons should be due to *objective danger* that is posed, rather than 'just in case'.	
3.1 Is assistance essential for eating? (Eating without assistance: food and implements may be provided by others)	**4**
3.2 Is assistance essential for using the toilet? (Using toilet without assistance: reach toilet/commode; undress sufficiently; clean self; dress and leave)	**4**
3.3 Is assistance essential for routine daily hygiene? (Routine hygiene includes only washing face, doing hair, cleaning teeth/fitting false teeth. Implements may be provided by others without considering this as assistance)	**4**
3.4 Is assistance essential for walking? (Walking without assistance: if absolutely necessary, able to walk indoors or around house or ward, may use any aid, however not requiring physical help or verbal instruction or supervision from another person)	**4**
4. INSTRUMENTAL ACTIVITIES OF DAILY LIVING Explanation: assistance includes physical assistance, verbal instruction, or supervision by another person. It may be considered *essential* when there is a need for physical help (by another person) with an activity or for supervision, or the patient needs prompting or reminding to do a task. The need for supervision for safety reasons should be due to *objective danger* that is posed, rather than 'just in case'.	
4.1 Is assistance essential for basic household chores which are important for daily life? (E.g. preparing a simple meal, doing the dishes, take out the garbage; exclude chores that do not need to be done every day)	**4**
4.2 Is assistance essential for local travel? (Local travel without assistance: the patient may drive or use public transport to get around. Ability to use a taxi is sufficient, provided the patient can manage to call and instruct the driver)	**4**
4.3 Is assistance essential for local shopping? (The patient is not able to buy groceries or necessities by him or herself)	3
5. PARTICIPATION IN USUAL SOCIAL ROLES Explanation: this section concerns impairment in fulfilment of major social roles (not social or financial circumstances).	
5.1 Is adjustment essential for duties/activities at home or at work/study because you are unable to perform these yourself (e.g. resulting in a change in the level of responsibility, a change from full-time to part-time work or a change in education)? (Work refers to both paid employment and voluntary work. Special arrangements which allow someone to return to work, even though normally he/she wouldn't be able to work, should be considered as adjustment of work.)	3
5.2 Do you occasionally need to avoid or reduce duties/activities at home or at work/study or do you need to spread these over time (while you are basically able to perform all those activities)?	2

5.3 Can you no longer take good care of loved ones as before? (Taking good care includes babysitting, looking after your partner, parents, grandchildren or dependent others.)	3
5.4 Since the COVID-19 diagnosis, have there been problems with relationships or have you become isolated? (These problems include communication problems, difficulties in relationships with people at home or at work/study, loss of friendships (increase in) isolation, etc.)	3
5.5 Are you restricted in participating in social and leisure activities? (Comprising hobbies and interests, including going to a restaurant, bar, cinema, going for walks, playing games, reading books, etc.)	2
6. SYMPTOM CHECKLIST Explanation: these can be any symptoms or problems reported by the patients or found on physical examination. Symptoms include but are not limited to: dyspnea, pain, fatigue, muscle weakness, memory loss, depression and anxiety.	
6.1 Do you report symptoms through which usual duties/activities need to be avoided, reduced or spread over time?	2
6.2 Do you report any symptoms, resulting from COVID-19, without experiencing functional limitations?	1
6.3 Do you have problems with relaxing or do you experience COVID-19 as a trauma? ('Trauma' is defined as: suffering from intrusive memories, flashbacks or avoidance responses, associated with having experienced COVID-19.)	1

Assigning a grade on the post-COVID-19 functional status scale

The overall rating is simply the poorest functional status indicated by the patient's answers (the highest grade corresponds with the most limitations). If a respondent has no limitations or symptoms, then the appropriate scale grade is 0.

11 REFERENCES

1. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media briefing-on-covid-19---11-march-2020.
2. Luo W, Yu H, Gou J, Li X, Sun Y, Li J, Liu L. Clinical pathology of critical patient with novel coronavirus pneumonia (COVID-19). *Preprints* 2020; published online Feb 27. 2020020407.
3. Fox SE, Akmatbekov A, Harbert JL, Li G, Brown JQ, Vander Heide RS. Pulmonary and cardiac pathology in Covid-19: the first autopsy series from New Orleans. *medRxiv* 2020; published online April 10. DOI:10.1101/2020.04.06.20050575
4. Becker RC. COVID-19 update: Covid-19-associated coagulopathy [published online ahead of print, 2020 May 15]. *J Thromb Thrombolysis* 2020;1-14. doi:10.1007/s11239-020-02134-3
5. Shah S, Shah K, Patel SB, Patel FS, Osman M, Velagapudi P, Turagam MK, Lakkireddy D, Garg J. Elevated D-dimer levels are associated with increased risk of mortality in COVID-19: A systematic review and meta-analysis. Cardiol Rev 2020 Jul 2 doi: 10.1097/CRD.0000000000000033.
6. Stanssens P, Bergum PW, Gansemans Y, Jespers L, Laroche Y, Huang S, Maki S, Messens J, Lauwereys M, Cappello M, Hotez PJ, Lasters I, Vlasuk GP. Anticoagulant repertoire of the hookworm Ancyclostoma caninum. *Proc Natl Acad Sci* USA 1996;93; 2149-2154.
7. Bergum PW, Cruikshank A, Maki SL, Kelly CR, Ruf W, Vlasuk GP. Role of zymogen and activated factor X as scaffolds for the inhibition of the blood coagulation factor VIIa-tissue factor complex by recombinant nematode anticoagulant protein c2. *J Biol Chem* 2001;276(13):10063-10071.
8. Lee AYY, Vlasuk GP. Recombinant nematode anticoagulant protein c2 and other inhibitors targeting blood coagulation factor VIIa/tissue factor. *J Intern Med* 2003; 254:313–321. PMID: 12974870
9. De Pont AC, Moons AH, de Jonge E, Meijers JCM, Vlasuk GP, Rote WE, Buller HR, van der Poll T, Levi M. Recombinant nematode anticoagulant protein c2, an inhibitor of tissue factor/factor VIIa, attenuates coagulation and the interleukin-10 response in human endotoxemia. *J Thromb Haemost* 2004;2(1):65-70.
10. Antoniak S, Mackman N. Multiple roles of the coagulation protease cascade during virus infection. *Blood* 2014;123(17):2605–2613.
11. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu H, Zhang Z. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost* 2020 doi: 10.1111/ jth.14859.
12. Geisbert TW, Hensley LE, Jahrling PB, Larsen T, Geisbert JB, Paragas J, Young HA, Fredeking TM, Rote WE, Vlasuk GP. Treatment of Ebola virus infection with a recombinant inhibitor of factor VIIa/tissue factor: a study in rhesus monkeys. *Lancet* 2003;362(9400):1953-8.
13. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheum* 2020. doi.org/10.1016/S2665-9913(20)30121-1.
14. Zelaya H, Rothmeier AS, Ruf W. Tissue factor at the crossroad of coagulation and cell signaling. J Thromb Haemost 2019: 16: 1941-52
15. Sutherland MR, Wolfram R, Pryzdial ELG. Tissue factor and glycoprotein C on herpes simplex virus type 1 are protease-activated receptor 2 cofactors that enhance infection. *Blood* 2012; 119:3638–45.
16. Sutherland MR, Simon AY, Shanina I, Horwitz MS, Ruf W, Pryzdial ELG. Virus envelope tissue factor promotes infection in mice. *J Thromb Haemost* 2019;17:482-491.
17. Lee A, Agnelli G, Büller H, Ginsberg J, Heit J, Rote W, Vlasuk G, Costantini L, Julian J, Comp P, van Der Meer J, Piovella F, Raskob G, Gent M. Dose-response study of recombinant factor VIIa/tissue factor

inhibitor recombinant nematode anticoagulant protein c2 in prevention of postoperative venous thromboembolism in patients undergoing total knee replacement. *Circulation* 2001;104(1):74-8.
18. Moons AH, Peters RJ, Bijsterveld NR, Piek JJ, Prins MH, Vlasuk GP, Rote WE, Büller HR. Recombinant nematode anticoagulant protein c2, an inhibitor of the tissue factor/factor VIIa complex, in patients undergoing elective coronary angioplasty. *J Am Coll Cardiol* 2003 Jun 18;41(12):2147-53.
19. Giugliano RP, Wiviott SD, Stone PH, Simon DI, Schweiger MJ, Bouchard A, Leesar MA, Goulder MA, Deitcher SR, McCabe CH, Braunwald E for the ANTHEM–TIMI-32 Investigators. Recombinant Nematode Anticoagulant Protein c2 in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome. The ANTHEM–TIMI-32 Trial. *J Am Coll Cardiol* 2007; 49 (25):2398-2407.
20. De Jonge E, Friederich PW, Vlasuk GP, Rote WE, Vroom MB, Levi M, van der Poll T. Activation of Coagulation of Administration of Recombinant Factor VIIA Elicits Interleukin 6 (IL-6) and IL-8 Release in Healthy Human Subjects. *Clin Diag Lab Immunol* 2003;10:495-7.
21. De Pont AC, Moons AH, de Jonge E, Meijers JC, Vlasuk GP, Rote WE, Buller HR, van der Poll T, Levi MJ. Recombinant nematode anticoagulant protein c2, an inhibitor of tissue factor VII, attenuates coagulation and the interleukin-10 response in human endotoxemia.*J Thromb Haemost* 2004;2:65-70.
22. Vlasuk GP, Bradbury A, Lopez-Kinninger L, Colón S, Bergum PW, Maki S, Rote WE. Pharmacokinetics and anticoagulant properties of the factor VIIa-tissue factor inhibitor recombinant Nematode Anticoagulant Protein c2 following subcutaneous administration in man. Dependence on the stoichiometric binding to circulating factor X. *Thromb Haemost* 2003;90(5):803-12.
23. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomized double-blind trial. Lancet 2010; 375: 807–15.
24. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or Enoxaparin for Thromboprophylaxis after Knee Replacement. *N Engl J Med* 2009;361:594-604.
25. Eriksson BI, Dahl OE, Rosencher N, Kurth A, van Kiijk CN, Frostick SP, Kalebo P, Christiansen AV, Hantel S, Hettiarachchi R, Schnee J, Buller HR. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007;5:2178–2185.
26. Freiderich PW, Levi M, Bauer KA, Vlasuk GP, Rote WE, Breederveld D, Keller T, Spataro M, Barzegar S, Buller HR. Ability of Recombinant Factor VIIA to Generate Thrombin During Inhibition of Tissue Factor in Human Subjects. *Circulation* 2001;103:2555-9.
27. Hannsson L, Hedner T, Dahlof B. Prospective Randomized Open Blinded End-point (PROBE) Study. A novel design for intervention trials. Blood Pressure 1992; 1: 113-119
28. Kohro T, Tsutomu Y. Cardiovascular clinical trials in Japan and controversies regarding prospective ransomized open-label blinded end-point design. Hypertension Research 2009; 32: 109-114
29. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease. MMWR 2020;69(13):382-386.
30. Spyropoulos AC, Connors J, Hunt B et al. Scientific and Standardization Committee Communication: Clinical Guidance on the Diagnosis, Prevention and Treatment of Venous Thromboembolism in Hospitalized Patients with COVID-19. J Thromb Haemost 2020; 2020; 18: 1859–65.
31. Klok FA, Boon GJAM, Barco S, Endres M, Geelhoed JJM, Knauss S, Rezek SA, Spruit A, Vehreschild J, Sigerink B. The Post-COVID-19 Functional Status (PCFS) Scale: a tool to measure functional status over time after COVID-19. *Eur Respir J* 2020. doi.org/10.1183/13993003.01494-2020.
32. https://www.who.int/health-topics/coronavirus#tab=tab_3 (accessed 1/28/2021)