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Rationale and design of a study to assess the safety and efficacy of rNAPc2 in COVID-19: the Phase 2b ASPEN-COVID-19 trial



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Background The interaction between thrombosis and inflammation appears central to COVID-19-associated coagulopathy and likely contributes to poor outcomes. Tissue factor is a driver of disordered coagulation and inflammatory signaling in viral infections and is important for viral replication; therefore, tissue factor may be an important therapeutic target in COVID-19.

Study Design ASPEN-COVID-19 (NCT04655586) is a randomized, prospective open-label blinded endpoint (PROBE), active comparator Phase 2b trial to evaluate the safety and efficacy of recombinant Nematode Anticoagulant Protein c2 (rNAPc2), a potent tissue factor inhibitor, in patients hospitalized with COVID-19 with elevated D-dimer levels. This report describes the design of the Phase 2b dose ranging and proof of concept study. Participants are randomly assigned, in a 1:1:2 ratio, to lower or higher dose rNAPc2 by subcutaneous injection on days 1, 3, and 5 or to heparin according to local standard of care; randomization is stratified by baseline D-dimer level (at 2X upper limit of normal). The primary efficacy endpoint for Phase 2b is proportional change in D-dimer concentration from baseline to Day 8 or day of discharge, whichever is earlier. The primary safety endpoint is major or non-major clinically relevant bleeding through Day 8. Phase 2b enrollment began in December 2020 and is projected to complete ~160 participants by Q4 2021.

Conclusions ASPEN-COVID-19 will provide important data on a novel therapeutic approach that may improve outcomes in hospitalized COVID-19 patients beyond available anticoagulants by targeting tissue factor, with potential effects on not only thrombosis but also inflammation and viral propagation. (*Am Heart J* 2022;246:136–143.)

Introduction

The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected over 200 million people and caused more than 4 million deaths worldwide as of September 2021¹. The underlying pathophysiology of COVID-19 appears to involve a severe inflammatory response and coagulopathy resulting in thrombosis despite conventional anticoagulation². Pulmonary micro- and macrothrombi in conjunction

with arterial and venous thrombi identified outside the lung indicate an aggressive hypercoagulable state characterized by elevated D-dimer³⁻⁵. Moreover, elevated plasma D-dimer has been associated with greater severity of disease and mortality in COVID-19⁶. Furthermore, prothrombotic autoantibodies, including pathogenic antiphospholipid antibodies, have been observed in COVID-19 and likened to a secondary antiphospholipid antibody syndrome⁷⁻¹⁰.

Numerous randomized trials of available anti-thrombotic agents for prevention of clinical thrombotic events in patients with COVID-19 have targeted the intrinsic and/or common coagulation pathway¹¹. Some have shown no benefit and have been associated with increased bleeding with higher intensity anticoagulation, while others have found a reduction in thrombotic risk when compared to prophylactic intensity anticoagulation among hospitalized patients with moderately severe disease¹². To date, no survival benefit of therapeutic anticoagulation has been shown among patients with severe disease¹³.

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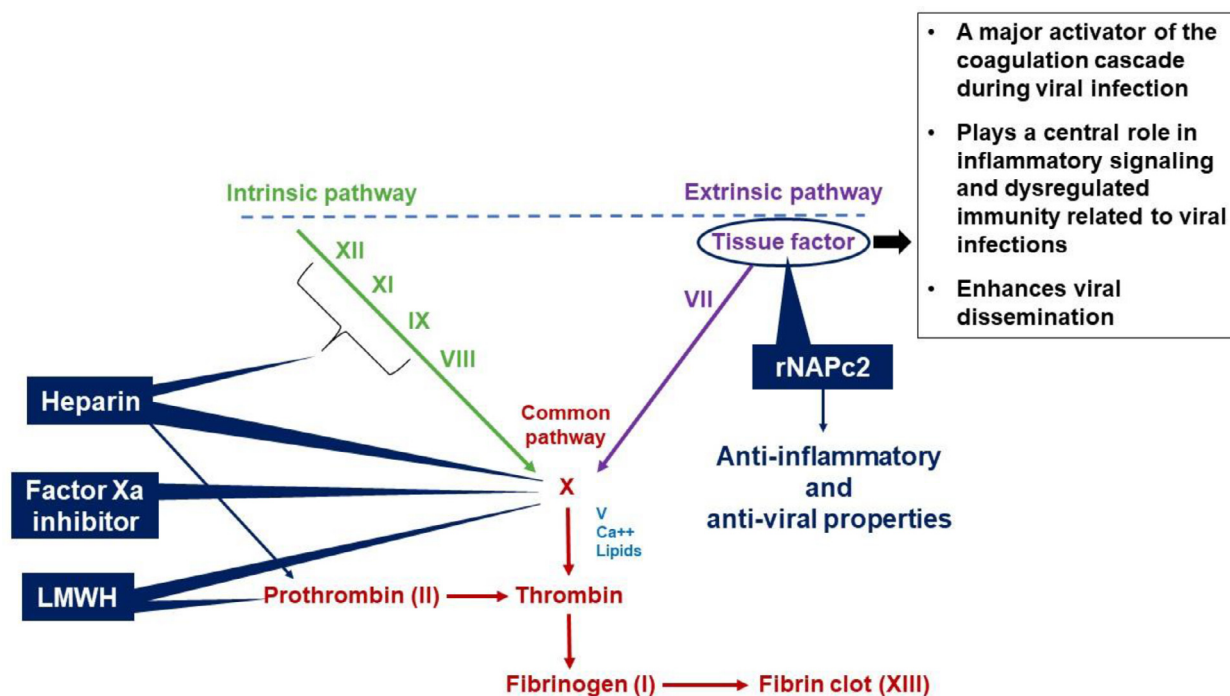
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Figure 1



Anticoagulation targets in viral coagulopathy. Agents currently under study for reduction of thrombotic risk in COVID-19 all target either the intrinsic and/or common coagulation pathways. Recombinant nematode anticoagulant protein c2 (rNAPc2) inhibits tissue factor and the extrinsic pathway. Given the prominent role of tissue factor in the viral propagation and viral-induced hypercoagulability, tissue factor may offer a more precise target in COVID-19 to both prevent thrombotic events and reduce viral progression, potentially speeding recovery.

This limited efficacy of antithrombotic agents targeting the intrinsic/common pathway may be related to the observed activation of multiple pro-coagulant mediators, especially tissue factor, in hypercoagulability associated with viral infections such as with coronaviruses¹⁴⁻¹⁷. Tissue factor complexed with activated factor VII is responsible for not only initiating the extrinsic coagulation pathway, particularly during viral infections, but also activating members of the protease activated receptor family that are important in inflammatory disorders such as sepsis^{14,18}. Incorporation of tissue factor into the viral envelope and involvement in viral dissemination have also been demonstrated in non-SARS-CoV-2 studies^{19,20}. Therefore, tissue factor may provide a novel target in the viral-mediated hypercoagulability observed in COVID-19.

Recombinant Nematode Anticoagulant Protein c2 (rNAPc2), a small recombinant protein cloned from the hematophagous hookworm *Ancylostoma caninum*, is a potent and long-acting inhibitor of tissue factor, binding first to factor X (or factor Xa) and then to the factor VIIa/tissue factor catalytic complex, thereby inhibiting the extrinsic coagulation pathway (Figure 1)²¹. In Ebola-infected non-human primates treated with rNAPc2, reductions in D-dimer, inflammatory biomarker response,

and viral load, and a trend for improvement in survival have been demonstrated²². Treatment with rNAPc2 in mice infected with Herpes simplex virus 1 reduces viral load¹⁹. Therefore, rNAPc2 has the potential to improve outcomes in COVID-19 through both anticoagulant and non-anticoagulant mechanisms, potentially improving disease recovery in hospitalized patients.

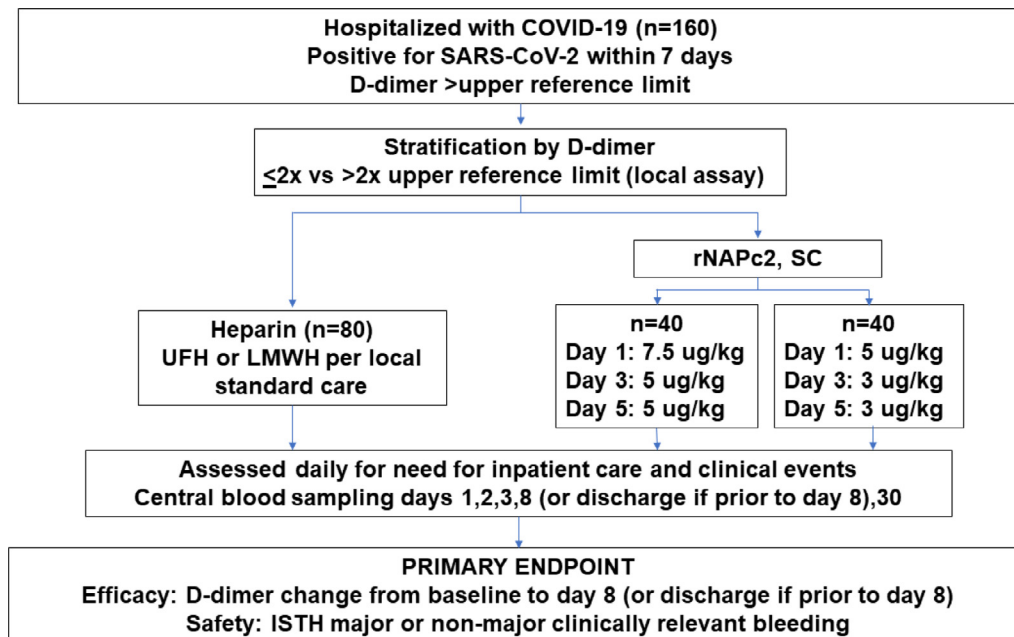
The Assessing Safety, hosPitalization and Efficacy of rNAPc2 in COVID-19 (ASPEN-COVID-19) study consists of sequential Phase 2b and Phase 3 trials designed to investigate the safety and efficacy of rNAPc2 in patients hospitalized with COVID-19 at elevated risk for thrombosis. The trial design for Phase 2b of ASPEN-COVID-19 is described herein.

Study design and population

The ASPEN-COVID-19 phase 2b study is a multicenter, prospective randomized, open-label blinded endpoint (PROBE) design, active comparator trial to assess the efficacy and safety of rNAPc2 compared with heparin in patients hospitalized with COVID-19 (Figure 2).

Selection criteria were designed to enroll a broadly representative population of adults hospitalized with

Figure 2



Study design for ASPEN-COVID-19 Phase 2b. ISTH, International Society of Haemostasis and Thrombosis; LMWH, low-molecular weight heparin; SC, subcutaneously; UFH, unfractionated heparin

COVID-19 at elevated thrombotic risk as reflected by elevated D-dimer. The study population was intended to include a range of disease severity, including critically ill patients requiring care in the intensive care unit and/or organ support, as well as patients managed with non-ICU-based care. Participants must be 18-90 years of age, weigh at least 50 kilograms, require inpatient medical care for COVID-19 as documented by a test indicating active infection, and have a systemic venous D-dimer plasma level elevated above the upper limit of normal per the local laboratory reference range. Key exclusion criteria include: high bleeding risk such as recent surgery, any medical indication for therapeutic anticoagulation, or concomitant use of dual antiplatelet therapy; significantly impaired renal function; inability to receive heparin (e.g. history of heparin-induced thrombocytopenia and thrombosis); and estimated life expectancy less than 72 hours. A complete list of inclusion and exclusion criteria is provided in [Table I](#).

Randomization is completed through use of a central computerized system, and study drug assignment is concealed from investigators until after eligibility is confirmed. Although open-label, investigators are instructed to maintain participant blinding, if possible. Participants are randomized in a 1:1:2 ratio to receive higher dose and therapeutic level rNAPc2 (7.5 ug/kg by subcutaneous injection on day 1, followed by 5 ug/kg on days 3 and 5)

approximating therapeutic anticoagulation²³, lower dose level rNAPc2 (5 ug/kg on day 1, followed by 3 ug/kg on days 3 and 5) providing intermediate dose anticoagulation²³, or heparin (low-molecular weight or unfractionated) administered according to local standard of care. Randomization is stratified by screening D-dimer concentration (less than or equal to vs. greater than twice the local laboratory upper reference limit).

Enrollment began in December 2020 and is expected to conclude in Q4 2021. The study is being conducted in accordance with all local laws and regulations and the ethical principles of the Declaration of Helsinki according to the International Council on Harmonization Good Clinical Practice guidelines. The study protocol and informed consent have been reviewed and approved by the corresponding health authorities, Institutional Review Boards, and Ethics Committees for all participating study sites. Enrolled participants provide informed consent for participation in the trial.

Treatment protocol and follow-up procedures

Treatment selection

The doses of rNAPc2 were selected to balance anti-thrombotic effects and bleeding risk based on data from over 700 participants in 3 separate phase 2 dose-ranging

Table 1. ASPEN-COVID-19 Inclusion/Exclusion criteria

Inclusion criteria

1. Age \geq 18 years and \leq 90 years at the Screening assessment
2. Weight \geq 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 7 days of hospitalization or screening assessment
5. D-dimer level $>$ upper limit of normal at screening
6. Provided electronic or written informed consent, either personally or through a legally authorized representative
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, and 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

Exclusion criteria

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/ μ L, current therapeutic anticoagulation for a medical indication other than COVID-19, 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/1.73m²
4. Known severe liver disease (e.g. bilirubin $>$ 3.5 mg/dL (60 μ mol/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 7 days of the Screening assessment or within 5 half-lives of the investigational agent, whichever is longer

studies examining rNAPc2 in patients with acute coronary syndrome²³, patients undergoing elective percutaneous coronary intervention²⁴, and patients following total knee arthroplasty²⁵. Pharmacokinetic (PK) data from prior rNAPc2 trials have demonstrated a consistently long half-life that increases with repeat dosing, with escalating dose levels after both the second (Day 3) and third (Day 5) doses; in this model, steady state is not reached within 8 days. For ASPEN-COVID-19, a loading dose was included to rapidly attain rNAPc2 plasma levels approximating those achieved at steady state, as COVID-19 patients ill enough to be hospitalized are at immediate risk for the conditions that lead to micro- or macrovascular thromboses. 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 μ g/kg to 1.75 at 5.0 μ g/kg and 2.1 at 7.5 μ g/kg. Based on these data, an initial dose of 5 μ g/kg followed by 3.0 μ g/kg on Days 3 and 5 was estimated to be equivalent to prophylactic dose heparin. A dose of 7.5 μ g/kg followed by 5 μ g/kg on days 3 and 5 was estimated to correlate with a higher intensity of anticoagulation approximating therapeutic heparin. Given the \sim 50-hour half-life of rNAPc, clinical effects of rNAPc2 are expected to begin to decline by day 8. Therefore, subjects randomized to rNAPc2 may be given standard of care heparin therapy beginning on day 8 per the discretion of the investigator. Dose selection for Phase 3 will be based on data from this Phase 2b study.

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 per standard of care. In light of institutional and international variation in use of anticoagulation for thromboprophylaxis in patients hospitalized with COVID-19, heparin-allocated participants will receive regimens per clinical care teams and according to local institutional practice.

Concomitant therapies

The protocol allows for treatment with standard therapies according to local practice, including approved antiviral and anti-inflammatory therapies. The protocol disallows treatment with any drug therapy not approved for use in COVID-19. If treatments such as systemic anticoagulants or dual antiplatelet therapy that might increase bleeding risk when combined with the study treatments are required for clinical indications, study drug will be discontinued.

Visit schedule and follow-up

Participants will be closely followed while hospitalized, including recording of clinical/adverse events, concomitant medications, and the Adaptive COVID-19 Treatment Trial (ACTT) ordinal scale for each day until hospital discharge²⁶. Blood samples will be obtained for central laboratory analysis of study biomarker endpoints on days 1 (prior to first study drug administration), 2, 3, 8

Table II. Safety and efficacy endpoints

Primary safety endpoint: CEC-adjudicated ISTH major or non-major clinically relevant bleeding through the earlier of Day 8 or two days after day of discharge if prior to Day 8. Each rNAPc2 dose will be compared with heparin-allocated patients.

Secondary safety endpoints:

- major or non-major clinically relevant bleeding with rNAPc2 vs. heparin through Day 30
- any bleeding through Day 8 and Day 30
- other adverse events

Primary efficacy endpoint: Proportional change in D-dimer level from baseline to Day 8 (or day of discharge if prior to Day 8) between the pooled rNAPc2 groups and the heparin group

Secondary efficacy endpoints:

- proportional change in D-dimer level from baseline to 24 hours post-dose (Day 2) and Day 3
- probability of discharge accompanied by ACTT ≥ 6 prior to Day 8
- change in biomarkers of inflammation and coagulation from baseline to Day 8 (or day of discharge if prior to Day 8)

Exploratory efficacy endpoints:

- Time to recovery defined as CEC-adjudicated ACTT score ≥ 6 by Day 30
- CEC-adjudicated clinical arterial and venous thrombotic events and death Healthcare resource utilization
- PCFS

ACTT, Adaptive COVID-19 Treatment Trial; CEC, clinical endpoint committee; ISTH, International Society on Thrombosis and Haemostasis; PCFS, Post-COVID Functional Status

(or day of discharge if prior to day 8), and 30. Blood will also be stored in a biorepository for future research for patients that consent to do so. The Post-COVID functional status (PCFS) scale will be assessed immediately after hospital discharge, if applicable, and on day 30²⁷. For those participants discharged from the hospital prior to day 30, a final follow-up visit at 30 days will include assessment of clinical/adverse events, concomitant medications, ACTT ordinal scale, and vital status, in addition to other day 30 visit activities as listed above.

Study endpoints

The primary safety endpoint for the trial is International Society of Thrombosis and Haemostasis (ISTH) major or non-major clinically relevant bleeding through day 8 (or day of discharge if earlier than day 8), comparing each rNAPc2 dosing regimen against heparin-allocated patients. The primary efficacy endpoint is proportional change in D-dimer level from baseline to Day 8 (or day of discharge if prior to Day 8) that will be compared between the pooled rNAPc2 groups and the heparin group. A complete listing of study endpoints is provided in [Table II](#). Clinical safety and efficacy events will be adjudicated by a blinded Clinical Events Committee (CEC) according to pre-specified definitions. Given the open-label trial design, blinded adjudication of these clinical endpoints is critical to reduce potential bias in the assessment of study outcomes.

Statistical considerations

Efficacy analyses will be conducted on all randomized patients using the principle of intention-to-treat; safety analyses will be conducted on all patients that received at least 1 dose of study drug and analyzed according to actual drug received. For the primary efficacy endpoint, proportional change in D-dimer, represented by percent change, will be based on data provided by the central laboratory paired samples. To reduce missingness, if the central laboratory values are not available, available paired local laboratory values will be used. Wilcoxon signed rank tests will be used to compare baseline vs. Day 8, or day of discharge if prior to day 8, values within each treatment group, and a Wilcoxon rank sum test will be used to compare proportional change from baseline to Day 8, or day of discharge if prior to day 8, between treatment groups. The primary outcome will be tested at a 2-sided significance level of 5%.

A sample size of ~100 subjects was originally planned to provide ~90% power for a pooled rNAPc2 vs heparin comparison assuming a standardized mean difference in D-dimer of 0.67 and a 2-sided Type 1 error of 5%. However, during ASPEN-COVID-19, clinical care for hospitalized COVID-19 patients has evolved to include use of concomitant therapies that might affect the primary D-dimer endpoint (e.g., steroids, remdesivir), COVID-19 vaccines that may modulate disease severity have been developed, and data have emerged regarding heterogeneity of antithrombotic therapies according to

severity of COVID-19^{12,13}. In addition, data may be missing due to issues with laboratory sampling. Given these developments and to ensure adequate and evaluable primary endpoint data, the sample size was subsequently increased to ~160 subjects. This sample size provides adequate power (>80%) for the primary efficacy endpoint across a range of effect sizes, ensuring inferences for the primary endpoint analysis will be robust given 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., comorbidities), and site-level covariates (e.g., country).

An independent Data and Safety Monitoring Committee (DSMC) is responsible for monitoring the safety of study participants throughout the trial. An analysis of safety was conducted after enrollment of ~30 participants, and the DSMC recommended continuation of the trial. When approximately 120 subjects have reached Day 8, a futility analysis and a conditional power analysis will be conducted. The DSMC may consider additional factors and request additional analyses to make decisions on trial conduct.

Study organization

Phase 2b of ASPEN-COVID-19 is being conducted at up to 24 sites in the United States, Argentina, and Brazil. An Executive Committee is responsible for oversight of the study and will submit study results for publication in a peer-reviewed journal. The trial is sponsored by ARCA *biopharma*, Inc. (Westminster, CO, United States) and conducted in partnership with CPC Clinical Research (Aurora, CO), a non-profit Academic Research Organization affiliated with the University of Colorado. International trial support is also provided by Estudios Clínicos Latinoamérica (Rosario, Argentina), Hospital Israelita Albert Einstein (São Paulo, Brazil), and Atlantis Clinical (São Paulo, Brazil). ASPEN-COVID-19 is registered on clinicaltrials.gov under NCT04655586. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Discussion

While vaccination against SARS-CoV-2 is ongoing worldwide, clinicians continue to face challenges in caring for patients hospitalized with COVID-19. In addition to issues with vaccine production, distribution, and uptake, SARS-CoV-2 variants pose a further serious threat to progress in containment and treatment of COVID-19. Despite current anticoagulation regimens, substantial residual thrombotic risk remains, particularly among severely ill patients¹³. Furthermore, available anticoagulants may not address important processes such as inflammation

and viral replication that contribute to COVID-19 associated morbidity and mortality. Ongoing efforts to mitigate thrombosis, inflammation, and viral dissemination have mainly focused on countering each of these processes individually. In contrast, rNAPc2 is a novel therapeutic with potential impact on all 3 and may therefore provide a therapy that more precisely addresses the pathophysiology underlying COVID-19.

ASPEN-COVID-19 is designed to assess the safety and efficacy of rNAPc2 in reducing thrombotic risk and potentially speeding recovery compared to standard of care thromboprophylaxis with heparin in patients hospitalized with COVID-19. rNAPc2 has shown an acceptable safety profile and antithrombotic promise in 3 completed Phase 2 studies. In subjects undergoing total knee replacement, rNAPc2 reduced the risk of deep venous thrombosis by as much as 50% more than historical rates observed with standard thromboprophylaxis, depending on the dose and timing of rNAPc2 administration²⁵. When given to subjects undergoing elective coronary intervention and receiving peri-procedural heparin, a single dose of rNAPc2 resulted in prolonged suppression of thrombin generation for up to 36 hours²⁴. In the setting of acute coronary syndrome, a condition with accelerated platelet activation and thrombin generation, rNAPc2 effectively suppressed thrombin generation and electrocardiogram evidence of ischemia²³. Notably, these studies demonstrated acceptable bleeding rates in populations undergoing invasive procedures, often with concurrent antiplatelet and anticoagulant therapies.

In contrast to the numerous completed and ongoing trials of available anticoagulants, rNAPc2 represents a novel mechanism acting via the extrinsic coagulation pathway that might more precisely address the pathophysiology seen in COVID-19. The trial endpoints are predicated on the potential for rNAPc2 to modulate multiple facets of SARS-CoV2 infection - thrombosis, inflammation, and viral propagation. Tissue factor activates the coagulation cascade, potentiates viral infectivity, and mediates inflammation associated with viral illness through protease-activated receptor signaling and activation of toll-like receptors^{28,29}. Importantly, the latter mechanism underlies viral triggering of cytokine storm in antiphospholipid syndrome³⁰. Importantly, Ebola and herpes simplex virus animal models have demonstrated the ability of rNAPc2 to lower tissue factor activity, virus titers, D-dimer concentrations, and inflammatory markers, as well as potentially improve survival rates compared to animals treated with placebo^{19,20,22}. The extent to which these preclinical studies may translate into clinical benefit for hospitalized patients with COVID-19 will be assessed in ASPEN-COVID-19.

In addition to hypercoagulable risk associated with viruses other than SARS-CoV-2, other potential applications for rNAPc2 include conditions such as cytokine storm associated with cancer therapies or antiphospho-

lipid antibody syndrome in which tissue factor may be a useful therapeutic target. The latter may be particularly relevant in the current study population, as pathogenic antiphospholipid antibodies operating through tissue factor have been observed in COVID-19^{10,31}; ASPEN-COVID-19 may provide important insight into whether tissue factor inhibition with rNAPc2 can prevent formation of these antiphospholipid antibodies and potentially mitigate longer-term thrombotic risk. Finally, the additional clinical experience gained in ASPEN-COVID-19 will build on the promising antithrombotic effects already observed in venous thromboprophylaxis, acute coronary syndrome, and elective cardiovascular procedures, as well as other anticoagulant trials in COVID-19.

Summary

Effective treatments for hospitalized patients with COVID-19 remain an important unmet need. The ASPEN-COVID-19 Phase 2b study has been designed to evaluate the safety of the novel tissue factor inhibitor rNAPc2 and its effects on biomarkers of thrombotic risk and inflammation in patients requiring inpatient care for COVID-19. Translation of favorable preclinical effects on viral infectivity and virus-induced inflammation into clinical benefits will be assessed as exploratory endpoints.

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