ARCA biopharma Reports Topline Results for ASPEN-COVID-19 Phase 2b Clinical Trial

- ***For the entire cohort of COVID-19 hospitalized patients, the pooled lower and higher rNAPc2 dose groups demonstrated a reduction compared to baseline in D-dimer levels of 16.8% versus 11.2% for standard of care heparin which was not statistically significant and consequently did not achieve the study primary endpoint***
- ***The treatment effects of rNAPc2 and heparin were different in Mild versus Severe categories of an adapted WHO COVID-19 Severity Scale, with generally decreasing D-dimer levels from baseline in Mild patients, but in Severe patients D-dimer levels were increasing in the Heparin group with no change in the rNAPc2 groups***
- ***rNAPc2 was well-tolerated at both doses***
- ***Company is now evaluating options for development of its assets, including partnering and other strategic options***

Westminster, CO, March 31, 2022 – ARCA biopharma, Inc. (Nasdaq: ABIO), today announced results for ASPEN-COVID-19, a 160 patient Phase 2b clinical trial evaluating rNAPc2, a highly potent and specific inhibitor of tissue factor, as a potential treatment for patients hospitalized with COVID-19. In the clinical trial, both doses of rNAPc2 demonstrated a treatment benefit for patients, however, neither dose achieved statistical significance for the primary efficacy endpoint of change in D-dimer level from Baseline to Day 8 compared to standard of care heparin.

This clinical trial used a 1:1:2 randomization between lower dose rNAPc2, higher dose rNAPc2 and standard of care heparin that was delivered in prophylactic doses in 93% of the patients. rNAPc2 patients received three sub-cutaneous (SC) doses on days 1, 3 and 5 and then received heparin beginning on day 8. This Phase 2b study was designed to understand the safety of the doses selected relative to standard of care, and to provide efficacy data that might support further study in a pivotal Phase 3 program.

For the entire cohort for pooled rNAPc2 versus heparin, in the intention to treat (ITT) population, rNAPc2 was associated with a change in D-dimer of -16.8 (-45.7, 36.8) %, P=0.41 compared to -11.2 (-36, 34.4) %, P=0.91 in the Heparin group (between groups P=0.47). For the per protocol analysis (N=81) of the 38 rNAPc2 patients who received all three doses and remained hospitalized long enough to have the day 8 end-of-efficacy period D-dimer levels measured, there was a reduction from baseline of -28.7 (-49.1,14.0) %, P=0.23, while the Heparin group change from baseline was an increase of 1.1 (-45.2,108) %, P=0.33; between groups P=0.33.

The clinical trial statistical analysis plan called for analysis of data stratified by a modified WHO COVID-19 Severity Scale that assigned randomized patients to either Mild or Severe groups. There was an imbalance by rNAPc2 dose group between these strata with more higher dose group

patients in the Severe stratum (15 vs 10 lower dose) and more lower dose in the Mild stratum. Because treatment effects were different in these strata, dose response had to be analyzed within each stratum. In the ITT analysis, WHO Mild patients (N= 84) had baseline median (IQR) D-dimer levels of 314 (206,473) D-Dimer Units (DDUs, ng/ml). D-dimer levels as percent change *decreased* at day 8 or hospital discharge in both the pooled high and low dose rNAPc2 arms (-32.7 (-44.7,4.3), P=0.009) and in the heparin arm (-16.8 (-36.0.0.5), P= 0.010); this decrease was statistically significant in the higher dose rNAPc2 group (-32.3 (-43.7,-2.4), P=0.016) but not in the lower dose group (-33.0 (-45.8,8.0), P=0.17). In contrast, in WHO Severe patients (N= 51, baseline DDU median 546 (318,872), P<0.0001 vs. Mild) D-dimer levels *increased* in the heparin group (% change 29.0 (-14.9,145), P=0.022) but *did not change* in the pooled rNAPc2 group (25.9 (-49.1,136), P=0.16) or in either rNAPc2 dose group (lower, -12.1(-50.2,498), P=0.84; higher, 36.8 (-41.7,136) P=0.13).

On the secondary endpoints measuring thrombotic events and time-to-recovery, there was a numerical imbalance in favor of rNAPc2 that was non-significant.

Dr. Michael Bristow, ARCA's President and Chief Executive Officer, commented, "Given the accumulating evidence on the clinical importance of thromboses in COVID-19 patients pointing to an important role for the tissue factor pathway in viral infection, inflammatory response and the development of coagulopathy, these clinical trial results are disappointing. While rNAPc2 did provide benefit to patients that was substantially equivalent to prophylactic heparin, neither the pooled dose groups nor either dose arm met the primary efficacy superiority endpoint. In the WHO Scale Severe category where most of the morbidity and mortality from COVID-19 resides, rNAPc2 attenuated the increase in D-dimer levels associated with heparin therapy. We are deeply grateful to all of the patients, their supporters, and investigators who participated in the ASPEN-COVID-19 study. We will continue to analyze the predefined clinical trial analyses, including important measurements such as antiphospholipid Abs. At this time, ARCA is not planning further clinical development of rNAPc2 in COVID-19 in a direct superiority comparison to heparin design. However, we believe the safety margin and apparent efficacy at the lower dose would not preclude a study design evaluating a prophylactic heparin-rNAPc2 combination. In addition, in view of the safety, ease of administration and efficacy for rNAPc2 seen in ASPEN-COVID-19, and lack of any issue related to heparin induced thrombocytopenia-like adverse effects, other indications which have implicated tissue factor in their pathogenesis may be considered as part of our review of strategic options."

Dr. Wolfram Ruf, Scientific Director of the Center for Thrombosis and Hemostasis at the Johannes Gutenberg University Medical Center Mainz, Germany, and Professor at Scripps Research, La Jolla, CA, and member of the ASPEN-COVID-19 Executive Committee, commented: "rNAPc2's efficacy to reduce D-dimer and venous and arterial thrombotic events similar to heparin shown in the ASPEN-COVID-19 study suggest that tissue factor is a likely driver for the coagulopathy seen in severe COVID-19 patients."

Dr. Marc Bonaca MD MPH, Executive Director of The Colorado Prevention Center and Professor of Medicine of University of Colorado, and a member of the ASPEN-COVID-19 Executive Committee stated, "These data support an acceptable safety profile of rNAPC2 at the doses chosen as compared to standard of care heparin. Although the clinical trial was not powered for clinical

efficacy and the overall impact on D-dimer was not statistically significant, the findings in the more severely ill patients, where we know higher doses of heparin are not effective, are exciting. We look forward to learning more about where this novel mechanism may benefit patients in COVID-19 and other disease states where tissue factor may play a key pathological role."

ASPEN-COVID-19 was a Phase 2b randomized, multi-center, international clinical trial that evaluated two dose regimens of rNAPc2 versus standard of care heparin in 160 hospitalized SARS-CoV-2 positive patients that also had an elevated D-dimer level. The primary endpoint of the clinical trial was the change in D-dimer level from baseline to Day 8 relative to standard of care heparin. D-dimer is a biomarker commonly used for assessing coagulation activation, which is commonly elevated in hospitalized COVID-19 patients and is associated with adverse clinical outcomes. Heparin is an anticoagulant commonly given to any patient hospitalized in the United States for COVID-19. Detailed information about the ASPEN-COVID-19 clinical trial is available at its listing on www.clinicaltrials.gov.

Summary efficacy results:
Change in D-dimer levels from baseline at Day 8:

- in ITT analysis, rNAPc2 combined dose arms median reduction of 16.8%, Heparin group reduction of 11.2% (P =0.47 between groups).
- Per protocol analysis (all 3 doses of rNAPc2 administered) reduction in D-dimer of 28.7% in rNAPc2 dose pooled group, heparin increased by 1.1% (P=0.33 between groups).
- WHO Severe patients Heparin group increase in D-dimer by 29.0%, P=0.022 within group; rNAPc2 change by 25.9%, P=0.16 within group.

On the secondary endpoint related to eligibility for hospital discharge (Time to recovery ACTT Score), the rNAPc2 combined arms log rank hazard ratio was 0.88 (0.62,1.23) compared to heparin, and the thrombosis events component of the composite clinical outcome endpoint yielded nine events in the heparin group versus six in the combined rNAPc2 groups (P= 0.44); neither result was statistically significant.

Summary safety results:
rNAPc2 was well-tolerated at both doses. There were no serious treatment-related adverse events and no dose dependent increase in adverse events was observed. There was no difference between rNAPc2 and standard-of-care heparin in major or non-major clinically relevant bleeding.

About ARCA biopharma
ARCA biopharma is dedicated to developing genetically and other targeted therapies for cardiovascular diseases through a precision medicine approach to drug development. The U.S. FDA has granted the Gencaro development program Fast Track designation and a Special Protocol Assessment (SPA) agreement. At present, ARCA is evaluating options for development of its assets, including partnering and other strategic options. For more information, please visit www.arcabio.com or follow the Company on LinkedIn.

Safe Harbor Statement
This press release contains "forward-looking statements" for purposes of the safe harbor provided by the Private Securities Litigation Reform Act of 1995. These statements include, but are not

limited to, statements regarding potential future development plans for Gencaro and rNAPc2, if any, the Company's review of strategic options, the expected features and characteristics of rNAPc2, and rNAPc2's potential to treat COVID-19, or any other RNA virus associated disease. Such statements are based on management's current expectations and involve risks and uncertainties. Actual results and performance could differ materially from those projected in the forward-looking statements as a result of many factors, including, without limitation, the risks and uncertainties associated with: ARCA's financial resources and whether they will be sufficient to meet its business objectives and operational requirements; ARCA may not be able to raise sufficient capital on acceptable terms, or at all, to continue development of rNAPc2 or Gencaro or to otherwise continue operations in the future; results of earlier clinical trials may not be confirmed in future clinical trials; the protection and market exclusivity provided by ARCA's intellectual property; risks related to the drug discovery and the regulatory approval processes; the Company's ability to complete a strategic transaction, and, the impact of competitive products and technological changes. These and other factors are identified and described in more detail in ARCA's filings with the Securities and Exchange Commission, including without limitation ARCA's annual report on Form 10-K for the year ended December 31, 2021, and subsequent filings. ARCA disclaims any intent or obligation to update these forward-looking statements.

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