Gencaro Atrial Fibrillation Phase 2B Results Selected for Publication in *Circulation: Arrhythmia and Electrophysiology*

- Analysis in full patient cohort shows Gencaro effect compared to standard of care
- In the GENETIC-AF entire cohort of heart failure patients treated with Gencaro, compared to patients treated with metoprolol succinate (TOPROL-XL), experienced:
  - a 36% reduction in cumulative atrial fibrillation burden with a 55% reduction in daily atrial fibrillation burden by the end of the study
  - a 32% reduction in the rate of rhythm control clinical interventions, and
  - a 39% increase in electrocardiograms demonstrating normal sinus rhythm
- Aspects of these data are the basis for the new patent issued by USPTO for use of Gencaro in treating atrial fibrillation in heart failure patients with ejection fractions greater than 40%, a patient population for whom there are few approved or effective drug therapies

Westminster, CO, July 28, 2021 – ARCA biopharma, Inc. (Nasdaq: ABIO), a biopharmaceutical company applying a precision medicine approach to developing genetically targeted therapies for cardiovascular diseases, today announced that the paper entitled "Bucindolol [Gencaro] Decreases AF Burden" (Jonathan Piccini, et al), which details a new analysis of the Gencaro Phase 2b data on atrial fibrillation (AF) burden and rhythm control interventions has been published in *Circulation: Arrhythmia and Electrophysiology*, a journal of the American Heart Association. In the Phase 2b superiority clinical trial, although the prespecified primary endpoint was not met, compared with metoprolol, Gencaro reduced AF burden, increased maintenance of sinus rhythm, and reduced the need for additional rhythm control interventions in patients with heart failure (HF) and the genotype which responds most favorably to Gencaro.

In the trial, the prevalence of electrocardiograms (ECGs) in normal sinus rhythm, AF interventions for rhythm control (electrical cardioversion, catheter ablation and Class III antiarrhythmic drugs), and biomarkers were evaluated in the overall population entering efficacy follow-up (N=257). AF burden was evaluated for 24 weeks in a device substudy (N=67) in which all patients had continuous monitoring of cardiac rhythm by implanted devices.

In 257 patients with HF, the mean age was 65.6 ± 10.0 years, 18% were female, mean left ventricular ejection fraction (LVEF) was 36%, and 51% had persistent AF. Cumulative 24-week AF burden was 24.4% (95% CI: 18.5, 30.2) for bucindolol and 36.7% (95% CI: 30.0, 43.5) for metoprolol (36% reduction, $p = 0.002$). Daily AF burden at the end of follow-up was 15.1% (95% CI: 3.2, 27.0) for bucindolol and 34.7% (95% CI: 17.9, 51.2) for metoprolol (55% reduction, $p < 0.001$). The prevalence of ECGs in normal sinus rhythm was 4.20 and 3.03 events per patient for the bucindolol and metoprolol groups, respectively (39% increase, $p < 0.001$); whereas the rate of AF rhythm control interventions was 0.56 and 0.82 events per patient for the bucindolol and metoprolol groups, respectively (32% reduction, $p = 0.011$). Reductions in plasma norepinephrine

(p = 0.038) and NT-proBNP (p = 0.009) were observed with bucindolol compared to metoprolol.

Jonathan Piccini, MD, Associate Professor of Medicine (Cardiology) and Director of the Cardiac Electrophysiology Section at the Duke University School of Medicine and first author of the paper stated, "Atrial fibrillation in heart failure patients is a growing and challenging problem that is badly in need of additional therapies, particularly those that substantially prevent atrial fibrillation while also improving heart failure. Compared to the GENETIC-AF primary endpoint of time to first AF event, the reduction in AF burden measured by continuous device monitoring in a subgroup, increase in sinus rhythm measured by ECG in all patients and the reduction in AF interventions gives a much more comprehensive evaluation of the relative efficacy of bucindolol vs. metoprolol. As clinical investigators, we are eager to take what we've learned in GENETIC-AF and apply it to the planned Phase 3 PRECISION-AF trial."

An additional analysis of these new data confined to patients with ejection fractions of 40% and above showed novel evidence of a clinically significant potential treatment effect for Gencaro in preventing and treating atrial fibrillation in these patients. Patients with this classification of heart failure, known as mildly reduced (HFmrEF) blending into preserved left ventricular ejection fraction (HFpEF) HF, have few approved or effective drug therapies. This novel result provided the basis for a new patent issued to ARCA by the United States Patent and Trademark Office (USPTO) in February 2021 for use of Gencaro in treating AF in the HF population that ARCA plans to enroll in Gencaro's planned Phase 3 development, a population that includes more than half of all HF patients in the United States and Europe. The Company believes this patent would provide effective patent coverage in the United States into 2039. ARCA has filed similar patent applications in other countries.

Dr. Michael Bristow, ARCA's President and Chief Executive Officer, commented, "Atrial fibrillation is common in patients with heart failure, where it complicates disease management, and is associated with worse outcomes, including greater rates of heart failure hospitalization, stroke, and death. AF burden is increasingly being recognized as a more sensitive measure of arrhythmia that is closely linked to key clinical outcomes. In the GENETIC-AF Phase 2b clinical trial device substudy and in the entire trial cohort, Gencaro demonstrated favorable treatment effects compared to the comparator arm. We believe these findings, and our observations that the AF prevention effects of Gencaro appear to persist or be enhanced in higher LVEF HF patients, provide the basis for the design of our Phase 3 trial, PRECISION-AF."

About ARCA biopharma

ARCA biopharma is dedicated to developing genetically targeted therapies for cardiovascular diseases through a precision medicine approach to drug development. ARCA is developing rNAPc2 as a potential treatment for diseases caused by RNA viruses, initially focusing on COVID-19. The U.S. FDA has granted Fast Track designation to the rNAPc2 development program, currently in Phase 2 clinical testing. ARCA is also developing Gencaro™ (bucindolol hydrochloride), an investigational, pharmacologically unique beta-blocker and mild vasodilator, as a potential treatment for atrial fibrillation in heart failure patients. ARCA has identified common genetic variations that it believes predict individual patient response to Gencaro, giving it the potential to be the first genetically targeted AF prevention treatment. The U.S. FDA has granted the Gencaro development program Fast Track designation and a Special Protocol Assessment

(SPA) agreement. 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 the potential future development plans for Gencaro and rNAPc2, the expected features and characteristics of Gencaro and rNAPc2, including the potential for genetic variations to predict individual patient response to Gencaro, Gencaro's potential to treat atrial fibrillation, rNAPc2's potential to treat COVID-19, future treatment options for patients with COVID-19 or AF, and the potential for Gencaro to be the first genetically targeted AF prevention treatment. 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 trials; the protection and market exclusivity provided by ARCA's intellectual property; risks related to the drug discovery and the regulatory approval process; 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, 2020, and subsequent filings. ARCA disclaims any intent or obligation to update these forward-looking statements.

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