Data on Gencaro Impact on Prevention of Bradycardia Published in *Heart Rhythm O2*

- Clinically important bradycardia is common in heart failure (HF) patients with persistent or paroxysmal atrial fibrillation (AF)
- In a Phase 2B clinical trial, the prevalence of clinically important bradycardia was statistically significantly lower for Gencaro™ compared to metoprolol

Westminster, CO, January 4, 2022 – 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 "Dose Limiting, Adverse Event Associated Bradycardia with β-blocker Treatment of Atrial Fibrillation in the GENETIC-AF Trial" (William Abraham, et al) has been published in Heart Rhythm O^2, a publication of the Hearth Rhythm Society. The paper details an analysis that examined the prevalence of bradycardia and its association with adverse events (AEs) and failure to achieve target dose in the GENETIC-AF Phase 2b clinical trial. In the genetically defined population of GENETIC-AF (all *ADRB1* Arg389Arg genotype), the prevalence of clinically important bradycardia was lower for Gencaro compared to metoprolol, with an incidence of heart rate (HR) <50 beats/min of 0.24 episodes/patient per 6 months compared to 0.57 episodes/patient per 6 months for metoprolol succinate ($P < .0001$). This translated to less dose reduction or limitation in the Gencaro group, with 75% of Gencaro subjects achieving target dose compared to 62% for metoprolol ($P < 0.0001$) and 13 bradycardia adverse events in the metoprolol group compared to one for Gencaro ($P = 0.001$).

The 267-patient GENETIC-AF clinical trial tested the hypothesis that pharmacogenetic inhibitory targeting of the higher function, 389 arginine (ADRB1 Arg389) variant of the beta1-adrenergic receptor (beta1-AR) by Gencaro would be more effective in preventing AF than inhibition by metoprolol succinate, a beta blocker without differentiated effects for the ADRB1 Arg389Gly polymorphism. In order to assess the prevalence and importance of bradyarrhythmias in AF-prone HF patients treated with beta blockers and to investigate potential differences between agents with different pharmacologic properties, the paper's authors compared HRs, prevalence of bradycardia, bradycardia association with AEs, target dose attainment, and dose reductions between the second-generation beta blocker metoprolol and the fourth-generation compound Gencaro in the GENETIC-AF trial. Patients randomized to metoprolol (n = 125) or Gencaro (n = 131) entering 24-week efficacy follow-up and receiving study medication were evaluated. Bradycardia was defined as an electrocardiogram (ECG) HR <60 beats per minute (bpm) and severe bradycardia <50 bpm.

Additional analyses determined that mean HR in sinus rhythm (SR) was 62.6 ± 12.5 bpm for metoprolol and 68.3 ± 11.1 bpm for Gencaro ($P < .0001$), but in AF HRs were not different (87.5 bpm vs 89.7 bpm, respectively). Bradycardia episodes (HR <60 bpm) per patient for Gencaro vs

metoprolol were 0.82 vs 2.08 (P < .001) with 98.9% of the episodes occurring in SR. Patients experiencing bradycardia had a 4.15-fold higher prevalence of study medication dose reduction (P <.0001) compared to patients without bradycardia. On multivariate analysis of 21 candidate bradycardia predictors including presence of a device with pacing capability, Gencaro treatment was associated with the greatest degree of prevention (Z odds ratio -4.24, P < .0001).

William T. Abraham, MD, FACP, FACC, College of Medicine Distinguished Professor, Division of Cardiovascular Medicine at The Ohio State University Wexner Medical Center and first author of the paper stated, "Heart failure patients with atrial fibrillation often have conduction system disorders, which may be worsened by beta-blocker therapy. Bradycardia and its necessary management by dose reduction or limitation may compromise efficacy for treating both AF and HF. In this analysis of the on-treatment cohort of GENETIC-AF, patients receiving metoprolol succinate compared to Gencaro experienced more bradycardia, more bradycardia-associated AEs, and more associated dose reductions resulting in an overall lower achievement of target dose. 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."

Dr. Michael Bristow, ARCA's President and Chief Executive Officer, commented, "Atrial fibrillation is common in patients with heart failure. This intersection is clinically important, as the presence of each disorder worsens the prognosis of the other, complicates disease management, and is associated with worse outcomes, including greater rates of heart failure hospitalization, stroke and death. The observations from this recent analysis reinforce the rationale for the development of atrial fibrillation therapeutic approaches that maintain sinus rhythm in heart failure patients, and also reverse or prevent the progression of heart failure, which is what we plan to evaluate in the upcoming Phase 3 PRECISION-AF trial."

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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