



**DOSE RESPONSE OF BETA-BLOCKERS IN ADRENERGIC RECEPTOR
POLYMORPHISM GENOTYPES PAPER PUBLISHED IN
CIRCULATION: GENOMIC AND PRECISION MEDICINE**

Westminster, CO, March 6, 2019 – [ARCA biopharma, Inc.](http://www.arcabio.com) (Nasdaq: ABIO), a biopharmaceutical company applying a precision medicine approach to developing genetically-targeted therapies for cardiovascular diseases, today announced that the paper “Dose Response of Beta-Blockers in Adrenergic Receptor Polymorphisms” was recently published (<https://www.ahajournals.org/doi/10.1161/CIRCGEN.117.002210>) in *Circulation: Genomic and Precision Medicine*, a journal of the American Heart Association.

The lead author on the paper is Duke University cardiologist Kishan S. Parikh and the senior author is Dr. Michael R. Bristow, ARCA’s Chief Executive Officer, formerly Chairman of the Substudies Committee in the [National Heart, Lung, and Blood Institute](http://www.nhlbi.nih.gov/health/clinical-trials/best) (NHLBI)-sponsored BEST (Beta-Blocker Evaluation of Survival Trial) trial.

In heart failure (HF) with reduced ejection fraction (HFrEF), two NHLBI sponsored clinical trials, BEST and HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise TrainNing), have reported an effectiveness interaction between the beta-1 adrenergic receptor (ADRB1) Arg389Gly polymorphism and beta-blockers. In the HF-ACTION DNA substudy, the Arg389 homozygous genotype (ADRB1 Arg389Arg) reported interaction was a decrease in all-cause mortality (ACM) in patients treated with high doses (>25 mg/day in carvedilol equivalents) versus no/low (0-25 mg/day) doses of conventional, HFrEF approved beta-blockers, primarily carvedilol and metoprolol (Fiuzat et al. *Eur J Heart Fail* 2013;15:258-6). In contrast, in BEST, bucindolol produced a reduction in ACM versus placebo in Arg389 homozygous advanced HFrEF patients treated mostly with high, target doses of the experimental beta-blocker (Liggett SB et al. *PNAS* 2006;103:11288-93). In the current Parikh et al. *Circulation: Genomic and Precision Medicine* paper, the authors used uniform methodology and the same dose range definitions for beta-blockers to investigate high (defined for bucindolol as >25 mg/day) versus no/low beta-blocker dose-ADRB1 Arg389Gly polymorphism interactions with major clinical end points in BEST and HF-ACTION, to further investigate pharmacogenetic interactions of beta-blockers.

The results indicated that compared to 389Gly genotypes, ADRB1 Arg389Arg subjects in each trial had less ACM with high- versus no/low-dose beta-blocker (BEST/bucindolol: hazard ratio [HR]=0.40 (0.24,0.65), P=0.0002; HF-ACTION beta-blockers: HR=0.45 (0.26,0.78) P = 0.005), compared to 389Gly genotypes (Gly carriers, high vs. no/low dose in both trials P>0.2). However, the basis for the more favorable effect of high vs. no/low dose groups in the Arg389Arg genotype differed between bucindolol and conventional beta-blockers. For conventional beta-blockers, the HR difference was due to increased mortality in the no/low dose group (HR vs. Gly carrier counterpart genotypes = 1.83 (1.13,2.97), P = 0.015) with no evidence of a favorable effect in the

high dose group (HR 0.84 (0.84,1.49), P = 0.55). In HF-ACTION, the ACM event rate was 21% in no/low dose Arg389Arg patients treated with conventional beta-blockers, compared to 10% in the high dose group, and respectively 14% and 13% in the no/low and high dose 389Gly carrier groups. In marked contrast, in the BEST DNA substudy no/low bucindolol was not associated with an increase in mortality in patients with an Arg389Arg genotype compared to 389 Gly carriers (HR 1.06 (0.73,1.53), P = 0.77). Rather, the advantage of bucindolol in high vs. no/low dose ADRB1 Arg389Arg patients was due to a pronounced differentiation of ACM prevention in the high dose group (HR 0.54 (0.33,0.90), P = 0.018 compared to Gly389 carrier subjects). Therefore, compared to Gly389 genotypes, no/low doses of conventional HF beta-blockers were associated with an 83% increase in ACM while high dose bucindolol produced a 60% decrease in ACM with no increase in ACM at no/low dose.

In the paper the authors concluded: “Beta-blocker dose effects on all-cause mortality risk may be observed for patients with HFrEF with an ADRB1 Arg389Arg genotype. The observed decreased risk compared with the alternative 389Gly carrier genotype may be because of a true reduction in event rates at high/target doses (bucindolol in BEST) or an increase in event rates with lower doses (other beta-blockers in HF-ACTION). These data support guideline recommendations that in HFrEF, beta-blockers should be used at the higher target doses used in all positive phase 3 trials.”

Dr. Bristow commented, “We believe these data provide further evidence that both beta-blocker dose and the ADRB1 Arg389Gly genotype are major determinants of the functionality of the beta-1 adrenergic receptor target of beta-blockers in the heart, and are important modulators of beta-blocker therapeutic responses in HFrEF patients. Moreover, the data support the idea that, depending on the beta-blocker and dose, ADRB1 Arg389Gly genotype can influence response in different directions. The observation that the ADRB1 Arg389Arg genotype may increase mortality in HFrEF patients treated with low doses of conventional, approved HF beta-blockers is potentially important, since substantial numbers of HF patients receive only low doses of these agents. We believe this finding needs to be evaluated in additional studies.”

About ARCA biopharma

ARCA biopharma is dedicated to developing genetically-targeted therapies for cardiovascular diseases through a precision medicine approach to drug development. ARCA’s lead product candidate, Gencaro™ (bucindolol hydrochloride), is an investigational, pharmacologically unique beta-blocker and mild vasodilator being developed for the potential treatment of atrial fibrillation in heart failure patients with mid-range ejection fraction. 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 Gencaro development program has been granted Fast Track designation by FDA. ARCA is also developing AB171, a thiol-substituted isosorbide mononitrate, as a potential genetically-targeted treatment for heart failure and peripheral arterial disease (PAD). For more information, please visit www.arcabio.com.

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, potential future development plans for Gencaro, the expected features and characteristics of Gencaro, including the potential for genetic variations to predict individual patient response to Gencaro, Gencaro's potential to treat atrial fibrillation (AF), future treatment options for patients with 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 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, 2018, and subsequent filings. ARCA disclaims any intent or obligation to update these forward-looking statements.

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