ARCA biopharma, Inc.
Form 10-K
March 21, 2017

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2016

or

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission File Number: 000-22873

ARCA BIOPHARMA, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	36-3855489
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

11080 CirclePoint Road, Suite 140, Westminster, CO 80020

(Address of Principal Executive Offices) (Zip Code)

(720) 940-2200

(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Exchange Act:

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock $0.001 par value	Nasdaq Capital Market

Securities registered pursuant to Section 12(g) of the Exchange Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in rule 405 of the Securities Act. Yes No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 and Section 15(d) of the Act. Yes No

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes No

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer," and "small reporting company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer		Accelerated filer
Non-accelerated filer	(Do not check if a smaller reporting company)	Smaller reporting company

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes No

The aggregate market value of the common stock held by non-affiliates of the Registrant on June 30, 2016, the last business day of the most recently completed second fiscal quarter, was $13,785,280 based on the last sale price of the common stock as reported on that day by the Nasdaq Capital Market.

As of March 17, 2017, the Registrant had 9,130,926 shares of common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's Definitive Proxy Statement, which will be filed with the Commission pursuant to Section 14A in connection with the 2017 Annual Meeting of Stockholders, are incorporated by reference into Part III of this Form 10-K.

TABLE OF CONTENTS

PART I		
Item 1.	Business	1
Item 1A.	Risk Factors	16
Item 1B.	Unresolved Staff Comments	36
Item 2.	Properties	36
Item 3.	Legal Proceedings	37
Item 4.	Mine Safety Disclosures	37
PART II		
Item 5.	Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	38
Item 6.	Selected Financial Data	39
Item 7.	Management's Discussion and Analysis of Financial Condition and Results of Operations	39
Item 7A.	Quantitative and Qualitative Disclosures About Market Risk	44
Item 8.	Financial Statements and Supplementary Data	45
	REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM, KPMG LLP	46
	BALANCE SHEETS	47
	STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS	48
	STATEMENTS OF STOCKHOLDERS' EQUITY	49
	STATEMENTS OF CASH FLOWS	50
	NOTES TO FINANCIAL STATEMENTS	51
Item 9.	Changes in and Disagreements with Accountants on Accounting and Financial Disclosure	64
Item 9A.	Controls and Procedures	64
Item 9B.	Other Information	64
PART III		
Item 10.	Directors, Executive Officers and Corporate Governance	65
Item 11.	Executive Compensation	65
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	65
Item 13.	Certain Relationships and Related Transactions, and Director Independence	65
Item 14.	Principal Accountant Fees and Services	65
PART IV		
Item 15.	Exhibits and Financial Statement Schedules	66
SIGNATURES		67

PART I

Item 1. Business

Some of the statements under “Business,” “Risk Factors,” “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and elsewhere in this Annual Report constitute forward-looking statements. In some cases, you can identify forward-looking statements by the following words: “may,” “will,” “could,” “would,” “should,” “expect,” “int “plan,” “anticipate,” “believe,” “estimate,” “predict,” “project,” “potential,” “continue,” “ongoing” or the negative of these ter comparable terminology, although not all forward-looking statements contain these words. Examples of these statements include, but are not limited to, statements regarding the following: the timing and results of any clinical trials, including GENETIC-AF, the potential that the data from at least 150 patients will support a recommendation that the GENETIC-AF trial transition to Phase 3 or completion of Phase 2B, the potential timeline for GENETIC-AF trial activities and related recommendations of the DSMB, potential timing for patient enrollment in the GENETIC-AF trial, the ongoing Gencaro trial for the prevention of atrial fibrillation, the potential for genetic variations to predict individual patient response to Gencaro, Gencaro’s potential to treat atrial fibrillation, future treatment options for patients with atrial fibrillation, and the potential for Gencaro to be the first genetically-targeted atrial fibrillation prevention treatment, the sufficiency of our current capital to reach certain of our corporate objectives, our ability to obtain additional funding when needed, including our ability to effect sales under the “at the market offering” agreement or enter into a strategic or other transaction, the extent to which our issued and pending patents may protect our products and technology, the potential of such product candidates to lead to the development of safe or effective therapies, our ability to enter into collaborations, our ability to maintain listing of our common stock on a national exchange, our future operating expenses, our future losses, our future expenditures, and the sufficiency of our cash resources to maintain operations. These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. While we believe that we have a reasonable basis for each forward-looking statement contained in this Annual Report, we caution you that these statements are based on a combination of facts and factors currently known by us and our projections of the future, about which we cannot be certain.

In addition, you should refer to the “Risk Factors” section of this Annual Report for a discussion of other important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this Annual Report will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all.

We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise. You are advised, however, to consult any further disclosures we make on related subjects in our Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and our website.

The terms “ARCA,” “the Company,” “we,” “us,” “our” and similar terms refer to ARCA biopharma, Inc.

Overview

We are a biopharmaceutical company applying a precision medicine approach to developing genetically-targeted therapies for cardiovascular diseases. Precision medicine refers to the tailoring of medical treatment to the individual characteristics of each patient through the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their

response to a specific treatment. Our lead product candidate, Gencaro™ (bucindolol hydrochloride), is an investigational, pharmacologically unique beta-blocker and mild vasodilator that we are developing for the potential treatment of patients with atrial fibrillation, or AF, and chronic heart failure with reduced left ventricular ejection fraction, or HFrEF. HFrEF constitutes an estimated 50-60% of the total heart failure, or HF population, with the remainder comprised of HF with preserved ejection fraction, or HFpEF. We believe that Gencaro's efficacy is enhanced in a specific genotype that is present in approximately fifty percent of the general population in the United States, and can be identified by a genetic test. We believe that with this genetic test, we may be able to predict individual patient response to Gencaro, potentially improving the efficacy of treatment for AF in HFrEF patients with this particular genotype. We believe that Gencaro, if approved, could potentially be a safer and more effective therapy for treating or preventing AF in patients with HFrEF and could be the first genetically-targeted AF treatment. We also believe that Gencaro may have market exclusivity based on patents and new chemical entity status, if approved in the United States, Europe or other markets.

We are conducting a Phase 2B/Phase 3 clinical superiority trial, known as GENETIC-AF, in which we are evaluating Gencaro for the treatment and prevention of AF in HFrEF patients. In our trial, HFrEF is defined as a left ventricular ejection fraction, or LVEF, of less than 50%. GENETIC-AF compares Gencaro to TOPROL-XL (metoprolol succinate), a drug approved for treating HFrEF that is also prescribed, but not approved, for treating AF in patients with HFrEF. Enrollment in GENETIC-AF is limited to patients that possess the specific genotype that we believe enhances Gencaro's potential therapeutic effects. Our current development of Gencaro

is, in part, based on a prospectively designed DNA substudy of adrenergic receptor polymorphisms in the BEST trial, a previous Phase 3 study of 2,708 HF patients. Based on data from the BEST trial, Gencaro showed potential evidence of enhanced efficacy in treating AF and in reducing mortality and hospitalizations in HF patients with this specific genotype. In 2015, the U.S. Food and Drug Administration, or FDA, designated the investigation of Gencaro for the prevention of AF in a genetically targeted heart failure population (HF patients with reduced LVEF) as a Fast Track development program.

AF, the most common sustained cardiac arrhythmia, is a potentially serious disorder in which the normally regular and coordinated contraction pattern of the heart's two small upper chambers, or the atria, becomes irregular, rapid and uncoordinated. AF commonly occurs together with HFrEF, with AF being both a cause and a result of HFrEF. By increasing heart rate and producing irregular cycle lengths, AF may contribute to the disease processes that leads to the progression of HFrEF and worsening clinical outcomes.

AF is considered an epidemic cardiovascular disease and a major public health burden. The estimated number of individuals with AF globally in 2010 was 33.5 million. According to the 2017 American Heart Association report on Cardiovascular Disease, approximately 5.2 million people in the United States had atrial fibrillation in 2015. Hospitalization rates for AF increased by 23% among U.S. adults from 2000 to 2010 and hospitalizations account for the majority of the economic cost burden associated with AF. In a global registry of AF patients, the rates of heart failure (of all types) ranged from 33% in patients with paroxysmal (episodes lasting 7 days or less) to 56% in patients with permanent AF.

We believe there is a significant need for drug therapies that are safe and effective for HFrEF patients with AF, as the existing drug therapies for the treatment or prevention AF have certain safety disadvantages in HFrEF patients, such as toxic or cardiovascular adverse effects. Most of the approved drugs for AF are contra indicated or have warnings in their prescribing information for such patients. Consequently, in the treatment and prevention of AF in HFrEF patients, we believe there is an unmet medical need for new treatments that have fewer side effects and are more effective than currently available therapies.

We believe that data from the BEST trial indicate that Gencaro may have a genetically regulated effect in reducing or preventing AF in HFrEF patients. A retrospective analysis of data from the BEST trial shows that all patients in the trial treated with Gencaro had a 41% reduction in the risk of new onset AF (time-to-event) compared to placebo ($p = 0.0004$). In a substudy in the trial, which considered only patients with the genotype believed to enhance Gencaro's efficacy (known as the beta-1 389 arginine homozygous genotype), patients treated with Gencaro experienced a 74% ($p = 0.0003$) reduction in risk of AF, based on the same analysis. In addition, the BEST study, the beta-1 389 arginine homozygous genotype Gencaro demonstrated enhanced efficacy in reducing mortality, hospitalizations, and ventricular tachycardia /ventricular fibrillation, or VT/VF. Furthermore, patients with a beta 1 389 arginine homozygous genotype who entered the trial in AF had statistically significant reductions in major cardiovascular or HF mortality/hospitalization composite endpoints, which we believe is the first and thus far only demonstration of effectiveness of a beta-blocker in reducing major HF events in HFrEF patients with permanent AF. We believe that in HFrEF patients, the therapeutic efficacy of TOPROL-XL is not enhanced in patients with a beta-1 389 arginine homozygous genotype, and we believe that Gencaro may be potentially unique in the beta-blocker class of drugs due to its apparent pharmacologic interaction with this beta-1 adrenergic receptor polymorphism. The beta-1 389 arginine homozygous genotype was present in about 47% of the patients in the BEST pharmacogenetic substudy, and we estimate it is present in about 50% of the U.S. general population.

GENETIC-AF is an adaptive, seamless design Phase 2B/Phase 3, multi-center, randomized, double-blind, clinical superiority trial comparing the safety and efficacy of Gencaro against an active comparator, the beta-blocker TOPROL-XL (metoprolol succinate), that seeks to enroll a combined total of approximately 620 patients. Eligible patients will have HFrEF, a history of paroxysmal AF (episodes lasting 7 days or less) or persistent AF (episodes

lasting more than 7 days and less than 1 year) in the past 6 months, and the beta-1 389 arginine homozygous genotype that we believe responds most favorably to Gencaro. A subset of patients in the trial will also undergo continuous heart rhythm monitoring to assess AF burden, which is defined as the amount of time per day that a patient experiences AF. These data will be collected via newly or previously implanted Medtronic, Inc. devices capable of assessing AF burden (for example, implantable loop recorders, pacemakers, cardioverter-defibrillators, or cardiac resynchronization therapy devices). The primary endpoint of the study is time to first event of symptomatic AF/atrial flutter, or AFL, or all-cause mortality. The combined Phase 2B/Phase 3 trial is designed for 90 percent power at a p-value of less than 0.01 significance level to detect a 25 percent reduction in the primary endpoint for patients in the Gencaro arm compared to patients in the TOPROL-XL arm. We received guidance from the FDA regarding the GENETIC-AF clinical trial prior to initiation of the trial. Based on this FDA guidance, we believe that a successful GENETIC-AF Phase 3 clinical trial, with a p-value of less than or equal to 0.01 could be sufficient evidence of efficacy upon which to base a New Drug Application, or NDA, when submitted with the prior Phase 3 BEST trial data, for the approval of Gencaro for an AF indication in HFrEF patients. A second trial may be required if the GENETIC-AF trial results produce a p-value greater than 0.01. The trial is currently enrolling patients in the United States, Canada and Europe.

The GENETIC-AF Data and Safety Monitoring Board, or DSMB, will perform a pre-specified interim analysis of unblinded efficacy data when at least 150 patients have evaluable data. A randomized patient has evaluable data either when they experience their first composite endpoint event, AF/AFL or all-cause mortality, or after completion of the 24-week primary endpoint follow-up period. The analysis will be conducted for detection of evidence of safety and superior efficacy of Gencaro versus the active comparator, TOPROL-XL.

The prospectively defined features of this analysis include an estimate of Gencaro effectiveness relative to TOPROL-XL and an assessment of safety as characterized by adverse events. The relative benefit estimate will utilize Bayesian statistical methods to calculate the predictive probability of the Phase 3 patient cohort hazard ratio based on the interim Phase 2B data. Prospectively defined ranges of predictive probabilities have been predetermined to define three potential outcomes based on the projection of the Phase 2B interim results:

1) transition the trial to Phase 3 based on a likelihood of achieving a statistically significant hazard ratio in favor of Gencaro (evidence of an efficacy signal consistent with pretrial assumptions) and enroll up to a total of 620 patients (including the Phase 2B patients);

2) completion of the Phase 2B stage of the trial including 24-week follow-up of all randomized subjects (approximately 250 patients), based on an intermediate result that is potentially favorable but does not support transition of the trial to Phase 3 or;

3) immediate termination of the trial due to futility.

We, in collaboration with the GENETIC-AF Steering Committee, will determine the next steps for the trial based on the DSMB recommendation from this interim analysis and on our available capital. The unblinded statistical data available to the DSMB will not be disclosed to us or the public. We randomized our 175th patient in the trial in March 2017. We project that the outcome of the DSMB interim analysis and recommendation will be available in the third quarter of 2017. In February 2016, we amended the trial protocol to allow for up to 250 patients to be enrolled in the Phase 2B portion of the trial, which is intended to enable the study to continue enrolling patients while the DSMB interim analysis is underway. Should the DSMB recommend that the study continue to Phase 3, the trial would continue enrolling to a total of approximately 620 patients (i.e., up to 250 patients in Phase 2B and 370 patients in Phase 3), subject to our obtaining sufficient financing to fund the Phase 3 portion of the trial.

In February 2016, the GENETIC-AF protocol was amended to simplify certain operational aspects of the trial. We believe these modifications facilitated site recruitment and enrollment in existing trial sites and additional sites in European countries, where we are expanding the study to support both the latter portion of Phase 2B, as well as the potential Phase 3 portion of the trial. We believe inclusion of European investigative sites will also support potential European regulatory submissions and partnering activity. We received no objections from the FDA and Health Canada on the protocol amendments prior to their implementation. As such, we believe that these changes do not fundamentally alter or impact previous regulatory agreements.

Our GENETIC-AF clinical trial of Gencaro requires a companion diagnostic test to identify the patient's receptor genotype. We have an agreement with Laboratory Corporation of America, or LabCorp, to provide the companion diagnostic test and services to support our GENETIC-AF trial. LabCorp has developed the genetic test and obtained an Investigational Device Exemption, or IDE, from the FDA for the companion diagnostic test which is being used in our GENETIC AF clinical trial. We retain all rights to the genetic test.

Medtronic, Inc., or Medtronic, a global healthcare solutions company, is collaborating with us on the GENETIC-AF trial. Under the collaboration with Medtronic, ARCA is conducting a substudy that includes continuous monitoring of the cardiac rhythms in a subset of patients enrolled during the trial, which is the basis for a supportive endpoint in the trial known as AF burden. The collaboration is administered by a joint ARCA-Medtronic committee. Medtronic uses its proprietary CareLink System to collect and analyze the cardiac rhythm data from the implanted Medtronic devices

and the data will be used by the DSMB as part of the interim analysis. Medtronic will support the reimbursement process for U.S. patients enrolled in the Phase 2B portion, and will provide financial support of unreimbursed costs for a certain number of U.S. patients in the Phase 2B portion up to a certain maximum amount per patient. If GENETIC-AF continues to Phase 3, we will continue to enroll additional patients, with Medtronic devices for monitoring and recording AF burden, in the substudy. Medtronic will provide the agreed upon CareLink System cardiac rhythm data collection and analysis for the Phase 3 portion of the substudy and support the reimbursement process.

We have been granted patents in the United States, Europe, and other jurisdictions for methods of treating AF and HF patients with Gencaro based on genetic testing. We believe our patent portfolio and new chemical entity exclusivity may provide market exclusivity for the indications of Gencaro that we may develop, into approximately 2030 or 2031 in the United States, Europe and other markets.

To support the continued development of Gencaro, in June 2015, we completed a private placement that raised approximately $34.2 million of net proceeds as additional funds for the Phase 2B portion of the GENETIC-AF trial and to support our ongoing operations. We are seeking to enroll up to 250 HFrEF patients in the Phase 2B portion of the GENETIC-AF trial, and we believe that our current cash and cash equivalents will be sufficient to fund our operations, at our projected cost structure, through the end of 2017. In January 2017, we entered into a sales agreement with an agent to sell, from time to time, our common stock having an aggregate offering price of up to $7.3 million, in an “at the market offering.” We are not obligated to make any sales of our common stock, and, as of March 17, 2017, we have sold an aggregate of 43,156 shares of our common stock pursuant to the terms of such sales agreement for aggregate gross proceeds of approximately $112,000, before paying commissions to our placement agent of approximately $3,000. However, changing circumstances may cause us to consume capital significantly faster or slower than we

currently anticipate. We have based these estimates on assumptions that may prove to be wrong, and we could exhaust our available financial resources sooner than we currently anticipate. If we continue to the Phase 3 portion of GENETIC-AF, we will be required to raise additional funds.

Our Strategy

Our mission is to become a leading biopharmaceutical company developing cardiovascular therapies, using genetic targeting, where possible, to enhance therapeutic response. To achieve this goal, we are pursuing the following strategies:

- Advance the development of Gencaro. We plan to advance the clinical development of Gencaro for AF in HFrEF patients by completing the GENETIC-AF clinical trial, which dependent upon the outcome of the DSMB interim analysis and our available capital, could transition to Phase 3 in 2017. Additional development opportunities for Gencaro potentially include indication expansion or new formulation development. We are also pursuing co-development partnerships for Gencaro.
- Raise additional funding or complete a strategic transaction. To support the continued clinical development of Gencaro, including the GENETIC-AF clinical trial, we expect to seek additional funding, including through the sale of public or private equity or debt securities, or through the completion of a strategic transaction.
- Build a cardiovascular pipeline. Our management and employees, including our chief executive officer, are experienced in cardiovascular research, molecular genetics and clinical development of cardiovascular therapies. We are seeking to leverage this expertise to identify, acquire and develop other cardiovascular products or candidates, particularly those with potential for pharmacogenetic based development.
- Leverage our existing assets. We are pursuing opportunities to leverage certain of our development-stage product candidates. These opportunities include collaborations with institutions conducting proof of concept studies and government funded development.

Atrial Fibrillation in Heart Failure Market Background and Opportunity

AF is a common and potentially serious cardiac rhythm disorder. In AF, the normally regular and coordinated contraction pattern of the heart’s two small upper chambers, or the atria, becomes irregular, rapid and uncoordinated. AF may produce uncomfortable symptoms, but can also have serious consequences. In addition to being a risk factor for stroke, AF can impair heart function by various mechanisms and lead to reduced cardiac function and progression of HF.

AF is considered an epidemic cardiovascular disease. According to the 2017 American Heart Association report on Cardiovascular Disease, approximately 5.2 million people in the United States had AF in 2015, with medical and indirect costs totaling an estimated $31 billion. Hospitalization rates for AF increased by 23% among U.S. adults from 2000 to 2010 and hospitalizations account for the majority of the economic cost burden associated with AF. The approved therapies for the treatment or prevention AF have certain safety disadvantages in HFrEF patients, such as toxic or cardiovascular adverse effects, and most of the approved drugs for AF are contra indicated or have warnings in their prescribing information for such patients. We believe there is an unmet medical need for new AF treatments that have fewer side effects than currently available therapies and are more effective, particularly in HFrEF patients.

AF often occurs in patients with HF. HF is also one of the most prevalent and serious cardiac disorders. In HF, cardiac function and circulatory output become impaired and cannot meet the body's metabolic demands under normal conditions. A common type of HF is HFrEF, where left ventricular systolic function is reduced and the chamber becomes enlarged. The prevalence of AF in patients with HFrEF can vary from approximately 5% to over 50%, depending on HF severity and other factors. In an analysis of patients with new onset HF (of all types) in the Framingham Heart Study, 57% also had AF. In a survey of over 10,000 AF patients from 26 countries conducted in 2009 and 2010, the incidence of HF (of all types) ranged from approximately 33% to over 55%, depending on whether the patient’s AF was paroxysmal, persistent or permanent. Therefore, there is a significant population of patients with both HF and AF, as well as HF patients at risk of developing AF.

AF and HFrEF are interrelated and share common disease processes. The presence of HFrEF makes it more likely AF will develop or perpetuate once it is initiated; in turn, AF in patients with HFrEF may predispose to HF progression including worsening of left ventricular dysfunction, increased hospitalization burden, and increased risk of death.

In treating AF, the risk of stroke is generally addressed through the use of anticoagulants. Beyond this, the goals of current medical therapy for AF are to maintain sinus rhythm or to control ventricular rate response in patients who cannot maintain sinus rhythm, in an effort to minimize patient symptoms and avoid the risk of further complications and disease progression. Current treatments include pharmaceutical therapy and device intervention. Device interventions, such as AF radiofrequency ablation or atrio-ventricular nodal ablation with pacemaker implantation, are considered second line therapy in treatment guidelines.

Addressing the rhythm and rate abnormalities of AF is believed to be particularly important in HFrEF patients because of the relationship between the presence of AF and HF progression. However, the current treatment options for controlling AF in these

patients have significant limitations. While anticoagulants are commonly prescribed to address the risk of stroke in AF patients, these drugs do not address the pathological effects of the irregular and rapid heartbeat that is the hallmark of AF. The drugs that are commonly used to control the rhythm disorder of AF, known as anti-arrhythmic drugs, have severe limitations in HFrEF patients. These drugs may have toxic or cardiovascular adverse effects, particularly with chronic use, and most are contraindicated or have warnings in their labels for use in HF patients.

Drugs in the class known as beta-blockers are commonly prescribed for treating HFrEF and to control rapid heart rate in HF patients with AF. Beta-blockers are generally safe for chronic use in these patients. However, the beta-blockers currently approved or used in HF patients are not approved for treating AF and have demonstrated mild efficacy in preventing AF. In addition, analyses of published trials indicate that current beta-blockers provide no significant benefit in improving clinical outcomes for patients with both AF and HFrEF.

We believe there is an unmet medical need for new therapeutics that may provide better treatment for patients with HFrEF and AF, which can safely treat the rhythm and rate disorders in these patients with greater efficacy, while improving their clinical outcomes and prognoses.

Gencaro

Gencaro (bucindolol hydrochloride) is an investigational, pharmacologically unique beta-blocker and mild vasodilator being developed for the treatment of AF. Gencaro is considered part of the beta-blocker class of compounds because of its property of blocking both beta-1 and beta-2, receptors in the heart. The blocking of these receptors prevents them from binding with other molecules, primarily the neurotransmitter norepinephrine, or NE, which activate these receptors. We believe that Gencaro is well-tolerated in cardiovascular patients because of its mild vasodilator effects. Originally developed by Bristol-Myers Squibb, or BMS, the active pharmaceutical ingredient, or API, in Gencaro, bucindolol hydrochloride, has been tested clinically in approximately 4,500 patients, including over 3,000 patients in seven clinical trials in HFrEF patients. Gencaro was the subject of a Phase 3 HF mortality trial in 2,708 patients, mostly in the United States, or the BEST trial. The BEST trial included a DNA bank of over 1,000 patients, which was used to evaluate the effect of genetic variation on patients' response to Gencaro.

At the time of the BEST trial, our scientific co-founders, Dr. Michael Bristow and Dr. Stephen Liggett, hypothesized that the unique pharmacologic properties of Gencaro would interact with common genetic variations of beta-1, beta-2 and alpha-2C, adrenergic receptors, which are important receptors that regulate cardiac or adrenergic (sympathetic) nerve function. They tested this hypothesis prospectively in a substudy conducted using data from the BEST DNA bank. On the basis of this study, Drs. Bristow and Liggett have determined that patients with certain variations in these receptors had substantially improved outcomes on primary and certain secondary clinical endpoints in the trial, such as mortality, HF progression, hospitalization and prevention of arrhythmias, relative to the counterpart genotype groups and the general patient population of the BEST trial. We believe that these genetically determined receptor variations, which are detectable using standard DNA testing technology, can serve as diagnostic markers for predicting enhanced therapeutic response to Gencaro, and potentially avoiding adverse events, in individual patients. We have patented our methods for treating AF and HF patients with Gencaro in the United States, Europe and other markets based on genetic testing.

Pharmacology and Pharmacogenetics

Gencaro's pharmacology appears to be different from other compounds in the beta-blocker class in several fundamental respects. First, the National Heart, Lung and Blood Institute of the National Institutes of Health, or NHLBI, and the Cooperative Studies Program of the Department of Veterans Affairs sponsored studies, or the Liggett-Bristow investigations, conducted by Drs. Bristow and Liggett indicated that in human myocardial preparations, Gencaro, but not other tested beta-blockers used to treat HF, predisposes to a shift in equilibrium of beta-1 389 arginine but not 389 glycine receptors from a constitutively active to an inactive state, a property known as inverse agonism. Second, other studies, including BEST, indicated that Gencaro lowers the systemic levels of the

neurotransmitter norepinephrine, or NE, released by cardiac and other adrenergic nerves. The beta-1 389 arginine receptor, 100% of the receptor population in patients with a 389 arginine homozygous genotype, has much higher affinity for binding to NE compared to 389 glycine receptors, and published data indicate that NE lowering from Gencaro is beneficial in patients who have only beta-1 389 arginine receptors. In contrast, patients with lower NE affinity beta-1 389 glycine genotypes may have blunting of efficacy from greater amounts of NE lowering. Third, Drs. Liggett and Bristow's investigations have revealed that NE lowering by Gencaro is in turn regulated by an adrenergic receptor polymorphism present in adrenergic nerve terminals, alpha-2C 322-325 insertion (Ins)/deletion (Del). The presence of 322-325 Del genotypes predisposes to greater amounts of Gencaro related NE lowering, which in the presence of beta-1 389 glycine genotypes can lead to compromise of efficacy. However, for patients with a beta-1 389 arginine homozygous genotype the high affinity of this receptor for NE means that any amount of NE lowering may be beneficial, and that it is not be necessary to take the alpha-2C 322-325 Ins/ Del genotype into consideration. As a result, the GENETIC-AF trial is targeted at patients with a beta-1 389 arginine homozygous genotype, which has been present in approximately 50% of screened patients. We believe that these properties and their pharmacogenetic implications for modulating effectiveness are unique to Gencaro, and if the drug is approved, will be described in in the prescribing information.

Gencaro has an important interaction with the beta-1 receptor found on muscle cells, or cardiac myocytes, of the heart. The general role of the beta-1 receptor and its downstream signaling cascades is to regulate the strength and rate of the heart's contractions. NE serves as an activator of the beta-1 receptor, causing the receptor to initiate signaling to the cardiac myocyte. Although this signaling may be beneficial to the failing heart in the short term, in chronic HFrEF patients the beta-1 receptor also initiates harmful, or cardiomyopathic, signaling which, over time, exacerbates the heart's structural and functional decline. Beta-blockers counteract this destructive process by reducing beta-1 receptor signaling and reversing abnormal patterns of gene expression. They do this by binding to the receptor and blocking NE molecules from binding and activating the signaling activity and, in Gencaro's case, by inactivating constitutively active (i.e. active in the absence of NE stimulation) beta-1 389 arginine receptors and lowering NE levels