ARCA biopharma, Inc.
Form 424B4
March 21, 2014
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Prospectus Supplement No. 18 **Filed pursuant to Rule 424(b)(4)**

(to Prospectus dated May 30, 2013) **Registration No. 333-187508**

125,000 Shares of Series A Convertible Preferred Stock

12,500,000 Shares of Common Stock Underlying the Preferred Stock

Warrants to Purchase up to 6,250,000 Shares of Common Stock and

6,250,000 Shares of Common Stock Underlying the Warrants

ARCA biopharma, Inc.

This prospectus supplement supplements the prospectus dated May 30, 2013 (the Prospectus), as supplemented by that certain Prospectus Supplement No. 1 dated July 17, 2013 (Supplement No. 1), by that certain Prospectus Supplement No. 2 dated July 19, 2013 (Supplement No. 2), by that certain Prospectus Supplement No. 3 dated July 24, 2013 (Supplement No. 3), by that certain Prospectus Supplement No. 4 dated July 30, 2013 (Supplement No. 4), by that certain Prospectus Supplement No. 5 dated August 6, 2013 (Supplement No. 5), by that certain Prospectus Supplement No. 6 dated September 4, 2013 (Supplement No. 6), by that certain Prospectus Supplement No. 7 dated September 23, 2013 (Supplement No. 7), by that certain Prospectus Supplement No. 8 dated October 29, 2013 (Supplement No. 8), by that certain Prospectus Supplement No. 9 dated November 6, 2013 (Supplement No. 9), by that certain Prospectus Supplement No. 10 dated November 13, 2013 (Supplement No. 10), by that certain Prospectus Supplement No. 11 dated November 21, 2013 (Supplement No. 11), by that certain Prospectus Supplement No. 12 dated December 5, 2013 (Supplement No. 12), by that certain Prospectus Supplement No. 13 dated January 8, 2014 (Supplement No. 13), by that certain Prospectus Supplement No. 14 dated February 10, 2014 (Supplement No. 14), by that certain Prospectus Supplement No. 15 dated February 12, 2014 (Supplement No. 15), by that certain Prospectus Supplement No. 16 dated February 18, 2014 (Supplement No. 16), and by that certain Prospectus Supplement No. 17 dated March 3, 2014 (Supplement No. 17 , and together with Supplement No. 1, Supplement No. 2, Supplement No. 3, Supplement No. 4, Supplement No. 5, Supplement No. 6, Supplement No. 7, Supplement No. 8, Supplement No. 9, Supplement No. 10, Supplement No. 11, Supplement No. 12, Supplement No. 13, Supplement No. 14, Supplement No. 15, and Supplement No. 16, the Supplements), which form a part of our Registration Statement on Form S-1 (Registration No. 333-187508). This prospectus supplement is being filed to update and supplement the information in the Prospectus and the Supplements with the information contained in our annual report on Form 10-K, filed with the Securities and Exchange Commission (the Commission) on March 20, 2014 (the Annual Report). Accordingly, we have attached the Annual Report to this prospectus supplement.

The Prospectus, the Supplements and this prospectus supplement relate to the offer and sale of up to 125,000 shares of Series A Convertible Preferred Stock (Preferred Stock) which are convertible into 12,500,000 shares of Common Stock, warrants to purchase up to 6,250,000 shares of our Common Stock and 6,250,000 shares of Common Stock underlying the warrants.

This prospectus supplement should be read in conjunction with the Prospectus and the Supplements. This prospectus supplement updates and supplements the information in the Prospectus and the Supplements. If there is any

inconsistency between the information in the Prospectus, the Supplements and this prospectus supplement, you should rely on the information in this prospectus supplement.

Our common stock is traded on the Nasdaq Global Market under the trading symbol ABIO. On March 20, 2014, the last reported sale price of our common stock was $2.06 per share.

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Investing in our securities involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading Risk Factors beginning on page 5 of the Prospectus and beginning on page 23 of our quarterly report on Form 10-Q for the quarterly period ended September 30, 2013 before you decide whether to invest in shares of our common stock.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if the Prospectus or this prospectus supplement is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus supplement is March 20, 2014

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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

x **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2013

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 x

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 x

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 x 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 x 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. x

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 x

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

The aggregate market value of the common stock held by non-affiliates of the Registrant on June 28, 2013, the last business day of the most recently completed second fiscal quarter, was $12,057,265 based on the last sale price of the common stock as reported on that day by the Nasdaq Capital Market.

As of March 17, 2014, the Registrant had 20,979,840 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 2014 annual meeting of stockholders, are incorporated by reference into Part III of this Form 10-K.

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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, intend, plan, anticipate, believe, estimate, predict, project, potential, continue, ongoing or the negative of these terms or other 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 the planned Gencaro trial for the prevention of atrial fibrillation-our ability to obtain additional funding 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 principally focused on developing genetically-targeted therapies for cardiovascular diseases. Our lead product candidate is Gencaro (bucindolol hydrochloride), a pharmacologically unique beta-blocker and mild vasodilator that we plan to evaluate in a new clinical trial for the treatment of atrial fibrillation, or AF, in patients with heart failure and/or left ventricular dysfunction, or HFREF. We have identified common genetic variations in receptors in the cardiovascular system that we believe interact with Gencaro s pharmacology and may predict patient response to the drug.

We plan to test this hypothesis in a Phase 2B/3 clinical trial of Gencaro, known as GENETIC-AF. We are pursuing this indication for Gencaro because data from the previously conducted Phase 3 HF trial of Gencaro in 2,708 HF patients, or the BEST trial, suggest that Gencaro may be successful in reducing or preventing AF.

AF is a disorder in which the normally regular and coordinated contraction pattern of the heart s two small upper chambers (the atria) becomes irregular and uncoordinated. The irregular contraction pattern associated with AF causes blood to pool in the atria, predisposing the formation of clots potentially resulting in stroke.

AF is considered an epidemic cardiovascular disease. The estimated number of individuals with AF globally in 2010 was 33.5 million. According to the 2014 American Heart Association report on Heart Disease and Stroke Statistics, the estimated number of individuals with AF in the U.S. in 2010 ranged from 2.7 million to 6.1 million people. AF increases the risk of stroke and may also contribute to worsening heart failure. The approved therapies for the treatment or prevention AF have certain 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.

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GENETIC-AF is planned as a multi-center, randomized, double-blind clinical trial designed to compare the safety and efficacy of Gencaro to an active comparator, the beta-blocker Toprol XL (metoprolol succinate), in HFREF patients recently diagnosed with persistent AF and having beta-1 389 arginine homozygous genotype, the genotype we believe responds most favorably to Gencaro. The primary endpoint of GENETIC-AF, time to recurrent symptomatic AF or all-cause mortality, will be measured over a twenty-four week period after a patient has been electrically cardioverted to restore normal heart rhythm.

We believe data from the BEST trial indicate that Gencaro may have a genetically regulated effect in reducing or preventing AF, whereas we believe the therapeutic benefit of Toprol XL does not appear to be enhanced in patients with this genotype. A retrospective analysis of data from the BEST trial shows that the entire cohort of patients in the BEST 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 the BEST DNA substudy, patients with the beta-1 389 arginine homozygous genotype experienced a 74% ($p = 0.0003$) reduction in risk of AF when receiving Gencaro, based on the same analysis. 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 US general population.

We have created an adaptive design for GENETIC-AF. It is anticipated that the trial will be initiated as a Phase 2B study in approximately 200 HFREF patients with recent onset, persistent AF who have the beta-1 389 arginine homozygous genotype that we believe responds most favorably to Gencaro. In addition to measuring the primary endpoint of recurrent symptomatic AF or all-cause mortality, an additional efficacy measure in the Phase 2B portion of GENETIC-AF will be AF burden, defined as a patient s percentage of time in AF per day, regardless of symptoms. All 200 patients in the Phase 2B portion of the trial will have either a newly or previously implanted Medtronic device that measures and records AF burden. The GENETIC-AF Data Safety Monitoring Board (DSMB) will analyze certain data from the Phase 2B portion of the trial and recommend based on a comparison to our pre-trial statistical assumptions, whether the trial should proceed to Phase 3 and seek to enroll an additional 420 patients. The DSMB will make their recommendation based on analysis of certain trial data after 200 patients have been enrolled and have completed 24 weeks of follow-up, the period for measuring the trial s primary end-point. The interim analysis will focus on available data regarding AF event rates, AF burden, and safety. Should the DSMB interim analysis conclude that the interim data is consistent with pre-trial statistical assumptions and indicates potential for achieving statistical significance for the Phase 3 endpoint, then the DSMB may recommend the study proceed to Phase 3. The DSMB may also recommend changes to the study design before the trial proceeds to Phase 3, or it may recommend that the study not proceed to Phase 3. Based on the DSMB recommendation, and other factors, including input from the trial s steering committee, the Company, in consultation with the trial s Trial Steering Committee, will make the final determination on the trial s development steps. The full Phase 2B/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 risk of AF recurrence or death in patients in the Gencaro arm compared to patients in the Toprol XL arm. The Company believes the Phase 2B portion of the study will take approximately two and one-half years to complete from the time the first patient is enrolled until the planned DSMB interim analysis of data from the initial 200 patients.

Our GENETIC-AF clinical trial of Gencaro requires a companion diagnostic test to identify the patient s receptor genotype. Accordingly, the GENETIC AF trial will require the use of a third party diagnostic service to perform the genetic testing. 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 will be used in our GENETIC-AF clinical trial.

Medtronic, Inc., a leader in medical technologies to improve the treatment of chronic diseases including cardiac rhythm disorders is collaborating with us on the planned GENETIC-AF trial. Under the collaboration with Medtronic,

ARCA plans to conduct a substudy that will include continuous monitoring of the cardiac rhythms of all 200 patients enrolled during the Phase 2B portion of the trial and approximately 100 additional patients in the Phase 3 portion of GENETIC-AF. The collaboration will be administered by a joint ARCA-Medtronic committee. Medtronic will use 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 patients enrolled in the Phase 2B portion, and will provide financial support of unreimbursed costs for a certain number of patients in the Phase 2B portion up to a certain maximum amount per patient. If GENETIC-AF proceeds to Phase 3, we will seek to enroll an additional 100 patients, with Medtronic devices for monitoring and recording AF burden, in the substudy. Medtronic will provide the agreed-on 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 U.S., Europe, and other jurisdictions for methods of treating AF and HF patients with Gencaro based on genetic testing, which we believe may provide market exclusivity for these uses of Gencaro into at least 2026 in the US and into 2025 in Europe. In addition we believe that if Gencaro is approved, a Gencaro patent will be eligible for patent term extension based on our current clinical trial plans which, if granted, may provide market exclusivity for Gencaro into 2029 or 2030 in the US and Europe.

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To support the continued development of Gencaro, we completed public equity offerings during 2013 that raised approximately $19.3 million of net proceeds. In February 2014 we completed a public equity offering that raised approximately $7.9 million of net proceeds as additional funds for the planned Phase 2B portion of the GENETIC-AF trial and to support our ongoing operations. In light of the significant uncertainties regarding clinical development timelines and costs for developing drugs such as Gencaro, we will need to raise a significant amount of additional capital to finance the completion of GENETIC-AF and our ongoing operations. We anticipate that our current cash and cash equivalents, including the net proceeds from our February 2014 equity offering, will be sufficient to fund our operations, at our projected cost structure, through at least the end of 2015. 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.

On January 27, 2009, we completed a business combination (the Merger) with ARCA Colorado in accordance with the terms of that Agreement and Plan of Merger and Reorganization, dated September 24, 2008, and amended on October 28, 2008 (as amended, the Merger Agreement), in which a wholly-owned subsidiary of Nuvelo, Inc. merged with and into ARCA Colorado, with ARCA Colorado continuing after the Merger as the surviving corporation and a wholly-owned subsidiary of Nuvelo, Inc. Immediately following the Merger, we changed our name from Nuvelo, Inc. to ARCA biopharma, Inc., and our common stock began trading on the Nasdaq Global Market under the symbol ABIO on January 28, 2009. On March 7, 2011, the listing of our common stock was transferred from the Nasdaq Global Market to the Nasdaq Capital Market.

On March 4, 2013, we filed a Certificate of Amendment to our Amended and Restated Certificate of Incorporation, to implement a six-for-one reverse split of our common stock, as previously authorized and approved at our special meeting of stockholders on February 25, 2013. On March 5, 2013, our common stock began trading on The NASDAQ Capital Market on a post-split basis.

The reverse split effected a proportionate adjustment to the per share exercise price and the number of shares issuable upon the exercise or settlement of all outstanding options and warrants to purchase shares of our common stock, and the number of shares reserved for issuance pursuant to our existing stock option plans were reduced proportionately. No fractional shares were issued as a result of the reverse split, and stockholders who otherwise would have been entitled to a fractional share received in lieu thereof, a cash payment based on the closing sale price of our common stock as reported on The NASDAQ Capital Market on March 4, 2013. The reverse split did not alter the par value of our common stock or modify any voting rights or other terms of the common stock.

Our Strategy

Our mission is to become a leading biopharmaceutical company developing cardiovascular therapies with an emphasis on genetically-targeted therapies. To achieve this goal, we are pursuing the following strategies:

Advance the development of Gencaro. We plan to focus our efforts on initiating and completing the GENETIC-AF Trial.

Raise additional funding or complete a strategic transaction. To support the continued clinical development of Gencaro, including the planned GENETIC-AF clinical trial, we expect to seek additional funding, through the sale of public or private equity or debt securities, or the completion of a strategic transaction.

Build a cardiovascular pipeline. Our management and employees, including our chief executive officer, have extensive experience 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, with an emphasis on pharmacogenetic applications.

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 Market Background and Opportunity

AF is a disorder in which the normally regular and coordinated contraction pattern of the heart s two small upper chambers becomes irregular and uncoordinated. The irregular contraction pattern associated with AF causes blood to pool in the heart s atria, predisposing to the formation of clots. These clots may travel from the heart and become lodged in the arteries leading to the brain and other organs, thereby blocking necessary blood flow and potentially resulting in stroke. In addition, we also believe that the development of AF in a HFREF patient can be associated with increased risk of death and other heart failure related adverse outcomes. AF is considered an epidemic cardiovascular disease. The estimated number of individuals with AF globally in 2010 was 33.5 million. According to the 2014 American Heart Association report on Heart Disease and Stroke Statistics, the estimated number of individuals with AF in the U.S. in 2010 ranged from 2.7 million to 6.1 million Approximately 300,000-400,000 treated AF patients currently receive a form of beta-blocker as pharmaceutical intervention.

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The goals of current medical therapy for AF are to maintain sinus rhythm or permanent AF control of the ventricular rate response, avoid the risk of complications including stroke and to minimize patient symptoms. Current treatments include pharmaceutical intervention and device intervention. There are several antiarrhythmic drugs approved by the FDA for the treatment and/or prevention of recurrent AF. However, these drugs have safety and/or administration concerns and all but one have contraindications or label warnings regarding their prescription in patients with HFREF.

Current device interventions for the treatment of AF include:

- Electrical cardioversion which is used to restore normal heart rhythm with administration of a direct current shock;
- Radiofrequency ablation which is effective in some patients for whom medications are ineffective; and,
- Atrial pacemakers which are implanted under the skin and then intravenously into the heart to regulate heart rhythm.

Gencaro

Gencaro (bucindolol hydrochloride) is a 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 the receptor from binding with other molecules, primarily the neurotransmitter norepinephrine (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. Gencaro was the subject of a Phase 3 HF mortality trial of over 2,700 patients, mostly in the U.S., known as 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 founding scientists, 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 U.S. and Europe based on genetic testing.

Pharmacology and Pharmacogenetics

Gencaro s pharmacology appears to be different from other compounds in the beta-blocker class in two fundamental respects. First, the National Heart, Lung and Blood Institute of the National Institutes of Health (NHLBI) and the Cooperative Studies Program of the Department of Veterans Affairs sponsored studies conducted by Drs. Bristow and Liggett indicated that in human myocardial preparations, Gencaro leads to inactivation of constitutively active (i.e. functional in the absence of bound agonist) beta-1 receptors through a mechanism separate from beta-blockade, in addition to inhibiting the binding activity of the beta-1 receptor like a typical beta-blocker. Second, other studies, including BEST, indicated that Gencaro lowers the systemic levels of the neurotransmitter NE, released by cardiac and other adrenergic nerves. These two properties interact with common genetic variations in two cardiac receptors, the beta-1 and alpha-2C receptors, to produce the unique pharmacogenetic profile of Gencaro. We believe that these two properties, and their pharmacogenetic implications, are unique to Gencaro.

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. 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 also inactivating certain beta-1 receptors that are constitutively active (active in the absence of NE stimulation) as well as by lowering NE levels.

There are two common genetic variations of the beta-1 receptor, each of which we estimate is present in approximately 50% of the U.S. population. One of these variations is known as the beta-1 389 arginine receptor variant, exclusively present in the beta-1 389 arginine homozygous or, genotype. Laboratory studies indicate that this variation results in a higher functioning beta-1 receptor, which has a greater ability to mediate the stimulatory effects of NE than the counterpart beta-1 389 glycine or beta-1 389 Gly version of the beta-1 receptor. In addition, the beta-1 389 arginine variant is also more likely to be constitutively active and signal the cardiac

myocyte to contract in the absence of NE. The beta-1 389 arginine receptor also has much higher affinity for NE as compared to the beta-1 389 glycine version, present in patients with either one or two copies of the beta-1 389 glycine gene allele (Gly carriers). Patients with the beta-1 389 glycine version, also present in approximately 50% of the U.S. population who are Gly carriers, results in a beta-1 receptor that is much lower functioning and, according to laboratory studies, has less probability of being in a constitutively active state and has lower NE affinity compared to the beta-1 389 arginine receptor.

We believe Gencaro has a powerful interaction with the higher-function beta-1 389 arginine variation of the beta-1 receptor. Laboratory studies show that constitutively active receptors will continue to signal in the presence of standard beta-blockade with neutral antagonists. Laboratory studies in isolated human heart preparations also show that Gencaro has the novel ability of being able to reduce the signaling of constitutively active receptors. We believe that this property contributes to the enhanced lowering of heart failure and arrhythmia event rates in HFREF patients who are beta-1 389 arginine homozygous genotype relative to individuals who are beta-1 389 Gly carriers or to the general population. In addition, we believe the unique NE lowering properties of Gencaro have a selectively beneficial effect in patients who have only beta-1 389 arginine receptors, because of the high affinity of these receptors for NE.

The efficacy of Gencaro also appears to be influenced by the alpha-2C receptor, located on the terminus of cardiac adrenergic nerves, at the neuromuscular junction with the cardiac myocyte. The role of this receptor is to modulate the release of NE at this junction, which in turn affects the activation of beta-1 receptors and the heart s activity. There are two important genetic variations of this receptor that appear to affect the effects of Gencaro; the alpha-2C -wild type , which is the normal functioning version of the receptor (approximately 87-90% of the U.S. general population), and the deletion variant , a version of the receptor that functions poorly (present in at least one copy in approximately 10-13% of the U.S. general population). The DNA substudy of patients from the BEST trial, conducted by Drs. Bristow and Liggett, indicated that these two variations of the alpha-2C receptor appear to affect Gencaro s heart failure and arrhythmia responses in HFREF patients only if the 389 Gly variant of the beta-1 receptor is also present; in patients with the beta-1 389 Gly variant, the wild type version of the alpha-2C receptor enhances clinical response, whereas the alpha-2C deletion variant reduces efficacy. When only the arginine version of the beta-1 receptor is present (beta-1 389 arginine homozygous genotype), the efficacy of Gencaro does not appear to depend on which version of the alpha-2C receptor is present.

The DNA substudy from the BEST HFREF trial indicated that the combinations of these receptor variations in individual patients appear to influence the response to Gencaro with respect to significant clinical endpoints. However, the beta-1 389 Arg/Arg variant appeared to have the most powerful beneficial effect on Gencaro heart failure and arrhythmia responses. While we believe that the beta-1 389 Gly carrier patients who also are alpha-2C wild type homozygotes may respond favorably to Gencaro, we believe that patients who possess only the beta-1 389 arginine variant (beta-1 389 arginine homozygous genotype) exhibit enhanced clinical responses to Gencaro, and should be the primary targeted population. The beta-1 389 arginine homozygous genotype constitutes an estimated 47-50% of the U.S. population.

The BEST trial

The NHLBI and Veterans Affairs Cooperative Studies funded BEST trial began in 1995. It was a double-blind, placebo-controlled, multi-center study of bucindolol s effect on reduction of mortality and morbidity in an advanced chronic HFREF population. The primary endpoint of the BEST trial was all cause mortality (ACM) and the pre-specified main secondary endpoint was progression of heart failure (HF), defined as death from HF, cardiac transplant, HF hospitalization, or emergency room visit for the treatment of worsening HF not requiring hospitalization. The trial was planned to run four and one-half years, and enroll 2,800 patients. The trial enrolled a total of 2,708 chronic HF patients, who were mostly from the United States. Under the umbrella of the BEST trial

substudies program, a DNA bank and substudy was created, and 1,040 of the BEST patients participated by providing blood for DNA analysis. The DNA bank provided data for the DNA substudy of BEST patients conducted by Drs. Bristow and Liggett.

In 1999, the BEST trial was terminated prior to the completion of follow-up, in response to a recommendation of the BEST trial Data and Safety Monitoring Board. The primary reason for termination was loss of investigator equipoise; in other words, the fact that the BEST investigators were no longer uncertain regarding the comparative therapeutic merits of giving a placebo versus giving a beta-blocker to a HFREF patient. Positive mortality results from two other HF trials involving other beta-blockers had been reported, and a substantial number of BEST trial investigators concluded that it was unethical to continue to give placebo to BEST trial participants. As a result, some investigators began to prescribe these other beta-blockers to patients in the trial, which threatened to destroy the trial s integrity; therefore the trial was terminated early.

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Clinical Results and the DNA Substudy

Following termination, the preliminary results of the study were analyzed and published. The preliminary determination and general perception were that the BEST trial had failed on the basis of not meeting its primary endpoint of ACM. The published values were a 10% risk reduction in mortality with a p-value of 0.10. Subsequently, we reanalyzed the results from BEST, in accordance with the FDA approved, pre-specified statistical analysis plans, which had not been performed by the sponsors of BEST when the trial was terminated. Our reanalysis appeared to show a 13% risk reduction on the primary endpoint of all-cause mortality in the BEST trial with a p-value of 0.053.

In 2003 and 2004, the results of the DNA substudy conducted by Drs. Bristow and Liggett began to be analyzed and released. The DNA substudy results indicated a significant enhancement of response on the major heart failure clinical endpoints from the BEST trial in patients with the beta-1 389 arginine homozygous genotype. The risk reduction on HF clinical efficacy endpoints such as mortality and hospitalization ranged from 34% to 48% in this genotype. In addition, in arrhythmia endpoints of atrial fibrillation or ventricular fibrillation/ventricular tachycardia, tracked by adverse events and surveillance ECGs, the risk reduction by bucindolol in the beta-1 389 arginine homozygous genotype appeared to be even greater, with hazard ratios of 74% for both endpoints.

Shown below are certain of the primary and secondary endpoint data from the BEST HF DNA substudy results, by genotype:

BEST Trial Clinical Responses by Genotype Groups

Endpoint	{beta-1 389 Arg/ Arg + any alpha-2C} Very Favorable Patient Type (47%)	{beta-1 389 Gly carrier+ alpha-2C Wt/Wt} Favorable Patient Type (40%)	{beta-1 389 Gly carrier + alpha-2C Del carrier} Unfavorable Patient Type (13%)
All Cause Mortality (ACM), TTE	i 38%*	i 25%	h 4%
Cardiovascular Mortality (CVM), TTE	i 48%*	i 40%*	h 11%
ACM + transplantation	i 43%*	i 24%	h 4%
HF (HF) Progression	i 34%**	i 20%	i 1%
HF Hosp days/patient	i 48%**	i 17%	h 19%
AF prevention (from AE and ECG db)	i 74%**	i 6%	h 33%
VT/VF prevention (from AE db)	i 74%**	i 49%*	i 24%

1 Covariate adjusted, transplant censored analysis with 1 hazard ratio estimates presented
*£ p<0.05; **p 0.007; TTE: Time To Event; CRF: Case Report Form; Adj.: Adjudicated

Analysis of BEST trial for AF

The BEST study data were further analyzed focusing on AF prevention, rate control in patients with persistent AF, and on clinical outcomes of patients with AF. Although there was no pre-determined AF endpoint, including reduction in risk of AF, in the BEST trial, according to our analysis of adverse events and surveillance ECG s during the trial, 7.9% of patients developed new onset AF, with a greater incidence observed in the placebo group (9.7%) compared to the bucindolol group (6.2%). This corresponded to a 36% reduction in the incidence of new onset AF (based on crude event rates) for patients receiving bucindolol ($p = 0.002$). In a time to event analysis, the risk of new onset AF was reduced by 41% ($p = 0.0004$) with bucindolol treatment. Patients in the BEST study with the beta-1 389 Arg/Arg genotype who received Gencaro had a 74% reduction in the risk of developing new onset AF ($p = 0.0003$).

Further published analyses of the data from BEST suggest that Gencaro may also have potential efficacy for other clinical endpoints and outcomes related to AF. A published analysis of the BEST data revealed that of the 303 patients in the BEST trial with established AF, 67% of those who received Gencaro achieved ventricular response rate control, defined as a resting heart rate of less than or equal to 80 beats per minute without symptomatic bradycardia ($p < 0.005$). In AF patients who achieved ventricular response rate control, Gencaro produced a 39% reduction ($p = 0.025$) in cardiovascular mortality/cardiovascular hospitalizations. In addition, Gencaro also improved cardiovascular clinical endpoints for those AF patients possessing the beta-1 389 arginine genotype that ARCA believes is most favorable for Gencaro response. In a substudy of 1,040 patients in BEST in which patient genotypes were analyzed, Gencaro was associated with a 72% decrease ($p = 0.039$) in cardiovascular mortality/cardiovascular hospitalizations in those 52 AF patients in the substudy with the beta-1 389 arginine homozygous genotype.

Analysis of the BEST Study data also shows that Gencaro has potential efficacy against the serious arrhythmias of VT/VF, which also appears to be genetically regulated. A published report demonstrated that patients in the BEST Trial who received Gencaro experienced a 58% reduction in the incidence of VT/VF ($p = 0.00006$), adjusted for the competing risk of mortality. In addition, the authors of this report determined that Gencaro reduced the incidence of VT/VF by 74% ($p = 0.00005$) in patients with the beta-1 389 arginine homozygous genotype.

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As with the overall study cohort, most patients (89%) in the 1,040 patient DNA substudy were free of AF (91% sinus rhythm, 9% other non-AF rhythms) at baseline. The proportion of patients free of AF at baseline was also similar in the two treatment groups for the overall DNA substudy cohort, as well as in the beta-1 389 genotype subgroups. In the BEST DNA substudy, the proportion of patients who developed new onset AF was similar compared to the overall study cohort for both the placebo group (11% and 10%, respectively) and the Gencaro group in the DNA substudy population compared to the overall study cohort (7% and 6%, respectively). Also, there was a similar reduction in new onset AF observed in the bucindolol group compared to placebo (43% and 41%, respectively, by time to event analysis). Therefore, the overall results from the genetic substudy population are consistent with the results from the overall study population.

In patients with all genotypes, the AF risk reduction of 41-43% by Gencaro in BEST is based on an analysis of adverse events and surveillance ECG s which was similar to AF risk reductions observed in a meta-analysis of data regarding seven placebo-controlled beta-blocker trials in HFREF patients. In the meta-analysis, beta-blockers appeared to reduce the incidence of new onset AF in all but one trial, with an overall relative risk reduction of 27%. Despite what we believe to be potential evidence for the prevention of AF in HFREF trials, no beta-blocker has FDA approval for use in this indication. However, the evidence of modest efficacy by beta-blockers approved for other indications will require that any Phase 3 trials with Gencaro will have an active beta-blocker comparator instead of a comparison against placebo. The Phase 2b/3 trial GENETIC-AF trial will only enroll patients with the beta-1 389 arginine homozygous genotype. In the BEST trial, the post hoc analysis of patients with the beta-1 389 arginine homozygous genotype who received Gencaro had a 74% reduction in the risk of developing AF. In another trial, the active comparator we plan to use in GENETIC-AF, metoprolol CR/XL, reduced the risk of developing AF by 48% in all genotypes. Because these are not the same trials, the results should not be relied on as direct comparisons. However, we believe that these two data points indicate that Gencaro may have an advantage in preventing AF when compared to metoprolol in GENETIC-AF, in part due to our plan to only enroll beta-1 389 arginine homozygous genotype patients who appear to respond best to Gencaro.

Clinical and Regulatory Strategy

The regulatory strategy for Gencaro is to conduct our adaptive design Phase 2b/3 clinical trial, GENETIC-AF, to obtain an AF approval in a genotype specific HFREF population. We will seek to enroll certain patients with the beta-1 389 arginine homozygous genotype in our AF clinical trial because our analysis of the BEST DNA substudy indicated this group had a 74% reduction in risk for new AF events.

We have created an adaptive design for GENETIC-AF. The trial will be initiated as a Phase 2B study in approximately 200 HFREF patients. Depending on the results of the Phase 2B portion, the trial could then be expanded to a Phase 3 study by enrolling an estimated additional 420 patients. The secondary endpoint of the Phase 2B portion of the trial will be AF burden, defined as a patient s percentage of time in AF per day, regardless of symptoms. Under our proposed trial design, all 200 patients in the Phase 2b portion of the trial will have AF burden measured by continuous monitoring, either by previously implanted cardiac resynchronization or defibrillation devices, or newly or previously inserted implantable loop recorders. When the first 200 patients have been enrolled and completed 24 weeks of follow-up, certain data related to the primary endpoint of recurrent symptomatic AF or all-cause mortality, and certain data related to the secondary endpoint of AF burden will be evaluated by the trial s Data and Safety Monitoring Board to determine if the interim data is consistent with pre-trail assumptions and if it indicates potential for achieving statistical significance for the Phase 3 endpoint. If the interim evaluation confirms our assumptions and acceptable safety is observed, the trial would then proceed to the Phase 3 portion and full enrollment.

We have received guidance from the FDA regarding our Phase 2B/3 clinical study comparing Gencaro to Toprol XL for the prevention of AF in approximately 620 patients. Based on this FDA guidance, we believe that a successful

GENETIC-AF Phase 3 clinical trial, with a p-value of less than 0.01, could be sufficient evidence of efficacy upon which to base a New Drug Application (NDA) for the approval of Gencaro for an AF indication in HFREF patients. Our Investigational New Drug (IND) application for atrial fibrillation, under which we anticipate our GENETIC-AF trial will be performed, has been accepted by FDA and is now active.

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The Gencaro Test

If approved, we believe that Gencaro will be the first cardiovascular drug to be integrated with a companion diagnostic to predict enhanced efficacy. We believe the drug label we will propose for Gencaro would identify the patient receptor genotype studied in the trial that can expect enhanced efficacy and, and that the label would recommend receptor genotype testing prior to initiation of therapy. Therefore, the commercialization of Gencaro may require an FDA approved diagnostic test for this genotype be available, the Gencaro Test. We believe the Genaro Test could be developed and commercialized through a preferred diagnostic provider, by the company marketing Gencaro, or a combination of approaches.

For our GENETIC-AF clinical trial, we have an agreement with LabCorp to provide the companion diagnostic test and services to support the trial. To provide those services, LabCorp has developed the genetic test and obtained from the FDA an Investigational Device Exemption, or IDE, for the companion diagnostic test we anticipate using in our GENETIC-AF clinical trial.

Licensing and Royalty Obligations

We have licensed worldwide rights to Gencaro, including all preclinical and clinical data from Cardiovascular Pharmacology and Engineering Consultants, LLC, or CPEC, who has licensed rights in Gencaro from BMS. In addition, we have sublicensed CPEC s rights from BMS. CPEC is a licensing entity which holds the rights of the biotechnology companies that were the commercial sponsors of the BEST trial. If the FDA grants marketing approval for Gencaro, the license agreements state that we are required to make a milestone payment of $8.0 million within six months after FDA approval. The license agreements also state that we are required to make milestone payments of up to $5.0 million in the aggregate upon regulatory marketing approval in Europe and Japan. The licenses state that our royalty obligations range from 12.5% to 25% of revenue from the related product based on achievement of specified product sales levels including a 5% royalty that CPEC is obligated to pay BMS. We have the right to buy down the royalties to a range of 12.5% to 17% by making a payment within six months of regulatory approval. We also have licensed worldwide rights to intellectual property covering the pharmacogenetic response of Gencaro based on the cardiac receptor polymorphisms, which is owned by the University of Colorado. We have no material future financial obligations under this license. We also have licensed exclusive, worldwide rights to develop and commercialize diagnostics for these receptor polymorphisms, for the purpose of prescribing Gencaro, from the licensee of these rights, the University of Cincinnati.

Development Pipeline

Our development activities are substantially focused on our lead product candidate, Gencaro, for the treatment of AF. We also believe, based upon data from the BEST trial, that Gencaro may have additional potential for the treatment of AF rate control, VT/VF and prevention of heart failure endpoints in HFREF patients. We do not expect to pursue development of Gencaro for disease indications beyond AF without entering into a strategic partnership or collaboration. We believe Gencaro has potential to address these additional indications, and that the clinical response of patients with these diseases may be genetically influenced, based on the same genetic markers we have identified for our proposed treatment of AF with Gencaro.

We also have exclusive pharmacogenetic and other patent rights to drug candidates that have potential indications in cardiovascular disease, oncology and other therapeutic areas, in both early and later stages of development. We may seek partners to assist us in the development of these candidates or who may license them. We may also seek funds to advance the development of the compounds on our own.

Competition

Current treatments include pharmaceutical intervention and device intervention. There are several antiarrhythmic drugs approved by the FDA for the treatment and/or prevention of recurrent AF. However, these drugs have safety and/or administration concerns and all but one have contraindications or label warnings regarding their prescription in patients with heart failure.

Considering that most of the approved drugs and device interventions for the treatment or prevention of AF have notable risks or adverse side effects, 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 patients with HF where the approved drugs are contra-indicated or have warnings regarding their prescribing information. We believe that Gencaro s prevention of AF in HF patients would provide this patient population a safer treatment option than other treatments currently approved by the FDA.

The pharmaceutical industry is highly competitive. We face significant competition from pharmaceutical companies and biotechnology companies that are researching and selling products designed to treat cardiovascular conditions. Most of these companies have significantly greater financial, product development, manufacturing, and commercial resources than we have.

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In addition, our proposed prescribing information for Gencaro includes a recommendation for genetic testing, which will add additional cost and procedures to the process of prescribing Gencaro, and which could make it more difficult for us to compete against existing therapies.

Manufacturing and Product Supply

Gencaro is a small molecule drug with an established manufacturing history. Multiple manufacturers of both the API and drug product have successfully produced Gencaro for use in clinical trials over the course of its clinical development. We outsource all manufacturing and analytical testing of the Gencaro API and drug product. We have selected third party contract manufacturing organizations on the basis of their technical and regulatory expertise. Our approach with our contract manufacturing partners has been to replicate the manufacturing processes that were used to support the prior pivotal clinical trial with Gencaro, and to minimize any changes from these baseline processes, thereby reducing technical and regulatory risk. We contracted with Groupe Novasep to complete the drug substance registration batches required for the Gencaro NDA. These batches were successful, and the resulting drug substance was used to supply the drug product registration campaign. Remaining inventory was placed in current Good Manufacturing Practice, or cGMP, storage to provide a backup supply for the planned GENETIC-AF trial, and for use as an initial source of drug substance to support eventual product launch, if approved.

For drug product production, we have contracted with Patheon, Inc. to manufacture the Gencaro tablets. Gencaro is produced in a tablet form, utilizing standard solid oral dosage processing techniques. Six separate dosage strengths are manufactured, with the maximum recommended dose of 50mg twice daily for patient weighing 75kg or less and 100mg twice daily for patients weighing more than 75kg. Registration batches were successfully completed by Patheon, Inc. and tablets from these runs have been placed in cGMP storage to supply the planned GENETIC-AF trial.

Our manufacturing focus for 2014 is to supply the blinded clinical trial materials for Gencaro and the comparator compound, and to manage the clinical distribution channels necessary for the successful execution of the planned GENETIC-AF trial.

Research and Development Expenses

Our research and development expenses totaled $2.9 million for the year ended December 31, 2013 as compared to $1.1 million for 2012, an increase of approximately $1.8 million. R&D expense in 2014 is expected to be substantially higher than 2013 as we initiate our planned GENETIC-AF clinical trial.

Government Regulation

Governmental authorities in the U.S. at the federal, state, and local levels and foreign countries extensively regulate, among other things, the research, development, testing, manufacture, labeling, promotion, advertising, marketing, distribution, sampling, and import and export of pharmaceutical and medical device products. In the U.S., the Food and Drug Administration (FDA) regulates these activities at the federal level pursuant to the Federal Food Drug and Cosmetic Act (FDCA) and the regulations promulgated thereunder. We anticipate that all of our products will require regulatory approval by governmental agencies prior to commercialization. The process of obtaining approval and the subsequent process of maintaining compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. In addition, these statutes, rules, regulations and policies may change and our products may be subject to new legislation or regulations. Both before and after approval or clearance, failure to comply with the requirements of the FDA and other state and federal statutes can lead to significant penalties or could disrupt our ability to manufacture and sell these products. In addition, the FDA could refuse to provide certificates needed to export our products if the agency determines that we

are not in compliance.

Premarket Approval of Drugs

FDA approval is required for marketing of any new drug, dosage form, indication, or strength. The steps required before new human therapeutic drug products are marketed in the U.S. and foreign countries include rigorous preclinical and clinical testing and other approval requirements by regulatory agencies, such as the FDA and comparable agencies in foreign countries. There is no guarantee that products will be approved in a specific timeframe or at all.

Preclinical Phase. Preclinical studies are generally conducted in the laboratory to identify potential drug candidates and to evaluate their potential efficacy and safety. These studies include laboratory evaluation of product chemistry, formulation and stability, as well as studies to evaluate short and long-term toxicity in animals. Preclinical studies are governed by numerous regulations, including but not limited to FDA s Good Laboratory Practices.

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Clinical Phase. Before human clinical trials can commence, an Investigational New Drug, or IND, application, submitted to FDA must become effective. For an IND to become effective, the applicant must submit, among other things, information on design of the proposed investigation, reports necessary to assess the safety of the drug for use in clinical investigation, and information on the chemistry and manufacturing of the drug, controls available for the drug, and primary data tabulations from animal or human studies. The clinical phase of development involves the performance of human studies, including adequate and well-controlled human clinical trials to establish the safety and efficacy of the product candidate for each proposed indication. Typically, clinical evaluation involves three sequential phases, which may overlap. During Phase 1, clinical trials are conducted with a relatively small number of subjects or patients to determine the early safety profile of a product candidate, as well as dose tolerance, absorption, and the pattern of drug distribution and drug metabolism. Phase 2 trials are conducted with groups of patients afflicted by a specific target disease to determine preliminary efficacy, optimal dosages and dosage tolerance and to identify possible adverse effects and safety risks. In Phase 3, larger-scale, multi- center trials are conducted with patients afflicted with a specific target disease over a longer term to confirm Phase 2 results and provide reliable and conclusive data supporting efficacy and safety of a drug as required by regulatory agencies for drug approval. The conduct of clinical trials is subject to extensive regulation. FDA may delay or suspend clinical trials through clinical holds.

NDA Submission. In the U.S., the results of preclinical and clinical testing along with chemistry, manufacturing and controls information, are submitted to the FDA in the form of an NDA. Under the current Prescription Drug User Fee Act, or PDUFA, after submission of an NDA and payment, or waiver, of the required fee, the FDA s goal is to review most standard NDAs within 10 months from the time that a sponsor s application is accepted as filed by FDA, which can occur within a 60-day window following the initial submission of the application. At the end of the 10 months, the FDA s goal is to issue a complete response, or approve the NDA. While FDA s goal is to issue a complete response within 10 months, the process may take longer than 10 months, particularly if multiple review cycles are required.

In responding to an NDA, the FDA may grant marketing approval or deny the application if the FDA determines that the application does not satisfy the statutory and regulatory approval criteria. A denial may include a request for additional information, including additional clinical data and/or an additional Phase 3 clinical trial. Data from clinical trials are not always conclusive and FDA may interpret data differently than we interpret data. Under the Food and Drug Modernization Act of 1997, the FDA is authorized to approve a drug based on a single adequate and well-controlled study if such study and other confirmatory data are sufficient to establish the drug s effectiveness. However, it has long been the FDA s general position that the standard of proof of a drug s effectiveness generally requires at least two well-controlled and adequate Phase 3 clinical studies demonstrating statistically significant results as compared to a placebo or active control (with p-values of less than 0.05) with respect to the primary endpoint or endpoints of the trial.

In addition, in accordance with current FDA law and regulations, the FDA may refer a drug to an advisory committee for review prior to approval. Most new compounds are referred to an FDA advisory committee, which could add additional time to the review process. There is no guarantee that the advisory committee will recommend approval of a drug candidate. In some cases, FDA may require completion, within a specified time period, of additional clinical studies after approval, referred to as Phase 4 clinical studies, to monitor the effect of a new product and may prevent or limit future marketing of the product based on the results of these post-marketing programs. Furthermore, prior to granting approval, the FDA generally conducts an inspection of the facilities, including outsourced facilities that will be involved in the manufacture, production, packaging, testing and control of the drug substance and finished drug product for compliance with current Good Manufacturing Practice, or cGMP, requirements.

If the FDA approves the NDA, the sponsor is authorized to begin commercialization of the drug in accordance with the approval. Even if the FDA approves the NDA, the FDA may decide later to suspend or withdraw product approval

if compliance with regulatory standards is not maintained or if safety problems are recognized after the product reaches the market. In addition, the FDA requires surveillance programs to monitor approved products that have been commercialized, and the agency has the power to require additional clinical studies, to require changes in labeling or to prevent further marketing of a product based on the results of these post-marketing programs. The FDA also has authority to request implementation of a risk evaluation and mitigation strategy, or REMS that could restrict distribution of Gencaro or require us to provide additional risk information to prescribers. Whether or not FDA approval has been obtained, approval of a product candidate by comparable foreign regulatory authorities is necessary prior to the commencement of marketing of a product candidate in those countries. The approval procedures vary among countries and can involve additional testing. The time required to obtain approval may differ from that required for FDA approval.

Post-approval Compliance. If regulatory approval for a drug or medical device is obtained, the product and the facilities manufacturing the product are subject to periodic inspection and continued regulation by regulatory authorities, including compliance with cGMP, as well as labeling, advertising, promotion, recordkeeping, and reporting requirements, including the reporting of adverse events. In addition, the FDA closely regulates the post-approval marketing and promotion of drugs, including standards and regulations for labeling, promotion to health care professionals, direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the Internet. Drugs may be marketed only for the approved indications and in accordance with the provisions of the approved labeling. Companies are responsible for compliance with such requirements and would be responsible to ensure that all contract manufacturing organizations who perform work for them also

comply with such requirements. Similarly, if a drug manufacturer hires contract sales representatives or consultants to promote its products, such organizations or individuals must comply with all of the same requirements applicable to the drug manufacturer. The FDA regularly inspects companies to determine compliance with cGMPs and other post-market requirements. Failure to comply with statutory requirements and the FDA s regulations can result in a variety of administrative or enforcement actions, including but not limited to an FDA Form 483 (which is issued by FDA at the conclusions of an inspection when an investigator has observed any conditions that may constitute violations), a public warning letter, suspension or withdrawal of regulatory approvals, product recalls, product detentions, refusal to provide export certificates, seizure of products and criminal prosecution.

Drug Price Competition and Patent Term Restoration Act of 1984. Under the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act, Congress created an abbreviated FDA review process for generic versions of pioneer (brand name) drug products. The Hatch-Waxman Act also provides for patent term restoration and the award, in certain circumstances, of non-patent marketing exclusivities.

Generic Drug Approval. The Hatch-Waxman Act established an abbreviated FDA review process for drugs that are shown to be equivalent to approved pioneer drugs. Approval for a generic drug is obtained by filing an abbreviated NDA, or ANDA. Generic drug applications are abbreviated because they generally do not include clinical data to demonstrate safety and effectiveness. Instead, an ANDA applicant must establish that its product is bioequivalent to an approved drug and that it is the same as the approved drug with respect to active ingredient(s), route of administration, dosage form, strength and recommended conditions of use (labeling). The FDA will approve the generic as suitable for an ANDA if it finds that the generic does not raise questions of safety and effectiveness as compared to the pioneer drug. A drug is not eligible for ANDA approval if the FDA determines that it is not equivalent to the pioneer drug or if it is intended for a different use. Any applicant who files an ANDA seeking approval of a generic version of an approved drug listed in FDA s Approved Drug Products with Therapeutic Equivalence Evaluations, or the Orange Book must certify to the FDA that (i) no patent information on the drug has been listed in the Orange Book; (ii) that each patent listed in the Orange Book for that approved drug has expired; (iii) FDA should approve the product on the date on which a listed patent expires; or (iv) that such patent is invalid, unenforceable or will not be infringed by the manufacture, use or sale of the generic drug. If the ANDA applicant makes a certification pursuant to (iv) above, or a Paragraph IV certification, and the NDA holder files an infringement suit against the ANDA applicant within 45 days of receiving the Paragraph IV notification, the NDA owner is entitled to an automatic 30-month stay of FDA s ability to approve the ANDA. This 30-month stay will end early upon any decision by a court that the patent is invalid, unenforceable or not infringed by the generic drug.

Patent Term Extension. While the term of a U.S. patent is 20 years from the earliest priority date of a patent application (excluding a provisional patent application) , a U.S. patent that covers subject matter requiring regulatory approval to market is eligible for an extension of that patent term. The Hatch-Waxman Act provides for the restoration of a portion of the patent term lost during product development and FDA review of an application. Patent Term Extension, or PTE, extends the term of an issued patent for generally 1) the length of the FDA approval process, i.e., the complete period of NDA review, and 2) half of the time spent in clinical trials, i.e., the investigational new drug (IND) period. However, the maximum period of restoration cannot exceed five years, or restore the total remaining term of the patent to greater than 14 years from the date of FDA approval of the product.

Under 35 U.S.C. § 156(a), a patent covering a method of using a product is eligible for PTE if the following conditions are met:

1) the patent has not yet expired;

2) the patent was not previously extended;

3) the patent owner submits an application for PTE that includes all necessary supporting information within 60 days of FDA approval;

4) the product was subject to regulatory review before its commercial marketing or use; and

5) the drug application is for the first permitted commercial marketing of the product.

We have obtained three U.S. patents (U.S. Patent Nos. 7,678,824; 8,080,578; 8,093,286), and have one pending U.S. patent application that generally concern methods for treating patients using Gencaro based on the presence of certain polymorphisms in the beta-1 and/or alpha-2C adrenergic receptors. We believe that, if approved by the FDA, one of the U.S. patents may be eligible for PTE, which could provide approximately 3 years or more of additional patent life based on our current clinical trial plans.

Patent Term Extension, known as a Supplementary Protection Certificate, or SPC, is a form of patent term extension that is available for pharmaceutical products approved for marketing in the European Union. We obtained a patent in Europe on methods for using Gencaro that is similar to the 824 patent (EP 1802775); this patent is in force in certain countries in Europe, including the United Kingdom, France, Germany, Italy and Spain. We believe that this patent may be eligible for an SPC, if Gencaro is approved for marketing in any European country in which the patent is in force, which could provide up to five years of additional patent life.

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Non-Patent Marketing Exclusivities. Separate and apart from patent protection, the Hatch-Waxman Act entitles approved drugs to various periods of non-patent statutory protection, known as marketing exclusivity. The Hatch-Waxman Act provides five years of new chemical entity marketing exclusivity to the first applicant to gain approval of an NDA for a product that contains an active moiety not found in any other approved product. This exclusivity means that another manufacturer cannot submit an ANDA or 505(b)(2) NDA until the marketing exclusivity period ends. This exclusivity protects the entire new chemical entity franchise, including all products containing the active ingredient for any use and in any strength or dosage form, but will not prevent the submission or approval of stand-alone NDAs where the applicants have conducted their own clinical studies to demonstrate safety and effectiveness. There is an exception, however, for a competitor that seeks to challenge a patent with a Paragraph IV certification. Four years into the five-year exclusivity period, a manufacturer who alleges that one or more of the patents listed with the NDA is invalid, unenforceable or not infringed may submit an ANDA or 505(b)(2) NDA for a generic or modified version of the product.

The Hatch-Waxman Act also provides three years of new use marketing exclusivity for the approval of NDAs, and supplements, where those applications contain the results of new clinical investigations (other than bioavailability studies) essential to the FDA s approval of the applications. Such applications may be submitted for new indications, dosage forms, strengths, or new conditions of use of approved products. So long as the studies are essential to the FDA s approval or were conducted by or for the applicant, this three-year exclusivity prohibits the final approval of ANDAs or 505(b)(2) NDAs for products with the specific changes associated with those studies. It does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for other products containing the same active ingredient, without those changes.

FDA Premarket Review of Medical Devices

Unless an exemption applies, each medical device that a company wishes to market in the U.S. requires either approval of a premarket approval application (PMA) or clearance of a premarket notification, commonly known as a 510(k) from the FDA. The FDA classifies medical devices into one of three classes. Devices deemed to pose lower risks are placed in either class I or II, which may require the manufacturer to submit to the FDA a 510(k) requesting permission to commercially distribute the device. Clearance of a 510(k) usually requires between three months and one year from the time of submission of the 510(k), although the process may take longer. The FDA s 510(k) clearance procedure is less rigorous than the PMA approval procedure, but is available only to companies who can establish that their device is substantially equivalent to a legally-marketed predicate device that was (i) on the market prior to the enactment of the Medical Device Amendments of 1976, (ii) reclassified from Class III to Class II, or (iii) has been cleared through the 510(k) procedure. 510(k)s must typically be supported by performance data, including preclinical data, bench testing, and in some cases, clinical data. Some low risk devices are exempted from this requirement. Devices deemed by the FDA to pose the greatest risks, or for which there is no predicate, are placed in class III, and require a PMA.

PMA Pathway. Generally, a PMA must be supported by extensive data and valid scientific evidence, including, but not limited to, technical, preclinical, clinical trials, manufacturing and labeling to demonstrate to the FDA s satisfaction a reasonable assurance of the safety and effectiveness of the device for its intended use. After a PMA is sufficiently complete, the FDA will accept the application and begin an in-depth review of the submitted information and will generally conduct a pre-approval inspection of the manufacturing facility or facilities to ensure compliance with FDA s Quality System Regulations (QSR). By statute, the FDA has 180 days to review the accepted application , although, generally, review of the application can take between one and three years, and it may take significantly longer. The PMA application process can be expensive, and there is a substantial user fee that must be paid to FDA in connection with the submission of a PMA application. If the FDA s evaluation of the PMA application or the manufacturing facility is not favorable, the FDA may deny approval of the PMA application or issue a not approvable letter. The

FDA may also require additional clinical trials, which can delay the PMA approval process by several years. In addition, if FDA discovers that an applicant has submitted false or misleading information, FDA may refuse to review submissions until certain requirements are met pursuant to its Application Integrity Policy (AIP). If the FDA approves the PMA, it may place restrictions on the device. After the PMA is approved, if significant changes are made to a device, its manufacturing or labeling, a PMA supplement containing additional information must be filed for prior FDA approval. PMA supplements often must be approved by FDA before the modification to the device, the labeling, or the manufacturing process may be implemented. Delays in receipt of or failure to receive such clearances or approvals, the loss of previously received clearances or approvals, or the failure to comply with existing or future regulatory requirements could have a material adverse effect on our business, financial condition and results of operations.

Clinical Trials. Clinical trials are generally required to support a PMA application and are sometimes required for 510(k) clearance. These trials generally require an Investigational Device Exemption, or IDE, application approved in advance by the FDA for a specified number of patients, unless the proposed study is deemed a non-significant risk study, which is eligible for an exemption from the IDE requirements. The IDE application must be supported by appropriate data, such as animal and laboratory testing results. Clinical trials may begin if the IDE application is approved by the FDA and the appropriate institutional review boards or IRBs at the clinical trial sites. Submission of an IDE application does not give assurance that the FDA will issue the IDE. If the IDE application is approved, there can be no assurance the FDA will determine that the data derived from the trials support the safety and effectiveness of the device or warrant the continuation of clinical trials. An IDE supplement must be submitted to and approved by the FDA before a sponsor or investigator may make a change to the investigational plan in such a way that may affect its scientific soundness, study indication or the rights, safety or welfare of human subjects. The trial must also comply with the FDA s regulations, including the requirement that informed consent be obtained from each subject. Even if a trial is completed, the results of clinical testing may not adequately demonstrate the safety and efficacy of the device or may otherwise not be sufficient to obtain FDA clearance to market the product in the United States.

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In Vitro Diagnostic Companion Diagnostic Devices. FDA has described IVD companion diagnostic devices as in vitro diagnostic devices that provide information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents of the therapeutic product. An IVD companion diagnostic device could be used to (i) identify patients who are most likely to benefit from a particular therapeutic product; (ii) identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product; or (iii) monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness. Although FDA s regulation of IVD companion diagnostic devices is evolving and implemented on a case-by-case basis, FDA s stated policy for a novel therapeutic product is that an IVD companion diagnostic device should be developed and approved or cleared contemporaneously to support the therapeutic product s safe and effective use. The clinical performance and clinical significance of the IVD companion diagnostic device is to be established using data from the clinical development program of the corresponding therapeutic product. FDA recognizes, however, that there may be cases where contemporaneous development may not be possible. With respect to the Gencaro Test, there is no assurance that we will be able to develop and obtain approval or clearance contemporaneously with Gencaro. Failure to develop the Gencaro Test or obtain clearance or approval could delay approval of Gencaro, if FDA regards the Gencaro Test as an IVD companion diagnostic test that is essential to the safe and effective use of Gencaro.

Continuing Regulation. After a device is placed on the market, numerous regulatory requirements apply to the manufacturer, or holder of a PMA approval. Unless subject to an exemption, medical devices distributed in the United States must be manufactured in compliance with the FDA s Quality System Regulations (QSRs) and current good manufacturing practices. These regulations govern the manufacturing process, including design, manufacture, testing, release, packaging, distribution, documentation and purchasing, as well as complaint handling, corrective and preventative actions and internal auditing. In complying with the QSRs, manufacturers must expend significant time, money and effort. Companies are also subject to other post-market and general requirements, including but not limited to product listing and establishment registration, post-market surveillance requirements, limitations on promotion, and requirements for recordkeeping and reporting of certain adverse events, malfunctions, corrections and removals. As discussed above, FDA regularly inspects companies to assess compliance with the QSRs and other post-market requirements. Failure to comply with these requirements can result in, among other things, adverse publicity, warning letters, and potential civil and criminal penalties. With respect to the Gencaro Test, we intend to seek a new or amended collaborative arrangement with a diagnostic company in which we could license them certain rights to perform the diagnostic test for patients with AF. As part of such arrangement, we will seek to have the diagnostic company take responsibility for compliance with the FDA s device approval and on-going regulatory requirements.

International Marketing Approvals. International sales of medical devices are subject to foreign government regulations, which vary substantially from country to country and are subject to change. The time required to obtain approval by a foreign country may be longer or shorter than that required for FDA clearance or approval, and the requirements may differ.

Other Regulatory Requirements. We are also subject to various federal, state and local laws, regulations and recommendations relating to safe working conditions, laboratory and manufacturing practices, the experimental use of animals and the use and disposal of hazardous or potentially hazardous substances, including radioactive compounds and infectious disease agents, used in connection with our work. The extent and character of governmental regulation that might result from future legislation or administrative action cannot be accurately predicted.

Medical Device Tax

In March 2010, the U.S. Congress adopted and President Obama signed into law comprehensive health care reform legislation. Among other initiatives, these laws impose significant new taxes on medical device makers in the form of a 2.3% excise tax on U.S. medical device sales, with certain exemptions, beginning on January 1, 2013. The Gencaro Test is likely to be subject to this tax.

Intellectual Property

The future success of our business will partly depend on our ability to maintain market exclusivity for Gencaro in the United States and important international markets, and for other products or product candidates that we may acquire or develop. We will rely on statutory protection, patent protection, trade secrets, know-how, and in-licensing of technology rights to maintain protection for our products.

We believe that both patent protection and data exclusivity statutes will give Gencaro market exclusivity in the U.S. and in major international markets. If approved by the FDA or international regulatory agencies, Gencaro will qualify as a New Chemical Entity, or NCE, as it has never received regulatory approval in any jurisdiction. As an NCE, Gencaro will enjoy market exclusivity in the United States and most international markets under data exclusivity statutes. These laws provide for an exclusivity period beginning from regulatory approval, during which any generic competitor is barred from submitting an application that relies on the data that has been submitted in connection with the approval of the NCE. In the U.S., the Hatch-Waxman Act provides for an initial period of up to five

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years from approval of the NCE, during which a generic application attempting to rely on the data submitted for the NCE cannot be filed with the FDA. This period can be effectively extended to seven and one-half years from FDA approval because a provision of the Hatch-Waxman Act provides for an automatic 30-month extension of the exclusivity period if we promptly pursue litigation against a company attempting to enter the market with a generic for a drug that is covered by a composition of matter or method of use patent.

Many international markets have data exclusivity statutes that are analogous to Hatch-Waxman and often more protective. The analogous statute in the European Medicines Evaluation Agency will, in general, provide Gencaro with a minimum of ten years of protection before such a generic application may be approved. Protection under Hatch-Waxman and other data exclusivity statutes is sometimes considered superior to patent protection, as the generic cannot be marketed during the period of exclusivity, thus eliminating the need to initiate patent infringement litigation with its accompanying risks and costs.

In addition to protection under data exclusivity statutes, we believe that Gencaro s patent portfolio provides an alternative protection to market exclusivity. We have been granted patents in the United States and Europe that claim the use of Gencaro in patients predicted to have a favorable response to the drug based on genetic polymorphisms in the genes encoding the beta-1 and/or alpha-2C receptors. We believe that this patent strategy may deter generic competition because of the threat of patent litigation or may exclude generic competition from the market until the patents expire if we are successful in litigation. Consequently, if our patent strategy is successful, we believe we may avoid generic competition with Gencaro in the U.S. or certain countries in Europe until at least the expiration of these patents, which would be no earlier than 2026 in the U.S and into 2025 in Europe. In addition, we believe that if Gencaro is approved, one of the U.S. patents may be entitled to an extension of its term and the European patent may be entitled to an extension through a supplemental protection certificate in one or more countries in Europe. The length of any such extension may vary by country. We cannot predict whether any such extensions will be granted, but if they are, they may provide market exclusivity for Gencaro into 2029 or 2030 in the U.S. and Europe.

We also have other potential patent rights in additional pharmacogenetic drug candidates having possible indications in cardiovascular disease, oncology, and other therapeutic areas; these are in both early and later stages of development. We may seek collaborators to assist us in the development of these candidates or we may seek to raise funds to advance the development of the compounds on our own.

Employees

As of December 31, 2013, we had 14 full-time employees. None of our employees are represented by any collective bargaining unit. We believe that we maintain good relations with our employees.

Corporate Information

On January 27, 2009, we completed a business combination (the Merger) with ARCA Colorado in accordance with the terms of that Agreement and Plan of Merger and Reorganization, dated September 24, 2008, and amended on October 28, 2008 in which a wholly-owned subsidiary of Nuvelo, Inc. merged with and into ARCA Colorado, with ARCA Colorado continuing after the Merger as the surviving corporation and a wholly-owned subsidiary of Nuvelo, Inc. Immediately following the Merger, we changed our name from Nuvelo, Inc. to ARCA biopharma, Inc. Nuvelo was originally incorporated as Hyseq, Inc. in Illinois in 1992 and reincorporated in Nevada in 1993. On January 31, 2003, Nuvelo merged with Variagenics, Inc., a publicly traded Delaware corporation based in Massachusetts, and, in connection with the merger, changed its name to Nuvelo, Inc. On March 25, 2004, Nuvelo was reincorporated from Nevada to Delaware. On January 27, 2009, in connection with the Merger with ARCA Colorado described above, Nuvelo changed its name to ARCA biopharma, Inc. Our principal offices are located in Westminster, Colorado.

On March 4, 2013, we filed a Certificate of Amendment to our Amended and Restated Certificate of Incorporation, to implement a six-for-one reverse split of our common stock, as previously authorized and approved at our special meeting of stockholders on February 25, 2013. On March 5, 2013, our common stock began trading on The NASDAQ Capital Market on a post-split basis.

The reverse split effected a proportionate adjustment to the per share exercise price and the number of shares issuable upon the exercise or settlement of all outstanding options and warrants to purchase shares of our common stock, and the number of shares reserved for issuance pursuant to our existing stock option plans were reduced proportionately. No fractional shares were issued as a result of the reverse split, and stockholders who otherwise would have been entitled to a fractional share received in lieu thereof, a cash payment based on the closing sale price of our common stock as reported on The NASDAQ Capital Market on March 4, 2013. The reverse split did not alter the par value of our common stock or modify any voting rights or other terms of the common stock.

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We file our annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934 electronically with the SEC. The public may read or copy any materials that have been filed with the SEC at the SEC s Public Reference Rooms at 100 F Street, N.E., Washington, D.C. 20549 on official business days during the hours of 10:00 a.m. and 3:00 p.m. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC maintains an Internet site that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. The address of that site is http://www.sec.gov.

You may obtain a free copy of our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports on our website at http://www.arcabiopharma.com on the earliest practicable date following the filing with the SEC or by contacting the Investor Relations Department at our corporate office by calling (720) 940-2200. Information found on our website is not incorporated by reference into this report.

Item 1A. ***Risk Factors***

An investment in ARCA s securities involves certain risks, including those set forth below and elsewhere in this report. In addition to the risks set forth below and elsewhere in this report, other risks and uncertainties not known to ARCA, that are beyond its control or that ARCA deems to be immaterial may also materially adversely affect ARCA s business operations. You should carefully consider the risks described below as well as other information and data included in this report.

Risks Related to Our Business and Financial Condition

Our management and our independent registered public accountant, in their report on our financial statements as of and for the year ended December 31, 2013, have concluded that due to our need for additional capital, and the uncertainties surrounding our ability to raise such funding, substantial doubt exists as to our ability to continue as a going concern.

Our audited consolidated financial statements for the fiscal year ended December 31, 2013 were prepared assuming that we will continue as a going concern. The going concern basis of presentation assumes that we will continue in operation for the foreseeable future and will be able to realize our assets and discharge our liabilities and commitments in the normal course of business and do not include any adjustments to reflect the possible future effects on the recoverability and classification of assets or the amounts and classification of liabilities that may result from our inability to continue as a going concern. Our management and our independent registered public accountants concluded as of December 31, 2013 that due to our need for additional capital, and the uncertainties surrounding our ability to raise such funding, substantial doubt exists as to our ability to continue as a going concern. In February 2014, the Company completed an equity financing transaction that raised aggregate net proceeds of $7.9 million. We believe our cash and cash equivalents balance as of December 31, 2013, together with the net proceeds from such equity financing, will be sufficient to fund our operations, at our projected cost structure, through at least the end of 2015. 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. We may be forced to reduce our operating expenses and raise additional funds to meet our working capital needs, principally through the additional sales of our securities or debt financings. However, we cannot guarantee that will be able to obtain sufficient additional funds when needed or that such funds, if available, will be obtainable on terms satisfactory to us. If we are unable to raise sufficient additional capital or complete a strategic transaction, we may be unable to continue to fund our operations, develop Gencaro or

our other product candidates, or realize value from our assets and discharge our liabilities in the normal course of business. If we cannot raise sufficient funds, we may have to liquidate our assets, and might realize significantly less than the values at which they are carried on our financial statements, and stockholders may lose all or part of their investment in our common stock.

We will need to raise substantial additional funds through public or private equity transactions and/or complete one or more strategic transactions, to continue development of Gencaro. If we are unable to raise such financing or complete such a transaction, we may not be able to continue operations.

In light of the expected development timeline to potentially obtain FDA approval for Gencaro, if at all, the substantial additional costs associated with the development of Gencaro, including the costs associated with the planned GENETIC-AF clinical trial, and the substantial cost of commercializing Gencaro, if it is approved, we will need to raise substantial additional funding through public or private equity transactions or a strategic combination or partnership. If we are delayed in obtaining funding or are unable to complete a strategic transaction, we may discontinue our development activities on Gencaro or discontinue our operations. Even if we are able to fund continued development and Gencaro is approved, we expect that we will need to complete a strategic transaction or raise substantial additional funding through public or private debt or equity securities to successfully commercialize Gencaro.

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We believe our cash and cash equivalents balance as of December 31, 2013, and the net proceeds from our equity financing completed in February 2014, will be sufficient to fund our operations, at our projected cost structure, through at least the end of 2015. 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.

Our liquidity, and our ability to raise additional capital or complete any strategic transaction, depends on a number of factors, including, but not limited to, the following:

- the costs and timing for additional clinical trials in order to gain possible FDA approval for Gencaro;
- progress of GENETIC-AF and enrollment and any data that may become available;
- the market price of our stock and the availability and cost of additional equity capital from existing and potential new investors;
- our ability to retain the listing of our common stock on the Nasdaq Capital Market;
- general economic and industry conditions affecting the availability and cost of capital;
- our ability to control costs associated with our operations;
- the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights; and
- the terms and conditions of our existing collaborative and licensing agreements.

The sale of additional equity or convertible debt securities would likely result in substantial dilution to our stockholders. If we raise additional funds through the incurrence of indebtedness, the obligations related to such indebtedness would be senior to rights of holders of our capital stock and could contain covenants that would restrict our operations. We also cannot predict what consideration might be available, if any, to us or our stockholders, in connection with any strategic transaction. Should strategic alternatives or additional capital not be available to us in the near term, or not be available on acceptable terms, we may be unable to realize value from our assets and discharge our liabilities in the normal course of business which may, among other alternatives, cause us to further delay, substantially reduce or discontinue operational activities to conserve our cash resources.

If we are not able to successfully develop, obtain FDA approval for and provide for the commercialization of Gencaro in a timely manner, we may not be able to continue our business operations.

We currently have no products that have received regulatory approval for commercial sale. The process to develop, obtain regulatory approval for and commercialize potential product candidates is long, complex and costly. We plan to conduct our Phase 2B clinical study of Gencaro in 200 hundred HFREF patients with AF, and it could expand to a Phase 3 clinical study of approximately 420 HFREF additional patients with AF. Clinical trials are typically lengthy, complex and expensive and we do not currently have the resources to fully fund such a trial.

Failure to demonstrate that a product candidate, particularly Gencaro, is safe and effective, or significant delays in demonstrating such safety and efficacy, would adversely affect our business. Failure to obtain marketing approval of Gencaro from appropriate regulatory authorities, or significant delays in obtaining such approval, would also adversely affect our business and could, among other things, preclude us from completing a strategic transaction or obtaining additional financing necessary to continue as a going concern.

Even if approved for sale, a product candidate must be successfully commercialized to generate value. We do not currently have the capital resources or management expertise to commercialize Gencaro and, as a result, will need to complete a strategic transaction, or, alternatively, raise substantial additional funds to enable commercialization of Gencaro, if it is approved. Failure to successfully provide for the commercialization of Gencaro, if it is approved, would damage our business.

Our clinical trials for our product candidates may not yield results that will enable us to further develop our products and obtain the regulatory approvals necessary to sell them.

We will receive regulatory approval for our product candidates only if we can demonstrate in carefully designed and conducted clinical trials that the product candidate is safe and effective. We do not know whether any future clinical trials, including the planned GENETIC-AF clinical trial for Gencaro, will demonstrate sufficient safety and efficacy to obtain the requisite regulatory approvals or will result in marketable products.

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For example, GENETIC-AF is designed to be an adaptive trial. The DSMB will analyze certain data from the Phase 2B portion and recommend whether the trial should proceed to Phase 3 and seek to enroll an additional 420 patients. The DSMB will make their recommendation after 200 patients have been enrolled and have completed 24 weeks of follow-up. The interim analysis will focus on data regarding AF event rates, AF burden, and safety. Should the DSMB interim analysis conclude the data is consistent with the pre-trial statistical assumptions and that the data indicates potential for achieving statistical significance for the Phase 3 endpoint, then the DSMB may recommend the study proceed to Phase 3. The DSMB may also recommend changes to the study design before potentially proceeding to Phase 3, or it may recommend that the study not proceed to Phase 3. The Company, in consultation with the trial s clinical steering committee and the DSMB, will make the final determination on the trial s development steps. If we do not see sufficient efficacy and safety in the Phase 2B portion of the trial, we will not initiate the Phase 3 portion of the trial.

Clinical trials are lengthy, complex and expensive processes with uncertain results. We have spent, and expect to continue to spend, significant amounts of time and money in the clinical development of our product candidates. We have never conducted a Phase 2 or Phase 3 clinical trial and do not currently have sufficient staff with the requisite experience to do so, and we therefore expect that we will have to rely on contract research organizations to conduct certain of our clinical trials. While certain of our employees have experience in designing and administering clinical trials, these employees have no such experience as employees of ARCA.

The results we obtain in preclinical testing and early clinical trials may not be predictive of results that are obtained in later studies. We may suffer significant setbacks in advanced clinical trials, even after seeing promising results in earlier studies. Based on results at any stage of clinical trials, we may decide to repeat or redesign a trial or discontinue development of one or more of our product candidates. If we fail to adequately demonstrate the safety and efficacy of our products under development, we will not be able to obtain the required regulatory approvals to commercialize our product candidates, and our business, results of operations and financial condition would be materially adversely affected.

Administering our product candidates to humans may produce undesirable side effects. These side effects could interrupt, delay or halt clinical trials of our product candidates and could result in the FDA or other regulatory authorities denying approval of our product candidates for any or all targeted indications.

If clinical trials for a product candidate are unsuccessful, we will be unable to commercialize the product candidate. If one or more of our clinical trials are delayed, we will be unable to meet our anticipated development timelines. Either circumstance could cause the market price of our common stock to decline.

We are relying on contract research organizations to conduct substantial portions of our GENETIC AF clinical trial, and as a result, we will be unable to directly control the timing, conduct and expense of the clinical trial.

We do not currently have sufficient staff with the requisite experience to conduct our clinical trial and are therefore relying primarily on third parties to conduct our clinical trial. We have contracted with Duke University , as our contract research organization (CRO) to conduct the clinical component of our GENETIC-AF trial. As a result of this contract, we will have less control over many details and steps of the trial, the timing and completion of the trial, the required reporting of adverse events and the management of data developed through the trial than would be the case if we were relying entirely upon our own staff. Communicating with outside parties can also be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. Outside parties, such as CROs, may have staffing difficulties, may undergo changes in priorities or may become financially distressed, adversely affecting their willingness or ability to conduct our trial. We may experience unexpected cost increases that are beyond our control. Problems with the timeliness or quality of the work of a CRO may lead us to seek to terminate the relationship and use

an alternative service provider. However, making this change may be costly and may delay ongoing trials, and contractual restrictions may make such a change difficult or impossible. Additionally, it may be impossible to find a replacement organization that can conduct clinical trials in an acceptable manner and at an acceptable cost.

Even though we are using a CRO to conduct our clinical trial, we have to devote substantial resources and rely on the expertise of our employees to manage the work being done by the CRO. We have never conducted a clinical trial and the inability of our current staff to adequately manage any CRO that we engage may exacerbate the risks associated with relying on a CRO.

If we encounter difficulties enrolling patients in our clinical trials, our trials could be delayed or otherwise adversely affected.

The GENETIC-AF clinical trial requires that we identify and enroll a large number of patients with the condition under investigation and the trial will enroll only those patients having a specific genotype, and only those patients who have or are willing to have a Medtronic device implanted for monitoring and recording AF burden data. Because of the rigorous enrollment criteria, we may not be able to enroll a sufficient number of patients to complete our clinical trial in a timely manner.

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Patient enrollment is affected by factors including:

- design of the protocol;
- the size of the patient population;
- eligibility criteria for the study in question;
- perceived risks and benefits of the drug under study;
- availability of competing therapies, including the off-label use of therapies approved for related indications;
- efforts to facilitate timely enrollment in clinical trials;
- the success of our personnel in making the arrangements with potential clinical trial sites necessary for those sites to begin enrolling patients;
- patient referral practices of physicians;
- availability of clinical trial sites;
- other clinical trials seeking to enroll subjects with similar profiles;
- the number of patients having the specific genotype needed for our trial; and
- the number of patients having, or willing to have, a Medtronic device implanted for monitoring and recording AF burden data.

If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay or terminate ongoing or planned clinical trials, either of which would have a negative effect on our business. Delays in enrolling patients in our clinical trials would also adversely affect our ability to generate any product, milestone and royalty revenues under collaboration agreements, if any, and could impose significant additional costs on us or on any future collaborators.

We may not achieve our projected development goals in the time frames we announce and expect.

We set goals for, and make public statements regarding, the timing of certain accomplishments, such as, the commencement and completion of clinical trials, particularly with respect to steps for commencing and continuing GENETIC-AF, the disclosure of trial results, the obtainment of regulatory approval and the sale of drug product, which we sometimes refer to as milestones. These milestones may not be achieved, and the actual timing of these events can vary dramatically due to a number of factors such as delays or failures in our clinical trials, disagreements with any collaborative partners, the uncertainties inherent in the regulatory approval process and manufacturing scale-up and delays in achieving manufacturing or marketing arrangements sufficient to commercialize our products. FDA approval of Gencaro, if it occurs, is expected to require years of additional clinical development, including the completion of genetic trials There can be no assurance that our genetic trials will be initiated or completed, or that we will make regulatory submissions or receive regulatory approvals as planned. If we fail to achieve one or more of these milestones as planned, our business will be materially adversely affected.

If we are not able to maintain the requirements for listing on the Nasdaq Capital Market, we could be delisted, which could have a materially adverse effect on our ability to raise additional funds as well as the price and liquidity of our common stock.

Our common stock is currently listed on the Nasdaq Capital Market. To maintain the listing of our common stock on the Nasdaq Capital Market we are required to meet certain listing requirements, including, among others, either: (i) a minimum closing bid price of $1.00 per share, a market value of publicly held shares (excluding shares held by our executive officers, directors and 10% or more stockholders) of at least $1 million and stockholders equity of at least $2.5 million; or (ii) a minimum closing bid price of $1.00 per share, a market value of publicly held shares (excluding shares held by our executive officers, directors and 10% or more stockholders) of at least $1 million and a total market value of listed securities of at least $35 million.

During 2012 our stock price fell below the Nasdaq Capital Market s minimum bid price requirements and we became subject to delisting from the exchange. On March 4, 2013 we executed a 1 for 6 reverse split of our common stock and have subsequently regained compliance with the minimum bid price requirements. In future periods, if we do not meet the minimum stockholders equity, minimum closing bid price requirements, or any other listing requirements, we would be subject to delisting from the Nasdaq Capital Market.

As of March 17, 2014, the closing price of our common stock was $2.07 per share, and the total market value of our listed securities was approximately $43.4 million. As of December 31, 2013, we had stockholders equity of $15.6 million.

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We expect to depend on existing and future collaborations with third parties for the development of some of our product candidates. If those collaborations are not successful, we may not be able to complete the development of these product candidates.

We currently have a collaboration agreement with Medtronic, Inc., or Medtronic for the support of our planned GENETIC-AF trial. Medtronic can terminate its collaboration with us for various reasons including uncured material breach, an ARCA bankruptcy, if, after FDA communication, it is reasonably concluded that the FDA will not allow GENETIC-AF to enroll or proceed, or if Medtronic s obligations are unilaterally expanded. We may seek additional third party collaborators for the development of Gencaro or other product candidates.

Under our current arrangement with Medtronic, we have limited control over the amount and timing of resources that they dedicate to the development of Gencaro. This is also likely to be true in any future collaboration with third parties. Our ability to generate revenues from these arrangements will depend on our collaborators abilities to successfully perform the functions assigned to them in these arrangements.

Collaborations involving our product candidates pose the following risks to us:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborator s strategic focus or available funding, or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our proprietary information or expose us to potential litigation;
- disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our product candidates or that result in costly litigation or arbitration that diverts management attention and resources;

collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates;

collaborators may elect to take over manufacturing rather than retain us as manufacturers and may encounter problems in starting up or gaining approval for their manufacturing facility and so be unable to continue development of product candidates;

we may be required to undertake the expenditure of substantial operational, financial and management resources in connection with any collaboration;

we may be required to issue equity securities to collaborators that would dilute our existing stockholders percentage ownership;

we may be required to assume substantial actual or contingent liabilities;

collaborators may not commit adequate resources to the marketing and distribution of our product candidates, limiting our potential revenues from these products; and

collaborators may experience financial difficulties.

We face a number of challenges in seeking additional collaborations. Collaborations are complex and any potential discussions may not result in a definitive agreement for many reasons. For example, whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator s resources and expertise, the terms and conditions of the proposed collaboration, and the proposed collaborator s evaluation of a number of factors, such as the design or results of our clinical trials, the potential market for our product candidates, the costs and complexities of manufacturing and delivering our product candidates to patients, the potential of competing products, the existence of uncertainty with respect to ownership or the coverage of our intellectual property, and industry and market conditions generally. If we were to determine that additional collaborations for our Gencaro development is necessary and were unable to enter into such collaborations on acceptable terms, we might elect to delay or scale back the development or commercialization of Gencaro in order to preserve our financial resources or to allow us adequate time to develop the required physical resources and systems and expertise ourselves.

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Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner, or at all. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. If a present or future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program could be delayed, diminished or terminated.

Our planned GENETIC-AF clinical trial will require the use of a third-party diagnostic services provider to administer the genetic test needed to identify the patient receptor genotypes of clinical trial participants, and as a result, we will be unable to directly control the timing, conduct and expense of the genetic test.

Our planned GENETIC-AF clinical trial of Gencaro requires a companion diagnostic test that identifies the patient s receptor genotype. The trial will only enroll those patients with the receptor that has the potential for enhanced efficacy, the beta-1 389 Arg receptor as detected by a beta-1 389 Arg/Arg genotype. Accordingly, the GENETIC-AF trial will require use of a third-party diagnostic service to perform the genetic testing. There has been limited experience in our industry in prospective development of companion diagnostics required to perform the required molecular profiling. We entered into an agreement with Laboratory Corporation of America, LabCorp, to provide the diagnostic services of the genetic test needed to support our GENETIC-AF trial. To provide those services, LabCorp obtained from the FDA an Investigational Device Exemption, or IDE, for the companion diagnostic test to be used in our Genetic AF clinical trial.

The FDA and similar regulatory authorities outside the United States regulate companion diagnostics. Companion diagnostics require separate or coordinated regulatory approval prior to commercialization. Changes to regulatory advice could delay our development programs or delay or prevent eventual marketing approval for our product candidates that may otherwise be approvable. In July 2011, the FDA issued draft guidance that stated that if safe and effective use of a therapeutic depends on an *in vitro* diagnostic, then the FDA generally will not approve the therapeutic unless the FDA approves or clears this *in vitro* companion diagnostic device at the same time that the FDA approves the therapeutic. The approval or clearance of the companion diagnostic would occur through the FDA s Center for Devices and Radiological Health. The draft guidance on companion diagnostics remains in draft form, and it is unclear how closely the final guidance, when published, will track the 2011 draft guidance. It is also difficult to predict how FDA will implement the guidance once finalized. For example, the draft guidance allows for flexibility by the FDA in the case of therapeutic products to treat serious conditions for which no alternative treatment exists and the benefits of using the companion diagnostic outweigh the risk, but it is unclear how this discretion will be applied by the agency. The FDA s evolving position on the topic of companion diagnostics could affect our clinical development programs that utilize companion diagnostics. In particular, the FDA may limit our ability to use retrospective data, otherwise disagree with our approaches to trial design, biomarker qualification, clinical and analytical validity, and clinical utility, or make us repeat aspects of a trial or initiate new trials.

Given our limited experience in developing diagnostics, we expect to rely primarily on third parties for their design and manufacture. If we, or any third parties that we engage to assist us, are unable to successfully develop companion diagnostics for our product candidates that require such diagnostics, or experience delays in doing so, the development of our product candidates may be adversely affected, our product candidates may not receive marketing approval and we may not realize the full commercial potential of any products that receive marketing approval. As a result, our business could be materially harmed.

We will need to establish a collaborative arrangement with a third-party diagnostics services provider to obtain marketing clearance or approval of the companion genetic test. There is no guarantee that the FDA will grant timely clearance or approval of the genetic test, if at all, and failure to obtain such timely clearance or approval would adversely affect our ability to market Gencaro.

The drug label we intend to seek for Gencaro would identify the patient receptor genotype for which the drug is approved. Accordingly, we believe developing a genetic test that is simple to administer and widely available will be critical to the successful commercialization of Gencaro and also to the ability to conduct our planned GENETIC-AF clinical trial. The genetic test will be subject to regulation by the FDA and by comparable agencies in various foreign countries. The process of complying with the requirements of the FDA and comparable agencies is costly, time consuming and burdensome.

Despite the time and expense expended, regulatory clearance or approval is never guaranteed. If regulatory clearance or approval is delayed, or if one or more third-party diagnostic services providers are unable to obtain FDA approval of the genetic test at all or in parallel with the approval of Gencaro, or are unable to commercialize the test successfully and in a manner that effectively supports the commercial efforts for Gencaro, or if the information concerning the differential response to Gencaro resulting from certain genetic variation is not included in the approval label for Gencaro, the commercial launch of Gencaro may be significantly and adversely affected.

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Regulatory approval will be required for the genetic test to be used in the GENETIC-AF trial and to support the commercialization of the test, if approved. Delays or failures in obtaining such regulatory approval, including any required validation analyses may prevent a third-party diagnostics provider from commercializing such genetic test and will adversely affect our business, operating results and prospects.

Before a genetic test can be used commercially, including in conjunction with Gencaro, if it is approved for marketing, the third-party diagnostics provider must obtain FDA Premarket Approval, or PMA, for such test. The FDA may require additional validation of the genetic test we plan to use in GENETIC-AF prior to any approval of Gencaro or the genetic test. We anticipate the genetic test will be required as a condition to prescribing Gencaro. There is no guarantee the FDA will approve the anticipated PMA submission for the genetic test. Even if the genetic test is eventually approved, performing additional validation work necessary to support the PMA, if required, for current or future genetic test products, including one associated with Gencaro, would require additional time and expense and the outcome would be uncertain. Moreover, such delays or increased costs or failures could adversely affect our business, operating results and prospects for commercializing the genetic test.

If a third-party diagnostics provider responsible for the genetic test or certain of its third-party suppliers fails to comply with ongoing FDA or other foreign regulatory authority requirements, or if there are unanticipated problems with the genetic test, these products could be subject to restrictions or withdrawal from use in trial or from the market.

Any diagnostic for which a third-party diagnostics provider obtains clearance or approval, and the manufacturing processes, reporting requirements, post-approval clinical data and promotional activities for such product, will be subject to continued regulatory review, oversight and periodic inspections by the FDA and other domestic and foreign regulatory bodies. With respect to the genetic test, to the extent applicable, any third-party diagnostics provider and certain of its suppliers will be required to comply with the FDA s Quality System Regulation, or QSR, and International Standards Organization, or ISO, requirements which cover the methods and documentation of the design, testing, production, control, quality assurance, labeling, packaging, storage and shipping of any product for which clearance or approval is obtained. Regulatory bodies, such as the FDA, enforce the QSR and other regulations through periodic inspections. The failure by a third-party diagnostics provider, or certain of its third-party manufacturers or suppliers, as the case may be, to comply with applicable statutes and regulations administered by the FDA and other regulatory bodies, or the failure to timely and adequately respond to any adverse inspectional observations or product safety issues, could result in, among other things, enforcement actions. If any of these actions were to occur, it could harm our reputation and cause product sales and profitability of Gencaro to suffer and may prevent us from generating revenue or utilizing the genetic test further in any clinical trial. Even if regulatory clearance or approval is granted, such clearance or approval may be subject to limitations on the intended uses for which the product may be marketed and reduce our potential to successfully commercialize the product and generate revenue from the product.

Future sales of Gencaro may suffer if its marketplace acceptance is negatively affected by the genetic test.

The genetic test is an important component of the commercial strategy for Gencaro in addition to being required to proceed with our planned AF trial. We believe that the genetic test helps predict patient response to Gencaro, and that this aspect of the drug is important to its ability to compete effectively with current therapies. The genetic test adds an additional step in the prescribing process, an additional cost for the patient and payors, the risk that the test results may not be rapidly available and the possibility that it may not be available at all to hospitals and medical centers. Although we anticipate that Gencaro, if approved in a timely manner, would be the first genetically-targeted cardiovascular drug, Gencaro will be one of a number of successful drugs in the beta-blocker class currently on the market. Prescribers may be more familiar with these other beta-blockers, and may be resistant to prescribing Gencaro as an AF therapy in patients with HF. Any one of these factors could affect prescriber behavior, which in turn may

substantially impede market acceptance of the genetic test, which could cause significant harm to Gencaro s ability to compete, and in turn harm our business.

Our failure to raise substantial additional funding or enter into a strategic transaction may materially and adversely affect our business.

Unless we are able to raise substantial additional funding for the development of Gencaro through other means, we will need to complete a strategic transaction to continue the development of Gencaro through the clinical development and commercialization phases, and to continue our other operations. The strategic transactions that we may consider include a potential combination or partnership. Our board of directors and management team has and will continue to devote substantial time and resources to obtaining additional capital or the consideration and implementation of any such strategic transaction. In addition, conditions in the financial markets may lead to an increased number of biotechnology companies that are also seeking to enter into strategic transactions, which may limit our ability to negotiate favorable terms for any such transaction. Further, our current employees do not have experience in the strategic transaction process, and our previous efforts to enter into a strategic transaction have not been successful. As a result of these and other factors, there is substantial risk that we may not be able to complete a strategic transaction on favorable terms, or at all. The failure to complete such a strategic transaction may materially and adversely affect our business.

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We may be limited in our ability to access sufficient funding through a private equity or convertible debt offering.

Nasdaq rules impose restrictions on our ability to raise funds through a private offering of our common stock, convertible debt or similar instruments without obtaining stockholder approval. Under Nasdaq rules, an offering of more than 20% of our total shares outstanding for less than the greater of book or market value requires stockholder approval unless the offering qualifies as a public offering for purposes of the Nasdaq rules. As of February 7, 2014 we had approximately 21 million shares of common stock outstanding, 20% of which is approximately 4.2 million shares. To the extent we seek to raise funds through a private offering of stock, convertible debt or similar instruments, we are limited in how much funding we could raise privately without requiring a stockholder vote. SEC rules impose restrictions on our ability to raise funds through the registered offering of our securities pursuant to our shelf registration statement on Form S-3. Under SEC rules, we are prohibited from selling securities under such registration statement if the aggregate market value of the securities sold thereunder in any twelve-month period exceeds one-third of the market value of our outstanding common stock held by non-affiliates. Our February 2014 equity financing substantially exhausted the availability under our shelf registration statement until the one year anniversary of such financing. In addition, we are currently subject to certain contractual rights of investors arising from our public and private equity financing transactions that limit the nature and price of future public and private financing transactions that we may effect. For example, in January 2013, we entered into separate subscription agreements with certain institutional investors in connection with a private investment in public equity, pursuant to which we sold shares of our common stock and warrants to purchase shares of our common stock to the investors. In connection with this transaction, we agreed that, subject to certain exceptions, we would not, while the warrants issued in such financing are outstanding, effect or enter into an agreement to effect any issuance of common stock or securities convertible into, exercisable for or exchangeable for common stock in a variable rate transaction, which means a transaction in which we issue or sell any convertible securities either (A) at a conversion price, exercise price or exchange rate or other price that is based upon and/or varies with the trading prices of, or quotations for, the shares of common stock at any time after the initial issuance of such convertible securities, or (B) with a conversion, exercise or exchange price that is subject to being reset at some future date after the initial issuance of the convertible securities or upon the occurrence of the specified or contingent events directly or indirectly related to our business or the market for our common stock. The restrictions imposed by the terms of our previous offerings, and that could be imposed in future offerings, may limit our access to capital on agreeable terms and delay or make impossible certain otherwise available equity financing opportunities and could severely restrict our access to the capital necessary to conduct our business.

Unless we are able to generate sufficient product revenue, we will continue to incur losses from operations and will not achieve or maintain profitability. We are years away from commercializing a product and generating product revenue.

Our historical losses have had and will continue to have an adverse effect on our stockholders equity and working capital, among other things. We are years away from commercializing a product and generating any product revenue. As a result, we expect to continue to incur significant operating losses for the foreseeable future. Even if we ultimately receive regulatory approval for Gencaro or our other product candidates, sales of such products may not generate sufficient revenue for it to achieve or maintain profitability. Because of the numerous risks and uncertainties associated with developing therapeutic drugs, we may experience larger than expected future losses and may never reach profitability.

Our product candidates are subject to extensive regulation, which can be costly and time-consuming, and unsuccessful or delayed regulatory approvals could increase our future development costs or impair our future revenue.

The preclinical and clinical development, testing, manufacture, safety, efficacy, labeling, storage, recordkeeping, and subsequent advertising, promotion, sale, marketing, and distribution, if approved, of our product candidates are subject to extensive regulation by the FDA and other regulatory authorities in the United States and elsewhere. These regulations also vary in important, meaningful ways from country to country. We are not permitted to market a potential drug in the United States until we receive approval of an NDA from the FDA. We have not received an NDA approval from the FDA for Gencaro or any of our other product candidates. There can be no guarantees with respect to our product candidates that clinical studies will adequately support an NDA, that the products will receive necessary regulatory approvals, or that they will prove to be commercially successful.

To receive regulatory approval for the commercial sale of any product candidates, we must demonstrate safety and efficacy in humans to the satisfaction of regulatory authorities through preclinical studies and adequate and well-controlled clinical trials of the product candidates. This process is expensive and can take many years, and failure can occur at any stage of the testing. Our failure to adequately demonstrate the safety and efficacy of our product candidates will prevent regulatory approval and commercialization of such products. In 2008, we submitted and the FDA accepted our NDA filing for Gencaro for the treatment of chronic HF. In 2009, the FDA issued a Complete Response Letter (CRL) in which the FDA stated that it could not approve the Gencaro NDA in its current form and specified actions required for approval of the NDA, including conducting an additional Phase 3 clinical trial of Gencaro in patients with HF. We plan to conduct a clinical study of Gencaro in HFREF patients to assess its efficacy in reducing or preventing AF. We currently anticipate that GENETIC-AF will begin patient enrollment in the first quarter of 2014. This trial is planned to begin as a Phase 2B study in approximately 200 patients and, depending on the outcome of the Phase 2B portion, may be expanded to a Phase 3 study with up to an estimated additional 420 patients. We believe the Phase 2B study would take approximately two and a half years to complete. This product candidate will require years of clinical development. Even if we conduct additional studies in accordance with further FDA guidance and submit or file a new or amended NDA, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval.

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In the event that we or our collaborators conduct preclinical studies that do not comply with Good Laboratory Practices or GLP or incorrectly design or carry out human clinical trials in accordance with Good Clinical Practices or GCP or those clinical trials fail to demonstrate clinical significance, it is unlikely that we will be able to obtain FDA approval for product development candidates. Our inability to successfully initiate and effectively complete clinical trials for any product candidate on schedule, or at all, will severely harm our business. Significant delays in clinical development could materially increase product development costs or allow our competitors to bring products to market before we do, impairing our ability to effectively commercialize any future product candidate. We do not know whether planned clinical trials will begin on time, will need to be redesigned or will be completed on schedule, if at all. Clinical trials can be delayed for a variety of reasons, including:

- delays or failures in obtaining regulatory authorization to commence a trial because of safety concerns of regulators relating to our product candidates or similar product candidates of our competitors or failure to follow regulatory guidelines;
- delays or failures in obtaining clinical materials and manufacturing sufficient quantities of the product candidates for use in trials;
- delays or failures in reaching agreement on acceptable terms with prospective study sites;
- delays or failures in obtaining approval of our clinical trial protocol from an institutional review board, or IRB, to conduct a clinical trial at a prospective study site;
- delays in recruiting patients to participate in a clinical trial, which may be due to the size of the patient population, eligibility criteria, protocol design, perceived risks and benefits of the drug, availability of other approved and standard of care therapies, availability of clinical trial sites;
- other clinical trials seeking to enroll subjects with similar profile;
- failure of our clinical trials and clinical investigators to be in compliance with the FDA s Good Clinical Practices;
- unforeseen safety issues, including negative results from ongoing preclinical studies;
- inability to monitor patients adequately during or after treatment;
- difficulty recruiting and monitoring multiple study sites;

failure of our third-party contract research organizations, clinical site organizations and other clinical trial managers, to satisfy their contractual duties, comply with regulations or meet expected deadlines; and

an insufficient number of patients who have, or are willing to have, a Medtronic device implanted for monitoring and recording AF burden data.

In addition, any approvals we may obtain may not cover all of the clinical indications for which we seek approval or permit us to make claims of superiority over currently marketed competitive products. Also, an approval might contain significant limitations in the form of narrow indications, warnings, precautions or contraindications with respect to conditions of use. If the FDA determines that a risk evaluation and mitigation strategy, or REMS, is necessary to ensure that the benefits of the drug outweigh the risks, we may be required to include as part of the NDA a proposed REMS that may include a package insert directed to patients, a plan for communication with healthcare providers, restrictions on a drug s distribution, or a Medication Guide, to provide better information to consumers about the drug s risks and benefits. Finally, an approval could be conditioned on our commitment to conduct further clinical trials, which we may not have the resources to conduct or which may negatively impact our financial situation.

The manufacture and tableting of Gencaro is done by third party suppliers, who must also meet current Good Manufacturing Practices, or cGMP, requirements and pass a pre-approval inspection of their facilities before we can obtain marketing approval.

All of our product candidates are prone to the risks of failure inherent in drug development. The results from preclinical animal testing and early human clinical trials may not be predictive of results obtained in later human clinical trials. Further, although a new product may show promising results in preclinical or early human clinical trials, it may subsequently prove unfeasible or impossible to generate sufficient safety and efficacy data to obtain necessary regulatory approvals. The data obtained from preclinical and clinical studies are susceptible to varying interpretations that may delay, limit or prevent regulatory approval, and the FDA and other regulatory authorities in the United States and elsewhere exercise substantial discretion in the drug approval process. The numbers, size and design of preclinical studies and clinical trials that will be required for FDA or other regulatory approval will vary depending on the product candidate, the disease or condition for which the product candidate is intended to be used and the regulations and guidance documents applicable to any particular product candidate. The FDA or other regulators can delay, limit or deny approval of any product candidate for many reasons, including, but not limited to:

Side effects;

Safety and efficacy;

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Defects in the design of clinical trials;

The fact that the FDA or other regulatory officials may not approve our or our third party manufacturer s processes or facilities; or

The fact that new regulations may be enacted by the FDA or other regulators may change their approval policies or adopt new regulations requiring new or different evidence of safety and efficacy for the intended use of a product candidate.

In light of widely publicized events concerning the safety of certain drug products, regulatory authorities, members of Congress, the Government Accountability Office, medical professionals and the general public have raised concerns about potential drug safety issues. These events have resulted in the withdrawal of certain drug products, revisions to certain drug labeling that further limit use of the drug products and establishment of risk management programs that may, for instance, restrict distribution of drug products. The increased attention to drug safety issues may result in a more cautious approach by the FDA to clinical trials and approval. Data from clinical trials may receive greater scrutiny with respect to safety and the product s risk/benefit profile, which may make the FDA or other regulatory authorities more likely to terminate clinical trials before completion, or require longer or additional clinical trials that may result in substantial additional expense, and a delay or failure in obtaining approval or approval for a more limited indication than originally sought. Aside from issues concerning the quality and sufficiency of submitted preclinical and clinical data, the FDA may be constrained by limited resources from reviewing and determining the approvability of the Gencaro NDA in a timely manner.

In pursuing clinical development of Gencaro for an AF indication, we will be required to amend the Gencaro HF NDA or prepare a new NDA. The FDA could approve Gencaro, but without including some or all of the prescribing information that we have requested. For instance, the FDA could approve Gencaro for AF in a more limited patient population or included additional warnings in the drug s label. This, in turn, could substantially and detrimentally impact our ability to successfully commercialize Gencaro and effectively protect our intellectual property rights in Gencaro.

If our product candidates receive regulatory approval, we would be subject to ongoing regulatory obligations and restrictions, which may result in significant expenses and limit our ability to develop and commercialize other potential products.

If a product candidate of ours is approved by the FDA or by another regulatory authority, we would be held to extensive regulatory requirements over product manufacturing, testing, distribution, labeling, packaging, adverse event reporting and other reporting to regulatory authorities, storage, advertising, marketing, promotion, distribution, and record keeping. Regulatory approvals may also be subject to significant limitations on the indicated uses or marketing of the product candidates. Potentially costly follow-up or post-marketing clinical studies may be required as a condition of approval to further substantiate safety or efficacy, or to investigate specific issues of interest to the regulatory authority. Previously unknown problems with the product candidate, including adverse events of unanticipated severity or frequency, may result in additional regulatory controls or restrictions on the marketing or use of the product or the need for post marketing studies, and could include suspension or withdrawal of the products from the market.

Furthermore, our third-party manufacturers and the manufacturing facilities that they use to make our product candidates are regulated by the FDA. Quality control and manufacturing procedures must continue to conform to cGMP after approval. Drug manufacturers and their subcontractors are required to register their facilities and products

manufactured annually with the FDA and certain state agencies and are subject to periodic unannounced inspections by the FDA, state and/or other foreign authorities. Any subsequent discovery of problems with a product, or a manufacturing or laboratory facility used by us or our collaborators, may result in restrictions on the product, or on the manufacturing or laboratory facility, including a withdrawal of the drug from the market or suspension of manufacturing. Any changes to an approved product, including the way it is manufactured or promoted, often require FDA approval before the product, as modified, can be marketed. We and our third-party manufacturers will also be subject to ongoing FDA requirements for submission of safety and other post-market information.

The marketing and advertising of our drug products by our collaborators or us will be regulated by the FDA, certain state agencies or foreign regulatory authorities. Violations of these laws and regulations, including promotion of our products for unapproved uses or failing to disclose risk information, are punishable by criminal and civil sanctions and may result in the issuance of enforcement letters or other enforcement action by the FDA, U.S. Department of Justice, state agencies, or foreign regulatory authorities that could jeopardize our ability to market the product.

In addition to the FDA, state or foreign regulations, the marketing of our drug products by us or our collaborators will be regulated by federal, state or foreign laws pertaining to health care fraud and abuse, such as the federal anti-kickback law prohibiting bribes, kickbacks or other remuneration for the order or recommendation of items or services reimbursed by federal health care programs. Many states have similar laws applicable to items or services reimbursed by commercial insurers. Violations of these laws are punishable by criminal and civil sanctions, including, in some instances, imprisonment and exclusion from participation in federal and state health care programs, including the Medicare, Medicaid and Veterans Affairs healthcare programs. Because of the far-reaching nature of these laws, we may be required to discontinue one or more of our practices to be in compliance with these laws. Health care fraud and abuse regulations are complex, and even minor irregularities can potentially give rise to claims that a statute or prohibition has been violated. Any violations of these laws, or any action against us for violations of these laws, even if we successfully defend against it, could have a material adverse effect on our business, financial condition and results of operations.

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We could also become subject to false claims litigation under federal statutes, which can lead to civil money penalties, restitution, criminal fines and imprisonment, and exclusion from participation in Medicare, Medicaid and other federal and state health care programs. These false claims statutes include the False Claims Act, which allows any person to bring a suit on behalf of the federal government alleging submission of false or fraudulent claims, or causing to present such false or fraudulent claims, under federal programs or contracts claims or other violations of the statute and to share in any amounts paid by the entity to the government in fines or settlement. These suits against pharmaceutical companies have increased significantly in volume and breadth in recent years. Some of these suits have been brought on the basis of certain sales practices promoting drug products for unapproved uses. This new growth in litigation has increased the risk that a pharmaceutical company will have to defend a false claim action, pay fines or restitution, or be excluded from the Medicare, Medicaid, Veterans Affairs and other federal and state healthcare programs as a result of an investigation arising out of such action. We may become subject to such litigation and, if we are not successful in defending against such actions, those actions may have a material adverse effect on our business, financial condition and results of operations. We could also become subject to false claims litigation and consumer protection claims under state statutes, which also could lead to civil monetary penalties, restitution, criminal fines and imprisonment, and exclusion from participation in state health care programs. Of note, over the past few years there has been an increased focus on the sales and marketing practices of the pharmaceutical industry at both the federal and state level. Additionally, the law or regulatory policies governing pharmaceuticals may change. New statutory requirements may be enacted or additional regulations may be adopted that could prevent or delay regulatory approval of our product candidates or limit our ability to commercialize our products. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from future legislation or administrative action, either in the U.S. or elsewhere.

If we, our collaborators or our third-party manufacturers fail to comply with applicable continuing regulatory requirements, our business could be seriously harmed because a regulatory agency may:

- issue untitled or warning letters;
- suspend or withdraw our regulatory approval for approved products;
- seize or detain products or recommend a product recall of a drug or medical device, or issue a mandatory recall of a medical device;
- refuse to approve pending applications or supplements to approved applications filed by us;
- suspend our ongoing clinical trials;
- restrict our operations, including costly new manufacturing requirements, or restrict the sale, marketing and/or distribution of our products;
- seek an injunction;

pursue criminal prosecutions;

close the facilities of our contract manufacturers; or

impose civil or criminal penalties.

Reliance on third parties to commercialize Gencaro could negatively impact our business. If we are required to establish a direct sales force in the U.S. and are unable to do so, our business may be harmed.

Commercialization of Gencaro, particularly the establishment of a sales organization, will require substantial additional capital resources. We currently intend to pursue a strategic partnership alternative for the commercialization of Gencaro, if it is approved, and we have suspended our efforts to build internal sales, marketing and distribution capabilities. If we elect to rely on third parties to sell Gencaro and any other products, then we may receive less revenue than if we sold such products directly. In addition, we may have little or no control over the sales efforts of those third parties. If we are unable to complete a strategic transaction, we would be unable to commercialize Gencaro or any other product candidate without substantial additional capital. Even if such capital were secured, we would be required to build internal sales, marketing and distribution capabilities to market Gencaro in the U.S. None of our current employees have experience in establishing and managing a sales force.

In the event we are unable to sell Gencaro and other selected product candidates, either directly or through third parties via a strategic transaction, the commercialization of Gencaro, if it is approved, may be delayed indefinitely.

We are dependent on our key personnel.

The success of our business is highly dependent on the principal members of our board of directors and executive management, including our President and Chief Executive Officer, Michael R. Bristow. The loss of the services of any such individual might seriously harm our product development, partnering and financing efforts. Recruiting and training personnel with the requisite skills is challenging and we compete for talent with companies that are larger and have more financial resources.

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We have no manufacturing capacity which puts us at risk of lengthy and costly delays of bringing our products to market.

We do not currently operate manufacturing facilities for clinical or commercial production of our product candidates, including their active pharmaceutical ingredients, or API. We have no experience in drug formulation or manufacturing, and we lack the resources and the capabilities to manufacture any of our product candidates on a clinical or commercial scale. We do not intend to develop facilities for the manufacture of product candidates for clinical trials or commercial purposes in the foreseeable future. We have contracted with Groupe Novasep to manufacture commercial quantities of the API for Gencaro. For drug production, we have contracted with Patheon, Inc. to manufacture the Gencaro tablets. These contract manufacturers may not perform as agreed or may not remain in the contract manufacturing business for the time required to successfully produce, store and distribute our products. In addition, these manufacturers may have staffing difficulties, may not be able to manufacture our products on a timely basis or may become financially distressed. In the event of errors in forecasting production quantities required to meet demand, natural disaster, equipment malfunctions or failures, technology malfunctions, strikes, lock-outs or work stoppages, regional power outages, product tampering, war or terrorist activities, actions of regulatory authorities, business failure, strike or other difficulty, we may be unable to find an alternative third-party manufacturer in a timely manner and the production of our product candidates would be interrupted, resulting in delays and additional costs, which could impact our ability to commercialize and sell our product candidates. We or our contract manufacturers may also fail to achieve and maintain required manufacturing standards, which could result in patient injury or death, product recalls or withdrawals, an order by governmental authorities to halt production, delays or failures in product testing or delivery, cost overruns or other problems that could seriously hurt our business. Contract manufacturers also often encounter difficulties involving production yields, quality control and quality assurance, as well as shortages of qualified personnel. In addition, our contract manufacturers are subject to ongoing inspections and regulation by the FDA, the U.S. Drug Enforcement Agency and corresponding foreign and state agencies and they may fail to meet these agencies acceptable standards of compliance. If our contract manufacturers fail to comply with applicable governmental regulations, such as quality control, quality assurance and the maintenance of records and documentation, we may not be able to continue production of the API or finished product. If the safety of any API or product supplied is compromised due to failure to adhere to applicable laws or for other reasons, this may jeopardize our regulatory approval for Gencaro and other product candidates, and we may be held liable for any injuries sustained as a result. Upon the occurrence of one of the aforementioned events, the ability to switch manufacturers may be difficult for a number of reasons, including:

- the number of potential manufacturers is limited and we may not be able to negotiate agreements with alternative manufacturers on commercially reasonable terms, if at all;
- long lead times are often needed to manufacture drugs;
- the manufacturing process is complex and may require a significant learning curve; and
- the FDA must approve any replacement prior to manufacturing, which requires new testing and compliance inspections.

Transitioning from a developmental stage company will require successful completion of a number of steps, many of which are outside of our control and, consequently, we can provide no assurance of our successful and timely

transition from a developmental stage company.

We are a development stage biopharmaceutical company with a limited operating history. To date we have not generated any product revenue and have historically funded our operations through investment capital. Our future growth depends on our ability to emerge from the developmental stage and successfully commercialize or provide for the commercialization of Gencaro and our other product candidates which in turn, will depend, among other things, on our ability to:

- conduct an additional clinical trial and develop and obtain regulatory approval for Gencaro or other product candidates;
- successfully partner a companion genetic test with the commercial launch of Gencaro;
- enter into a strategic transaction enabling the continued development and commercialization of Gencaro, or alternatively, raise significant additional capital to enable these activities;
- pursue additional indications for Gencaro and develop other product candidates, including other cardiovascular therapies; and
- obtain commercial quantities of Gencaro or other product candidates at acceptable cost levels.

Any one of these factors or other factors discussed in this report could affect our ability to successfully commercialize Gencaro and other product candidates, which could impact our ability to earn sufficient revenues to transition from a developmental stage company and continue our business.

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If approved by the FDA, Gencaro will be entering a competitive marketplace and may not succeed.

Gencaro is a new type of beta-blocker and vasodilator being developed for AF. While we anticipate that this drug, if approved, would be the first genetically-targeted cardiovascular drug, and potentially the only beta-blocker approved for AF, Gencaro will be one of a number of accepted treatments for AF. In addition, our proposed prescribing information for Gencaro is expected to include a requirement for genetic testing of the patient to ascertain if they have the genotype that we believe responds most favorably to Gencaro. This additional step will add incremental cost and procedures to prescribing Gencaro, which could make it more difficult to compete against existing therapies.

Our commercial opportunity may be reduced or eliminated if competitors develop and commercialize products that are safer, more effective, have fewer side effects, are more convenient or are less expensive than Gencaro. If products with any of these properties are developed, or any of the existing products are better marketed, then prescriptions of Gencaro by physicians and patient use of Gencaro could be significantly reduced or rendered obsolete and noncompetitive. Further, public announcements rega