ARCA biopharma, Inc.
Form 10-K
March 27, 2009
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2008

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.)
8001 Arista Place, Suite 200 Broomfield, CO (Address of Principal Executive Offices)	80021 (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 Global 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 þ

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 þ

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 þ 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. þ

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 þ

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

The aggregate market value of the common stock held by non-affiliates of the Registrant on June 30, 2008, the last business day of the most recently completed second fiscal quarter, was $29,925,354 based on the last sale price of the common stock as reported on that day by the Nasdaq Global Market.

As of March 17, 2009, the Registrant had 7,567,399 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 2009 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***

We have included or incorporated by reference into this Annual Report on Form 10-K statements that may constitute forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. Forward-looking statements may be identified by words including anticipate, plan, believe, intend, estimate, expect, should, may, potential and similar expressions. Such statements are based on our management s current expecta involve risks and uncertainties. Our actual results and performance could differ materially from those projected in the forward-looking statements as a result of many factors discussed in this Annual Report, including those set forth in this Item 1, as well as under Item 1A. Risk Factors and Item 7. Management s Discussion and Analysis of Financial Condition and Results of Operations. We do not intend to update any of the forward-looking statements after the date of this Annual Report to conform these statements to actual results unless required by law.

Merger Transaction

On January 27 2009, ARCA biopharma, Inc., formerly known as Nuvelo, Inc., or Nuvelo, completed the merger contemplated by that Agreement and Plan of Merger and Reorganization, dated September 24, 2008, as amended October 28, 2008, by and among Nuvelo, Dawn Acquisition Sub, Inc., a wholly-owned subsidiary of Nuvelo, or Merger Sub, and ARCA biopharma, Inc., or ARCA, a privately held developmental-stage biopharmaceutical company based in Broomfield, Colorado, which merger agreement, as amended, is referred to herein as the Merger Agreement.

In accordance with the Merger Agreement, immediately prior to the consummation of the merger, Nuvelo effected a reverse stock split of its common stock. Pursuant to this reverse stock split, each 20 shares of Nuvelo s common stock that were issued and outstanding immediately prior to the merger were converted into one share of Nuvelo s common stock. In addition, pursuant to the Merger Agreement, Merger Sub merged with and into ARCA, with ARCA continuing after the merger as the surviving corporation and a wholly owned subsidiary of Nuvelo. Immediately following the merger, Nuvelo changed its name to ARCA biopharma, Inc. On January 28, 2009, ARCA s common stock began trading on the Nasdaq Global Market under the new symbol ABIO.

The business combination is treated as a reverse merger for accounting purposes, and as such, historical financial information included in our future filings with the SEC will be the financial information of ARCA as the accounting acquirer in the merger. However, since the merger was consummated after the end of the period covered by this report, the historical financial information included in this report is that of Nuvelo prior to the merger and not that of ARCA.

Unless the context otherwise requires, all references herein to ARCA, the Company, we, us and our refer to ARCA both before and after the completion of the merger, and all references to Nuvelo refer to Nuvelo and its business prior to the completion of the merger and the name change. All share and per share amounts contained in this report give effect to the reverse stock split completed in connection with the merger.

Nuvelo s Business Prior to the Merger

Prior to the completion of the merger, Nuvelo was developing drugs for acute cardiovascular disease, gastro-intestinal, or GI, diseases and other debilitating medical conditions. Its development pipeline included NU172, a direct thrombin inhibitor that has completed Phase I development for use as a short-acting anticoagulant during medical or surgical procedures, and Phase I clinical candidate NU206, a recombinant, secreted protein for the potential treatment of GI, diseases, including inflammatory bowel disease, mucositis and bone disease.

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On March 17, 2008, Nuvelo announced its decision to discontinue clinical development of its clinical-stage product candidate, alfimeprase, and restructure its operations in order to make additional resources available for its other research and development programs. As part of the restructuring plan, Nuvelo reduced its workforce by approximately 19% and recorded a restructuring expense of $2.5 million, including $1.3 million of termination benefits and $1.2 million of non-cash stock-based compensation expense.

Overview

ARCA is a biopharmaceutical company whose principal focus is developing genetically-targeted therapies for heart failure and other cardiovascular diseases.

ARCA s lead product candidate is Gencaro™ (bucindolol hydrochloride), a pharmacologically unique beta-blocker and mild vasodilator, which is under review by the U.S. Food and Drug Administration, or FDA, for chronic heart failure, or HF. ARCA also plans to pursue several significant follow-on indications for Gencaro. Gencaro is an oral tablet formulation, dosed twice daily. ARCA has identified common genetic variations, or genetic markers, that predict patient response to Gencaro. Subject to approval by the FDA, ARCA, through its collaboration with Laboratory Corporation of America, or LabCorp, anticipates introducing a test for these genetic markers with the market launch of Gencaro, potentially making Gencaro the first genetically-personalized cardiovascular drug. When prescribed using the test for these markers, ARCA believes that Gencaro can become an important new therapy for many chronic heart failure patients, with the potential for positive clinical outcomes in a defined genetic subpopulation, and good tolerability. In September 2008, the FDA formally accepted for filing ARCA s New Drug Application, or NDA, for Gencaro as a potential treatment for HF. In accordance with the Prescription Drug User Free Act, or PDUFA, the FDA s goal is to complete its review of the Gencaro NDA by May 31, 2009, and ARCA anticipates an FDA decision on the approvability of Gencaro in the second or third quarter of 2009. Gencaro was the subject of a major North America based heart failure Phase III trial, known as BEST, which ARCA believes will provide the primary basis for approval of Gencaro in the U.S.

Chronic heart failure is one of the largest health care problems in the United States and the rest of the world. Beta-blockers are part of the current standard of care for HF, and are considered to be among the most effective drug classes for the disease. However, a significant percentage of eligible patients in the United States is not being treated, or does not tolerate or respond well to those beta-blockers currently approved for the treatment of HF. ARCA believes that new therapies for which patient response can be predicted before a drug is prescribed can help improve the current standard of practice in the treatment of HF.

ARCA has collaborated with LabCorp to develop the Gencaro Test, a companion test for the genetic markers that predict clinical response to Gencaro. The proposed use of the Gencaro Test, if approved by the FDA, will be to enable a physician to determine, prior to therapy, whether a patient is likely to have a good response to Gencaro. LabCorp has developed the Gencaro Test to be administered using a blood test or a cheek swab, and to provide prompt results to the treating physician. The Gencaro Test was submitted through the Premarket Approval, or PMA, process in January 2009, and an FDA decision on approval, based on FDA guidance, is expected in conjunction with the FDA decision on Gencaro. ARCA intends to closely coordinate the commercial launch of Gencaro and the Gencaro Test with LabCorp.

ARCA holds worldwide rights to Gencaro and plans to commercialize the drug in the U.S. through its own specialized sales force. ARCA s commercial effort in the United States will focus on cardiologists specializing in heart failure, and selected other physicians. ARCA intends to seek partners to assist it in commercializing Gencaro in international markets. ARCA believes that Gencaro will have market exclusivity under federal and international laws following commercial launch, and will also potentially have protection under patent applications, which ARCA believes would substantially extend market exclusivity. ARCA also plans to pursue several significant follow-on indications for Gencaro, including various forms of cardiac arrhythmias.

ARCA is also evaluating continued development of NU172, a novel, short-acting anticoagulant. ARCA believes that NU172 may have potential as a new therapy in indications where heparin paired with its antidote,

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protamine, is the current standard of care, such as coronary artery bypass graft (CABG) surgery, kidney dialysis and a variety of vascular surgical and coronary interventions. NU172 recently completed a successful Phase Ib study. ARCA is currently exploring collaborations for the other research and development programs that Nuvelo had conducted prior to the merger.

ARCA believes that its expertise in cardiovascular pathophysiology and genetics, and its clinical and commercial experience, will enable it to identify and develop other cardiovascular therapies, with an emphasis on those that may be personalized using genetic markers. ARCA is currently exploring such opportunities.

Market Opportunity

HF is one of the world s most significant health care challenges. Industry sources estimate that about 6 million Americans have HF and nearly 550,000 new patients are diagnosed annually. In addition, HF is the underlying reason for approximately 12 to 15 million annual visits to physicians, 6.5 million annual hospital days and over $34 billion in direct and indirect healthcare costs. Some sources estimate that the number of chronic heart failure patients in countries within the European Union is significantly higher than in the U.S.

Medical therapy has made progress in treating HF, but morbidity and mortality remain high. The current standard of care for HF involves the use of various therapies that operate to inhibit the activity of the renin-angiotensin-aldosterone system (these include angiotensin converting enzyme, or ACE, inhibitors, angiotensin II receptor blockers, or ARB s, and aldosterone receptor antagonists), diuretics, and drugs in the class known as beta-blockers.

Beta-blockers are named for their characteristic mechanism of binding to certain receptors in the nervous system of the heart, and in doing so blocking those receptors from being activated by binding with other molecules. This drug class is part of the current standard of care in patients with HF and left ventricular dysfunction. The American Heart Association and the American College of Cardiology physician guidelines for the treatment of HF state the following:

Beta-blockers should be prescribed to all patients with stable heart failure due to reduced left ventricular ejection fraction, unless they have a contraindication to their use or have been shown to be unable to tolerate treatment with the drugs. Because of favorable effects of beta-blockers on survival and disease progression, treatment with a beta-blocker should be initiated as soon as left ventricular dysfunction is diagnosed.

The benefits of beta-blockade are well established. Beta blockers are potentially usable by a majority of the HF population, they are effective in reducing mortality, and they are considered to be the most effective drugs overall for the treatment of HF. However, many patients who could potentially benefit from therapy are not being treated. It is estimated that approximately 40% of eligible HF patients in the U.S., and 50% in the European Union, are not being treated with beta-blockers. Further, it is believed that a substantial portion of patients being treated with beta-blockers are not receiving the target dose. Based on analysis of this market and expert opinion, ARCA believes this lack of adoption may be due in part to the fact that a significant percentage of chronic heart failure patients do not tolerate one or more of the beta-blockers currently approved for HF, or do not respond well to them.

In addition, due to the fact that patients respond unevenly to beta-blockers, it is difficult to predict what a particular patient s response is likely to be in advance of therapy. This uncertainty creates special problems in the context of HF. The current standard of practice in administering a beta-blocker for HF involves a lengthy, often months-long process, in which the patient is gradually moved from a low initial dose up to one that has been proven to be clinically beneficial. This extended protocol is necessary because the therapeutic mechanism of this drug class inhibits processes in the failing heart that, while deleterious over the long term, initially provide support for diminished cardiac function. Thus, the dosage must be increased slowly to allow the patient to adjust to the therapy, and it may be months before it is known whether the patient will both tolerate the therapy and will benefit from it.

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During this process, the patient may feel worse and exhibit no objective benefit. However, it can be difficult for the physician to determine whether this is due to the mechanism of the drug class, or whether it is a problem with the particular drug. A serious adverse event, such as hospitalization for an acute episode, or death, may be the first substantial evidence that the patient is not responding well to the particular therapy. ARCA believes that many HF patients on beta-blockers never reach their target dose, whether due to actual side effects or the perception that the patient is not benefiting. Some patients simply do not respond, after enduring this long and potentially difficult process. Unfortunately, the physician has no good method to determine, in advance of therapy, whether a patient is likely to benefit, introducing an element of trial and error into the use of these agents that is frustrating to prescribers, potentially harmful to patients and costly to payors. ARCA believes that a new HF therapy that includes a simple test to identify those patients likely to benefit, can help alleviate some of the problems encountered with the current standard of practice.

ARCA Strategy

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

Obtain FDA approval for Gencaro for the treatment of chronic heart failure and initiate U.S. commercialization. ARCA believes that Gencaro has a clinical record that supports its approvability. Gencaro s NDA was accepted for filing by the FDA in September 2008. ARCA expects a decision by the FDA on the approvability of Gencaro in the second or third quarter of 2009. If Gencaro is approved, ARCA currently intends to market it in the United States as the first pharmacogenetic cardiovascular therapy through its own sales force. ARCA plans to differentiate Gencaro based on its pharmacogenetic profile, unique mode of action, the Gencaro Test s expected ability to predict response, favorable tolerability and improved clinical endpoints. ARCA plans to support its commercialization effort with a publication strategy, appropriate contacts with key opinion leaders, a heart failure patient registry and an effective reimbursement strategy, in compliance with applicable federal requirements.

Build a specialty sales and marketing capability. In anticipation of the potential commercial launch of Gencaro in the U.S., ARCA is building a specialty sales and marketing organization, focusing on cardiologists that specialize in heart failure, and other physicians who treat heart failure or are influential in this setting. ARCA s management and employees, including its chief executive officer and its executive vice president in charge of commercialization, have extensive experience in the commercialization of cardiovascular therapies, including specialty sales and marketing organizations. ARCA also intends to use this sales and marketing organization to commercialize future product candidates in the U.S.

Expand Gencaro indications. ARCA plans to pursue clinical development of several potential additional indications for Gencaro, including the prevention of several forms of arrhythmia. ARCA believes these indications have pharmacogenetic potential, reasonable clinical development paths, will help differentiate Gencaro, and could potentially be successfully marketed by the specialty sales and marketing organization ARCA is currently building.

Develop NU172. ARCA s second investigational compound under consideration is NU172, a novel, short-acting anticoagulant that ARCA is evaluating for development as a potential new therapy in indications where heparin paired with its antidote, protamine, are the current standard of care, such as CABG surgery, kidney dialysis and a variety of vascular surgical and coronary interventions. NU172 recently completed a successful Phase Ib study.

Build a cardiovascular pipeline. ARCA s management and employees, including its chief executive officer and chief science and medical officer, have extensive experience in cardiovascular research, molecular genetics, cardiovascular clinical development, and the commercialization of cardiovascular

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therapies. ARCA intends to leverage this expertise to seek to identify, acquire, develop and commercialize other cardiovascular products or candidates, with an emphasis on pharmacogenetic applications.

Gencaro

Gencaro (bucindolol hydrochloride) is a pharmacologically unique beta-blocker and mild vasodilator which is under review by the FDA for the treatment of chronic heart failure. ARCA also plans to pursue several significant follow-on indications for Gencaro. Gencaro is considered part of the beta-blocker class because of its property of blocking both beta-1, or $ß_1$ and beta-2, or $ß_2$ receptors in the cardiac nervous system from binding with other molecules that activate these receptors. Because of its mild vasodilator effects, Gencaro is well-tolerated in patients with advanced HF. Originally developed by Bristol-Myers Squibb, or BMS, the active pharmaceutical ingredient, or API, in Gencaro, bucindolol has been tested clinically in approximately 4,500 patients. Gencaro was the subject of a Phase III heart failure mortality trial of over 2,700, mostly U.S. patients, known as the BEST trial. The BEST trial included a DNA bank of over 1,000 patients, which was used to conduct studies of the effect of genetic variation on bucindolol response.

At the time of the BEST trial, ARCA s founding scientists, Dr. Michael Bristow and Dr. Stephen Liggett, hypothesized that the unique pharmacologic properties of Gencaro would interact with common genetic variations or polymorphisms of the $ß_1$, and alpha2C, or $\propto_{2C}$, receptors, which are important receptors that regulate cardiac 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 determined that patients with certain variations, or polymorphisms, in these receptors had substantially improved outcomes on primary and certain secondary clinical endpoints in the trial, such as mortality, heart failure progression and hospitalization, relative to the general patient population of the BEST trial. ARCA believes that these polymorphisms, which are detectable using standard genetic testing technology, can serve as diagnostic markers for predicting enhanced therapeutic response to Gencaro, and avoiding adverse events, in individual patients.

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Pharmacology and Pharmacogenetics

Gencaro s pharmacology appears to be different from other compounds in the beta-blocker class in two fundamental respects. First, studies conducted by ARCA researchers indicate that in human myocardial preparations, Gencaro significantly inactivates high functioning ß$_1$ receptors through a mechanism separate from ß$_1$-blockade, in addition to inhibiting the binding activity of the ß$_1$ receptor like a typical beta-blocker. Second, these same ARCA studies indicate that Gencaro lowers the systemic levels of the neurotransmitter norepinephrine, or NE, which is released by cardiac and other sympathetic nerves. These two properties interact with common genetic variations in two cardiac receptors, the ß$_1$ and $\propto_{2C}$ receptors, to produce the unique pharmacogenetic profile of Gencaro. ARCA believes that these two properties, and their pharmacogenetic implications, are unique to Gencaro. These receptors, their genetic variants, and the biological system in which they function, are illustrated below:

Gencaro has an important interaction with the ß$_1$ receptor found on muscle cells, or cardiac myocytes, of the heart. The general role of the ß$_1$ 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 β 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 heart failure patients the ß$_1$ receptor also initiates harmful, or cardiomyopathic, signaling which, over time, exacerbates the heart s functional and structural decline. Beta-blockers counteract this destructive process by reducing βreceptor 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 the constitutively active (active in the absence of NE stimulation) state of certain ß$_1$ receptors.

There are two common genetic variations of the ß$_1$ receptor, each of which ARCA estimates is present in approximately 50% of the U.S. population. One of these variations is known as the βArg/Arg variant. Laboratory studies indicate that this variation results in a higher functioning ß$_1$ receptor, one which has a greater ability to mediate the stimulatory effects of NE. In addition, this variation is also more likely to be constitutively active and signal the cardiac myocyte to contract in the absence of NE. Heart failure patients with this genotype may have the potential for greater cardiomyopathic ß$_1$ signaling. The other variation, the βGly carrier , also present in about 50% of the U.S. population, results in a ß$_1$ receptor that is much lower functioning and, according to laboratory studies, has less probability of being in a constitutively active state compared to the ß$_1$-Arg/Arg receptor.

Gencaro has a powerful interaction with the higher-functioning ß$_1$-Arg/Arg variation of the ß$_1$ receptor. Laboratory studies show that constitutively active receptors will continue to signal in the presence of standard beta-blockade. Laboratory studies in isolated human heart preparations also show that Gencaro has the unusual

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ability of being able to stop the signaling of constitutively active receptors. ARCA believes that individuals with the $ß_1$-Arg/Arg genotype potentially will recognize an enhanced therapeutic response to Gencaro because of the greater potential for active state, cardiomyopathic signaling among individuals with this genotype, and the larger reduction in signaling that these individuals experience when taking Gencaro, relative to individuals with the $ß_1$-Gly carrier genotype.

The other receptor that appears to give Gencaro its pharmacogenetic properties is the $\propto_{2C}$ receptor. This receptor is located on the terminus of the sympathetic cardiac nerve, at its junction with the cardiac myocyte. The role of this receptor is to modulate the amount of NE that is present at this junction, which in turn affects the activation of $ß_1$ receptors and the heart s activity. There are two important genetic variations of this receptor that appear to affect the performance of Gencaro. Approximately 10-13% of the general population in the U.S. has a modified $\propto_{2C}$ receptor resulting from at least one modified gene that functions poorly. Patients with this variant, also known as the deletion variant , or $\propto_{2C}$ 322 325 DEL, are believed to have a diminished ability to regulate the amount of NE released by the cardiac nerve. The remaining 85% of the population has a normal functioning version of this receptor, referred to as the $\propto_{2C}$-wild type.

Individuals with the deletion variant of the $\propto_{2C}$ receptor tend to have abnormally high levels of NE in their cardiac nervous system. Gencaro, unlike other ß-blocking agents, exhibits the pharmacologic property of sympatholysis , or the ability to lower systemic NE levels, through effects that are mediated at least in part by blockade of $ß_2$ receptors residing on sympathetic nerve terminals. Therefore, when chronic heart failure patients with the deletion variant of the $\propto_{2C}$ receptor are treated with Gencaro, some of them may be more likely to experience an exaggerated lowering of NE resulting from Gencaro interacting with this variant, leading to a loss of efficacy. This risk may be more pronounced with late stage chronic heart failure patients, who are more dependent on high NE levels to support cardiac function. In contrast to those with the $\propto_{2C}$ deletion variant, the majority of patients with the $\propto_{2C}$-wild type variant appear to experience only a mild reduction in NE levels from Gencaro. In these patients, mild NE lowering by Gencaro appears to have a favorable therapeutic effect. In addition, patients with the $ß_1$-Arg/Arg genotype can tolerate the greater amount of NE lowering associated with $\propto_{2C}$ DEL genotypes, and in these patients any amount of sympatholysis appears to be beneficial.

The DNA substudy of patients from the BEST trial conducted by Drs. Bristow and Liggett indicated that the combinations of these polymorphisms in individual patients appear to influence the response to Gencaro with respect to significant clinical endpoints. As a result, ARCA anticipates three broad treatment groups for Gencaro:

- The very favorable group, constituting an estimated 47-50% of the U.S. population and comprised of patients with the $ß_1$-Arg/Arg genotype. ARCA believes these individuals may have an enhanced therapeutic response to Gencaro because of its effect on this higher-functioning/constitutively active $ß_1$ receptor variant, and a favorable response to NE lowering, regardless of their $\propto_{2C}$ receptor genotype and the degree of bucindolol-associated sympatholysis.

- A second favorable group, constituting an estimated 40% of the U.S. population, and comprised of individuals with the $ß_1$-Gly carrier $ß_1$ receptor and wild-type $\propto_{2c}$ receptor. ARCA believes these individuals will benefit therapeutically from Gencaro (although not as much as the very favorable group), because of Gencaro s enhanced efficacy in the wild-type $\propto_{2C}$ receptor population, combined with some (although reduced) efficacy in $ß_1$-Gly carriers.

- A third and much smaller, unfavorable group, constituting about 10-13% of the U.S. population, comprised of individuals with both $ß_1$-Gly carrier $ß_1$ receptors and the deletion variant $\propto_{2C}$ receptors. In these patients, compensatory support to the failing heart may be compromised when Gencaro is administered, likely due to the inability of the lower functioning $ß_1$-Gly carrier $ß_1$ receptor to compensate for marked NE lowering from the deletion variant $\propto_{2C}$ receptor. Clinical data suggest Gencaro should not be administered to these patients.

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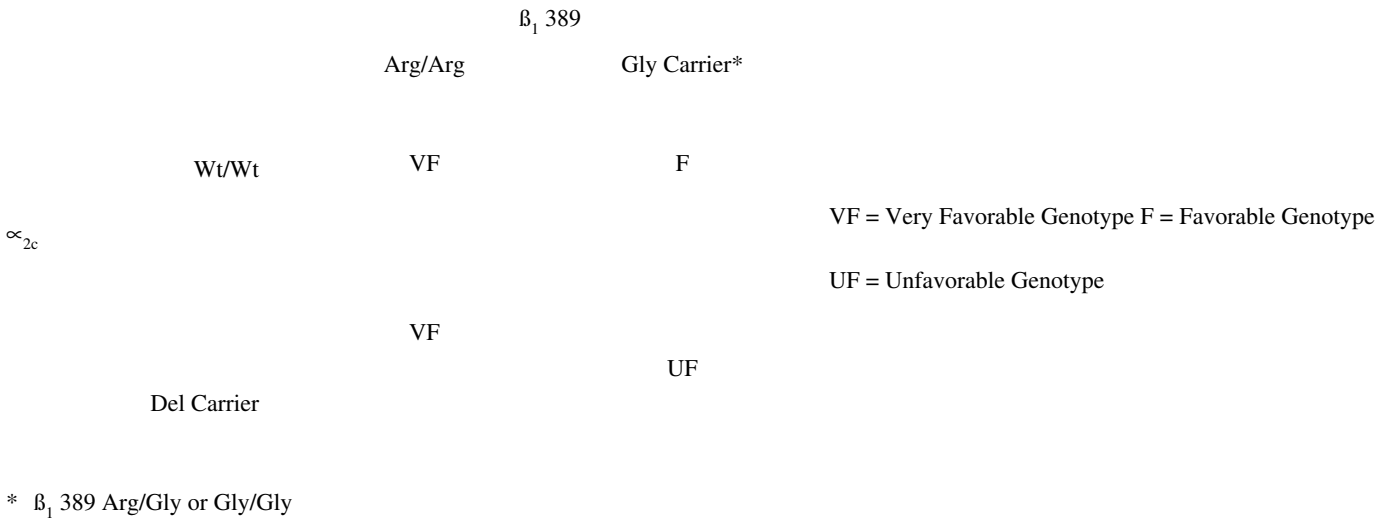
Diagram of subgroups based on ß$_1$ - and ∝$_{2c}$-AR genotype status:



* ß$_1$ 389 Arg/Gly or Gly/Gly

∝$_{2c}$ 322-325 Wt/Del or Del/Del

The BEST Trial

Bucindolol was originally developed by BMS for hypertension, and was licensed in the early 1990 s to Intercardia, a biopharmaceutical company. Around the time of completion of the Phase II clinical trials with bucindolol, a group of leading heart failure researchers proposed to the U.S. Department of Veteran Affairs Cooperative Clinical Studies Program that a large mortality study of beta-blockers be conducted in chronic heart failure. This grant application was approved, and shortly thereafter the U.S. National Heart, Lung and Blood Institute agreed to join in the sponsorship of the trial, known as the Beta-Blocker Evaluation of Survival Trial, or BEST. The Steering Committee of the BEST trial selected bucindolol as the agent to be tested against placebo, and Intercardia joined the trial as a sponsor.

The BEST trial was a double-blind, placebo-controlled, multi-center study of bucindolol on mortality and morbidity in an advanced chronic heart failure population. Most of the patients were from the United States. The basis for the selection of bucindolol as the tested ß-blocker included its Phase II clinical results and its high tolerability in more advanced HF patients. The trial was planned to run four and one-half years, and enroll 2,800 patients. 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.

The BEST trial began in 1995 and enrolled a total of 2,708 chronic heart failure patients. The patients were the most advanced clinical heart failure population ever studied in a large mortality trial, based on baseline systolic blood pressure and other criteria, and clinical stability was not an entry criterion for the trial. The primary endpoint of the BEST trial was total mortality and the pre-specified main secondary endpoint was progression of heart failure, defined as heart failure death, cardiac transplant, heart failure hospitalization, or emergency room visit for the treatment of worsening heart failure not requiring hospitalization. Other pre-specified secondary endpoints included death from cardiovascular causes, a composite of death or heart transplantation, heart failure hospitalization, improvement in left ventricular ejection fraction, incidence of myocardial infarction, quality of life, and any change in the need for concomitant heart failure therapy, including administration of intravenous inotropic agents, intravenous diuretics, or increase in doses of orally-administered diuretics.

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 HF patient. Positive mortality results from two other heart failure 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

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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. At the time the BEST study was terminated, approximately 70% of the trial information was available, with 2,708 of a projected 2,800 patients enrolled and 797 out of 916 deaths reported. A companion trial to the BEST trial, known as the BEAT trial, studying European patients with left ventricular dysfunction and a history of heart attack, was terminated when BEST was terminated, with approximately 10% of trial information available (including 343 of 2,000 patients enrolled and 53 out of 630 deaths reported).

Following termination, the preliminary results of both studies 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 total mortality. The published values were a 10% risk reduction in mortality with a p-value of 0.10.

Clinical Results and the DNA Substudy

In 2003 and 2004, the results of the DNA substudy conducted by Drs. Bristow and Liggett began to be released and analyzed. The DNA substudy results indicated a significant enhancement of response on the major clinical endpoints from the BEST trial in patients with the very favorable genotype. The risk reduction on clinical efficacy endpoints such as mortality and hospitalization ranged from approximately 35% to approximately 48% in this genotype. In addition, in arrhythmia endpoints of atrial fibrillation or ventricular fibrillation tracked by safety analyses, the risk reduction by bucindolol in the very favorable genotype appeared to be even greater, by 62-70%. Also, beginning in 2005, ARCA began to more fully analyze the overall BEST results in accordance with FDA-approved, pre-specified statistical plans, which had not been done by the sponsors when the BEST trial was terminated. For example, as re-analyzed by ARCA in accordance with the statistical plan, there appeared to be a 13% risk reduction on the primary endpoint in the BEST trial of mortality for the entire patient population taking bucindolol, with a p-value of 0.053. In addition, the pre-specified main secondary endpoint, reduction in the progression of heart failure, had not been analyzed when the BEST trial ended. As analyzed by ARCA, the results of the BEST trial indicated a 20% risk reduction on this secondary endpoint for the entire patient population taking bucindolol, that was highly statistically significant (p = 0.00003). The endpoint of heart failure progression, in similar forms, was the original basis of approval for the two beta-blockers currently approved in the U.S. for HF.

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

BEST Clinical Responses[1] by Genotype Groups

Endpoint	**Very Favorable patients**	Favorable patients	Unfavorable patients
(% of study population)	**(47%)**	(40%)	(13%)
All Cause Mortality (ACM), TTE	**i38%***	i25%	h4%
Cardiovascular Mortality (CVM), TTE	**i48%***	i40%*	h11%
ACM + transplantation	**i43%***	i24%	h4%
Heart failure (HF) Morbidity & Mortality, CRF, TTE	**i34%****	i20%	i1%
HF M&M, TTE (Adj.)	**i42%****	i27%	i16%
HF Hosp days/patient	**i48%****	i17%	h19%
AF prevention (from AE db)	**i62%***	i11%	i4%
VT/VF prevention (from AE db)	**i70%****	i44%	i9%

1 Covariate adjusted, transplant censored analysis

* p<0.05; **p≤0.007; TTE: Time To Event; CRF: Case Report Form; Adj.: Adjudicated

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While the results of the DNA substudy of the BEST trial indicate that Gencaro s efficacy varies by genotype with the most robust clinical effects found in patients with the very favorable genotype, they also indicate that patients with the favorable genotype may also benefit from the drug. The results of the DNA substudy indicate that patients in the unfavorable genotype group are not recommended for Gencaro. ARCA estimates that approximately 10-13% of the U.S. HF patient population falls into the unfavorable genotype group. In addition to these results, there was a 45-47% reduction in myocardial infarction in all patients in the BEST trial taking bucindolol. This result, which is unique to Gencaro, was supported by the limited results of the companion BEAT trial in Europe, in which Gencaro, with only approximately 10% of the trial information available, demonstrated a statistically significant improvement in combined myocardial infarction endpoints versus placebo, in patients with left ventricular dysfunction and a history of myocardial infarction.

Regulatory Strategy

In 2005, ARCA approached the FDA to discuss the results of the DNA substudy and ARCA s revised analysis of data from the BEST trial, as well as the prospect of an NDA for Gencaro for the treatment of HF. Through a number of meetings over the next several years, ARCA received guidance from the FDA on the potential NDA and the coordination of the NDA with a potential application for approval of the Gencaro Test.

The regulatory strategy for Gencaro and the Gencaro Test has been guided by this interaction with the FDA. In the NDA submitted for Gencaro, it is ARCA s position that Gencaro is approvable based on the full clinical program associated with its development, including data from the total patient cohort population in the BEST trial. The Gencaro clinical development program encompassed numerous clinical studies, including four randomized and placebo controlled studies in patients with HF or myocardial infarction, of which two, the BEST and BEAT trials, evaluated rigorous clinical endpoints, including mortality, hospitalization and myocardial infarction. The remaining clinical studies include the Phase II study conducted by BMS for the treatment of hypertension, several safety studies in other patient populations and a Phase I program in healthy subjects. The NDA presents the pharmacogenetic data from the DNA substudy conducted by Drs. Bristow and Liggett as important to the prescribing information in the proposed label for Gencaro, but not as the basis for its approval.

ARCA believes that the clinical trial results for Gencaro, including the results of the BEST trial and DNA substudy, demonstrate the efficacy and safety of Gencaro for treatment of patients with HF, both for decreasing the risk of mortality and cardiovascular or heart failure hospitalization, and also for reducing the risk of ischemic events and myocardial infarction. The primary endpoint of mortality (when analyzed in accordance with the pre-specified plan) was reduced in all BEST trial patients on bucindolol by 13%, with a p-value of 0.053. While the FDA typically views significance as a p-value of less than 0.05, the Gencaro p-value is within the range found sufficient for approval based on certain FDA precedent. This primary endpoint result is enhanced by the response of the BEST trial patient population with respect to eight secondary endpoints, all of which were positive and statistically significant. As pre-specified with FDA, heart failure progression was the most important secondary endpoint, and was positive and statistically significant; a heart failure progression endpoint was FDA s basis of approval for the two beta-blockers approved for HF. ARCA also believes that other statistical analyses and the attributes of the BEST trial itself add to its credibility.

ARCA believes Gencaro s status as a beta-blocker adds further support to its clinical record, as this class has a well-established record of safety and efficacy. The results of the BEST trial are supported by qualitatively consistent results from almost every trial in the beta-blocker class for the treatment of HF. ARCA believes the use of class effects to support marketing approval of Gencaro by the FDA is consistent with prior precedent, especially within the precedent of approvals in cardiovascular and heart-specific therapies.

ARCA believes that the pharmacogenetic data generated from the DNA substudy conducted by Drs. Bristow and Liggett create a separate public health rationale for approval of Gencaro. These DNA substudy results are not the primary basis for approval as set forth in the Gencaro NDA, but ARCA believes they will represent an important part of the prescribing information in the label being sought for Gencaro. ARCA believes the genetic

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results will provide physicians with a tool to help predict individual patient response prior to therapy. This unique attribute of Gencaro represents a new approach in treating HF, one that ARCA believes has the potential to improve the standard of care.

Licensing and Partnership Obligations

ARCA has 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; ARCA has 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. Under this license agreement, ARCA is obligated under the CPEC license to make an $8.0 million milestone payment within 180 days after receiving approval from the FDA. ARCA also has the obligation under the CPEC license to make milestone payments of up to $13.0 million in the aggregate upon regulatory marketing approval in the U.S., Europe and Japan. Under the CPEC and BMS licenses, ARCA is obligated to pay royalties based on a percentage of annual sales of Gencaro in any jurisdiction worldwide, which in the aggregate are likely to average from the mid- to high-teens depending on actual annual sales. ARCA has an option to reduce these royalty rates by making a lump-sum payment.

ARCA has also licensed worldwide rights to intellectual property covering the pharmacogenetic response of bucindolol hydrochloride based on the cardiac receptor polymorphisms, which is owned by the University of Colorado. ARCA has no material future financial obligations under this license. ARCA has also licensed the nonexclusive rights to develop and commercialize diagnostics for these receptor polymorphisms, for the purpose of prescribing Gencaro, from the licensee of these rights, CardioDx, Inc. ARCA has certain milestone and royalty obligations under this license agreement, which have been assumed by LabCorp under the parties collaboration agreement.

The Gencaro Test

If cleared or approved, ARCA believes that Gencaro will be the first cardiovascular drug to be integrated with a companion diagnostic to predict enhanced efficacy. The drug label being sought for Gencaro would identify the patient receptor genotypes that can expect enhanced efficacy, as well as those with a likelihood of a standard beta-blocker response and the small unfavorable subgroup with a low probability of benefit. The label being sought would recommend receptor genotype testing prior to initiation of therapy. Accordingly, ARCA believes it is critical to the successful commercialization of Gencaro to develop a companion genetic test that is simple to administer and widely available.

ARCA has collaborated with LabCorp to develop and commercialize the Gencaro Test. Under the terms of the collaboration, which has a 10-year term, ARCA has licensed to LabCorp the rights to commercialize a receptor genotype diagnostic for the $ß_1$ and $\propto_{2c}$ polymorphisms. In return, LabCorp has agreed to develop the Gencaro Test, obtain FDA clearance or approval of the Gencaro Test, and commercially launch the Gencaro Test in parallel with the commercial launch of Gencaro and in coordination with ARCA s commercial plan. LabCorp has assumed all financial obligations of ARCA s license for the diagnostic technology, and retains all the economic benefits.

LabCorp has developed the commercial method for the Gencaro Test, which will use either a blood draw or a cheek swab to obtain a sample. ARCA believes that the Gencaro Test involves a straightforward genetic test that relies on well-validated technology. Based on FDA guidance, LabCorp has submitted a PMA regulatory submission, which was formally accepted by the FDA in January 2009, with the expectation of a decision on approval in the second or third quarter of 2009. LabCorp and ARCA believe that no further clinical trials will be required for the Gencaro Test submission, though there is no guarantee that FDA will not require additional clinical data. The clinical basis for the Gencaro Test will be the clinical studies discussed in ARCA s NDA for Gencaro, which the LabCorp submission cross-references.

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ARCA and LabCorp are developing a joint commercialization and marketing plan, which addresses commercial performance metrics such as turnaround time and distribution, the coordination of the drug and diagnostic sales and marketing programs, and strategies for third-party reimbursement.

Marketing and Sales

ARCA s strategy is to market Gencaro as the first pharmacogenetically targeted cardiovascular therapy for HF patients. For the U.S. market, ARCA currently plans to build its own specialized sales force, which it expects to be experienced in heart failure and cardiovascular drug sales. Cardiologists specializing in heart failure and selected other physicians will be the focus of ARCA s specialty sales force. ARCA believes a relatively small number of cardiologists and other heart failure specialists treat a significant percentage of HF patients, and, ARCA believes, also have a disproportionate influence on the prescribing practices of other health care providers that treat HF. Accordingly, ARCA believes that the HF market may be successfully targeted by a specialized sales strategy. Commercialization of Gencaro in the U.S. will require substantial additional capital resources. If sufficient capital is not available on acceptable terms, we may consider alternative commercialization strategies.

Additional elements of ARCA s U.S. marketing and sales strategy include:

Publication plan. ARCA has developed a plan that it believes is consistent with applicable federal laws and regulations.

National and regional key opinion leader development. ARCA plans to develop appropriate contacts with key decision makers in the heart failure market.

Registry. ARCA intends to develop an observational database integrating genetic and HF data.

Reimbursement. ARCA plans to implement a comprehensive reimbursement plan for Gencaro and the Gencaro Test in connection with the commercial launch of both products and in compliance with applicable federal requirements.

ARCA holds world-wide rights to Gencaro and has filed its patent applications covering Gencaro in the major international pharmaceutical markets. ARCA plans to accelerate its international commercialization strategy for Gencaro in 2009, by obtaining guidance from foreign regulatory agencies and engaging in discussions with potential international partners.

Competition

If approved, Gencaro will compete against existing beta-blockers approved for HF and their generic equivalents. Currently, there are two beta-blockers (three branded formulations) approved for the treatment of HF in the U.S.:

TOPROL-XL®;

Coreg® and Coreg CR® (a sustained release formulation)

TOPROL-XL and immediate release Coreg have generic equivalents commercially available in the U.S. (Metoprolol Succinate and Carvedilol respectively). It is anticipated that both of these generic equivalents will be priced at less than the price of Gencaro. During the 12-month period ended January 31, 2009, total sales of beta-blockers approved for use in HF were approximately $4.6 billion in the U.S., with generic formulations accounting for a substantial majority of the market. ARCA estimates up to 50% of these revenues could be attributable to patients with heart failure. While reports vary on the proportion of the beta-blocker market represented by heart failure, ARCA believes HF contributes to a significant portion of the U.S. market.

The companies that sell the existing therapies are much larger than ARCA and have much greater resources. In addition, ARCA s proposed prescribing information for Gencaro includes a recommendation for genetic

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testing, which will add additional cost and procedures to the process of prescribing Gencaro, and which could make it more difficult for ARCA to compete against existing therapies.

Additionally, Gencaro may also compete against existing therapies whose follow-on indications may include treatment for HF. For example, Forest Laboratories may apply for approval to use Bystolic, a drug currently used to treat high blood pressure, for treatment of heart failure. If approved for treatment of heart failure, Gencaro may not be successful in competing against Bystolic, an already well-known name brand.

Other Potential Indications for Gencaro

ARCA is exploring the potential of Gencaro for the prevention of atrial fibrillation, and/or ventricular tachycardia/ventricular fibrillation. ARCA believes these could be attractive follow-on indications. ARCA believes that data from the BEST trial suggests that Gencaro has potential for these indications, and that the clinical response is also pharmacogenetic, based on the same genetic markers that stratify response on HF endpoints.

Development Pipeline

ARCA intends to leverage its management s experience in cardiovascular research, genetics, clinical development, and commercialization to acquire and develop other cardiovascular products or candidates, with an emphasis on pharmacogenetic applications. ARCA is evaluating further clinical development of NU172, a novel, short-acting anticoagulant, as a potential new therapy in indications where heparin paired with its antidote, protamine, are the current standard of care, such as CABG surgery, kidney dialysis and a variety of vascular surgical and coronary interventions.

NU172 is an aptamer, a single-stranded nucleic acid that forms a well-defined, three-dimensional shape conceptually similar to an antibody. NU172 was designed to directly inhibit thrombin s ability to stimulate blood clot formation in the setting of medical or surgical procedures where human blood is exposed to foreign materials. ARCA believes that NU172 has potential as a therapy for use in CABG surgeries, kidney dialysis, and other vascular and coronary interventions. Approximately 450,000 CABG procedures and 50 million dialysis procedures are performed annually in the U.S. In these procedures, heparin is often paired with its antidote protamine as the anticoagulation effect of heparin needs to be reversed once the procedure has been completed. Data from the Phase I trial and preclinical studies suggest that NU172 has the potential to produce rapid and predictable onset and offset of anticoagulation, work in stagnant blood, avoid thrombocytopenia, and has the potential for non-renal clearance. These studies also suggest that NU172 may have a short half-life in patients, giving it the potential to be rapidly reversed without the need for an antidote.

The development of NU172 is subject to a collaboration agreement with Archemix Corporation, under which ARCA is responsible for development and worldwide commercialization of NU172 and other potential product candidates that may be developed under this collaboration. In February 2008, Nuvelo paid Archemix a $1.0 million milestone fee in connection with the dosing of the first patient in the Phase I trial for NU172. If ARCA enrolls the first patient in a Phase II trial of NU172, ARCA will be obligated to pay Archemix a $3.0 million milestone fee.

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. ARCA outsources all manufacturing and analytical testing of the API of Gencaro and the drug product. Third party contract manufacturing organizations have been selected by ARCA on the basis of their technical and regulatory expertise. ARCA s approach with its contract manufacturing partners has been to replicate the manufacturing processes that were used to support the pivotal clinical trials with Gencaro, and to minimize any changes from these baseline processes, thereby reducing technical and regulatory risk.