

ARCA biopharma, Inc.
Form 424B5
January 25, 2019
Table of Contents

**As Filed Pursuant to Rule 424(b)(5)
Registration No. 333-217459**

PROSPECTUS SUPPLEMENT

(To Prospectus Dated May 10, 2017)

\$2,499,876

Common Stock

On January 25, 2019, we entered into an amendment, or the Amendment No. 2, to our Capital on Demand Sales Agreement, dated as of January 11, 2017 as amended on August 21, 2017, or the Original Agreement and, together with the Amendment No. 2, the Sales Agreement, with JonesTrading Institutional Services LLC, or JonesTrading. Under the Amendment No. 2, we increased the maximum aggregate offering price of the shares of our common stock, \$0.001 par value per share, that we may issue and sell from time to time under the Sales Agreement, as amended, from \$10,242,863 to \$12,742,739. This prospectus supplement only relates to such additional shares of common stock.

As of January 25, 2019, we have sold an aggregate of \$10,083,445 of our common stock under the Sales Agreement pursuant to our registration statement on Form S-3 filed with the Securities and Exchange Commission, or the SEC, on April 4, 2014 (File No. 333-195054) and our registration statement on Form S-3 filed with the SEC on May 10, 2017 (File No. 333-217459). As a result of the limitations discussed below and the current public float of our common stock, and in accordance with the terms of the Sales Agreement, we may offer and sell shares of our common stock having an aggregate offering price of up to \$2,499,876 under this prospectus supplement and accompanying prospectus from time to time through JonesTrading.

We are subject to General Instruction I.B.6 of Form S-3, which limits the amounts that we may sell under the registration statement of which this prospectus supplement and the accompanying prospectus forms a part. Pursuant to General Instruction I.B.6 of Form S-3, in no event will we sell securities registered on the registration statement of which this prospectus supplement and accompanying prospectus is a part in a public primary offering with a value exceeding more than one-third of our public float in any 12-month period if our public float, measured in accordance with such instruction, remains below \$75.0 million. As of January 24, 2019, the aggregate market value of our common stock held by non-affiliates, or the public float, was \$7,499,629, which was calculated based on 13,760,788 shares of our outstanding common stock held by non-affiliates as of the date of January 24, 2019 at a price of \$0.545 per share, which was the closing price of our common stock on the NASDAQ Capital Market, or the Exchange, on November 28, 2018. As of the date hereof, we have sold no shares of our common stock pursuant to General Instruction I.B.6 of Form S-3 during the 12 calendar months prior to and including the date of this prospectus supplement.

Our common stock is listed on the Exchange under the symbol ABIO. On January 24, 2019, the last reported sale price of our common stock was \$0.425 per share.

Sales of our common stock, if any, under this prospectus supplement and accompanying prospectus may be made in sales deemed to be at the market offerings as defined in Rule 415 promulgated under the Securities Act of 1933, as amended, or the Securities Act. JonesTrading is not required to sell any specific number or dollar amount of securities, but will act as a sales agent using commercially reasonable efforts consistent with its normal trading and sales practices, on mutually agreed terms between JonesTrading and us. There is no arrangement for funds to be received in any escrow, trust or similar arrangement.

The compensation to JonesTrading for sales of common stock sold pursuant to the Sales Agreement will be an amount equal to 3.0% of the gross proceeds of any shares of common stock sold under the Sales Agreement. In connection with the sale of the common stock on our behalf, JonesTrading will be deemed to be an underwriter within the meaning of the Securities Act and the compensation of JonesTrading will be deemed to be underwriting commissions or discounts. We have also agreed to provide indemnification and contribution to JonesTrading with respect to certain liabilities, including liabilities under the Securities Act or the Exchange Act of 1934, as amended, or the Exchange Act.

Investing in our securities involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading Risk Factors on page S-6 of this prospectus supplement and under similar headings in the accompanying prospectus and other documents that are incorporated by reference into this prospectus supplement and accompanying prospectus.

NEITHER THE SECURITIES AND EXCHANGE COMMISSION NOR ANY STATE SECURITIES COMMISSION HAS APPROVED OR DISAPPROVED OF THESE SECURITIES OR DETERMINED IF THIS PROSPECTUS SUPPLEMENT OR THE ACCOMPANYING PROSPECTUS ARE TRUTHFUL OR COMPLETE. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

JonesTrading

The date of this prospectus supplement is January 25, 2019.

Table of Contents

TABLE OF CONTENTS

PROSPECTUS SUPPLEMENT	
<u>ABOUT THIS PROSPECTUS SUPPLEMENT</u>	S-1
<u>PROSPECTUS SUPPLEMENT SUMMARY</u>	S-2
<u>THE OFFERING</u>	S-5
<u>RISK FACTORS</u>	S-6
<u>FORWARD-LOOKING STATEMENTS</u>	S-9
<u>USE OF PROCEEDS</u>	S-11
<u>DILUTION</u>	S-12
<u>PLAN OF DISTRIBUTION</u>	S-13
<u>LEGAL MATTERS</u>	S-15
<u>EXPERTS</u>	S-15
<u>WHERE YOU CAN FIND MORE INFORMATION</u>	S-15
<u>INCORPORATION OF CERTAIN INFORMATION BY REFERENCE</u>	S-16
PROSPECTUS	
<u>ABOUT THIS PROSPECTUS</u>	1
<u>PROSPECTUS SUMMARY</u>	2
<u>RISK FACTORS</u>	8
<u>FORWARD-LOOKING STATEMENTS</u>	8
<u>USE OF PROCEEDS</u>	10
<u>DESCRIPTION OF SECURITIES TO BE REGISTERED</u>	11
<u>DESCRIPTION OF CAPITAL STOCK</u>	11
<u>DESCRIPTION OF DEBT SECURITIES</u>	17
<u>DESCRIPTION OF WARRANTS</u>	24
<u>LEGAL OWNERSHIP OF SECURITIES</u>	26
<u>PLAN OF DISTRIBUTION</u>	30
<u>LEGAL MATTERS</u>	32
<u>EXPERTS</u>	32
<u>WHERE YOU CAN FIND MORE INFORMATION</u>	32
<u>INCORPORATION OF CERTAIN INFORMATION BY REFERENCE</u>	33

Table of Contents

ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in the accompanying prospectus the statement in the document having the later date modifies or supersedes the earlier statement.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreement, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

We have not, and JonesTrading has not, authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus supplement, in the accompanying prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We and JonesTrading take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you.

This prospectus supplement and accompanying prospectus do not constitute an offer to sell, or a solicitation of an offer to purchase, the securities offered by this prospectus supplement and the accompanying prospectus in any jurisdiction to or from any person to whom or from whom it is unlawful to make such offer or solicitation of an offer in such jurisdiction. You should assume that the information appearing in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and in any free writing prospectus that we have authorized for use in connection with this offering is accurate only as of the date of those respective documents. It is important for you to read and consider all information contained in this prospectus supplement and in the accompanying prospectus, including the documents incorporated by reference herein and therein, in making your investment decision. You should also read and consider the information in the documents to which we have referred you in the sections entitled *Where You Can Find More Information* and *Incorporation of Certain Information by Reference* in this prospectus supplement and in the accompanying prospectus.

Other than in the United States, no action has been taken by us or JonesTrading that would permit a public offering of the securities offered by this prospectus supplement and accompanying prospectus in any jurisdiction where action for that purpose is required. The securities offered by this prospectus supplement and accompanying prospectus may not be offered or sold, directly or indirectly, nor may this prospectus supplement, accompanying prospectus or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus supplement and accompanying prospectus comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus supplement and accompanying prospectus. This prospectus supplement and accompanying prospectus do not constitute an offer to sell or a solicitation of an offer to buy any securities offered by

this prospectus supplement and accompanying prospectus in any jurisdiction in which such an offer or a solicitation is unlawful.

S-1

Table of Contents**PROSPECTUS SUPPLEMENT SUMMARY**

*This summary highlights certain information about us, this offering and selected information contained elsewhere in or incorporated by reference into this prospectus supplement and accompanying prospectus. This summary is not complete and does not contain all of the information that you should consider before deciding whether to invest in our common stock. For a more complete understanding of our company and this offering, we encourage you to read and consider carefully the more detailed information in this prospectus supplement and accompanying prospectus, including the information incorporated by reference in this prospectus supplement and accompanying prospectus, and the information included in any prospectus supplement or free writing prospectus that we have authorized for use in connection with this offering, including the information under the heading *Risk Factors* in this prospectus supplement on page S-6 and in the documents incorporated by reference into this prospectus supplement and accompanying prospectus.*

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

Company Overview

We are a biopharmaceutical company applying a precision medicine approach to developing genetically-targeted therapies for cardiovascular diseases. Precision medicine refers to the tailoring of medical treatment to the individual characteristics of each patient through the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment. Our lead product candidate, Gencaro (bucindolol hydrochloride), is an investigational, pharmacologically unique beta-blocker and mild vasodilator that we are developing to treat atrial fibrillation, or AF, in certain patients who also have heart failure, or HF.

Gencaro has a mechanism of action that we believe is unique in the beta-blocker drug class and is modulated by a specific genotype. We estimate this genotype is present in about 50% of the North American and European general populations. We believe that Gencaro's potential efficacy is enhanced in treating patients who have this genotype and, if Gencaro is approved by the U.S. Food and Drug Administration, or the FDA, Gencaro could potentially be a safe and effective therapy for treating AF in patients who have HF. We also believe that Gencaro will have market exclusivity based on patents and new chemical entity status, if approved in the United States, Europe or other markets.

In February 2018, we reported the results of our Phase 2B clinical trial, known as GENETIC-AF, in which we evaluated Gencaro for the prevention of AF recurrence in patients with HF and a left ventricular ejection fraction, or LVEF, < 0.50. This population included 267 patients that had HF with reduced LVEF < 0.40, or HF_{rEF}, or HF with mid-range LVEF ³ 0.40 and < 0.50, or HF_{mrEF}. GENETIC-AF compared Gencaro to TOPROL-XL (metoprolol succinate), a drug approved for treating HF_{rEF} that is also prescribed, but not approved, for treating AF in patients with HF_{rEF}. There are no approved or guideline recommended drug therapies for HF_{mrEF} patients, which constituted approximately one-half of the GENETIC-AF population.

GENETIC-AF showed a similar treatment effect for the two drugs in the overall population for prevention of AF recurrence. However, additional analyses prespecified in the statistical analysis plan showed statistically significant treatment effects in favor of Gencaro in the majority of the Phase 2B population (N=196; HR=0.54; p = 0.011). Gencaro also showed statistically significant treatment effects compared to TOPROL-XL for the prevention of AF recurrence in a subset of these patients with HF_{mrEF} (N=91; HR=0.42; p = 0.017). We plan to conduct a pivotal Phase 3 trial, known as PRECISION-AF, evaluating Gencaro in HF_{mrEF} patients because of Gencaro's potential treatment effect in these patients, the unmet medical need, and the near-term path to potential regulatory approval in this indication.

We are seeking a Special Protocol Assessment, or SPA, agreement with the FDA. The FDA's SPA process is designed to facilitate the FDA's review and approval of drugs by allowing FDA to evaluate the proposed design and size of certain clinical trials that are intended to form the primary basis for determining a drug product's efficacy and safety. Upon specific request by a clinical trial sponsor, FDA will evaluate the protocol and respond to a sponsor's questions regarding, among other things, primary efficacy endpoints, trial conduct and data analysis, within 45 days of receipt of the request. FDA ultimately assesses whether the protocol design and planned analysis of the trial are acceptable to support regulatory approval of the product candidate for the indication studied. An SPA agreement can potentially reduce the regulatory risk of bringing a drug to market.

In July 2018, we received guidance from the FDA, following an End-of-Phase 2 meeting regarding the Phase 3 program for Gencaro. Based on review of the Phase 2B GENETIC-AF trial results, as well as its alignment with previous Phase 3

Table of Contents

pharmacogenetic substudy data from the BEST trial, a previous Phase 3 study of HF patients, the FDA stated that data from a single pivotal Phase 3 clinical trial may be sufficient to support approval of Gencaro for the treatment of AF in patients with HF and the beta-1 389 arginine homozygous genotype. In consultation with the FDA, we developed key elements for a Phase 3 clinical trial needed to support a potential New Drug Application, or NDA, details of which were submitted to the FDA for evaluation and confirmation via the FDA's SPA process.

In late October 2018, we received a No Agreement letter from the FDA on our SPA request. After further correspondence and following provision of information regarding the SPA, we met with the FDA in December 2018 and the FDA agreed to reconsider our SPA request. In December 2018, we submitted an amendment to the original SPA request that addressed the feedback and guidance from the FDA on the target population for our planned Phase 3 clinical trial. In January 2019, we received a No Agreement letter in response to the SPA amendment. In January 2019, addressing the FDA's new guidance, we refined the design and statistical power for our planned Phase 3 clinical trial and resubmitted our SPA request to the FDA.

Our SPA request, as resubmitted, details a single adequate and well-controlled Phase 3 clinical trial (PRECISION-AF) designed as a double-blind, active-controlled, multicenter, international, study comparing Gencaro with TOPROL-XL (metoprolol succinate) for the prevention of recurrent AF or all-cause mortality, or ACM, in HFmrEF patients. Eligible patients will have HFmrEF, a recent AF event and the genotype which responds most favorably to Gencaro. The primary endpoint of the submitted trial will be time to first event of atrial fibrillation/atrial flutter or ACM during a 26-week follow-up period. Subject to the FDA's approval of our SPA request and securing significant additional financing, we anticipate initiating PRECISION-AF in the fourth quarter of 2019. We expect to receive the FDA's response to our SPA request in February 2019.

On April 11, 2018, we received notification from the Exchange of potential delisting of our shares from the Nasdaq Capital Market because the closing bid price of our common stock had not met the minimum closing bid price of \$1.00 per share during the preceding 30 days. On October 9, 2018, we received a written notification from the Exchange granting an additional 180 calendar day period, until April 8, 2019, to regain compliance with the minimum bid price requirement. The minimum bid price requirement will be met if our common stock has a closing bid of at least \$1.00 per share for a minimum of 10 consecutive business days during the 180 day period. This second 180 day period relates exclusively to the bid price deficiency and we could be delisted during the 180 day period for failure to maintain compliance with any other listing requirements that occurs during the 180 day period.

On October 18, 2018, we held a special meeting of its stockholders, at which our stockholders approved a series of certificates of amendment to our restated certificate of incorporation, as amended, to effect a reverse split of our outstanding common stock, at a ratio of between 1-for-3 and 1-for-20, inclusive, and to authorize our board of directors to, for a period of up to one-year, to select and file such a certificate of amendment to effect such a reverse split of our outstanding common stock, if, in the judgment of our board of directors, it is deemed necessary. Our board of directors has not selected a ratio for the reverse split.

Risks Associated with our Business

Our business is subject to numerous risks and uncertainties, including those highlighted in the section titled "Risk Factors" immediately following this prospectus supplement summary and those described under similar headings in the documents incorporated by reference into this prospectus supplement and accompanying prospectus. These risks include:

We requested an SPA from the FDA relating to our planned Phase 3 program for Gencaro, and we cannot guarantee that the FDA will issue an agreement on the SPA request. Even if we do obtain the FDA's agreement, an SPA would not guarantee approval of Gencaro or any other particular outcome from regulatory review.

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.

If we are not able to regain compliance with the closing bid requirement in such period, we may be subject to delisting from the Nasdaq Capital Market. If delisted it could substantially impact our access to the capital markets, and any limitation on market liquidity or reduction in the price of the common stock as a result of that delisting could adversely affect our ability to raise capital on acceptable terms, or at all.

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

Table of Contents

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

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 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.

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.

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

Corporate Information

On January 27, 2009, we completed a business combination, or the Merger, with Nuvelo, Inc. Immediately following the Merger, we changed our name from Nuvelo, Inc. to ARCA biopharma, Inc. Our principal offices are located in Westminster, Colorado, and our telephone number is (720) 940-2200. Our website address is www.arcabio.com. We do not incorporate the information on our website into this prospectus supplement or accompanying prospectus, and you should not consider it part of this prospectus supplement or accompanying prospectus. For further information regarding us and our financial information, you should refer to our recent filings with the SEC. See [Where You Can Find More Information](#) and [Incorporation of Certain Information by Reference](#).

Each of ARCA, ARCA biopharma, Gencaro and Gencaro Test is a registered trademark of ARCA biopharma, Inc. Each of the other trademarks, trade names or service marks appearing in this prospectus supplement and accompanying prospectus belongs to its respective holder.

Table of Contents

THE OFFERING

Common Stock Offered By Us	Shares of our common stock having an aggregate offering price of up to \$2,499,876.
Common Stock to be Outstanding After this Offering	19,805,886 shares, based on an assumed offering price of \$0.425 per share, the last reported sale price of our common stock on the Exchange on January 24, 2019.
Manner of Offering	At the market offering that may be made from time to time through or to our sales agent, JonesTrading, as sales agent or principal. See Plan of Distribution on page S-13 of this prospectus supplement.
Use of Proceeds	We currently intend to use the net proceeds from the sale of the securities under this prospectus supplement and accompanying prospectus for general corporate purposes, including clinical trials, research and development expenses and general and administrative expenses. See Use of Proceeds on page S-11 of this prospectus supplement.
Risk Factors	Investing in our common stock involves significant risks. See Risk Factors on page S-6 of this prospectus supplement and under similar headings in the accompanying prospectus and the other documents incorporated by reference into this prospectus supplement and accompanying prospectus.

NASDAQ Capital Market Symbol ABIO

The above discussion and table are based on 13,923,825 shares of our common stock outstanding as of September 30, 2018 and excludes:

604,265 shares of our common stock issuable upon the exercise of stock options outstanding as of September 30, 2018, at a weighted average exercise price of \$5.47 per share;

2,669,855 shares of our common stock issuable upon exercise of warrants outstanding as of September 30, 2018, at a weighted average exercise price of \$7.07 per share;

233 shares of our common stock issuable upon the settlement of restricted stock units outstanding as of September 30, 2018; and

615,976 shares of our common stock reserved for issuance under our equity incentive, non-employee director stock award and employee stock purchase plans as of September 30, 2018.

S-5

Table of Contents

RISK FACTORS

*Investing in our common stock involves significant risks, some of which are described below. You should carefully consider these risks, as well as the other information in this prospectus supplement, accompanying prospectus and any free writing prospectus authorized in connection with this offering, including documents incorporated by reference, such as our most recent annual report on Form 10-K and quarterly reports on Form 10-Q filed with the SEC, and in other documents that we have filed or subsequently file with the SEC that are incorporated by reference, before deciding whether to invest in our common stock. Each of the risk factors could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our securities, and the occurrence of any of these risks might cause you to lose all or part of your investment. Additional risks not presently known to us or that we currently believe are immaterial may also significantly impair our business operations. Please also read carefully the section below titled *Forward-Looking Statements*.*

Additional Risks Related to this Offering

If you purchase our common stock in this offering, you may incur immediate dilution in the book value of your investment.

The offering price per share in this offering may exceed the net tangible book value per share of our common stock outstanding prior to this offering. Assuming that an aggregate of 5,882,061 shares of our common stock are sold at a price of \$0.425 per share, the last reported sale price of our common stock on the Exchange on January 24, 2019, for aggregate gross proceeds of \$2,499,876, and after deducting commissions and estimated offering expenses payable by us, you would experience immediate dilution of \$(0.07) per share, representing the difference between our as adjusted net tangible book value per share as September 30, 2018 after giving effect to this offering and the assumed offering price. If we were to sell shares of our common stock in this offering at a price per share greater than our net tangible book value, it would result in dilution of your investment. The exercise of outstanding stock options and warrants or the settlement of outstanding restricted stock units would result in further dilution of your investment. See the section entitled *Dilution* below for a more detailed illustration of the dilution you may incur if you participate in this offering. Because the sales of the shares offered hereby will be made directly into the market or in negotiated transactions, the prices at which we sell these shares will vary and these variations may be significant. Purchasers of the shares we sell, as well as our existing shareholders, will experience significant dilution if we sell shares at prices significantly below the price at which they invested.

Future sales or the possibility of future sales of our common stock may depress the market price of our common stock.

Sales in the public market of substantial amounts of our common stock could depress prevailing market prices of our common stock. As of September 30, 2018, approximately 13.9 million shares of common stock were outstanding, and all of these shares are freely transferable without restriction or further registration under the Securities Act, except for shares held by our directors, officers and other affiliates and unregistered shares held by non-affiliates. The sale of these additional shares, or the perception that such sales may occur, could depress the market price of our common stock.

As of September 30, 2018, approximately 2.7 million shares of our common stock were issuable upon the exercise of outstanding warrants. Once a warrant is exercised, if the shares of our common stock issued upon the exercise of any such warrant are not available for sale in the open market without further registration under the Securities Act, then the holder can arrange for the resale of shares either by invoking any applicable registration rights, causing the shares to be registered under the Securities Act and thus freely transferable, or by relying on an exemption to the Securities

Act. For instance, in July 2015, we filed a registration statement on Form S-3 which registered for resale an aggregate of 2.4 million shares of our common stock issuable upon exercise of outstanding warrants. If these registration rights, or similar registration rights that may apply to securities we may issue in the future, are exercised, it could result in additional sales of our common stock in the market, which may have an adverse effect on our stock price.

As of September 30, 2018, there were approximately 604,000 shares of our common stock which may be issued upon the exercise of outstanding stock options and the settlement of restricted stock units, and we anticipate that we will continue to issue stock option and restricted stock unit awards to our employees and consultants in the fiscal year ended December 31, 2019 and thereafter. If and when these options are exercised and these restricted stock units are vested, such shares will be available for sale in the open market without further registration under the Securities Act. The existence of these outstanding options and restricted stock units may negatively affect our ability to complete future equity financings at acceptable prices and on acceptable terms. The exercise of those options and settlement of the restricted stock units, and the prompt resale of shares of our common stock received, may also result in downward pressure on the price of our common stock.

Table of Contents

In the absence of a significant strategic transaction, we will need to raise significant additional capital to finance the research, development and commercialization of Gencaro. If future securities offerings occur, they would dilute our current stockholders' equity interests and could reduce the market price of our common stock.

We have implemented anti-takeover provisions that could discourage, prevent or delay a takeover, even if the acquisition would be beneficial to our stockholders.

Provisions of our certificate of incorporation and bylaws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us, even if doing so would benefit our stockholders. These provisions:

establish a classified board of directors so that not all members of our board may be elected at one time;

authorize the issuance of up to approximately 5 million additional shares of preferred stock that could be issued by our board of directors to increase the number of outstanding shares and hinder a takeover attempt;

limit who may call a special meeting of stockholders;

prohibit stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders; and

establish advance notice requirements for nominations for election to our board of directors or for proposing matters that can be acted upon at a stockholder meeting.

Specifically, our certificate of incorporation provides that all stockholder action must be effected at a duly called meeting and not by a written consent. The bylaws provide, however, that our stockholders may call a special meeting of stockholders only upon a request of stockholders owning at least 50% of our outstanding common stock. These provisions of our certificate of incorporation and bylaws could discourage potential acquisition proposals and could delay or prevent a change in control. We designed these provisions to reduce our vulnerability to unsolicited acquisition proposals and to discourage certain tactics that may be used in proxy fights. These provisions, however, could also have the effect of discouraging others from making tender offers for our shares. As a consequence, they also may inhibit fluctuations in the market price of our shares that could result from actual or rumored takeover attempts. Such provisions also may have the effect of preventing changes in our management.

We are permitted to issue shares of our preferred stock without stockholder approval upon such terms as our board of directors determines. Therefore, the rights of the holders of our common stock are subject to, and may be adversely affected by, the rights of the holders of our preferred stock that may be issued in the future. In addition, the issuance of preferred stock could have a dilutive effect on the holdings of our current stockholders.

We are subject to the Delaware anti-takeover laws regulating corporate takeovers. These anti-takeover laws prevent a Delaware corporation from engaging in a merger or sale of more than 10% of its assets with any stockholder, including all affiliates and associates of the stockholder, who owns 15% or more of the corporation's outstanding voting stock, for three years following the date that the stockholder acquired 15% or more of the corporation's stock unless:

the board of directors approved the transaction where the stockholder acquired 15% or more of the corporation's stock;

after the transaction in which the stockholder acquired 15% or more of the corporation's stock, the stockholder owned at least 85% of the corporation's outstanding voting stock, excluding shares owned by directors, officers and employee stock plans in which employee participants do not have the right to determine confidentially whether shares held under the plan will be tendered in a tender or exchange offer; or

on or after this date, the merger or sale is approved by the board of directors and the holders of at least two-thirds of the outstanding voting stock that is not owned by the stockholder.

The provisions of our governing documents and current Delaware law may collectively:

lengthen the time required for a person or entity to acquire control of us through a proxy contest for the election of a majority of our board of directors;

discourage bids for our common stock at a premium over market price; and

generally deter efforts to obtain control of us.

S-7

Table of Contents

Our management might apply the net proceeds from this offering in ways with which you do not agree and in ways that may impair the value of your investment.

We currently intend to use the net proceeds from the sale of the securities under this prospectus supplement and accompanying prospectus for general corporate purposes, including clinical trials, potential in-licensing agreements, research and development expenses and general and administrative expenses. Our management has broad discretion as to the use of these proceeds and you will be relying on the judgment of our management regarding the application of these proceeds. We might apply these proceeds in ways with which you do not agree, or in ways that do not yield a favorable return. If our management applies these proceeds in a manner that does not yield a significant return, if any, on our investment of these net proceeds, it could compromise our ability to pursue our growth strategy and adversely affect the market price of our common stock.

Table of Contents

FORWARD-LOOKING STATEMENTS

This prospectus supplement and accompanying prospectus, the documents incorporated by reference and any free writing prospectus that we have authorized for use in connection with this offering contain forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act. These are based on our management's current beliefs, expectations and assumptions about future events, conditions and results and on information currently available to us. Discussions containing these forward-looking statements may be found, among other places, in the Sections entitled Business, Risk Factors and Management's Discussion and Analysis of Financial Condition and Results of Operations incorporated by reference from our most recent annual report on Form 10-K and quarterly reports on Form 10-Q, as well as any amendments thereto, filed with the SEC.

Any statements in this prospectus supplement and accompanying prospectus or incorporated herein, about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and are forward-looking statements. These forward-looking 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 prospectus supplement and accompanying prospectus, 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. As a result of these factors, we cannot assure you that the forward-looking statements in this prospectus supplement and accompanying prospectus or documents incorporated by reference 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. You should not place undue reliance on these forward-looking statements, which apply only as of the date of this prospectus supplement. You should read this prospectus supplement and accompanying prospectus and the documents incorporated by reference completely and with the understanding that our actual future results may be materially different from what we expect.

These forward-looking statements include, but are not limited to, statements regarding:

the timing and results of any clinical trials, including PRECISION-AF, any potential future PRECISION-AF trials, the potential for genetic variations to predict individual patient response to Gencaro, Gencaro's potential to treat AF, future treatment options for patients with AF, and the potential for Gencaro to be the first genetically-targeted atrial fibrillation prevention treatment;

our requested SPA from the FDA relating to our planned Phase 3 program for Gencaro does not guarantee that the FDA will issue an agreement on the SPA. Even if we do obtain the FDA's agreement on our SPA in the time we estimate, an SPA would not guarantee approval of Gencaro or any other particular outcome from regulatory review;

our ability to obtain U.S. and foreign regulatory approval for our product candidates and the ability of our product candidates to meet existing or future regulatory standards;

our expectations regarding federal, state and foreign regulatory requirements;

the therapeutic benefits and effectiveness of our product candidates;

the accuracy of our estimates of the size and characteristics of the markets that may be addressed by our product candidates;

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;

Table of Contents

our ability to compete with other companies that are or may be developing or selling products that are competitive with our product candidates;

anticipated trends and challenges in our potential markets; and

our ability to attract and retain key personnel.

In some cases, you can identify forward-looking statements by the words may, might, can, will, to be, could, should, expect, intend, plan, objective, anticipate, believe, estimate, predict, project, potential, ongoing, or the negative of these terms, or other comparable terminology intended to identify statements about the future, although not all forward-looking statements contain these words. 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.

You should refer to the Risk Factors section, or under similar heading, contained in this prospectus supplement, accompanying prospectus, the documents incorporated by reference and any related free writing prospectus for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements.

Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to revise any forward-looking statements to reflect events or developments occurring after the date of this prospectus supplement, even if new information becomes available in the future.

Table of Contents

USE OF PROCEEDS

Pursuant to the terms of the Sales Agreement, we may issue and sell shares of our common stock from time to time through or to JonesTrading, acting as sales agent or principal. Because there is no minimum offering amount required as a condition to close this offering, the actual total public offering amount, commissions and proceeds to us, if any, are not determinable at this time. There can be no assurance that we will sell any shares under or fully utilize the Sales Agreement with JonesTrading as a source of financing.

We currently intend to use the net proceeds from the sale of the securities under this prospectus supplement and accompanying prospectus for general corporate purposes, including clinical trials, potential in-licensing agreements, research and development expenses and general and administrative expenses. We may also use a portion of the net proceeds to invest in or acquire businesses or technologies that we believe are complementary to our own, although we have no current plans, commitments or agreements with respect to any acquisitions as of the date of this prospectus supplement. Pending these uses, we will have broad discretion in the way that we use the net proceeds of this offering.

Table of Contents**DILUTION**

Our net tangible book value as of September 30, 2018 was approximately \$7.5 million, or \$0.536 per share. Net tangible book value per share is determined by dividing our total tangible assets, less total liabilities, by the number of shares of our common stock outstanding as of September 30, 2018. Dilution with respect to net tangible book value per share represents the difference between the amount per share paid by purchasers of shares of common stock in this offering and the net tangible book value per share of our common stock immediately after this offering.

After giving effect to the sale of 5,882,061 shares of our common stock in this offering at an assumed offering price of \$0.425 per share, the last reported sale price of our common stock on the Exchange on January 24, 2019, and after deducting estimated offering commissions and offering expenses payable by us, our as adjusted net tangible book value as of September 30, 2018 would have been approximately \$9.8 million, or \$0.495 per share. This represents an immediate decrease in net tangible book value of \$0.041 per share to existing stockholders and immediate dilution of \$(0.07) per share to investors purchasing our common stock in this offering at the public offering price. The following table illustrates this dilution on a per share basis:

Assumed public offering price per share	\$ 0.425
Net tangible book value per share of as September 30, 2018	\$ 0.536
Decrease in net tangible book value per share attributable to this offering	\$ (0.041)
As adjusted net tangible book value per share as of September 30, 2018, after giving effect to this offering	\$ 0.495
Dilution per share to investors purchasing our common stock in this offering	\$ (0.07)

The above discussion and table are based on 13,923,825 shares of our common stock outstanding as of September 30, 2018 and excludes:

604,265 shares of our common stock issuable upon the exercise of stock options outstanding as of September 30, 2018, at a weighted average exercise price of \$5.47 per share;

2,669,855 shares of our common stock issuable upon exercise of warrants outstanding as of September 30, 2018, at a weighted average exercise price of \$7.07 per share;

233 shares of our common stock issuable upon the settlement of restricted stock units outstanding as of September 30, 2018; and

615,976 shares of our common stock reserved for issuance under our equity incentive, non-employee director stock award and employee stock purchase plans as of September 30, 2018.

The table above assumes for illustrative purposes that an aggregate of 5,882,061 shares of our common stock are sold during the term of the Sales Agreement with JonesTrading at a price of \$0.425 per share, the last reported sale price of

our common stock on the Exchange on January 24, 2019, for aggregate gross proceeds of \$2,499,876. The shares subject to the Sales Agreement with JonesTrading are being sold from time to time at various prices. An increase of \$0.10 per share in the price at which the shares are sold from the assumed offering price of \$0.525 per share shown in the table above, assuming all of our common stock in the aggregate amount of \$2,499,876 during the term of the Sales Agreement with JonesTrading is sold at that price, would increase our adjusted net tangible book value per share after the offering to \$0.525 per share and would have no dilution in net tangible book value per share to new investors in this offering, after deducting commissions and estimated aggregate offering expenses payable by us. A decrease of \$0.10 per share in the price at which the shares are sold from the assumed offering price of \$0.325 per share shown in the table above, assuming all of our common stock in the aggregate amount of \$2,499,876 during the term of the Sales Agreement with JonesTrading is sold at that price, would decrease our adjusted net tangible book value per share after the offering to \$0.45 per share and would decrease the dilution in net tangible book value per share to new investors in this offering to \$(0.13) per share, after deducting commissions and estimated aggregate offering expenses payable by us. This information is supplied for illustrative purposes only.

To the extent that options or warrants outstanding as of September 30, 2018 have been or may be exercised or other shares issued, investors purchasing our common stock in this offering may experience further dilution. In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

Table of Contents

PLAN OF DISTRIBUTION

On January 25, 2019, we entered into an amendment (Amendment No. 2) to Capital on Demand Sales Agreement, dated January 11, 2017, as amended on August 21, 2017 (the Original Agreement and together with Amendment No. 2, the Sales Agreement) with JonesTrading, pursuant to which we may, from time to time, offer and sell shares of our common stock having an aggregate offering price of up to \$12,742,739. Sales of our common stock, if any, under this prospectus supplement and accompanying prospectus may be made in sales deemed to be at the market offerings as defined in Rule 415 promulgated under the Securities Act.

As a result of the limitations discussed below and the current public float of our common stock, and in accordance with the terms of the Sales Agreement, we may offer and sell shares of our common stock having an aggregate offering price of up to \$2,499,876 from time to time through or to JonesTrading, as sales agent or principal. Pursuant to General Instruction I.B.6 of Form S-3, in no event will we sell securities registered on the registration statement of which this prospectus supplement is a part in a public primary offering with a value exceeding more than one-third of our public float in any 12-month period if our public float, measured in accordance with such instruction, remains below \$75.0 million. As of January 24, 2019, the aggregate market value of our common stock held by non-affiliates, or the public float, was \$7,499,629, which was calculated based on 13,760,788 shares of our outstanding common stock held by non-affiliates as of the date of January 24, 2019 at a price of \$0.545 per share, which was the closing price of our common stock on the Exchange on November 28, 2018. As of the date hereof, we have sold no shares of our common stock pursuant to General Instruction I.B.6 of Form S-3 during the 12 calendar months prior to and including the date of this prospectus supplement. Sales of the shares of common stock, if any, may be made on the Exchange at market prices and such other sales as agreed upon by us and JonesTrading. The Amendment No. 2 has been filed as an exhibit to our Current Report on Form 8-K filed with the SEC on January 25, 2019.

Each time we wish to issue and sell common stock, we will notify JonesTrading of the number of shares to be issued, the dates on which such sales are anticipated to be made, any minimum price below which sales may not be made and other sales parameters as we deem appropriate. Once we have so instructed JonesTrading, unless JonesTrading declines to accept the terms of the notice, JonesTrading has agreed, subject to the terms and conditions of the Sales Agreement, to use its commercially reasonable efforts consistent with its normal trading and sales practices to sell such shares up to the amount specified on such terms. We may instruct JonesTrading not to sell shares of common stock if the sales cannot be effected at or above the price designated by us in any such instruction. We or JonesTrading may suspend the offering of shares of common stock being made through JonesTrading under the Sales Agreement upon proper notice to the other party.

We will pay JonesTrading commissions for its services in acting as agent in the sale of our common stock. JonesTrading may effect sales to or through dealers, and such dealers may receive compensation in the form of discounts, concessions or commissions from JonesTrading and/or purchasers of shares of common stock for whom they may act as agents or to whom they may sell as principal. JonesTrading will be entitled to compensation at a commission rate equal to 3.0% of the aggregate gross sales price of the shares sold. Because there is no minimum offering amount required as a condition to close this offering, the actual total public offering amount, commissions and proceeds to us, if any, are not determinable at this time. We have also agreed to reimburse JonesTrading for certain specified expenses, including the fees and disbursements of its legal counsel in an aggregate amount (inclusive of expenses paid in connection with entering into the Sales Agreement) not to exceed \$65,000, as provided in the Sales Agreement. As of the effective date of the Amendment, the Company has reimbursed \$38,000 of such expenses to JonesTrading. We estimate that the total expenses for this offering (inclusive of expenses paid in connection with entering into the Sales Agreement), excluding compensation and reimbursements payable to JonesTrading under the terms of the Sales Agreement, will be approximately \$55,000.

Settlement for sales of common stock will occur on the second business day following the date on which any sales are made or such earlier day as is industry practice for regular-way trading, or on some other date that is agreed upon by us and JonesTrading in connection with a particular transaction, in return for payment of the net proceeds to us. There is no arrangement for funds to be received in an escrow, trust or similar arrangement.

In connection with the sale of the common stock on our behalf, JonesTrading will be deemed to be an underwriter within the meaning of the Securities Act and the compensation of JonesTrading will be deemed to be underwriting commissions or discounts. We have agreed to provide indemnification and contribution to JonesTrading against certain civil liabilities, including liabilities under the Securities Act.

S-13

Table of Contents

Our common stock is listed on the Exchange and trades under the symbol ABIO. The transfer agent of our common stock is Computershare Trust Company, N.A.

JonesTrading and/or its affiliates have in the past and may in the future provide various investment banking and other financial services for us for which services they may in the future receive customary fees.

S-14

Table of Contents

LEGAL MATTERS

The validity of the common stock offered by this prospectus supplement will be passed upon by Cooley LLP, Broomfield, Colorado. Duane Morris LLP, New York, New York, is counsel for JonesTrading in connection with this offering.

EXPERTS

The financial statements of ARCA biopharma, Inc. as of December 31, 2017 and 2016, and for the years then ended, have been incorporated by reference herein and in the registration statement in reliance upon the report of KPMG LLP, independent registered public accounting firm, incorporated by reference herein, and upon the authority of said firm as experts in accounting and auditing. The audit report covering the December 31, 2017 financial statements contains an explanatory paragraph that states that the Company's recurring losses from operations and the need and uncertainty related to raising additional capital to fund its clinical development programs raises substantial doubt about the Company's ability to continue as a going concern. The financial statements do not include any adjustments that might result from the outcome of that uncertainty.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus supplement and accompanying prospectus is part of a registration statement on Form S-3 we filed with the SEC. This prospectus supplement and accompanying prospectus does not contain all of the information set forth in the registration statement or the exhibits to the registration statement. For further information with respect to us and the securities we are offering under this prospectus supplement and accompanying prospectus, we refer you to the registration statement and the exhibits and schedules filed as a part of the registration statement. Whenever a reference is made in this prospectus supplement or accompanying prospectus to any of our contracts, agreements or other documents, the reference may not be complete and you should refer to the exhibits that are a part of the registration statement or the exhibits to the reports or other documents incorporated by reference into this prospectus supplement and accompanying prospectus for a copy of such contract, agreement or other document. You should rely only on the information contained in this prospectus supplement, accompanying prospectus or incorporated by reference. We have not authorized anyone else to provide you with different information. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus supplement or accompanying prospectus is accurate as of any date other than the date on the front page of this prospectus supplement or the date on the front page of the accompanying prospectus, as applicable, regardless of the time of delivery of this prospectus supplement and accompanying prospectus or any sale of the securities offered by this prospectus supplement and accompanying prospectus.

We file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy the registration statement, as well as any other document filed by us with the SEC, at the SEC's Public Reference Room at 100 F Street NE, Washington, D.C. 20549. You can also request copies of these documents by writing to the SEC and paying a fee for the copying cost. You may obtain information on the operation of the Public Reference Room by calling the SEC at (800) SEC-0330. The SEC maintains a website that contains reports, proxy statements and other information regarding issuers that file electronically with the SEC, including ARCA biopharma. The address of the SEC website is www.sec.gov.

We maintain a website at www.arcabio.com. Information contained in or accessible through our website does not constitute a part of this prospectus supplement or accompanying prospectus.

Table of Contents

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference information from other documents that we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus supplement and accompanying prospectus. Information in this prospectus supplement and accompanying prospectus supersedes information incorporated by reference that we filed with the SEC prior to the date of this prospectus supplement and accompanying prospectus, while information that we file later with the SEC will automatically update and supersede the information in this prospectus supplement and accompanying prospectus. We incorporate by reference into this prospectus supplement and the registration statement of which this prospectus supplement and accompanying prospectus is a part the information or documents listed below that we have filed with the SEC (Commission File No. 000-22873):

our annual report on Form 10-K for the year ended December 31, 2017, filed with the SEC on March 22, 2018;

the information specifically incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2017 from our definitive proxy statement on Schedule 14A (other than information furnished rather than filed) filed with the SEC on April 18, 2018;

our quarterly reports on Form 10-Q for the quarterly periods ended March 31, 2018, filed with the SEC on May 8, 2018; June 30, 2018, filed with the SEC on August 9, 2018; and September 30, 2018, filed with the SEC on November 14, 2018;

our Current Reports on Form 8-K filed with the SEC on January 8, 2018; February 26, 2018; March 5, 2018; April 16, 2018; April 23, 2018; May 29, 2018; June 5, 2018; July 31, 2018; September 18, 2018; October 9, 2018; October 18, 2018; December 20, 2018 and January 25, 2019; and

the description of our common stock set forth in our registration statement on Form 8-A filed with the SEC on July 23, 1997, including any amendments thereto or reports filed for the purpose of updating such description.

We also incorporate by reference any future filings (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items unless such Form 8-K expressly provides to the contrary) made with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, including (i) those made after the date of the initial filing of the registration statement of which this prospectus supplement and accompanying prospectus is a part and prior to effectiveness of such registration statement, and (ii) those made after the date of this prospectus supplement until we file a post-effective amendment that indicates the termination of the offering of the securities covered by this prospectus supplement and accompanying prospectus, and will become a part of this from the date that such documents are filed with the SEC. Information in such future filings updates and supplements the information provided in this prospectus supplement and accompanying prospectus. Any statements in any such future filings will automatically be deemed to modify and supersede any information in any document we previously filed with the SEC that is incorporated or deemed to be incorporated herein by reference to the extent that statements in the later filed document modify or replace such earlier statements.

We will furnish without charge to you, on written or oral request, a copy of any or all of the documents incorporated by reference, including exhibits to these documents. You should direct any requests for documents to ARCA biopharma, Inc., Attention: Secretary, 11080 CirclePoint Road, Suite 140, Westminster, Colorado 80020. Our phone number is (720) 940-2200. In addition, all of the documents incorporated by reference into this prospectus supplement and accompanying prospectus may be accessed via the Internet at our website: <http://www.arcabio.com>.

This prospectus supplement and accompanying prospectus is part of a registration statement we filed with the SEC. That registration statement and the exhibits filed along with the registration statement contain more information about us and the shares in this offering. Because information about documents referred to in this prospectus supplement and accompanying prospectus is not always complete, you should read the full documents which are filed as exhibits to the registration statement. You may read and copy the full registration statement and its exhibits at the SEC's public reference rooms or its website.

Table of Contents

PROSPECTUS

\$75,000,000

Common Stock

Preferred Stock

Debt Securities

Warrants

From time to time, we may offer and sell up to \$75,000,000 of any combination of the securities described in this prospectus, either individually or in combination with other securities. We may also offer common stock or preferred stock upon conversion of debt securities, common stock upon conversion of preferred stock, or common stock, preferred stock or debt securities upon the exercise of warrants.

This prospectus provides a general description of securities we may offer. Each time we offer and sell securities, we will provide the specific terms of these offerings and securities in one or more supplements to this prospectus. We may also authorize one or more free writing prospectuses to be provided to you in connection with these offerings. The prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus. You should carefully read this prospectus, the applicable prospectus supplement and any related free writing prospectus, as well as the documents incorporated by reference, before buying any of the securities being offered.

Our common stock is listed on The NASDAQ Capital Market under the trading symbol ABIO. On May 9, 2017, the last reported sale price of our common stock was \$2.40 per share. The applicable prospectus supplement will contain information, where applicable, as to other listings, if any, on The NASDAQ Capital Market or other securities exchange of the securities covered by the applicable prospectus supplement.

INVESTING IN OUR SECURITIES INVOLVES A HIGH DEGREE OF RISK. YOU SHOULD REVIEW CAREFULLY THE RISKS AND UNCERTAINTIES DESCRIBED UNDER THE HEADING RISK FACTORS CONTAINED IN THE APPLICABLE PROSPECTUS SUPPLEMENT AND IN ANY FREE WRITING PROSPECTUS WE HAVE AUTHORIZED FOR USE IN CONNECTION WITH A SPECIFIC OFFERING, AND UNDER SIMILAR HEADINGS IN THE DOCUMENTS THAT ARE INCORPORATED BY REFERENCE INTO THIS PROSPECTUS AS DESCRIBED ON PAGE 33.

THIS PROSPECTUS MAY NOT BE USED TO CONSUMMATE A SALE OF SECURITIES UNLESS ACCOMPANIED BY A PROSPECTUS SUPPLEMENT.

The securities may be sold directly by us to investors, through agents designated from time to time or to or through underwriters or dealers, on a continuous or delayed basis. For additional information on the methods of sale, you should refer to the section entitled "Plan of Distribution" in this prospectus. If any agents or underwriters are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such agents or underwriters and any applicable fees, commissions, discounts and over-allotment options will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds we expect to receive from such sale will also be set forth in a prospectus supplement.

NEITHER THE SECURITIES AND EXCHANGE COMMISSION NOR ANY STATE SECURITIES COMMISSION HAS APPROVED OR DISAPPROVED OF THESE SECURITIES OR DETERMINED IF THIS PROSPECTUS IS TRUTHFUL OR COMPLETE. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

The date of this prospectus is May 10, 2017.

Table of Contents

TABLE OF CONTENTS

<u>ABOUT THIS PROSPECTUS</u>	1
<u>PROSPECTUS SUMMARY</u>	2
<u>RISK FACTORS</u>	8
<u>FORWARD-LOOKING STATEMENTS</u>	8
<u>USE OF PROCEEDS</u>	10
<u>DESCRIPTION OF SECURITIES TO BE REGISTERED</u>	11
<u>DESCRIPTION OF CAPITAL STOCK</u>	11
<u>DESCRIPTION OF DEBT SECURITIES</u>	17
<u>DESCRIPTION OF WARRANTS</u>	24
<u>LEGAL OWNERSHIP OF SECURITIES</u>	26
<u>PLAN OF DISTRIBUTION</u>	30
<u>LEGAL MATTERS</u>	32
<u>EXPERTS</u>	32
<u>WHERE YOU CAN FIND MORE INFORMATION</u>	32
<u>INCORPORATION OF CERTAIN INFORMATION BY REFERENCE</u>	33

Table of Contents

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or SEC, utilizing a shelf registration process. Under this shelf registration process, we may offer and sell shares of our common stock and preferred stock, various series of debt securities and/or warrants to purchase any of such securities, either individually or in combination with other securities, in one or more offerings, up to a total dollar amount of \$75,000,000. This prospectus provides you with a general description of the securities we may offer.

Each time we offer securities under this prospectus, we will provide a prospectus supplement that will contain more specific information about the terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change any of the information contained in this prospectus or in the documents that we have incorporated by reference into this prospectus. We urge you to read carefully this prospectus, together with any applicable prospectus supplement and any free writing prospectus we have authorized for use in connection with a specific offering, and the information incorporated herein by reference as described under the heading **Incorporation of Certain Information by Reference**, before buying any of the securities being offered.

This prospectus may not be used to consummate a sale of securities unless it is accompanied by a prospectus supplement.

You should rely only on the information contained in, or incorporated by reference into, this prospectus and any applicable prospectus supplement, along with the information contained in any free writing prospectus we have authorized for use in connection with a specific offering. We have not authorized anyone to provide you with different or additional information. We are not making an offer to sell or seeking an offer to buy securities under this prospectus or any applicable prospectus supplement and any related free writing prospectus in any jurisdiction where the offer or sale is not permitted.

The information appearing in this prospectus, any applicable prospectus supplement or any related free writing prospectus, and the documents incorporated by reference herein and therein, is accurate only as of the date on the front of the document and any information we have incorporated by reference is accurate only as of their respective dates, regardless of the time of delivery of this prospectus, any applicable prospectus supplement or any related free writing prospectus, or any sale of a security. Our business, financial condition, results of operations and prospects may have changed since those dates.

This prospectus contains summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been filed, will be filed or will be incorporated by reference as exhibits to the registration statement of which this prospectus is a part, and you may obtain copies of those documents as described below under the section entitled **Where You Can Find More Information**.

This prospectus incorporates by reference, and any prospectus supplement or free writing prospectus may contain and incorporate by reference, industry, statistical and market data from our own internal estimates and research as well as from industry and general publications and research, surveys and studies conducted by third parties. Industry publications, studies and surveys generally state that they have been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe that each of these studies and publications is reliable, we have not independently verified statistical, market and industry data from

third-party sources. While we believe our internal company research is reliable and the market definitions are appropriate, neither such research nor these definitions have been verified by any independent source.

1.

Table of Contents**PROSPECTUS SUMMARY**

This summary highlights selected information contained elsewhere in this prospectus or incorporated by reference in this prospectus, and does not contain all of the information that you need to consider in making your investment decision. You should carefully read the entire prospectus, the applicable prospectus supplement and any related free writing prospectus, including the risks of investing in our securities discussed under the heading Risk Factors contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus. You should also carefully read the information incorporated by reference into this prospectus, including our financial statements, and the exhibits to the registration statement of which this prospectus is a part.

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

Overview

We are a biopharmaceutical company applying a precision medicine approach to developing genetically-targeted therapies for cardiovascular diseases. Precision medicine refers to the tailoring of medical treatment to the individual characteristics of each patient through the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment. Our lead product candidate, Gencaro (bucindolol hydrochloride), is an investigational, pharmacologically unique beta-blocker and mild vasodilator that we are developing for the potential treatment of patients with atrial fibrillation, or AF, and chronic heart failure with reduced left ventricular ejection fraction, or HFrEF. HFrEF constitutes an estimated 50-60% of the total heart failure with the remainder comprised of HF with preserved ejection fraction. We believe that Gencaro's efficacy is enhanced in a specific genotype that is present in approximately fifty percent of the general population in the United States, and can be identified by a genetic test. We believe that with this genetic test, we may be able to predict individual patient response to Gencaro, potentially improving the efficacy of treatment for AF in HFrEF patients with this particular genotype. We believe that Gencaro, if approved, could potentially be a safer and more effective therapy for treating or preventing AF in patients with HFrEF and could be the first genetically-targeted AF treatment. We also believe that Gencaro may have market exclusivity based on patents and new chemical entity status, if approved in the United States, Europe or other markets.

We are conducting a Phase 2B/Phase 3 clinical superiority trial, known as GENETIC-AF, in which we are evaluating Gencaro for the treatment and prevention of AF in HFrEF patients. In our trial, HFrEF is defined as a left ventricular ejection fraction, or LVEF, of less than 50%. GENETIC-AF compares Gencaro to TOPROL-XL (metoprolol succinate), a drug approved for treating HFrEF that is also prescribed, but not approved, for treating AF in patients with HFrEF. Enrollment in GENETIC-AF is limited to patients that possess the specific genotype that we believe enhances Gencaro's potential therapeutic effects. Our current development of Gencaro is, in part, based on a prospectively designed DNA substudy of adrenergic receptor polymorphisms in the BEST trial, a previous Phase 3 study of 2,708 HF patients. Based on data from the BEST trial, Gencaro showed potential evidence of enhanced efficacy in treating AF and in reducing mortality and hospitalizations in HF patients with this specific genotype. In 2015, the U.S. Food and Drug Administration, or FDA, designated the investigation of Gencaro for the prevention of AF in a genetically targeted heart failure population (HF patients with reduced LVEF) as a Fast Track development program.

AF, the most common sustained cardiac arrhythmia, is a potentially serious disorder in which the normally regular and coordinated contraction pattern of the heart's two small upper chambers, or the atria, becomes irregular, rapid and uncoordinated. AF commonly occurs together with HFrEF, with AF being both a cause and a result of HFrEF. By

increasing heart rate and producing irregular cycle lengths, AF may contribute to the disease processes that leads to the progression of HFrEF and worsening clinical outcomes.

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

2.

Table of Contents

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

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

GENETIC-AF is an adaptive, seamless design Phase 2B/Phase 3, multi-center, randomized, double-blind, clinical superiority trial comparing the safety and efficacy of Gencaro against an active comparator, the beta-blocker TOPROL-XL (metoprolol succinate), that seeks to enroll a combined total of approximately 620 patients. Eligible patients will have HFrEF, a history of paroxysmal AF (episodes lasting 7 days or less) or persistent AF (episodes lasting more than 7 days and less than 1 year) in the past 6 months, and the beta-1 389 arginine homozygous genotype that we believe responds most favorably to Gencaro. A subset of patients in the trial will also undergo continuous heart rhythm monitoring to assess AF burden, which is defined as the amount of time per day that a patient experiences AF. These data will be collected via newly or previously implanted Medtronic, Inc. devices capable of assessing AF burden (for example, implantable loop recorders, pacemakers, cardioverter-defibrillators, or cardiac resynchronization therapy devices). The primary endpoint of the study is time to first event of symptomatic AF/atrial flutter, or AFL, or all-cause mortality. The combined Phase 2B/Phase 3 trial is designed for 90 percent power at a p-value of less than 0.01 significance level to detect a 25 percent reduction in the primary endpoint for patients in the Gencaro arm compared to patients in the TOPROL-XL arm. We received guidance from the FDA regarding the GENETIC-AF clinical trial prior to initiation of the trial. Based on this FDA guidance, we believe that a successful GENETIC-AF Phase 3 clinical trial, with a p-value of less than or equal to 0.01 could be sufficient evidence of efficacy upon which to base a New Drug Application when submitted with the prior Phase 3 BEST trial data, for the approval of Gencaro for an AF indication in HFrEF patients. A second trial may be required if the GENETIC-AF trial results produce a p-value greater than 0.01. The trial is currently enrolling patients in the United States, Canada and Europe.

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

superior efficacy of Gencaro versus the active comparator, TOPROL-XL.

The prospectively defined features of this analysis include an estimate of Gencaro effectiveness relative to TOPROL-XL and an assessment of safety as characterized by adverse events. The relative benefit estimate will utilize Bayesian statistical methods to calculate the predictive probability of the Phase 3 patient cohort hazard ratio

3.

Table of Contents

based on the interim Phase 2B data. Prospectively defined ranges of predictive probabilities have been predetermined to define three potential outcomes based on the projection of the Phase 2B interim results:

- 1) transition the trial to Phase 3 based on a likelihood of achieving a statistically significant hazard ratio in favor of Gencaro (evidence of an efficacy signal consistent with pretrial assumptions) and enroll up to a total of 620 patients (including the Phase 2B patients);
- 2) completion of the Phase 2B stage of the trial including 24-week follow-up of all randomized subjects (approximately 250 patients), based on an intermediate result that is potentially favorable but does not support transition of the trial to Phase 3 or;
- 3) immediate termination of the trial due to futility.

We, in collaboration with the GENETIC-AF Steering Committee, will determine the next steps for the trial based on the DSMB recommendation from this interim analysis and on our available capital. The unblinded statistical data available to the DSMB will not be disclosed to us or the public. We randomized our 200th patient in the trial in April 2017. We project that the outcome of the DSMB interim analysis and recommendation will be available in September of 2017. In February 2016, we amended the trial protocol to allow for up to 250 patients to be enrolled in the Phase 2B portion of the trial, which is intended to enable the study to continue enrolling patients while the DSMB interim analysis is underway. Should the DSMB recommend that the study continue to Phase 3, the trial would continue enrolling to a total of approximately 620 patients (i.e., up to 250 patients in Phase 2B and 370 patients in Phase 3), subject to our obtaining sufficient financing to fund the Phase 3 portion of the trial.

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

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

Medtronic, Inc., or Medtronic, a global healthcare solutions company, is collaborating with us on the GENETIC-AF trial. Under the collaboration with Medtronic, ARCA is conducting a substudy that includes continuous monitoring of the cardiac rhythms in a subset of patients enrolled during the trial, which is the basis for a supportive endpoint in the trial known as AF burden. The collaboration is administered by a joint ARCA-Medtronic committee. Medtronic uses its proprietary CareLink System to collect and analyze the cardiac rhythm data from the implanted Medtronic devices and the data will be used by the DSMB as part of the interim analysis. Medtronic will support the reimbursement process for U.S. patients enrolled in the Phase 2B portion, and will provide financial support of unreimbursed costs for a certain number of U.S. patients in the Phase 2B portion up to a certain maximum amount per patient. If

GENETIC-AF continues to Phase 3, we will continue to enroll additional patients, with Medtronic devices for monitoring and recording AF burden, in the substudy. Medtronic will provide the agreed upon CareLink System cardiac rhythm data collection and analysis for the Phase 3 portion of the substudy and support the reimbursement process.

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

To support the continued development of Gencaro, in June 2015, we completed a private placement that raised approximately \$34.2 million of net proceeds as additional funds for the Phase 2B portion of the GENETIC-AF trial and to support our ongoing operations. We are seeking to enroll up to 250 HFrEF patients in the Phase 2B portion

4.

Table of Contents

of the GENETIC-AF trial, and we believe that our current cash and cash equivalents will be sufficient to fund our operations, at our projected cost structure, through the end of 2017. In January 2017, we entered into a sales agreement with an agent to sell, from time to time, our common stock having an aggregate offering price of up to \$7.3 million, in an at the market offering. We are not obligated to make any sales of our common stock, and, as of May 9, 2017, we have sold an aggregate of 144,977 shares of our common stock pursuant to the terms of such sales agreement for aggregate gross proceeds of approximately \$380,625, before paying commissions to our placement agent of approximately \$11,000. However, changing circumstances may cause us to consume capital significantly faster or slower than we currently anticipate. We have based these estimates on assumptions that may prove to be wrong, and we could exhaust our available financial resources sooner than we currently anticipate. If we continue to the Phase 3 portion of GENETIC-AF, we will be required to raise additional funds.

Company Information

On January 27, 2009, we completed a business combination, or the Merger, between Nuvelo, Inc., or Nuvelo, a corporation originally incorporated in 1992, and its subsidiary, ARCA biopharma, Inc. Immediately following the Merger, we changed our name from Nuvelo, Inc. to ARCA biopharma, Inc. Our principal offices are located in Westminster, Colorado.

Our principal offices are located at 11080 CirclePoint Road, Suite 140, Westminster, Colorado 80020. Our telephone number is (720) 940-2200. Our internet address is <http://www.arcabio.com>. We do not incorporate the information on our website into this prospectus, and you should not consider it part of this prospectus. For further information regarding us and our financial information, you should refer to our recent filings with the Securities and Exchange Commission, or the SEC. See [Where You Can Find More Information](#) and [Incorporation of Certain Information by Reference](#).

Each of ARCA, ARCA biopharma, Gencaro and Gencaro Test is a registered trademark of ARCA biopharma, Inc. Each of the other trademarks, trade names or service marks appearing in this prospectus belongs to its respective holder.

The Securities We May Offer

We may offer shares of our common stock and preferred stock, various series of debt securities and/or warrants to purchase any of such securities, either individually or in combination with other securities, with a total value of up to \$75,000,000 from time to time under this prospectus, together with the applicable prospectus supplement and any related free writing prospectus, at prices and on terms to be determined by market conditions at the time of any offering. This prospectus provides you with a general description of the securities we may offer. Each time we offer a type or series of securities under this prospectus, we will provide a prospectus supplement that will describe the specific amounts, prices and other important terms of the securities, including, to the extent applicable:

designation or classification;

aggregate principal amount or aggregate offering price;

maturity date, if applicable;

original issue discount, if any;

rates and times of payment of interest or dividends, if any;

redemption, conversion, exercise, exchange or sinking fund terms, if any;

ranking;

restrictive covenants, if any;

5.

Table of Contents

conversion or exchange prices or rates, if any, and, if applicable, any provisions for changes to or adjustments in the conversion or exchange prices or rates and in the securities or other property receivable upon conversion or exchange; and

material or special U.S. federal income tax considerations, if any.

The applicable prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change any of the information contained in this prospectus or in the documents we have incorporated by reference. However, no prospectus supplement or free writing prospectus will offer a security that is not registered and described in this prospectus at the time of the effectiveness of the registration statement of which this prospectus is a part.

THIS PROSPECTUS MAY NOT BE USED TO CONSUMMATE A SALE OF SECURITIES UNLESS IT IS ACCOMPANIED BY A PROSPECTUS SUPPLEMENT.

We may sell the securities directly to investors or to or through agents, underwriters or dealers. We, and our agents or underwriters, reserve the right to accept or reject all or part of any proposed purchase of securities. If we do offer securities to or through agents or underwriters, we will include in the applicable prospectus supplement:

the names of those agents or underwriters;

applicable fees, discounts and commissions to be paid to them;

details regarding over-allotment options, if any; and

the net proceeds to us.

Common Stock. We may issue shares of our common stock from time to time. The holders of our common stock are entitled to one vote for each share held of record on all matters submitted to a vote of stockholders. Under our Bylaws, our stockholders do not have cumulative voting rights. Because of this, the holders of a majority of the shares of common stock entitled to vote in any election of directors can elect all of the directors standing for election, if they should so choose. Subject to preferences that may be applicable to any outstanding shares of preferred stock, the holders of common stock are entitled to receive ratably such dividends as may be declared by our board of directors out of legally available funds. Upon our liquidation, dissolution or winding up, holders of our common stock are entitled to share ratably in all assets remaining after payment of liabilities and the liquidation preferences of any outstanding shares of preferred stock. Holders of common stock have no preemptive rights and no right to convert their common stock into any other securities. There are no redemption provisions applicable to our common stock. The rights, preferences and privileges of the holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate in the future. In this prospectus, we have summarized certain general features of the common stock under *Description of Capital Stock* *Common Stock*. We urge you, however, to read the applicable prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) related to any common stock being offered.

Preferred Stock. We may issue shares of our preferred stock from time to time, in one or more series. Under our certificate of incorporation, our board of directors has the authority to designate up to 5,000,000 shares of preferred stock, \$0.001 par value per share, in one or more series and to fix the privileges, preferences and rights of each series of preferred stock, any or all of which may be greater than the rights of the common stock. If we sell any new series of preferred stock under this prospectus and any applicable prospectus supplement, our board of directors will determine the designations, voting powers, preferences and rights of the preferred stock being offered, as well as the qualifications, limitations or restrictions thereof, including dividend rights, conversion rights, preemptive rights, terms of redemption or repurchase, liquidation preferences, sinking fund terms and the number of shares constituting any series or the designation of any series. Preferred stock may be convertible into our common stock or other securities of ours, or may be exchangeable for debt securities. Conversion may be mandatory or at the holder's option and would be at prescribed conversion rates. We will file as an exhibit to the registration statement of which

6.

Table of Contents

this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of the certificate of designation that describes the terms of the series of preferred stock that we are offering before the issuance of the related series of preferred stock. In this prospectus, we have summarized certain general features of the preferred stock under *Description of Capital Stock Preferred Stock*. We urge you, however, to read the applicable prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) related to the series of preferred stock being offered, as well as the complete certificate of designation that contains the terms of the applicable series of preferred stock.

Debt Securities. We may issue debt securities from time to time, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. The senior debt securities will rank equally with any other unsecured and unsubordinated debt. The subordinated debt securities will be subordinate and junior in right of payment, to the extent and in the manner described in the instrument governing the debt, to all of our senior indebtedness. Convertible debt securities will be convertible into or exchangeable for our common stock or our other securities. Conversion may be mandatory or at the holder's option and would be at prescribed conversion rates.

The debt securities will be issued under an indenture that we will enter into with a national banking association or other eligible party, as trustee. In this prospectus, we have summarized certain general features of the debt securities under *Description of Debt Securities*. We urge you, however, to read the applicable prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) related to the series of debt securities being offered, as well as the complete indenture and any supplemental indentures that contain the terms of the debt securities. We have filed the form of indenture as an exhibit to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

Warrants. We may issue warrants for the purchase of common stock, preferred stock and/or debt securities in one or more series. We may issue warrants independently or in combination with common stock, preferred stock and/or debt securities. In this prospectus, we have summarized certain general features of the warrants under *Description of Warrants*. We urge you, however, to read the applicable prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) related to the particular series of warrants being offered, as well as the form of warrant and/or the warrant agreement and warrant certificate, as applicable, that contain the terms of the warrants. We have filed the forms of the warrant agreements and forms of warrant certificates containing the terms of the warrants that we may offer as exhibits to the registration statement of which this prospectus is a part. We will file as exhibits to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of warrant and/or the warrant agreement and warrant certificate, as applicable, that contain the terms of the particular series of warrants we are offering, and any supplemental agreements, before the issuance of such warrants.

Warrants may be issued under a warrant agreement that we enter into with a warrant agent. We will indicate the name and address of the warrant agent, if any, in the applicable prospectus supplement relating to a particular series of warrants.

Table of Contents

RISK FACTORS

An investment in our securities involves a high degree of risk. Before you make a decision to invest in our securities, you should consider carefully the risks described in the section entitled "Risk Factors" contained in the applicable prospectus supplement and in our most recent Annual Report on Form 10-K and Quarterly Report on Form 10-Q filed with the SEC, as well as any amendment or update thereto reflected in subsequent filings with the SEC or in any Current Report on Form 8-K we may file. The risks described in these documents are not the only ones we face, but those that we consider to be material. There may be other unknown or unpredictable economic, business, competitive, regulatory or other factors that could have material adverse effects on our future results. Past financial performance may not be a reliable indicator of future performance, and historical trends should not be used to anticipate results or trends in future periods. If any of these risks actually occur, our business, operating results, prospects or financial condition could be materially and adversely affected. This could cause the trading price of our securities to decline and you may lose part or all of your investment. Moreover, the risks described are not the only ones that we face. Additional risks not presently known to us or that we currently deem immaterial may also affect our business, operating results, prospects or financial condition.

FORWARD-LOOKING STATEMENTS

This prospectus, any accompanying prospectus supplements, the documents incorporated by reference and any free writing prospectus that we have authorized for use in connection with this offering contain forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act. These are based on our management's current beliefs, expectations and assumptions about future events, conditions and results and on information currently available to us. Discussions containing these forward-looking statements may be found, among other places, in the Sections entitled "Business," "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" incorporated by reference from our most recent Annual Report on Form 10-K and Quarterly Reports on Form 10-Q, as well as any amendments thereto, filed with the SEC.

Any statements in this prospectus, any accompanying prospectus supplements or incorporated herein, about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and are forward-looking statements. These forward-looking 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 prospectus and any accompanying prospectus supplements, 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. As a result of these factors, we cannot assure you that the forward-looking statements in this prospectus, any accompanying prospectus supplements or documents incorporated by reference 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. You should not place undue reliance on these forward-looking statements, which apply only as of the date of this prospectus. You should read this prospectus, any accompanying prospectus supplement and the documents incorporated by reference completely and with the understanding that our actual future results may be materially different from what we expect.

These forward-looking statements include, but are not limited to, statements regarding:

the timing and results of any clinical trials, including GENETIC-AF, any potential future GENETIC-AF trials, the ongoing Gencaro trial for the prevention of AF, the potential for genetic variations to predict individual patient response to Gencaro, Gencaro's potential to treat AF, future treatment options for patients with AF, and the potential for Gencaro to be the first genetically-targeted atrial fibrillation prevention treatment;

our ability to obtain U.S. and foreign regulatory approval for our product candidates and the ability of our product candidates to meet existing or future regulatory standards;

our expectations regarding federal, state and foreign regulatory requirements;

8.

Table of Contents

the therapeutic benefits and effectiveness of our product candidates;

the accuracy of our estimates of the size and characteristics of the markets that may be addressed by our product candidates;

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;

our ability to compete with other companies that are or may be developing or selling products that are competitive with our product candidates;

anticipated trends and challenges in our potential markets; and

our ability to attract and retain key personnel.

In some cases, you can identify forward-looking statements by the words may, might, can, will, to be, could, should, expect, intend, plan, objective, anticipate, believe, estimate, predict, project, potential, ongoing, or the negative of these terms, or other comparable terminology intended to identify statements about the future, although not all forward-looking statements contain these words. 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.

You should refer to the Risk Factors section, or under similar heading, contained in this prospectus, accompanying prospectus supplement, the documents incorporated by reference and any related free writing prospectus for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements.

Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to revise any forward-looking statements to reflect events or developments occurring after the date of this prospectus, even if new information becomes available in the future.

9.

Table of Contents

USE OF PROCEEDS

We will retain broad discretion over the use of the net proceeds from the sale of the securities offered by this prospectus. Except as described in any applicable prospectus supplement or in any free writing prospectus we have authorized for use in connection with a specific offering, we currently intend to use the net proceeds from the sale of the securities under this prospectus, if any, for general corporate purposes, including clinical trials, research and development expenses and general and administrative expenses. We will set forth in the prospectus supplement applicable to a specific offering our intended use for the net proceeds received from the sale of any securities in that offering.

The amounts and timing of our use of the net proceeds from any offerings hereunder will depend on a number of factors, such as the timing and progress of our clinical trials and research and development efforts, the timing of regulatory approval of our product candidates, if any, the timing and progress of any partnering and collaboration efforts, technological advances and the competitive environment for our product candidates. As of the date of this prospectus, we cannot specify with certainty all of the particular uses for the net proceeds to us from offerings hereunder. Accordingly, our management will have broad discretion in the timing and application of these proceeds. Pending application of the net proceeds as described above, we intend to temporarily invest the proceeds in short-term, interest-bearing instruments.

Table of Contents

DESCRIPTION OF SECURITIES TO BE REGISTERED

DESCRIPTION OF CAPITAL STOCK

General

As of the date of this prospectus, our amended and restated certificate of incorporation, as amended, or the Restated Certificate, authorizes us to issue 100,000,000 shares of common stock, par value \$0.001 per share, and 5,000,000 shares of preferred stock, \$0.001 par value per share. As of December 31, 2016, 9,082,366 shares of common stock were outstanding and no shares of preferred stock were outstanding.

The following summary description of our capital stock is based on the provisions of our Restated Certificate, our second amended and restated bylaws, or the Bylaws, and applicable provisions of the Delaware General Corporation Law. This information may not be complete in all respects and is qualified entirely by reference to the applicable provisions of our Restated Certificate, our Bylaws and the Delaware General Corporation Law. For information on how to obtain copies of our Restated Certificate and Bylaws, which are exhibits to the registration statement of which this prospectus is a part, see [Where You Can Find More Information](#).

Common Stock

Voting Rights. Each holder of our common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders, including the election of directors; provided, however, holders of our common stock may not, unless otherwise required by law, vote on any amendment to our Restated Certificate that relates solely to the terms of one or more series of preferred stock that we may issue if the holders of such preferred stock are entitled to vote on such amendment. In all such matters other than the election of directors, the affirmative vote of the majority of shares present in person, by remote communication, or represented by proxy at a meeting of the stockholders and entitled to vote generally on the subject matter shall be the act of the stockholders. Directors shall be elected by a plurality of the votes of the shares present in person, by remote communication, or represented by proxy at a meeting of the stockholders and entitled to vote generally on the election of directors. Our stockholders do not have cumulative voting rights in the election of directors. Accordingly, holders of a majority of the voting shares are able to elect all of the directors to be elected at any particular time.

Dividends. Subject to preferences that may be applicable to any then outstanding preferred stock, holders of our common stock are entitled to receive dividends, if any, as may be declared from time to time by our board of directors out of legally available funds.

Liquidation. In the event of our liquidation, dissolution or winding up, holders of our common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities and the satisfaction of any liquidation preference granted to the holders of any then outstanding shares of preferred stock.

Rights and Preferences. Holders of our common stock have no preemptive, conversion, subscription or other rights, and there are no redemption provisions applicable to our common stock. The rights, preferences and privileges of the holders of our common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of our preferred stock that we may designate in the future.

Preferred Stock

Pursuant to our Restated Certificate, our board of directors has the authority, without further action by our stockholders, to issue up to 5,000,000 shares of preferred stock, \$0.001 par value per share, in one or more series, to establish from time to time the number of shares to be included in each such series, and to fix the designations, powers, preferences, privileges and relative participating, optional or special rights and the qualifications, limitations or restrictions thereof, including dividend rights, conversion rights, preemptive rights, voting rights, terms of

11.

Table of Contents

redemption and repurchase, liquidation preferences and sinking fund terms, any or all of which may be greater than the rights of the common stock. Preferred stock may be convertible into our common stock or other securities of ours, or may be exchangeable for debt securities. Conversion may be mandatory or at the holder's option and would be at prescribed conversion rates. Because our board of directors, without stockholder approval, can issue preferred stock with voting, conversion or other rights, preferred stock could be issued quickly with terms calculated to delay or prevent a change in control of our company or make removal of management more difficult. Additionally, the issuance of preferred stock may have the effect of decreasing the market price of the common stock and may adversely affect the voting power of holders of common stock and reduce the likelihood that common stockholders will receive dividend payments and payments upon liquidation.

The following is a summary of terms of our preferred stock. For a complete description, you should refer to the provisions of our Restated Certificate and Bylaws and the resolutions containing the terms of each class or series of the preferred stock which have been or will be filed with the SEC at or prior to the time of issuance of such class or series of preferred stock and described in any applicable prospectus supplement. Any applicable prospectus supplement may also state that any of the terms set forth herein are inapplicable to such series of preferred stock, provided that the information set forth in such prospectus supplement does not constitute material changes to the information herein such that it alters the nature of the offering or the securities offered.

Our board of directors will fix the rights, preferences, privileges, qualifications and restrictions of the preferred stock of each series that we sell under this prospectus and applicable prospectus supplements in the certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of any certificate of designation that describes the terms of the series of preferred stock we are offering before the issuance of the related series of preferred stock. This description will include:

the title and stated value;

the number of shares we are offering;

the liquidation preference per share;

the purchase price per share;

the dividend rate per share, dividend period and payment dates and method of calculation for dividends;

whether dividends will be cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;

our right, if any, to defer payment of dividends and the maximum length of any such deferral period;

the procedures for any auction and remarketing, if any;

the provisions for a sinking fund, if any;

the provisions for redemption or repurchase, if applicable, and any restrictions on our ability to exercise those redemption and repurchase rights;

any listing of the preferred stock on any securities exchange or market;

whether the preferred stock will be convertible into our common stock or other securities of ours, including warrants, and, if applicable, the conversion period, the conversion price, or how it will be calculated, and under what circumstances it may be adjusted;

12.

Table of Contents

whether the preferred stock will be exchangeable for debt securities, and, if applicable, the exchange period, the exchange price, or how it will be calculated, and under what circumstances it may be adjusted;

voting rights, if any, of the preferred stock;

preemptive rights, if any;

restrictions on transfer, sale or other assignment, if any;

a discussion of any material or special United States federal income tax considerations applicable to the preferred stock;

the relative ranking and preferences of the preferred stock as to dividend rights and rights if we liquidate, dissolve or wind up our affairs;

any limitations on issuances of any class or series of preferred stock ranking senior to or on a parity with the series of preferred stock being issued as to dividend rights and rights if we liquidate, dissolve or wind up our affairs; and

any other specific terms, rights, preferences, privileges, qualifications or restrictions of the preferred stock. When we issue shares of preferred stock under this prospectus, upon our receipt of the purchase price for such shares, the shares will be fully paid and nonassessable and will not have, or be subject to, any preemptive or similar rights. Unless we specify otherwise in the applicable prospectus supplement, the preferred stock will rank, with respect to dividends and upon our liquidation, dissolution or winding up:

senior to all classes or series of our common stock and to all of our equity securities ranking junior to the preferred stock;

on a parity with all of our equity securities the terms of which specifically provide that the equity securities rank on a parity with the preferred stock; and

junior to all of our equity securities the terms of which specifically provide that the equity securities rank senior to the preferred stock.

The term "equity securities" does not include convertible debt securities.

The Delaware General Corporation Law provides that the holders of any class or series of preferred stock will have the right to vote separately as a class on any proposed amendment to the Restated Certificate that would alter or

change the powers, preferences or special rights of the holders of such class or series of preferred stock so as to affect them adversely. This right is in addition to any voting rights that may be provided for in the applicable certificate of designation.

The issuance of preferred stock could adversely affect the voting power of holders of common stock and reduce the likelihood that common stockholders will receive dividend payments and payments upon liquidation. The issuance could have the effect of decreasing the market price of the common stock. The issuance of preferred stock also could have the effect of delaying, deterring or preventing a change in control of us.

Stock Options

As of December 31, 2016, there were 1,252,798 shares of common stock reserved for issuance under our equity incentive plans. Of this number, 629,629 shares were reserved for issuance upon exercise of outstanding options and 30,739 shares were reserved for issuance upon the vesting of outstanding restricted stock units as of December 31, 2016.

Table of Contents

Anti-Takeover Effects of Provisions of Delaware Law and Our Charter Documents

Certificate of Incorporation and Bylaws

Our Restated Certificate and Second Amended and Restated Bylaws, or Bylaws, include a number of provisions that may deter or impede hostile takeovers or changes of control or management. These provisions include:

Issuance of Undesignated Preferred Stock. Under our Restated Certificate, our board of directors has the authority, without further action by the stockholders, to issue up to 5,000,000 shares of undesignated preferred stock with rights and preferences, including voting rights, designated from time to time by the board of directors. The existence of authorized but unissued shares of preferred stock enables our board of directors to make it more difficult or to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise.

Classified Board. Our Restated Certificate provides for a classified board of directors consisting of three classes of directors, with staggered three-year terms. Only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms. This provision may have the effect of delaying a change in control of the board.

Board of Directors Vacancies. Our Restated Certificate and Bylaws authorize only our board of directors to fill vacant directorships, unless our board of directors determines by resolution that the stockholders shall fill such vacant directorships. In addition, the number of directors constituting our board of directors may be set only by resolution adopted by a majority vote of our entire board of directors. These provisions prevent a stockholder from increasing the size of our board of directors and gaining control of our board of directors by filling the resulting vacancies with its own nominees.

Stockholder Action; Special Meetings of Stockholders. Our Restated Certificate provides that our stockholders may not take action by written consent, but may only take action at annual or special meetings of our stockholders. Under our Bylaws, stockholders are not permitted to cumulate their votes for the election of directors. Our Bylaws further provide that special meetings of the stockholders may be called by the chief executive officer, president, the board of directors, or by holders of common stock who hold, in the aggregate, not less than fifty percent (50%) of the outstanding shares of common stock for the purpose or purposes stated in the call of the meeting. These provisions may prevent stockholders from corporate actions as stockholders at times when they otherwise would like to do so.

Advance Notice Requirements for Stockholder Proposals and Director Nominations. Our Bylaws provide advance notice procedures for stockholders seeking to bring business before our annual meeting of stockholders, or to nominate candidates for election as directors at our annual meeting of stockholders. Our Bylaws also specify certain requirements as to the form and content of a stockholder's notice. These provisions may make it more difficult for our stockholders to bring matters before our annual meeting of stockholders or to nominate directors at our annual meeting of stockholders.

These provisions are intended to enhance the likelihood of continued stability in the composition of our board of directors and its policies and to discourage certain types of transactions that may involve an actual or threatened acquisition of us. These provisions are designed to reduce our vulnerability to an unsolicited acquisition proposal. The provisions also are intended to discourage certain tactics that may be used in proxy fights. However, these provisions could have the effect of discouraging others from making tender offers for our shares and, as a consequence, they may also reduce fluctuations in the market price of our shares that could result from actual or rumored takeover attempts.

Section 203 of the Delaware General Corporation Law

We are subject to Section 203 of the Delaware General Corporation Law. Section 203 generally prohibits certain Delaware corporations from engaging, under certain circumstances, in a business combination with any interested stockholder for a period of three years following the time that such stockholder became an interested stockholder, unless:

prior to such time the board of directors approved either the business combination or transaction which resulted in the stockholder becoming an interested stockholder;

Table of Contents

upon consummation of the transaction which resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares outstanding (a) shares owned by persons who are directors and also officers and (b) employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or

at or subsequent to such time the business combination is approved by the board of directors and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66-2/3% of the outstanding voting stock which is not owned by the interested stockholder.

Section 203 defines a business combination to include:

any merger or consolidation involving the corporation and the interested stockholder;

any sale, lease, exchange, mortgage, pledge, transfer or other disposition (in one transaction or a series of transactions) involving the interested stockholder of 10% or more of the assets of the corporation (or its majority-owned subsidiary);

subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;

subject to exceptions, any transaction involving the corporation that has the effect, directly or indirectly, of increasing the proportionate share of the stock or any class or series of the corporation beneficially owned by the interested stockholder; and

the receipt by the interested stockholder of the benefit, directly or indirectly (except proportionately as a stockholder of such corporation), of any loans, advances, guarantees, pledges or other financial benefits, other than certain benefits set forth in Section 203, provided by or through the corporation.

In general, Section 203 defines an interested stockholder as any entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation and any entity or person that is an affiliate or associate of such entity or person.

A Delaware corporation may opt out of these provisions with an express provision in its original certificate of incorporation or an express provision in its certificate of incorporation or bylaws resulting from a stockholders amendment approved by a majority of the outstanding voting shares. We have not opted out of these provisions and do not plan to do so. The statute could prohibit or delay mergers or other takeover or change in control attempts and, accordingly, may discourage attempts to acquire us.

Potential Effects of Authorized but Unissued Stock

Our shares of common stock and preferred stock available for future issuance without stockholder approval. We may utilize these additional shares for a variety of corporate purposes, including future public offerings to raise additional capital, to facilitate corporate acquisitions or payment as a dividend on the capital stock.

The existence of unissued and unreserved common stock and preferred stock may enable our board of directors to issue shares to persons friendly to current management or to issue preferred stock with terms that could render more difficult or discourage a third-party attempt to obtain control by means of a merger, tender offer, proxy contest or otherwise, thereby protecting the continuity of our management. In addition, our board of directors has the discretion to determine designations, rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences of each series of preferred stock, all to the

Table of Contents

fullest extent permissible under the Delaware General Corporation Law and subject to any limitations set forth in our certificate of incorporation. The purpose of authorizing the board of directors to issue preferred stock and to determine the rights and preferences applicable to such preferred stock is to eliminate delays associated with a stockholder vote on specific issuances. The issuance of preferred stock, while providing desirable flexibility in connection with possible financings, acquisitions and other corporate purposes, could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from acquiring, a majority of our outstanding voting stock.

Amendments to Governing Documents

Generally, the amendment of our Restated Certificate requires approval by our board of directors and a majority vote of stockholders, provided that the provisions of our Restated Certificate relating to (i) the requirement that all stockholder action be taken only at a duly called annual meeting or special meeting; (ii) the authority and power of the board of directors and the procedure required to amend our Bylaws; (iii) the percentage of the shares necessary to amend the Restated Certificate; (iv) the elimination of directors' personal liability for monetary damages arising from their negligence and gross negligence; and (v) indemnification of directors, officers and other persons requires approval of our stockholders holding at least 66-2/3% of our capital stock then outstanding and entitled to vote. Any amendment to our Bylaws requires the approval of either a majority of our board of directors or approval of our stockholders holding at least 66-2/3% of our capital stock then outstanding and entitled to vote.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company N.A. The transfer agent for any series of preferred stock that we may offer under this prospectus will be named and described in the prospectus supplement for that series.

Listing on the NASDAQ Capital Market

Our common stock is listed on the NASDAQ Capital Market under the symbol ABIO.

Table of Contents

DESCRIPTION OF DEBT SECURITIES

We may issue debt securities from time to time, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. While the terms we have summarized below will apply generally to any debt securities that we may offer under this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement. The terms of any debt securities offered under a prospectus supplement may differ from the terms described below. Unless the context requires otherwise, whenever we refer to the indenture, we also are referring to any supplemental indentures that specify the terms of a particular series of debt securities.

We will issue the debt securities under the indenture that we will enter into with the trustee named in the indenture. The indenture will be qualified under the Trust Indenture Act of 1939, as amended, or the Trust Indenture Act. We have filed the form of indenture as an exhibit to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

The following summary of material provisions of the debt securities and the indenture is subject to, and qualified in its entirety by reference to, all of the provisions of the indenture applicable to a particular series of debt securities. We urge you to read the applicable prospectus supplements and any related free writing prospectuses related to the debt securities that we may offer under this prospectus, as well as the complete indenture that contains the terms of the debt securities.

General

The indenture does not limit the amount of debt securities that we may issue. It provides that we may issue debt securities up to the principal amount that we may authorize and may be in any currency or currency unit that we may designate. Except for the limitations on consolidation, merger and sale of all or substantially all of our assets contained in the indenture, the terms of the indenture do not contain any covenants or other provisions designed to give holders of any debt securities protection against changes in our operations, financial condition or transactions involving us.

We may issue the debt securities issued under the indenture as discount securities, which means they may be sold at a discount below their stated principal amount. These debt securities, as well as other debt securities that are not issued at a discount, may be issued with original issue discount, or OID, for U.S. federal income tax purposes because of interest payment and other characteristics or terms of the debt securities. Material U.S. federal income tax considerations applicable to debt securities issued with OID will be described in more detail in any applicable prospectus supplement.

We will describe in the applicable prospectus supplement the terms of the series of debt securities being offered, including:

the title of the series of debt securities;

any limit upon the aggregate principal amount that may be issued;

the maturity date or dates;

the form of the debt securities of the series;

the applicability of any guarantees;

whether or not the debt securities will be secured or unsecured, and the terms of any secured debt;

17.

Table of Contents

whether the debt securities rank as senior debt, senior subordinated debt, subordinated debt or any combination thereof, and the terms of any subordination;

if the price (expressed as a percentage of the aggregate principal amount thereof) at which such debt securities will be issued is a price other than the principal amount thereof, the portion of the principal amount thereof payable upon declaration of acceleration of the maturity thereof, or if applicable, the portion of the principal amount of such debt securities that is convertible into another security or the method by which any such portion shall be determined;

the interest rate or rates, which may be fixed or variable, or the method for determining the rate and the date interest will begin to accrue, the dates interest will be payable and the regular record dates for interest payment dates or the method for determining such dates;

our right, if any, to defer payment of interest and the maximum length of any such deferral period;

if applicable, the date or dates after which, or the period or periods during which, and the price or prices at which, we may, at our option, redeem the series of debt securities pursuant to any optional or provisional redemption provisions and the terms of those redemption provisions;

the date or dates, if any, on which, and the price or prices at which we are obligated, pursuant to any mandatory sinking fund or analogous fund provisions or otherwise, to redeem, or at the holder's option to purchase, the series of debt securities and the currency or currency unit in which the debt securities are payable;

the denominations in which we will issue the series of debt securities, if other than denominations of \$1,000 and any integral multiple thereof;

any and all terms, if applicable, relating to any auction or remarketing of the debt securities of that series and any security for our obligations with respect to such debt securities and any other terms which may be advisable in connection with the marketing of debt securities of that series;

whether the debt securities of the series shall be issued in whole or in part in the form of a global security or securities, the terms and conditions, if any, upon which such global security or securities may be exchanged in whole or in part for other individual securities and the depositary for such global security or securities;

if applicable, the provisions relating to conversion or exchange of any debt securities of the series and the terms and conditions upon which such debt securities will be so convertible or exchangeable, including the conversion or exchange price, as applicable, or how it will be calculated and may be adjusted, any mandatory or optional (at our option or the holders' option) conversion or exchange features, the applicable

conversion or exchange period and the manner of settlement for any conversion or exchange;

if other than the full principal amount thereof, the portion of the principal amount of debt securities of the series which shall be payable upon declaration of acceleration of the maturity thereof;

additions to or changes in the covenants applicable to the particular debt securities being issued, including, among others, the consolidation, merger or sale covenant;

additions to or changes in the events of default with respect to the securities and any change in the right of the trustee or the holders to declare the principal, premium, if any, and interest, if any, with respect to such securities to be due and payable;

additions to or changes in or deletions of the provisions relating to covenant defeasance and legal defeasance;

18.

Table of Contents

additions to or changes in the provisions relating to satisfaction and discharge of the indenture;

additions to or changes in the provisions relating to the modification of the indenture both with and without the consent of holders of debt securities issued under the indenture;

the currency of payment of debt securities if other than U.S. dollars and the manner of determining the equivalent amount in U.S. dollars;

whether interest will be payable in cash or additional debt securities at our or the holders' option and the terms and conditions upon which the election may be made;

the terms and conditions, if any, upon which we will pay amounts in addition to the stated interest, premium, if any and principal amounts of the debt securities of the series to any holder that is not a United States person for federal tax purposes;

any restrictions on transfer, sale or assignment of the debt securities of the series; and

any other specific terms, preferences, rights or limitations of, or restrictions on, the debt securities, any other additions or changes in the provisions of the indenture, and any terms that may be required by us or advisable under applicable laws or regulations.

Conversion or Exchange Rights

We will set forth in any applicable prospectus supplement the terms on which a series of debt securities may be convertible into or exchangeable for our common stock or our other securities. We will include provisions as to settlement upon conversion or exchange and whether conversion or exchange is mandatory, at the option of the holder or at our option. We may include provisions pursuant to which the number of shares of our common stock or our other securities that the holders of the series of debt securities receive would be subject to adjustment.

Consolidation, Merger or Sale

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the indenture will not contain any covenant that restricts our ability to merge or consolidate, or sell, convey, transfer or otherwise dispose of our assets as an entirety or substantially as an entirety. However, any successor to or acquirer of such assets (other than a subsidiary of ours) must assume all of our obligations under the indenture or the debt securities, as appropriate.

Events of Default under the Indenture

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the following are events of default under the indenture with respect to any series of debt securities that we may issue:

if we fail to pay any installment of interest on any series of debt securities, as and when the same shall become due and payable, and such default continues for a period of 90 days; provided, however, that a valid extension of an interest payment period by us in accordance with the terms of any indenture supplemental thereto shall not constitute a default in the payment of interest for this purpose;

if we fail to pay the principal of, or premium, if any, on any series of debt securities as and when the same shall become due and payable whether at maturity, upon redemption, by declaration or otherwise, or in any payment required by any sinking or analogous fund established with respect to such series; provided, however, that a valid extension of the maturity of such debt securities in accordance with the terms of any indenture supplemental thereto shall not constitute a default in the payment of principal or premium, if any;

if we fail to observe or perform any other covenant or agreement contained in the debt securities or the indenture, other than a covenant specifically relating to another series of debt securities, and our failure

Table of Contents

continues for 90 days after we receive written notice of such failure, requiring the same to be remedied and stating that such is a notice of default thereunder, from the trustee or holders of at least 25% in aggregate principal amount of the outstanding debt securities of the applicable series; and

if specified events of bankruptcy, insolvency or reorganization occur.

If an event of default with respect to debt securities of any series occurs and is continuing, other than an event of default specified in the last bullet point above, the trustee or the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series, by notice to us in writing, and to the trustee if notice is given by such holders, may declare the unpaid principal of, premium, if any, and accrued interest, if any, due and payable immediately. If an event of default specified in the last bullet point above occurs with respect to us, the principal amount of and accrued interest, if any, of each issue of debt securities then outstanding shall be due and payable without any notice or other action on the part of the trustee or any holder.

The holders of a majority in principal amount of the outstanding debt securities of an affected series may waive any default or event of default with respect to the series and its consequences, except defaults or events of default regarding payment of principal, premium, if any, or interest, unless we have cured the default or event of default in accordance with the indenture. Any waiver shall cure the default or event of default.

Subject to the terms of the indenture, if an event of default under an indenture shall occur and be continuing, the trustee will be under no obligation to exercise any of its rights or powers under such indenture at the request or direction of any of the holders of the applicable series of debt securities, unless such holders have offered the trustee reasonable indemnity. The holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee, or exercising any trust or power conferred on the trustee, with respect to the debt securities of that series, provided that:

the direction so given by the holder is not in conflict with any law or the applicable indenture; and

subject to its duties under the Trust Indenture Act, the trustee need not take any action that might involve it in personal liability or might be unduly prejudicial to the holders not involved in the proceeding.

A holder of the debt securities of any series will have the right to institute a proceeding under the indenture or to appoint a receiver or trustee, or to seek other remedies only if:

the holder has given written notice to the trustee of a continuing event of default with respect to that series;

the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series have made written request;

such holders have offered to the trustee indemnity satisfactory to it against the costs, expenses and liabilities to be incurred by the trustee in compliance with the request; and

the trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series other conflicting directions within 90 days after the notice, request and offer.

These limitations do not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, the debt securities.

We will periodically file statements with the trustee regarding our compliance with specified covenants in the indenture.

Table of Contents

Modification of Indenture; Waiver

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, we and the trustee may change an indenture without the consent of any holders with respect to specific matters:

to cure any ambiguity, defect or inconsistency in the indenture or in the debt securities of any series;

to comply with the provisions described above under Description of Debt Securities Consolidation, Merger or Sale;

to provide for uncertificated debt securities in addition to or in place of certificated debt securities;

to add to our covenants, restrictions, conditions or provisions such new covenants, restrictions, conditions or provisions for the benefit of the holders of all or any series of debt securities, to make the occurrence, or the occurrence and the continuance, of a default in any such additional covenants, restrictions, conditions or provisions an event of default or to surrender any right or power conferred upon us in the indenture;

to add to, delete from or revise the conditions, limitations, and restrictions on the authorized amount, terms, or purposes of issue, authentication and delivery of debt securities, as set forth in the indenture;

to make any change that does not adversely affect the interests of any holder of debt securities of any series in any material respect;

to provide for the issuance of and establish the form and terms and conditions of the debt securities of any series as provided above under Description of Debt Securities General to establish the form of any certifications required to be furnished pursuant to the terms of the indenture or any series of debt securities, or to add to the rights of the holders of any series of debt securities;

to evidence and provide for the acceptance of appointment under any indenture by a successor trustee; or

to comply with any requirements of the SEC in connection with the qualification of any indenture under the Trust Indenture Act.

In addition, under the indenture, the rights of holders of a series of debt securities may be changed by us and the trustee with the written consent of the holders of a majority in aggregate principal amount of the outstanding debt securities of each series that is affected. However, unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, we and the trustee may make the following changes only with the consent of each holder of any outstanding debt securities affected:

extending the fixed maturity of any debt securities of any series;

reducing the principal amount, reducing the rate of or extending the time of payment of interest, or reducing any premium payable upon the redemption of any series of any debt securities; or

reducing the percentage of debt securities, the holders of which are required to consent to any amendment, supplement, modification or waiver.

Discharge

Each indenture provides that we can elect to be discharged from our obligations with respect to one or more series of debt securities, except for specified obligations, including obligations to:

provide for payment;

Table of Contents

- register the transfer or exchange of debt securities of the series;
- replace stolen, lost or mutilated debt securities of the series;
- pay principal of and premium and interest on any debt securities of the series;
- maintain paying agencies;
- hold monies for payment in trust;
- recover excess money held by the trustee;
- compensate and indemnify the trustee; and
- appoint any successor trustee.

In order to exercise our rights to be discharged, we must deposit with the trustee money or government obligations sufficient to pay all the principal of, any premium, if any, and interest on, the debt securities of the series on the dates payments are due.

Form, Exchange and Transfer

We will issue the debt securities of each series only in fully registered form without coupons and, unless we provide otherwise in the applicable prospectus supplement, in denominations of \$1,000 and any integral multiple thereof. The indenture provides that we may issue debt securities of a series in temporary or permanent global form and as book-entry securities that will be deposited with, or on behalf of, The Depository Trust Company, or DTC, or another depository named by us and identified in a prospectus supplement with respect to that series. To the extent the debt securities of a series are issued in global form and as book-entry, a description of terms relating to any book-entry securities will be set forth in the applicable prospectus supplement.

At the option of the holder, subject to the terms of the indenture and the limitations applicable to global securities described in the applicable prospectus supplement, the holder of the debt securities of any series can exchange the debt securities for other debt securities of the same series, in any authorized denomination and of like tenor and aggregate principal amount.

Subject to the terms of the indenture and the limitations applicable to global securities set forth in the applicable prospectus supplement, holders of the debt securities may present the debt securities for exchange or for registration of transfer, duly endorsed or with the form of transfer endorsed thereon duly executed if so required by us or the security registrar, at the office of the security registrar or at the office of any transfer agent designated by us for this purpose. Unless otherwise provided in the debt securities that the holder presents for transfer or exchange, we will impose no service charge for any registration of transfer or exchange, but we may require payment of any taxes or other governmental charges.

We will name in the applicable prospectus supplement the security registrar, and any transfer agent in addition to the security registrar, that we initially designate for any debt securities. We may at any time designate additional transfer agents or rescind the designation of any transfer agent or approve a change in the office through which any transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

If we elect to redeem the debt securities of any series, we will not be required to:

issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or

Table of Contents

register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

Information Concerning the Trustee

The trustee, other than during the occurrence and continuance of an event of default under an indenture, undertakes to perform only those duties as are specifically set forth in the applicable indenture. Upon an event of default under an indenture, the trustee must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs. Subject to this provision, the trustee is under no obligation to exercise any of the powers given it by the indenture at the request of any holder of debt securities unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur.

Payment and Paying Agents

Unless we otherwise indicate in the applicable prospectus supplement, we will make payment of the interest on any debt securities on any interest payment date to the person in whose name the debt securities, or one or more predecessor securities, are registered at the close of business on the regular record date for the interest.

We will pay principal of and any premium and interest on the debt securities of a particular series at the office of the paying agents designated by us, except that unless we otherwise indicate in the applicable prospectus supplement, we will make interest payments by check that we will mail to the holder or by wire transfer to certain holders. Unless we otherwise indicate in the applicable prospectus supplement, we will designate the corporate trust office of the trustee as our sole paying agent for payments with respect to debt securities of each series. We will name in the applicable prospectus supplement any other paying agents that we initially designate for the debt securities of a particular series. We will maintain a paying agent in each place of payment for the debt securities of a particular series.

All money we pay to a paying agent or the trustee for the payment of the principal of or any premium or interest on any debt securities that remains unclaimed at the end of two years after such principal, premium or interest has become due and payable will be repaid to us, and the holder of the debt security thereafter may look only to us for payment thereof.

Governing Law

The indenture and the debt securities will be governed by and construed in accordance with the laws of the State of New York, except to the extent that the Trust Indenture Act is applicable.

Table of Contents

DESCRIPTION OF WARRANTS

The following description, together with the additional information we may include in any applicable prospectus supplements, summarizes the material terms and provisions of the warrants that we may offer under this prospectus and the related warrant agreements and warrant certificates. While the terms summarized below will apply generally to any warrants that we may offer, we will describe the particular terms of any series of warrants in more detail in the applicable prospectus supplement. If we indicate in the prospectus supplement, the terms of any warrants offered under that prospectus supplement may differ from the terms described below. However, no prospectus supplement shall fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness. Specific warrant agreements will contain additional important terms and provisions and will be incorporated by reference as an exhibit to the registration statement that includes this prospectus or as an exhibit to a report that we file with the SEC.

General

We will describe in the applicable prospectus supplement the terms of the series of warrants, including:

the offering price and aggregate number of warrants offered;

the currency for which the warrants may be purchased;

if applicable, the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each such security or each principal amount of such security;

if applicable, the date on and after which the warrants and the related securities will be separately transferable;

in the case of warrants to purchase debt securities, the principal amount of debt securities purchasable upon exercise of one warrant and the price at, and currency in which, this principal amount of debt securities may be purchased upon such exercise;

in the case of warrants to purchase common stock or preferred stock, the number of shares of common stock or preferred stock, as the case may be, purchasable upon the exercise of one warrant and the price at which these shares may be purchased upon such exercise;

the effect of any merger, consolidation, sale or other disposition of our business on the warrant agreements and the warrants;

the terms of any rights to redeem or call the warrants;

any provisions for changes to or adjustments in the exercise price or number of securities issuable upon exercise of the warrants;

the dates on which the right to exercise the warrants will commence and expire;

the manner in which the warrant agreements and warrants may be modified;

any material or special U.S. federal income tax consequences of holding or exercising the warrants;

the terms of the securities issuable upon exercise of the warrants; and

any other specific terms, preferences, rights or limitations of or restrictions on the warrants.

Table of Contents

Before exercising their warrants, holders of warrants will not have any of the rights of holders of the securities purchasable upon such exercise, including:

in the case of warrants to purchase debt securities, the right to receive payments of principal of, or premium, if any, or interest on, the debt securities purchasable upon exercise or to enforce covenants in the applicable indenture; or

in the case of warrants to purchase common stock or preferred stock, the right to receive dividends, if any, or payments upon our liquidation, dissolution or winding up or to exercise voting rights, if any.

Exercise of Warrants

Each warrant will entitle the holder to purchase the securities that we specify in the applicable prospectus supplement at the exercise price that we describe in the applicable prospectus supplement. Unless we otherwise specify in the applicable prospectus supplement, holders of the warrants may exercise the warrants at any time up to 5:00 P.M. eastern time on the expiration date that we set forth in the applicable prospectus supplement. After the close of business on the expiration date, unexercised warrants will become void.

Holders of the warrants may exercise the warrants by delivering the warrant certificate representing the warrants to be exercised together with specified information, and paying the required amount to the warrant agent in immediately available funds, as provided in the applicable prospectus supplement. We will set forth on the reverse side of the warrant certificate and in the applicable prospectus supplement the information that the holder of the warrant will be required to deliver to the warrant agent.

Upon receipt of the required payment and the warrant certificate properly completed and duly executed at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement, we will issue and deliver the securities purchasable upon such exercise. If fewer than all of the warrants represented by the warrant certificate are exercised, then we will issue a new warrant certificate for the remaining amount of warrants. If we so indicate in the applicable prospectus supplement, holders of the warrants may surrender securities as all or part of the exercise price for warrants.

Enforceability of Rights by Holders of Warrants

Each warrant agent will act solely as our agent under the applicable warrant agreement and will not assume any obligation or relationship of agency or trust with any holder of any warrant. A single bank or trust company may act as warrant agent for more than one issue of warrants. A warrant agent will have no duty or responsibility in case of any default by us under the applicable warrant agreement or warrant, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a warrant may, without the consent of the related warrant agent or the holder of any other warrant, enforce by appropriate legal action its right to exercise, and receive the securities purchasable upon exercise of, its warrants.

Outstanding Warrants

As of December 31, 2016, there were outstanding warrants to purchase 3,686,894 shares of our common stock, having an exercise price ranging from \$6.10 to \$818.23, with a weighted average exercise price per share of \$8.82. Any of the outstanding warrants may be exercised by applying the value of a portion of the warrant, which is equal to the number

of shares issuable under the warrant being exercised multiplied by the fair market value of the security receivable upon the exercise of the warrant, less the per share price, in lieu of payment of the exercise price per share.

The warrants will expire, if not exercised, at various times between June 22, 2017 and June 16, 2022.

Table of Contents

LEGAL OWNERSHIP OF SECURITIES

We can issue securities in registered form or in the form of one or more global securities. We describe global securities in greater detail below. We refer to those persons who have securities registered in their own names on the books that we or any applicable trustee, depository or warrant agent maintain for this purpose as the holders of those securities. These persons are the legal holders of the securities. We refer to those persons who, indirectly through others, own beneficial interests in securities that are not registered in their own names, as indirect holders of those securities. As we discuss below, indirect holders are not legal holders, and investors in securities issued in book-entry form or in street name will be indirect holders.

Book-Entry Holders

We may issue securities in book-entry form only, as we will specify in the applicable prospectus supplement. This means securities may be represented by one or more global securities registered in the name of a financial institution that holds them as depository on behalf of other financial institutions that participate in the depository's book-entry system. These participating institutions, which are referred to as participants, in turn, hold beneficial interests in the securities on behalf of themselves or their customers.

Only the person in whose name a security is registered is recognized as the holder of that security. Securities issued in global form will be registered in the name of the depository or its participants. Consequently, for securities issued in global form, we will recognize only the depository as the holder of the securities, and we will make all payments on the securities to the depository. The depository passes along the payments it receives to its participants, which in turn pass the payments along to their customers who are the beneficial owners. The depository and its participants do so under agreements they have made with one another or with their customers; they are not obligated to do so under the terms of the securities.

As a result, investors in a book-entry security will not own securities directly. Instead, they will own beneficial interests in a global security, through a bank, broker or other financial institution that participates in the depository's book-entry system or holds an interest through a participant. As long as the securities are issued in global form, investors will be indirect holders, and not holders, of the securities.

Street Name Holders

We may terminate a global security or issue securities in non-global form. In these cases, investors may choose to hold their securities in their own names or in street name. Securities held by an investor in street name would be registered in the name of a bank, broker or other financial institution that the investor chooses, and the investor would hold only a beneficial interest in those securities through an account he or she maintains at that institution.

For securities held in street name, we or any applicable trustee or depository will recognize only the intermediary banks, brokers and other financial institutions in whose names the securities are registered as the holders of those securities, and we or any applicable trustee or depository will make all payments on those securities to them. These institutions pass along the payments they receive to their customers who are the beneficial owners, but only because they agree to do so in their customer agreements or because they are legally required to do so. Investors who hold securities in street name will be indirect holders, not holders, of those securities.

Legal Holders

Our obligations, as well as the obligations of any applicable trustee and of any third parties employed by us or a trustee, run only to the legal holders of the securities. We do not have obligations to investors who hold beneficial interests in global securities, in street name or by any other indirect means. This will be the case whether an investor chooses to be an indirect holder of a security or has no choice because we are issuing the securities only in global form.

For example, once we make a payment or give a notice to the holder, we have no further responsibility for the payment or notice even if that holder is required, under agreements with depository participants or customers or by

Table of Contents

law, to pass it along to the indirect holders but does not do so. Similarly, we may want to obtain the approval of the holders to amend an indenture, to relieve us of the consequences of a default or of our obligation to comply with a particular provision of the indenture or for other purposes. In such an event, we would seek approval only from the holders, and not the indirect holders, of the securities. Whether and how the holders contact the indirect holders is up to the holders.

Special Considerations for Indirect Holders

If you hold securities through a bank, broker or other financial institution, either in book-entry form or in street name, you should check with your own institution to find out:

the performance of third party service providers;

how it handles securities payments and notices;

whether it imposes fees or charges;

how it would handle a request for the holders' consent, if ever required;

whether and how you can instruct it to send you securities registered in your own name so you can be a holder, if that is permitted in the future;

how it would exercise rights under the securities if there were a default or other event triggering the need for holders to act to protect their interests; and

if the securities are in book-entry form, how the depository's rules and procedures will affect these matters.

Global Securities

A global security is a security that represents one or any other number of individual securities held by a depository. Generally, all securities represented by the same global securities will have the same terms.

Each security issued in book-entry form will be represented by a global security that we deposit with and register in the name of a financial institution or its nominee that we select. The financial institution that we select for this purpose is called the depository. Unless we specify otherwise in the applicable prospectus supplement, DTC will be the depository for all securities issued in book-entry form.

A global security may not be transferred to or registered in the name of anyone other than the depository, its nominee or a successor depository, unless special termination situations arise. We describe those situations below under the section entitled "Special Situations When a Global Security Will Be Terminated" in this prospectus. As a result of these

arrangements, the depositary, or its nominee, will be the sole registered owner and holder of all securities represented by a global security, and investors will be permitted to own only beneficial interests in a global security. Beneficial interests must be held by means of an account with a broker, bank or other financial institution that in turn has an account with the depositary or with another institution that does. Thus, an investor whose security is represented by a global security will not be a holder of the security, but only an indirect holder of a beneficial interest in the global security.

If the prospectus supplement for a particular security indicates that the security will be issued in global form only, then the security will be represented by a global security at all times unless and until the global security is terminated. If termination occurs, we may issue the securities through another book-entry clearing system or decide that the securities may no longer be held through any book-entry clearing system.

Table of Contents

Special Considerations for Global Securities

The rights of an indirect holder relating to a global security will be governed by the account rules of the investor's financial institution and of the depository, as well as general laws relating to securities transfers. We do not recognize an indirect holder as a holder of securities and instead deal only with the depository that holds the global security.

If securities are issued only in the form of a global security, an investor should be aware of the following:

an investor cannot cause the securities to be registered in his or her name, and cannot obtain non-global certificates for his or her interest in the securities, except in the special situations we describe below;

an investor will be an indirect holder and must look to his or her own bank or broker for payments on the securities and protection of his or her legal rights relating to the securities, as we describe above;

an investor may not be able to sell interests in the securities to some insurance companies and to other institutions that are required by law to own their securities in non-book-entry form;

an investor may not be able to pledge his or her interest in a global security in circumstances where certificates representing the securities must be delivered to the lender or other beneficiary of the pledge in order for the pledge to be effective;

the depository's policies, which may change from time to time, will govern payments, transfers, exchanges and other matters relating to an investor's interest in a global security;

we and any applicable trustee have no responsibility for any aspect of the depository's actions or for its records of ownership interests in a global security, nor do we or any applicable trustee supervise the depository in any way;

the depository may, and we understand that DTC will, require that those who purchase and sell interests in a global security within its book-entry system use immediately available funds, and your broker or bank may require you to do so as well; and

financial institutions that participate in the depository's book-entry system, and through which an investor holds its interest in a global security, may also have their own policies affecting payments, notices and other matters relating to the securities.

There may be more than one financial intermediary in the chain of ownership for an investor. We do not monitor and are not responsible for the actions of any of those intermediaries.

Special Situations When a Global Security Will Be Terminated

In a few special situations described below, the global security will terminate and interests in it will be exchanged for physical certificates representing those interests. After that exchange, the choice of whether to hold securities directly or in street name will be up to the investor. Investors must consult their own banks, brokers or other financial institutions to find out how to have their interests in securities transferred to their own name, so that they will be direct holders. We have described the rights of holders and street name investors above.

Unless we provide otherwise in any applicable prospectus supplement, the global security will terminate when the following special situations occur:

if the depositary notifies us that it is unwilling, unable or no longer qualified to continue as depositary for that global security and we do not appoint another institution to act as depositary within 90 days;

if we notify any applicable trustee that we wish to terminate that global security; or

Table of Contents

if an event of default has occurred with regard to securities represented by that global security and has not been cured or waived.

The applicable prospectus supplement may also list additional situations for terminating a global security that would apply only to the particular series of securities covered by the applicable prospectus supplement. When a global security terminates, the depository, and not we or any applicable trustee, is responsible for deciding the names of the institutions that will be the initial direct holders.

Table of Contents

PLAN OF DISTRIBUTION

We may sell the securities from time to time pursuant to underwritten public offerings, direct sales to the public, negotiated transactions, block trades or a combination of these methods. We may sell the securities to or through underwriters or dealers, through agents, or directly to one or more purchasers. We may distribute securities from time to time in one or more transactions:

at a fixed price or prices, which may be changed;

at market prices prevailing at the time of sale;

at prices related to such prevailing market prices; or

at negotiated prices.

We may also sell equity securities covered by this registration statement in an at the market offering as defined in Rule 415 under the Securities Act. Such offering may be made into an existing trading market for such securities in transactions at other than a fixed price, either:

on or through the facilities of The NASDAQ Capital Market or any other securities exchange or quotation or trading service on which such securities may be listed, quoted or traded at the time of sale; and/or

other than on The NASDAQ Capital Market or such other securities exchanges or quotation or trading services

Such at the market offerings, if any, may be conducted by underwriters acting as principal or agent.

A prospectus supplement or supplements (and any related free writing prospectus that we may authorize to be provided to you) will describe the terms of the offering of the securities, including, to the extent applicable:

the name or names of the underwriters, if any;

the purchase price of the securities or other consideration therefor, and the proceeds, if any, we will receive from the sale;

any over-allotment options under which underwriters may purchase additional securities from us;

any agency fees or underwriting discounts and other items constituting agents or underwriters compensation;

any public offering price;

any discounts or concessions allowed or reallocated or paid to dealers; and

any securities exchange or market on which the securities may be listed.

Only underwriters named in the prospectus supplement will be underwriters of the securities offered by the prospectus supplement.

If underwriters are used in the sale, they will acquire the securities for their own account and may resell the securities from time to time in one or more transactions at a fixed public offering price or at varying prices determined at the time of sale. The obligations of the underwriters to purchase the securities will be subject to the conditions set forth in the applicable underwriting agreement. We may offer the securities to the public through

Table of Contents

underwriting syndicates represented by managing underwriters or by underwriters without a syndicate. Subject to certain conditions, the underwriters will be obligated to purchase all of the securities offered by the prospectus supplement, other than securities covered by any over-allotment option. Any public offering price and any discounts or concessions allowed or reallocated or paid to dealers may change from time to time. We may use underwriters with whom we have a material relationship. We will describe in the prospectus supplement, naming the underwriter, the nature of any such relationship.

We may sell securities directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of securities and we will describe any commissions we will pay the agent in the applicable prospectus supplement. Unless the applicable prospectus supplement states otherwise, our agent will act on a best-efforts basis for the period of its appointment.

We may authorize agents or underwriters to solicit offers by certain types of institutional investors to purchase securities from us at the public offering price set forth in the applicable prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. We will describe the conditions to these contracts and the commissions we must pay for solicitation of these contracts in the prospectus supplement.

We may provide agents and underwriters with indemnification against civil liabilities, including liabilities under the Securities Act, or contribution with respect to payments that the agents or underwriters may make with respect to these liabilities. Agents and underwriters may engage in transactions with, or perform services for, us in the ordinary course of business.

All securities we may offer, other than common stock, will be new issues of securities with no established trading market. Any underwriters may make a market in these securities, but will not be obligated to do so and may discontinue any market making at any time without notice. We cannot guarantee the liquidity of the trading markets for any securities.

Any underwriter may engage in over-allotment, stabilizing transactions, short-covering transactions and penalty bids in accordance with Regulation M under the Exchange Act. Over-allotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum price. Syndicate-covering or other short-covering transactions involve purchases of the securities, either through exercise of the over-allotment option or in the open market after the distribution is completed, to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a stabilizing or covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

Any underwriters or agents that are qualified market makers on The NASDAQ Capital Market may engage in passive market making transactions in the common stock on The NASDAQ Capital Market in accordance with Regulation M under the Exchange Act, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the common stock. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker's bid, however, the passive market maker's bid must then be lowered when certain purchase limits are exceeded. Passive market making may stabilize the market price of the securities at a level above that which might otherwise prevail in the open market and, if commenced, may be discontinued at any time.

In compliance with guidelines of the Financial Industry Regulatory Authority, or FINRA, the maximum consideration or discount to be received by any FINRA member or independent broker dealer may not exceed 8% of the aggregate amount of the securities offered pursuant to this prospectus and the applicable prospectus supplement.

Table of Contents

LEGAL MATTERS

Unless otherwise indicated in the applicable prospectus supplement, the validity of the securities offered by this prospectus, and any supplement thereto, will be passed upon for us by Cooley LLP, Broomfield, Colorado.

EXPERTS

The financial statements of ARCA biopharma, Inc. as of December 31, 2016 and 2015, and for each of the years in the two-year period ended December 31, 2016, have been incorporated by reference herein and in the registration statement in reliance upon the report of KPMG LLP, independent registered public accounting firm, incorporated by reference herein, and upon the authority of said firm as experts in accounting and auditing. The audit report covering the December 31, 2016, financial statements contains an explanatory paragraph that states that the Company's recurring losses from operations and the need and uncertainty related to raising additional capital to fund its clinical development programs raises substantial doubt about the Company's ability to continue as a going concern. The financial statements do not include any adjustments that might result from the outcome of that uncertainty.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus is part of a registration statement on Form S-3 we filed with the SEC. This prospectus does not contain all of the information set forth in the registration statement or the exhibits to the registration statement. For further information with respect to us and the securities we are offering under this prospectus, we refer you to the registration statement and the exhibits and schedules filed as a part of the registration statement. Whenever a reference is made in this prospectus to any of our contracts, agreements or other documents, the reference may not be complete and you should refer to the exhibits that are a part of the registration statement or the exhibits to the reports or other documents incorporated by reference into this prospectus for a copy of such contract, agreement or other document. You should rely only on the information contained in this prospectus, any accompanying prospectus supplement or incorporated by reference. We have not authorized anyone else to provide you with different information. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus or any accompanying prospectus supplement is accurate as of any date other than the date on the front page of this prospectus and the date on the front page of the applicable accompanying prospectus supplement, as applicable, regardless of the time of delivery of this prospectus and any accompanying prospectus supplement or any sale of the securities offered by this prospectus and any accompanying prospectus supplement.

We file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy the registration statement, as well as any other document filed by us with the SEC, at the SEC's Public Reference Room at 100 F Street NE, Washington, D.C. 20549. You can also request copies of these documents by writing to the SEC and paying a fee for the copying cost. You may obtain information on the operation of the Public Reference Room by calling the SEC at (800) SEC-0330. The SEC maintains a website that contains reports, proxy statements and other information regarding issuers that file electronically with the SEC, including ARCA biopharma. The address of the SEC website is www.sec.gov.

We maintain a website at www.arcabio.com. Information contained in or accessible through our website does not constitute a part of this prospectus or any accompanying prospectus supplement.

Table of Contents

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference information from other documents that we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus. Information in this prospectus supersedes information incorporated by reference that we filed with the SEC prior to the date of this prospectus, while information that we file later with the SEC will automatically update and supersede the information in this prospectus. We incorporate by reference into this prospectus and the registration statement of which this prospectus is a part the information or documents listed below that we have filed with the SEC (Commission File No. 000-22873):

our Annual Report on Form 10-K for the year ended December 31, 2016, filed with the SEC on March 21, 2017;

the information specifically incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2016 from our definitive proxy statement on Schedule 14A (other than information furnished rather than filed) filed with the SEC on April 21, 2017;

our Current Reports on Form 8-K filed with the SEC on January 11, 2017, January 18, 2017, February 21, 2017, March 1, 2017, March 6, 2017 and April 26, 2017; and

the description of our common stock set forth in our registration statement on Form 8-A filed with the SEC on July 23, 1997, including any amendments thereto or reports filed for the purpose of updating such description.

We also incorporate by reference any future filings (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items unless such Form 8-K expressly provides to the contrary) made with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, including (i) those made after the date of the initial filing of the registration statement of which this prospectus is a part and prior to effectiveness of such registration statement, and (ii) those made after the date of this prospectus until we file a post-effective amendment that indicates the termination of the offering of the securities covered by this prospectus, and will become a part of this from the date that such documents are filed with the SEC. Information in such future filings updates and supplements the information provided in this prospectus. Any statements in any such future filings will automatically be deemed to modify and supersede any information in any document we previously filed with the SEC that is incorporated or deemed to be incorporated herein by reference to the extent that statements in the later filed document modify or replace such earlier statements.

We will furnish without charge to you, on written or oral request, a copy of any or all of the documents incorporated by reference, including exhibits to these documents. You should direct any requests for documents to ARCA biopharma, Inc., Attention: Secretary, 11080 CirclePoint Road, Suite 140, Westminster, Colorado 80020. Our phone number is (720) 940-2200. In addition, all of the documents incorporated by reference into this prospectus may be accessed via the Internet at our website: <http://www.arcabio.com>.

This prospectus is part of a registration statement we filed with the SEC. That registration statement and the exhibits filed along with the registration statement contain more information about us and the shares in this offering. Because

information about documents referred to in this prospectus is not always complete, you should read the full documents which are filed as exhibits to the registration statement. You may read and copy the full registration statement and its exhibits at the SEC's public reference rooms or its website.

Table of Contents

\$2,499,876

Common Stock

Prospectus Supplement

JonesTrading

January 25, 2019