GENOCEA BIOSCIENCES, INC.
Form 424B2
July 30, 2015

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Filed Pursuant to Rule 424(b)(2)
Registration No. 333-203981

Prospectus Supplement
(To Prospectus dated May 14, 2015)

3,850,000 Shares

Common Stock

We are offering 3,850,000 shares of our common stock. Our common stock is listed on The NASDAQ Global Market under the symbol "GNCA." On July 28, 2015, the last reported sale price of our common stock on The NASDAQ Global Market was $14.57 per share.

We are an "emerging growth company" as defined under the federal securities laws and, as such, we may elect to comply with certain reduced public company reporting requirements.

Investing in our common stock involves a high degree of risk. Please read "Risk Factors" beginning on page S-8 of this prospectus supplement and in the documents incorporated by reference into this 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 supplement or the accompanying prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

	PER SHARE	*TOTAL*
Public offering price	**$ 13.00**	**$ 50,050,000**
Underwriting discounts and commissions	**$ 0.78**	**$ 3,003,000**
Proceeds to us (after expenses)	**$ 12.22**	**$ 47,047,000**

Delivery of the shares of common stock is expected to be made on or about August 4, 2015. We have granted the underwriters an option for a period of 30 days to purchase up to 577,500 additional shares of our common stock. If the underwriters exercise the option in full, the total underwriting discounts and commissions payable by us will be $3,453,450, and the total proceeds to us, before expenses, will be $54,104,050.

Joint Book-Running Managers

Cowen and Company **Piper Jaffray** **Stifel**

Co-Manager

Needham & Company

Prospectus Supplement dated July 30, 2015

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ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying prospectus relate to part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, using a shelf registration process. Both this prospectus supplement and the accompanying prospectus include or incorporate by reference important information about us, our common stock and other information you should know before investing. You should read both this prospectus supplement and the accompanying prospectus as well as additional information described under "Where You Can Find More Information" in the accompanying prospectus before making an investment decision.

We have not authorized any dealer, agent or other person to give any information or to make any representation other than those contained or incorporated by reference in this prospectus supplement and the accompanying prospectus. You must not rely upon any information or representation not contained or incorporated by reference in this prospectus supplement or the accompanying prospectus. This prospectus supplement and the accompanying prospectus do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which they relate, nor do this prospectus supplement and the accompanying prospectus constitute an offer to sell or the solicitation of an offer to buy securities in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction. You should not assume that the information contained in this prospectus supplement and the accompanying prospectus is accurate on any date subsequent to the date set forth on the front of the document or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference, even though this prospectus supplement and any accompanying prospectus is delivered or securities are sold on a later date.

This prospectus supplement may add to, update or change the information in the accompanying prospectus. If information in this prospectus supplement is inconsistent with information in the accompanying prospectus, this prospectus supplement will apply and will supersede that information in the accompanying prospectus.

Unless otherwise indicated or unless the context requires otherwise, all references in this prospectus supplement to "Genocea," "we," "us" and "our" refer to Genocea Biosciences, Inc.

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PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information included or incorporated by reference in this prospectus supplement and the accompanying prospectus and does not contain all of the information that may be important to you. You should carefully review this entire prospectus supplement and the accompanying prospectus, including the risk factors and financial statements included and incorporated by reference in this prospectus supplement and the accompanying prospectus.

Overview

We are a biopharmaceutical company that discovers and develops novel vaccines and immunotherapies to address diseases with significant unmet needs. We use our proprietary discovery platform, ATLAS, to rapidly design vaccines and immunotherapies that act, in part, through T cell (or cellular) immune responses, in contrast to approved vaccines and immunotherapies, which are designed to act primarily through B cell (or antibody) immune responses. We believe that by harnessing T cells we can develop first-in-class vaccines and immunotherapies to address diseases where T cells are central to the control of the disease.

We have two product candidates in Phase 2 clinical development: GEN-003, an immunotherapy for the treatment of genital herpes, and GEN-004, a universal vaccine for the prevention of pneumococcal infections. We also have active research and pre-clinical development programs for diseases including genital herpes, chlamydia and malaria. We are also investigating the application of ATLAS to immuno-oncology target discovery.

GEN-003 Phase 2 immunotherapy for genital herpes

Our lead program is GEN-003, a Phase 2 candidate therapeutic vaccine, or immunotherapy, that we are developing to treat genital herpes infections. Data from our double-blind, placebo-controlled, dose-escalating Phase 1/2a trial for GEN-003 represented the first reported instance of a therapeutic vaccine working against an infectious disease, and we have identified a dose in our Phase 2 trial which has showed an even greater reduction in viral shedding than the best dose in the Phase 1/2a trial.

Final analysis of the data from the Phase 1/2a trial showed that, for the best performing 30 µg dose group, there was a sustained reduction in the viral shedding rate. After completion of dosing for this group, the viral shedding rate fell by 52% versus baseline and, at six months after the final dose, the shedding rate remained at 40% below baseline. The reduction in the genital lesion rate after completion of the third dose was greatest for the 30 µg dose group at 48%. After six months, the reduction from baseline in genital lesion rate for this dose group was 65% and, after 12 months, the genital lesion rate was 42% lower than baseline. GEN-003 was well tolerated over the 12 months of this trial. We believe the six-month duration of reduced viral shedding and genital lesion rates may be clinically meaningful.

Having identified a dose that, according to company-sponsored market research, delivers clinically meaningful efficacy in magnitude and durability, we are now conducting a 310-subject Phase 2 dose optimization trial. The objective of this trial is to confirm the results of the best performing dose in the Phase 1/2a trial and to test six other combinations of proteins and adjuvant to determine the optimal dose for future trials and potentially improve on the current profile of GEN-003.

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In May 2015 we announced positive top-line data from the Phase 2 trial. Subjects were randomized to one of six dosing groups of either 30 µg or 60 µg per protein paired with one of three adjuvant doses (25 µg, 50 µg, or 75 µg). A seventh group received placebo. Subjects received three doses of GEN-003 or placebo at 21-day intervals. Baseline viral shedding and genital lesion rates were established for each subject in a 28-day observation period prior to the commencement of dosing by collecting 56 genital swab samples (two per day), which were analyzed for the presence of HSV-2 DNA, and by recording the days on which genital lesions were present. During the 28-day observation period immediately after completion of dosing, the best dose of 60 µg per protein / 75 µg of Matrix-M2 adjuvant demonstrated a highly statistically significant ($p<0.0001$) 55% reduction from baseline in the viral shedding rate, the primary endpoint of the trial and a measure of anti-viral activity. All dose combinations tested, including the successful 30 µg per protein / 50 µg of adjuvant dose from the prior Phase 1/2a trial, demonstrated a statistically significant viral shedding rate reduction versus baseline and only the lowest dose combination did not demonstrate a statistically significant reduction versus placebo. In a planned secondary analysis to assess impact on patient-reported genital lesion rates, all dose groups, including the placebo group, demonstrated a statistically significant reduction from baseline. The study showed the GEN-003 was well tolerated, with no serious adverse events related to the vaccine. Furthermore, there was no difference in discontinuations in patient dosing due to adverse events across the different treatment arms. Data from the six-month and 12-month observation periods in this trial is expected in the fourth quarter of 2015 and the first quarter of 2016, respectively.

If GEN-003 successfully completes clinical development and is approved, we believe it would represent an important new treatment option for patients with genital herpes.

GEN-004 Phase 2 universal vaccine for the prevention of pneumococcal infections

We are also developing a second T cell-stimulating vaccine candidate, GEN-004, a potential universal *Streptococcus pneumoniae*, or pneumococcus, vaccine to protect against the leading cause of infectious disease mortality worldwide. GEN-004 is designed to stimulate T helper 17 (T_H17) cells, a rare cell type that provides immunity at epithelial and mucosal surfaces, in the nasopharynx to prevent colonization by pneumococcus.

In June 2014, we announced top-line data from a Phase 1 clinical trial for GEN-004. This trial met its safety, tolerability and immunogenicity goals including measurable increases in the blood of T_H17 cells. We initiated a Phase 2a trial in September 2014 to demonstrate that GEN-004 can reduce the frequency, magnitude or duration of colonization of pneumococcus in the nasopharynx in healthy adults. We expect to announce results from this trial in the fourth quarter of 2015.

ATLAS Platform

Vaccines represent a major healthcare success story, having eradicated or significantly reduced the global prevalence of many infectious diseases. To date, all approved vaccines have been developed primarily to elicit B cell responses. However, there remain many diseases for which no effective vaccines or only partially effective vaccines exist. A major reason is that the organisms that cause these infections largely evade the antibody immune response generated by B cells, which can generally only address pathogens in the bloodstream. Such organisms may reside in host cells or mucosal surfaces of the nose and throat. To address these pathogens, vaccines targeting responses from the T cell arm of the immune system may present the solution. Furthermore, the importance of the T cell arm of the immune system is increasingly understood to be critical in the treatment of certain cancers.

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We believe T cell target discovery has been particularly challenging for two reasons. First, the diversity of human T cell responses contrasts with the generally uniform B cell responses in humans. Second, the number of candidate targets for T cell responses can be exponentially greater than for B cell responses. These complexities represent fundamental barriers that traditional vaccine discovery tools, which rely largely on empirically selecting the potential targets from the proteins of a pathogen and iteratively testing them in animal models, have not been able to address.

We have designed the ATLAS platform to overcome these T cell target discovery challenges. We believe ATLAS represents the most comprehensive high throughput system for T cell vaccine and immunotherapy discovery in the biopharmaceutical industry. ATLAS is designed to mimic the T cell arm of the human immune system in a laboratory setting. Using ATLAS, we are able to measure T cell responses to the entire set of protein targets for a specific pathogen in blood samples from large, genetically diverse populations, allowing us to identify vaccine and immunotherapy targets associated with protective T cell responses to disease. By comparing antigens identified in individuals who naturally control their infection with those who do not, we can select the antigens that may have the best likelihood of inducing protective T cell immune responses.

We believe we are a leader in the field of T cell vaccine and immunotherapy discovery and development. Our management and scientific teams possess considerable experience in vaccine, immunotherapy and anti-infective research, manufacturing, clinical development and regulatory matters.

Our Product Candidate Pipeline

The following table describes our current development programs:

Vaccine Candidate	Program	Stage of Development	Next Milestone	Anticipated Timeline
GEN-003	Genital herpes Therapeutic	Phase 2	Phase 2b dose optimization trial six-month data	Fourth quarter of 2015
GEN-004	Pneumococcus Prophylaxis	Phase 2a	Complete Phase 2a trial	Fourth quarter of 2015
GEN-005	Malaria Prophylaxis	Research	Initiate pre-clinical studies	Second half of 2015
GEN-002	HSV-2 Prophylaxis	Pre-clinical	File investigational new drug application (IND)	2017
GEN-001	Chlamydia Prophylaxis	Pre-clinical	File IND	2018

Our Team

Our management and scientific teams possess considerable experience in vaccine and anti-infective research, manufacturing, clinical development and regulatory matters. We have also assembled a team of leading advisors, led by George Siber, M.D., to guide the further development of our programs. Previously, Dr. Siber was the Chief Scientific Officer of Wyeth Vaccines, where he led the development of several first-in-class vaccines including Prevnar. He is also an inventor of Respigam and Cytogam, antibodies to treat and protect against respiratory syncytial virus and cytomegalovirus, respectively. Dr. Siber is one of our directors and chairs our Scientific Advisory Board.

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Our Strategy

Our objective is to be the leading T cell vaccine and immunotherapy company. Key components of our strategy are:

§ **Continue to rapidly advance our lead vaccine candidate, GEN-003.** GEN-003 is a potential first-in-class therapeutic vaccine candidate we are developing to treat genital herpes infections, for which we are currently conducting a Phase 2b trial to optimize the vaccine dose. We reported positive top-line data from the immediate post dosing 28-day observation period in May 2015. We identified an improved dose of 60 µg per protein / 75 µg of adjuvant, which demonstrated a highly statistically significant reduction ($p<0.0001$) from baseline in the viral shedding rate (55%) and genital lesion rate (60%). Data from the six-month and 12-month observation periods in this trial is expected in the fourth quarter of 2015 and the first quarter of 2016, respectively.

Following improvements that we have made to the manufacturing process for GEN-003, we intend to commence a small Phase 2b bridging study in the fourth quarter of 2015. Viral shedding and genital lesion rate data from this bridging study is expected in the first quarter of 2016.

In the second half of 2016, we intend to commence a Phase 2b dose regimen study and a Phase 2b study to investigate the potential benefits of using GEN-003 in combination with oral antiviral medicines. We also intend to conduct an end-of-Phase 2 meeting with the FDA in the fourth quarter of 2016.

We retain all rights to GEN-003 and plan to advance this program through regulatory approval and, if approved, commercialize this vaccine through a focused commercial effort in the United States. Outside the United States, we intend to evaluate partnerships for GEN-003 opportunistically.

§ **Continue to rapidly advance GEN-004.** Our second clinical-stage product candidate is GEN-004, a vaccine candidate designed to prevent infections caused by all strains of pneumococcus. We are currently conducting a Phase 2a clinical trial seeking to demonstrate that GEN-004 can reduce colonization of pneumococcus in the nasopharynx in healthy adults. Results from this trial are expected in the fourth quarter of 2015. We believe this trial could provide the first evidence in humans that a T cell vaccine, with potential to become a universal vaccine, can reduce colonization by pneumococcus. We intend to commence a further Phase 1/2 trial of GEN-004 in toddlers in the first half of 2016. We retain all rights to this program, other than certain rights we have granted in developing countries, and intend to evaluate partnerships for GEN-004 opportunistically.

§ **Advance our discovery stage and pre-clinical novel vaccine programs.** We expect similarly to advance our novel pre-clinical prophylactic vaccine and immunotherapy programs against chlamydia, HSV-2 and malaria through human proof of concept. We will seek partnerships opportunistically for late-stage development and commercialization of such programs.

§ **Utilize ATLAS, our vaccine discovery platform, to develop additional T cell vaccine candidates in infectious disease and oncology.** We intend to continue to use ATLAS to discover and advance novel T cell vaccines. Since we begin our vaccine candidate discovery process by profiling human populations exposed to a pathogen, and use these

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subjects' own cells to comprehensively screen the entire proteome of the pathogens, we believe we have a better chance of identifying vaccines or immunotherapies likely to protect against pathogens of interest. We will also continue to actively investigate, either alone or through partnerships, the applicability of ATLAS to cancer immunotherapies.

Recent Developments

We are currently finalizing our financial results for the fiscal quarter ended June 30, 2015. While complete financial information and operating data are not available, based on information currently available, we estimate that as of June 30, 2015, we had approximately $74.6 million of cash and cash equivalents and marketable securities. These preliminary estimates have been prepared by, and are the responsibility of, our management. Our independent registered public accounting firm, Ernst & Young LLP, has not audited or reviewed, and does not express an opinion with respect to these estimates. Our actual cash and cash equivalents and marketable securities as of June 30, 2015 may differ from these estimates due to the completion of our closing procedures with respect to the fiscal quarter ended June 30, 2015, final adjustments and other developments that may arise between now and the time the financial results for the fiscal year are finalized. We expect to complete our closing procedures with respect to the fiscal quarter ended June 30, 2015 after this offering is consummated. Accordingly, our financial statements as of and for the fiscal quarter ended June 30, 2015 will not be available until after this offering is completed.

Corporate Information

We were incorporated in the state of Delaware in August 2006 as Genocea, Inc., and we subsequently changed our name to Genocea Biosciences, Inc. Our principal executive offices are located at Cambridge Discovery Park, 100 Acorn Park Drive, 5th Floor, Cambridge, Massachusetts 02140, and our telephone number is (617) 876-8191. Our Internet website is www.genocea.com. We have included our website address in this prospectus solely as an inactive textual reference. The information on, or that can be accessed through, our website is not part of this prospectus, and you should not rely on any such information in making the decision whether to purchase our common stock.

Genocea® and the Genocea logo are our registered trademarks. The other trademarks, trade names and service marks appearing in this prospectus are the property of their respective owners.

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THE OFFERING

Common stock offered by us	3,850,000 shares
Common stock to be outstanding after this offering	27,987,395 shares
Use of proceeds	We intend to use the net proceeds from this offering to: fund the clinical development of GEN-003 and GEN-004, continue investment in new research programs, and the balance for other general corporate purposes.
Risk factors	See "Risk Factors" beginning on page S-8 and other information included or incorporated by reference in this prospectus supplement and the accompanying prospectus for a discussion of factors you should carefully consider before deciding to invest in shares of our common stock.
Underwriters' option	The underwriters have an option for a period of 30 days to purchase additional 577,500 shares of our common stock.
NASDAQ Global Market symbol	GNCA

The number of shares of our common stock to be outstanding after this offering as reflected above is based on 24,137,395 actual shares of our common stock outstanding as of March 31, 2015.

The number of shares of our common stock to be outstanding after this offering as reflected above excludes:

- 2,763,129 shares of common stock issuable upon exercise of stock options outstanding at March 31, 2015 at a weighted-average exercise price of $7.48 per share;
- 77,603 shares of common stock issuable upon the exercise of warrants outstanding at March 31, 2015 at a weighted-average exercise price of $8.21 per share;
- 313,692 shares of common stock reserved for future issuance under our 2014 Equity Incentive Plan at March 31, 2015;
- 185,154 shares of common stock reserved for future issuance under our 2014 Employee Stock Purchase Plan at March 31, 2015; and
- 14,896 shares of unvested restricted stock subject to repurchase by us at March 31, 2015.

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RISK FACTORS

An investment in our common stock involves significant risks. For a discussion of the factors that you should carefully consider before deciding to purchase any of our common stock, please review the risk factors below and those included in the documents incorporated by reference in this prospectus supplement, including Item 1A. Risk Factors included in our Annual Report on Form 10-K for the year ended December 31, 2014. In addition, please read "Forward-Looking Statements" in this prospectus supplement, where we describe additional uncertainties associated with our business and the forward-looking statements included or incorporated by reference in this prospectus supplement and the accompanying prospectus. Please note that additional risks not currently known to us or that we currently deem immaterial may also impair our business and operations.

Additional Risks Related to This Offering

We may allocate the net proceeds from this offering in ways that you and other stockholders may not approve.

We currently intend to use the net proceeds of this offering to fund the clinical development of GEN-003 and GEN-004, continue investment in new research programs, and the balance for other general corporate purposes. This expected use of the net proceeds from this offering represents our intentions based upon our current plans and business conditions. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development efforts, the status of and results from clinical trials, as well as any collaborations that we may enter into with third parties for our product candidates, and any unforeseen cash needs. Because of the number and variability of factors that will determine our use of the proceeds from this offering, their ultimate use may vary substantially from their currently intended use. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering and could spend the proceeds in ways that do not necessarily improve our operating results or enhance the value of our common stock. See "Use of Proceeds."

If you purchase our common stock in this offering, you will incur immediate and substantial dilution in the book value of your shares.

The public offering price of our common stock is substantially higher than the net tangible book value per share of our common stock. Therefore, if you purchase shares of our common stock in this offering, you will pay a price per share that substantially exceeds our net tangible book value per share after this offering. After giving effect to the sale of 3,850,000 shares of our common stock in this offering based on a public offering price of $13.00 per share, less the estimated underwriting discounts and commissions, and estimated offering expenses payable by us and based on a net tangible book value per share of our common stock of $2.89 as of March 31, 2015, if you purchase shares in this offering, you will suffer immediate and substantial dilution of $8.83 per share in the net tangible book value of common stock purchased. To the extent shares are issued under outstanding options, restricted stock units or the warrants issued to Hercules Technology Growth Capital, Inc. or future sales are made pursuant to our equity sales agreement with Cowen and Company, LLC, you will incur further dilution. See "Dilution" for a more detailed description of the dilution to new investors in the offering.

Investors in this offering may experience future dilution.

In order to raise additional capital, we may in the future offer additional shares of our common stock or other securities convertible into, or exchangeable for, our common stock at prices that may not be the same as the price per share in this offering. We cannot assure you that we will be able to

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sell shares of our common stock or other related securities in any other offering at a price per share that is equal to or greater than the price per share paid by investors in this offering. If the price per share at which we sell additional shares of our common stock or related securities in future transactions is less than the price per share in this offering, investors who purchase our common stock in this offering will suffer a dilution in their investment.

A significant portion of our total outstanding shares may be sold into the market at any time, which could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock.

Upon the completion of this offering, approximately 5,192,146 shares of our common stock beneficially owned by our officers and directors will be subject to lock-up agreements with the underwriters that prohibit, subject to certain exceptions, the disposal or pledge of, or the hedging against, any of their common stock or securities convertible into or exchangeable for shares of common stock for a period of 90 days after the date of this prospectus supplement. However, all of the shares sold in this offering and the remaining shares of our common stock outstanding prior to this offering will not be subject to lock-up agreements with the underwriters and, except to the extent such shares are held by our affiliates, will be freely tradable. In addition, the holders of a significant number of the shares outstanding, as of our initial public offering, have registration rights pursuant to which they may require us, upon request of holders of at least 50% of such shares, to register their securities for resale under the Securities Act of 1933 (including prior to the expiration of the 90-day lock up period referenced above). The market price of our common stock could decline as a result of sales by our stockholders in the market following completion of this offering or the perception that these sales could occur. These factors could also make it difficult for us to raise additional capital by selling stock.

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FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the other documents we have filed with the SEC that are incorporated by reference herein contain forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. In particular, you should consider the numerous risks described in our Annual Report on Form 10-K for the year ended December 31, 2014 incorporated by reference in this prospectus, and in the "Risk Factors" section in this prospectus supplement.

Although we believe the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, level of activity, performance or achievements. You should not rely upon forward-looking statements as predictions of future events. Unless required by law, we will not undertake and we specifically disclaim any obligation to release publicly the result of any revisions which may be made to any forward-looking statements to reflect events or circumstances after the date of such statements or to reflect the occurrence of events, whether or not anticipated. In that respect, we wish to caution readers not to place undue reliance on any such forward-looking statements, which speak only as of the date they are made.

This prospectus supplement, the accompanying prospectus and the other documents we have filed with the SEC that incorporated by reference herein include statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. Industry publications and third party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe these industry publications and third party research, surveys and studies are reliable, we have not independently verified such data.

The risks and uncertainties regarding our forward-looking statements include, among other things:

- risks related to our ability to progress any product candidates in preclinical or clinical trials;
- risks related to the scope, rate and progress of our preclinical studies and clinical trials and other research and development activities;
- the uncertainty of clinical trial results and the fact that current results may not be predictive of future results, even if the data from preclinical studies or clinical trials is positive;
- risks that our product candidates may not prove to be safe and efficacious;
- the risk that we may not be able to enter into future collaborations with industry partners and the government and the terms, timing and success of any such collaboration;
- risks relating to the cost of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights;

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- risks related to the competition for clinical resources and patient enrollment from drug candidates in development by other companies with greater resources and visibility;
- risks related to the rate of cash utilized by us in our business and the period for which existing cash will be able to fund such operation; and
- risks related to our ability to obtain adequate financing in the future through product licensing, co-promotional arrangements, public or private equity or debt financing or otherwise; general business conditions; competition; business abilities and judgment of personnel; and the availability of qualified personnel.

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USE OF PROCEEDS

We estimate that the net proceeds we will receive from this offering will be approximately $46.9 million, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise their option to purchase additional shares in full, we estimate that the net proceeds from this offering will be approximately $54.0 million.

We intend to use the net proceeds from this offering for the following purposes:

- 55% to fund clinical development for GEN-003;
- 10% to fund clinical development of GEN-004;
- 15% to continue investment in new research programs, including oncology; and
- 20% for general corporate purposes.

We believe that the net proceeds from this offering, together with our existing cash and cash equivalents and investments, will be sufficient to fund our projected operating expenses and capital expenditures to into the second half of 2017, allowing us to advance our Research and Development programs as follows:

- GEN-003: To obtain data from the six and 12 month observation periods from the ongoing Phase 2b trial, safety and efficacy data from the planned bridging study, top-line data from the planned dose regimen and antiviral combination trials and to conduct an end of Phase 2 meeting with the FDA in the fourth quarter of 2016.
- GEN-004: To obtain data from the ongoing Phase 2a human challenge study and advance GEN-004 into its next clinical study.
- Research and pre-clinical: To continue our existing pre-clinical program investments and to invest in further infectious disease and oncology discovery research programs using our ATLAS platform.

Our expected use of the net proceeds from this offering represents our intentions based upon our current plans and business conditions. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development efforts, the status of and results from clinical trials, as well as any collaborations that we may enter into with third parties for our product candidates, and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering. We have no current understandings, agreements or commitments for any material acquisitions or licenses of any compounds, product candidates or technology.

Pending our use of the net proceeds from this offering, we intend to invest the net proceeds in a variety of capital preservation investments, including short-term, investment-grade, interest-bearing instruments and U.S. government securities.

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DILUTION

If you invest in our common stock in this offering, your ownership interest will be diluted immediately to the extent of the difference between the public offering price per share of our common stock and the pro forma net tangible book value per share of our common stock after this offering.

Our historical net tangible book value as of March 31, 2015 was $69.7 million, or $2.89 per share of our common stock. Historical net tangible book value per share represents the amount of our total tangible assets less total liabilities, divided by 24,137,395 shares of our common stock outstanding.

After giving effect to the sale of 3,850,000 shares of common stock by us, at a public offering price of $13.00 per share, less the underwriting discounts and commissions and estimated offering expenses payable by us, our pro forma net tangible book value as of March 31, 2015 would have been approximately $116.6 million, or approximately $4.17 per share. This represents an immediate increase in pro forma net tangible book value per share of $1.28 to existing stockholders and immediate dilution of $8.83 in pro forma net tangible book value per share to new investors purchasing common stock in this offering.

Dilution per share to new investors is determined by subtracting pro forma net tangible book value per share after this offering from the public offering price per share paid by new investors. The following table illustrates this dilution on a per share basis.

Public offering price per share		$ 13.00
Net tangible book value per share as of March 31, 2015	$ 2.89	
Increase in net tangible book value per share attributable to new investors	$ 1.28	
Pro forma net tangible book value per share after this offering		$ 4.17
Dilution per share to new investors		$ 8.83

If the underwriters exercise their option to purchase additional shares or if any additional shares are issued under outstanding options, restricted stock or the warrants issued to Hercules Technology Growth Capital, Inc., you will experience further dilution.

The number of shares of our common stock to be outstanding upon completion of this offering as reflected in the foregoing dilution calculations excludes:

- 2,763,129 shares of common stock issuable upon exercise of stock options outstanding at March 31, 2015 at a weighted-average exercise price of $7.48 per share;
- 77,603 shares of common stock issuable upon the exercise of warrants outstanding at March 31, 2015 at a weighted-average exercise price of $8.21 per share;
- 313,692 shares of common stock reserved for future issuance under our 2014 Equity Incentive Plan at March 31, 2015;
- 185,154 shares of common stock reserved for future issuance under our 2014 Employee Stock Purchase Plan at March 31, 2015; and
- 14,896 shares of unvested restricted stock subject to repurchase by us at March 31, 2015.

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UNDERWRITING

Cowen and Company, LLC, Piper Jaffray & Co. and Stifel, Nicolaus & Company, Incorporated are acting as joint book-running managers of the offering and as representatives of the underwriters named below. Subject to the terms and conditions stated in the underwriting agreement dated the date of this prospectus, each underwriter named below has severally agreed to purchase, and we have agreed to sell to that underwriter, the number of shares set forth opposite the underwriter's name.

Underwriter	Number of Shares
Cowen and Company, LLC	1,405,250
Piper Jaffray & Co.	1,289,750
Stifel, Nicolaus & Company, Incorporated	770,000
Needham & Company, LLC	385,000
Total	3,850,000

The underwriting agreement provides that the obligations of the underwriters to purchase the shares included in this offering are subject to approval of legal matters by counsel and to other conditions. The underwriters are obligated to purchase all the shares (other than those covered by the option to purchase described below) if they purchase any of the shares.

Shares sold by the underwriters to the public will be offered at the price set forth on the cover of this prospectus. Any shares sold by the underwriters to securities dealers may be sold at a discount from the public offering price not to exceed $0.468 per share. If all the shares are not sold at the offering price, the underwriters may change the offering price and the other selling terms. The representatives have advised us that the underwriters do not intend to make sales to discretionary accounts.

If the underwriters sell more shares than the total number set forth in the table above, we have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus, to purchase up to 577,500 additional shares at the public offering price of $13.00 per share, less the underwriting discount. To the extent the option is exercised, each underwriter must purchase a number of additional shares approximately proportionate to that underwriter's initial purchase commitment. Any shares issued or sold under the option will be issued and sold on the same terms and conditions as the other shares that are the subject of this offering.

We, our officers and directors, certain of our employees and our other stockholders have agreed that, for a period of 90 days from the date of this prospectus, we and they will not, without the prior written consent of Cowen and Company, LLC, Piper Jaffray & Co. and Stifel, Nicolaus & Company, Incorporated, dispose of or hedge any shares or any securities convertible into or exchangeable for our common stock; provided, however, that we may sell shares of our common stock pursuant to our $50 million at-the-market sales program beginning 60 days after the date of this prospectus. Cowen and Company, LLC, Piper Jaffray & Co. and Stifel, Nicolaus & Company, Incorporated in their sole discretion may release any of the securities subject to these lock-up agreements at any time.

Our common stock is listed on The NASDAQ Global Market under the symbol "GNCA".

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The following table shows the underwriting discounts and commissions that we are to pay to the underwriters in connection with this offering. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase.

	Paid by Genocea	
	No Exercise	Full Exercise
Per share	$ 0.78	$ 0.78
Total	$ 3,003,000	$ 3,453,450

We estimate that our portion of the total expenses of this offering will be $146,000. We have agreed to reimburse the underwriters for certain expenses in an amount up to $30,000.

In connection with the offering, the underwriters may purchase and sell shares in the open market. Purchases and sales in the open market may include short sales, purchases to cover short positions, which may include purchases pursuant to the option to purchase, and stabilizing purchases.

- Short sales involve secondary market sales by the underwriters of a greater number of shares than they are required to purchase in the offering.
  - "Covered" short sales are sales of shares in an amount up to the number of shares represented by the underwriters' option to purchase.
  - "Naked" short sales are sales of shares in an amount in excess of the number of shares represented by the underwriters' option to purchase.
- Covering transactions involve purchases of shares either pursuant to the underwriters' option to purchase or in the open market in order to cover short positions.
  - To close a naked short position, the underwriters must purchase shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the shares in the open market after pricing that could adversely affect investors who purchase in the offering.
  - To close a covered short position, the underwriters must purchase shares in the open market or must exercise the option to purchase. In determining the source of shares to close the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the option to purchase.
- Stabilizing transactions involve bids to purchase shares so long as the stabilizing bids do not exceed a specified maximum.

Purchases to cover short positions and stabilizing purchases, as well as other purchases by the underwriters for their own accounts, may have the effect of preventing or retarding a decline in the market price of the shares. They may also cause the price of the shares to be higher than the price that would otherwise exist in the open market in the absence of these transactions. The underwriters may conduct these transactions on The NASDAQ Global Market, in the over-the-counter market or otherwise. If the underwriters commence any of these transactions, they may discontinue them at any time.

Other Relationships

The underwriters are full-service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, principal investment, hedging, financing and brokerage activities. Certain of the underwriters and their respective affiliates may, from time to time, engage in transactions with and

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perform services for us in the ordinary course of their business for which they may receive customary fees and reimbursement of expenses. In the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (which may include bank loans and/or credit default swaps) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investments and securities activities may involve securities and/or instruments of ours or our affiliates. The underwriters and their affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act, or to contribute to payments the underwriters may be required to make because of any of those liabilities.

Notice to Prospective Investors in the European Economic Area

In relation to each member state of the European Economic Area that has implemented the Prospectus Directive (each, a relevant member state), with effect from and including the date on which the Prospectus Directive is implemented in that relevant member state (the relevant implementation date), an offer of shares described in this prospectus may not be made to the public in that relevant member state other than:

- to any legal entity which is a qualified investor as defined in the Prospectus Directive;
- to fewer than 100 or, if the relevant member state has implemented the relevant provision of the 2010 PD Amending Directive, 150 natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the relevant Dealer or Dealers nominated by us for any such offer; or
- in any other circumstances falling within Article 3(2) of the Prospectus Directive,

provided that no such offer of shares shall require us or any underwriter to publish a prospectus pursuant to Article 3 of the Prospectus Directive.

For purposes of this provision, the expression an "offer of securities to the public" in any relevant member state means the communication in any form and by any means of sufficient information on the terms of the offer and the shares to be offered so as to enable an investor to decide to purchase or subscribe for the shares, as the expression may be varied in that member state by any measure implementing the Prospectus Directive in that member state, and the expression "Prospectus Directive" means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the relevant member state) and includes any relevant implementing measure in the relevant member state. The expression 2010 PD Amending Directive means Directive 2010/73/EU.

The sellers of the shares have not authorized and do not authorize the making of any offer of shares through any financial intermediary on their behalf, other than offers made by the underwriters with a view to the final placement of the shares as contemplated in this prospectus. Accordingly, no purchaser of the shares, other than the underwriters, is authorized to make any further offer of the shares on behalf of the sellers or the underwriters.

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Notice to Prospective Investors in the United Kingdom

This prospectus is only being distributed to, and is only directed at, persons in the United Kingdom that are qualified investors within the meaning of Article 2(1)(e) of the Prospectus Directive that are also (i) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the Order) or (ii) high net worth entities, and other persons to whom it may lawfully be communicated, falling within Article 49(2)(a) to (d) of the Order (each such person being referred to as a "relevant person"). This prospectus and its contents are confidential and should not be distributed, published or reproduced (in whole or in part) or disclosed by recipients to any other persons in the United Kingdom. Any person in the United Kingdom that is not a relevant person should not act or rely on this document or any of its contents.

Notice to Prospective Investors in Israel

In the State of Israel this prospectus shall not be regarded as an offer to the public to purchase shares of common stock under the Israeli Securities Law, 5728 - 1968, which requires a prospectus to be published and authorized by the Israel Securities Authority, if it complies with certain provisions of Section 15 of the Israeli Securities Law, 5728-1968, including, inter alia, if: (i) the offer is made, distributed or directed to not more than 35 investors, subject to certain conditions (the "Addressed Investors"); or (ii) the offer is made, distributed or directed to certain qualified investors defined in the First Addendum of the Israeli Securities Law, 5728 - 1968, subject to certain conditions (the "Qualified Investors"). The Qualified Investors shall not be taken into account in the count of the Addressed Investors and may be offered to purchase securities in addition to the 35 Addressed Investors. The company has not and will not take any action that would require it to publish a prospectus in accordance with and subject to the Israeli Securities Law, 5728 - 1968. We have not and will not distribute this prospectus or make, distribute or direct an offer to subscribe for our common stock to any person within the State of Israel, other than to Qualified Investors and up to 35 Addressed Investors. Qualified Investors may have to submit written evidence that they meet the definitions set out in of the First Addendum to the Israeli Securities Law, 5728 - 1968. In particular, we may request, as a condition to be offered common stock, that Qualified Investors will each represent, warrant and certify to us and/or to anyone acting on our behalf: (i) that it is an investor falling within one of the categories listed in the First Addendum to the Israeli Securities Law, 5728 - 1968; (ii) which of the categories listed in the First Addendum to the Israeli Securities Law, 5728 - 1968 regarding Qualified Investors is applicable to it; (iii) that it will abide by all provisions set forth in the Israeli Securities Law, 5728 - 1968 and the regulations promulgated thereunder in connection with the offer to be issued common stock; (iv) that the shares of common stock that it will be issued are, subject to exemptions available under the Israeli Securities Law, 5728 - 1968: (a) for its own account; (b) for investment purposes only; and (c) not issued with a view to resale within the State of Israel, other than in accordance with the provisions of the Israeli Securities Law, 5728 - 1968; and (v) that it is willing to provide further evidence of its Qualified Investor status. Addressed Investors may have to submit written evidence in respect of their identity and may have to sign and submit a declaration containing, inter alia, the Addressed Investor's name, address and passport number or Israeli identification number.

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MATERIAL UNITED STATES FEDERAL INCOME AND ESTATE TAX CONSIDERATIONS FOR NON-U.S. HOLDERS OF SHARES OF OUR COMMON STOCK

The following is a summary of certain material United States federal income and estate tax considerations relating to the purchase, ownership, and disposition of shares of our common stock by a non-U.S. holder (as defined below) that acquires our common stock in this offering and holds it as a capital asset within the meaning of Section 1221 of the Internal Revenue Code of 1986, as amended, or the Code. For purposes of this summary, a "non-U.S. holder" is a beneficial owner of our common stock that, for United States federal income tax purposes, is an individual, corporation, estate or trust other than:

- an individual who is a citizen or resident of the United States;
- a corporation, or any other organization taxable as a corporation for United States federal income tax purposes, that is created or organized under the laws of the United States, any state thereof, or the District of Columbia;
- an estate the income of which is subject to United States federal income taxation regardless of its source; or
- a trust if (1) a court within the United States is able to exercise primary supervision over the trust's administration and one or more United States persons (as defined in the Code) have the authority to control all substantial decisions of that trust, or (2) the trust has in effect a valid election under the applicable Treasury regulations to be treated as a United States person.

A modified definition of "non-U.S. holder" applies for United States federal estate tax purposes (as discussed below).

This summary is based upon the Code, Treasury regulations promulgated or proposed thereunder, judicial decisions, rulings, and administrative interpretations thereof, all as of the date hereof and all of which are subject to change, possibly with retroactive effect. The foregoing are subject to differing interpretations which could affect the tax consequences described herein. This summary does not purport to be a complete analysis of all the potential tax considerations relevant to non-U.S. holders of our common stock. In addition, this summary does not address all aspects of United States federal income and estate taxation that may be applicable to non-U.S. holders in light of their particular circumstances or status, nor does it address specific tax considerations that may be relevant to particular persons (including, for example, financial institutions, broker-dealers, insurance companies, partnerships or other pass-through entities, certain United States expatriates, tax-exempt organizations, pension plans, "controlled foreign corporations," "passive foreign investment companies," corporations that accumulate earnings to avoid United States federal income tax, persons in special situations, such as those who have elected to mark securities to market or those who hold shares of our common stock as part of a straddle, hedge, conversion transaction, synthetic security or other integrated investment, persons that have a "functional currency" other than the U.S. dollar, or holders subject to the alternative minimum tax). In addition, except as explicitly addressed herein with respect to estate tax, this summary does not address certain estate and any gift tax considerations or considerations under the tax laws of any state, local or non-United States jurisdiction.

If a partnership (including any entity or arrangement treated as a partnership for United States federal income tax purposes) owns our common stock, the tax treatment of a person treated as a partner in the partnership for United States federal income tax purposes generally will depend upon the status of the partner and the activities of the partnership. Partnerships and other entities that are

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treated as partnerships for United States federal income tax purposes and persons holding our common stock through a partnership or other entity treated as a partnership for United States federal income tax purposes should consult their tax advisors.

There can be no assurance that the Internal Revenue Service, or IRS, will not challenge one or more of the tax consequences described herein, and we have not obtained, nor do we intend to obtain, a ruling from the IRS or an opinion of counsel with respect to the United States federal income or estate tax consequences to a non-U.S. holder of the purchase, ownership or disposition of our common stock.

THIS SUMMARY IS FOR GENERAL INFORMATION ONLY AND IS NOT INTENDED TO BE TAX ADVICE. YOU ARE URGED TO CONSULT YOUR TAX ADVISOR REGARDING THE UNITED STATES FEDERAL INCOME AND ESTATE TAXATION, STATE, LOCAL, AND NON-UNITED STATES TAXATION AND OTHER TAX CONSEQUENCES OF THE PURCHASE, OWNERSHIP, AND DISPOSITION OF OUR COMMON STOCK, INCLUDING THE CONSEQUENCES UNDER ANY APPLICABLE TAX TREATY.

Distributions on our shares of our common stock

We do not currently expect to pay dividends. In the event we do make a distribution of cash or property with respect to our common stock, any such distributions generally will constitute dividends for United States federal income tax purposes to the extent of our current or accumulated earnings and profits, as determined under United States federal income tax principles, and will be subject to withholding as described in the next paragraph below. If a distribution exceeds our current and accumulated earnings and profits, the excess will be treated as a tax-free return of the non-U.S. holder's investment, up to such holder's adjusted tax basis in shares of our common stock. Any remaining excess will be treated as capital gain, subject to the tax treatment described below in "Gain on Sale, exchange or other taxable disposition of our common stock." Any distribution described in this paragraph would also be subject to the discussion below in "Additional withholding and reporting requirements."

Any dividends paid to a non-U.S. holder with respect to shares of our common stock generally will be subject to withholding of United States federal tax at a 30% rate unless such non-U.S. holder provides us or our agent, as the case may be, with the appropriate IRS Form W-8 prior to the payment of dividends, such as:

- IRS Form W-8BEN or W-8BEN-E, as applicable (or successor form), certifying, under penalties of perjury, that such non-U.S. holder is entitled to a reduction in withholding under an applicable income tax treaty, or
- IRS Form W-8ECI (or successor form) certifying, under penalties of perjury that a dividend paid on our common stock is not subject to withholding tax because it is effectively connected with the conduct of a trade or business in the United States of the non-U.S. holder (and, if required by an applicable income tax treaty, is attributable to a permanent establishment or fixed base maintained in the U.S.) (in which case such dividend generally will be subject to graduated United States federal income tax rates on a net income basis as described below).

The certification requirement described above also may require a non-U.S. holder that provides an IRS form or that claims treaty benefits to provide its United States taxpayer identification number.

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Each non-U.S. holder is urged to consult its own tax advisor about the specific methods for satisfying these requirements. A claim for exemption will not be valid if the person receiving the applicable form has actual knowledge or reason to know that the statements on the form are false.

If dividends are "effectively connected" with the conduct of a trade or business in the United States of a non-U.S. holder (and, if required by an applicable income tax treaty, are attributable to a permanent establishment or fixed base maintained by such non-U.S. holder in the United States), the non-U.S. holder, although exempt from the withholding tax described above (provided that the certifications described above are satisfied), will generally be subject to United States federal income tax on such dividends on a net income basis in the same manner as if it were a resident of the United States. In addition, if the non-U.S. holder is taxable as a corporation for United States federal income tax purposes, such holder may, under certain circumstances, be subject to an additional "branch profits tax" equal to 30% (unless reduced by an applicable income tax treaty) of its effectively connected earnings and profits for the taxable year.

If a non-U.S. holder is eligible for a reduced rate of United States federal withholding tax pursuant to an applicable income tax treaty, such holder may obtain a refund or credit of any amounts withheld in excess of that rate by timely filing an appropriate refund claim with the IRS.

Gain on sale, exchange or other taxable disposition of shares of our common stock

Subject to the discussion below under "Additional withholding and reporting requirements," a non-U.S. holder generally will not be subject to United States federal income tax or withholding tax on gain realized upon a sale, exchange or other taxable disposition of shares of our common stock (including a redemption, but only if the redemption would be treated as a sale or exchange rather than a distribution for United States federal income tax purposes) unless:

(1) the gain is "effectively connected" with the conduct of a trade or business of the non-U.S. holder in the United States (and, if required by an applicable income tax treaty, the gain is attributable to a permanent establishment or fixed base maintained in the United States);

(2) the non-U.S. holder is an individual who is present in the United States for 183 or more days in the taxable year of the disposition and meets certain other conditions; or

(3) we are or have been a "United States real property holding corporation", or USRPHC, for United States federal income tax purposes at any time within the shorter of the five-year period preceding the disposition and the non-U.S. holder's holding period for our common stock (the "relevant period").

If the first exception applies, the non-U.S. holder generally will be subject to United States federal income tax on a net income basis with respect to such gain in the same manner as if such holder were a resident of the United States. In addition, if the non-U.S. holder is a corporation for United States federal income tax purposes, such gains may, under certain circumstances, also be subject to an additional "branch profits tax" at a 30% rate (or at a lower rate under an applicable income tax treaty).

If the second exception applies, the non-U.S. holder generally will be subject to United States federal income tax at a rate of 30% (unless an applicable income tax treaty provides otherwise) on the amount by which such non-U.S. holder's capital gains allocable to United States sources exceed capital losses allocable to United States sources during the taxable year of the disposition.

With respect to the third exception above, although there can be no assurances, we believe we currently are not, and we do not anticipate becoming, a USRPHC for United States federal income tax purposes. However, because the determination of whether we are a USRPHC depends on the

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fair market value of our United States real property interests relative to the fair market value of our other trade or business assets and our foreign real property interests, there can be no assurance that we will not become a USRPHC in the future. Generally, a corporation is a USRPHC only if the fair market value of its United States real property interests (as defined in the Code) equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business. Even if we are or become a USRPHC, a non-U.S. holder would not be subject to U.S. federal income tax on a sale, exchange or other taxable disposition of our common stock by reason of our status as a USRPHC so long as (i) our common stock continues to be regularly traded on an established securities market (within the meaning of Section 897(c)(3) of the Code) during the calendar year in which such disposition occurs and (ii) such non-U.S. holder does not own and is not deemed to own (directly, indirectly or constructively) more than 5% of our common stock at any time during the relevant period. If we are a USRPHC and the requirements of (i) or (ii) are not met, gain on the disposition of shares of our common stock generally will be taxed in the same manner as gain that is effectively connected with the conduct of a U.S. trade or business, except that the "branch profits tax" will not apply.

Additional withholding and reporting requirements

Legislation (commonly referred to as "FATCA") imposes United States federal withholding at a rate of 30% on payments to certain non-U.S. entities (including financial intermediaries), including dividends on, and the gross proceeds from, dispositions of our common stock, unless various information reporting and due diligence requirements, which are different from and in addition to the certification requirements described elsewhere in this discussion, have been satisfied (generally relating to ownership by U.S. persons of interests in or accounts with those non-U.S. entities). These requirements may be met by satisfying the requirements of an intergovernmental agreement between the United States and a foreign country where a holder or intermediary is located. The withholding rules applicable to payments of dividends is currently in effect, and the withholding rules will apply to gross proceeds from dispositions of our common stock beginning January 1, 2017. Although Treasury regulations implementing FATCA have been finalized, certain aspects of these rules remain unclear and subject to change. Non-U.S. holders should consult their tax advisors regarding the possible implications of FATCA on their investment in our common stock.

Information reporting and backup withholding

We must report annually to the IRS and to each non-U.S. holder the gross amount of the distributions on our common stock paid to such holder and the tax withheld, if any, with respect to such distributions, regardless of whether withholding was required. A non-U.S. holder will generally be subject to backup withholding on dividends paid to such holder unless such holder furnishes a valid IRS Form W-8BEN or W-8BEN-E, as applicable (or such other applicable form and documentation as required by the Code or the Treasury regulations), certifying under penalties of perjury that it is a non-U.S. holder (and the payor does not have actual knowledge or reason to know that such holder is a United States person as defined under the Code), or such holder otherwise establishes an exemption. Dividends paid to non-U.S. holders subject to the United States federal withholding tax, as described above in "Distributions on shares of our common stock," generally will be exempt from U.S. backup withholding.

Information reporting and, depending on the circumstances, backup withholding will apply to the payment of the proceeds of a sale or other disposition of shares of our common stock by a non-U.S. holder effected by or through the United States office of any broker, United States or foreign, unless the holder certifies that it is not a United States person (as defined under the Code) and satisfies certain other requirements, or otherwise establishes an exemption. Generally, information reporting and backup withholding will not apply to a payment of disposition proceeds to a non-U.S. holder

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where the transaction is effected outside the United States through a non-United States office of a broker. However, for information reporting purposes, dispositions effected through a non-United States office of a broker with substantial United States ownership or operations generally will be treated in a manner similar to dispositions effected through a United States office of a broker. Prospective investors should consult their own tax advisors regarding the application of the information reporting and backup withholding rules to them.

Copies of the information returns may be made available to the tax authorities in the country in which the non-U.S. holder resides or is incorporated under the provisions of an applicable treaty or agreement.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules may be allowed as a credit against a non-U.S. holder's United States federal income tax liability, if any, and may entitle such holder to a refund, provided that an appropriate claim is timely filed with the IRS.

Federal estate taxes

Shares of our common stock held (or treated as held) by an individual who is not a United States citizen or resident (as specifically determined for United States federal estate tax purposes) at the time of such individual's death generally will be included in the holder's gross estate for United States federal estate tax purposes, unless an applicable estate tax or other treaty provides otherwise, and, therefore, may be subject to United States federal estate tax.

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INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" into this prospectus supplement the information 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 information in documents that we file later with the SEC will automatically update and supersede information in this prospectus supplement. We incorporate by reference into this prospectus supplement the documents listed below and any future filings made by us with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act, except for information "furnished" under Items 2.02, 7.01 or 9.01 on Form 8-K or other information "furnished" to the SEC which is not deemed filed and not incorporated in this prospectus supplement, until the termination of the offering of securities described in the applicable prospectus supplement. We hereby incorporate by reference the following documents:

- Our Annual Report on Form 10-K for the year ended December 31, 2014, as filed with the SEC on February 27, 2015;
- Our Quarterly Report on Form 10-Q for the quarter ended March 31, 2015, as filed with the SEC on May 8, 2015;
- Our Current Reports on Form 8-K filed with the SEC on February 27, 2015, March 12, 2015, May 20, 2015 (except for Item 7.01), June 8, 2015 and June 19, 2015; and
- Description of our common stock, which is contained in the Registration Statement on Form 8-A, as filed with the SEC on January 30, 2014, as supplemented by the Description of Common Stock found on page 10 of the accompanying prospectus and including any amendments or reports filed for the purpose of updating such description.

You may request a copy of these filings, at no cost, by writing or telephoning us at the following address:

Investor Relations
100 Acorn Park Drive, 5th Floor,
Cambridge, Massachusetts 02140,
(617) 876-8191
email address: ir@genocea.com

Copies of these filings are also available, without charge, on the SEC's website at www.sec.gov and on our website at www.genocea.com as soon as reasonably practicable after they are filed electronically with the SEC. The information contained on our website is not a part of this prospectus supplement.

LEGAL MATTERS

The validity of the shares of common stock offered hereby is being passed upon for us by Ropes & Gray LLP, Boston, Massachusetts. Cooley, LLP, Boston, Massachusetts will pass upon certain legal matters relating to this offering for the underwriters.

EXPERTS

The financial statements of Genocea Biosciences, Inc. appearing in Genocea Biosciences, Inc.'s Annual Report (Form 10-K) for the year ended December 31, 2014, have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon, included therein, and incorporated herein by reference. Such financial statements are incorporated herein by reference in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

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PROSPECTUS

$250,000,000

Common Stock

Preferred Stock

Warrants

We may offer and sell from time to time, in one or more series or issuances and on terms that we will determine at the time of the offering, any combination of the securities described in this prospectus, up to an aggregate amount of $250.0 million.

We will provide specific terms of any offering in a supplement to this prospectus. Any prospectus supplement may also add, update, or change information contained in this prospectus. You should carefully read this prospectus and the applicable prospectus supplement as well as the documents incorporated or deemed to be incorporated by reference in this prospectus before you purchase any of the securities offered hereby.

These securities may be offered and sold in the same offering or in separate offerings; to or through underwriters, dealers, and agents; or directly to purchasers. The names of any underwriters, dealers, or agents involved in the sale of our securities and their compensation will be described in the applicable prospectus supplement.

Our common stock is traded on The NASDAQ Global Market under the symbol "GNCA." On May 6, 2015, the closing price of our common stock was $9.81.

Investing in our securities involves risks. See "Risk Factors" on page 6, and any applicable prospectus supplement, and under similar headings in the other documents that are incorporated by reference into this prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

Prospectus dated May 14, 2015

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You should rely only on the information contained in, or incorporated by reference into, this prospectus. We have not authorized anyone to give you information different from that contained in this prospectus. We are not making an offer to sell these securities in any jurisdiction where the offer is not permitted. The information contained in this prospectus is accurate only as of the date on the front cover of this prospectus, regardless of when this prospectus is delivered or when any sale of our securities occurs. Our business, financial condition, results of operations and prospects may have changed since that date.

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ABOUT THIS PROSPECTUS

This prospectus is a part of a registration statement that we filed with the Securities and Exchange Commission (the "SEC") using a "shelf" registration process. Under this shelf registration process, we may offer to sell any combination of the securities described in this prospectus in one or more offerings up to a total dollar amount of $250.0 million. Each time we sell securities under this shelf registration, we will provide a prospectus supplement that will contain specific information about the terms of that offering. The prospectus supplement may also add, update or change information contained in this prospectus. You should read both this prospectus and the applicable prospectus supplement, including all documents incorporated herein by reference, together with additional information described under "Where You Can Find More Information" below.

This prospectus does not include all of the information that is in the registration statement. We omitted certain parts of the registration statement from this prospectus as permitted by the SEC. We refer you to the registration statement and its exhibits for additional information about us and the securities that may be sold under this prospectus.

We have not authorized any dealer, agent or other person to give any information or to make any representation other than those contained or incorporated by reference in this prospectus and any accompanying prospectus supplement. You must not rely upon any information or representation not contained or incorporated by reference in this prospectus or an accompanying prospectus supplement. This prospectus and the accompanying prospectus supplement, if any, do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which they relate, nor do this prospectus and the accompanying prospectus supplement constitute an offer to sell or the solicitation of an offer to buy securities in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction. You should not assume that the information contained in this prospectus and the accompanying prospectus supplement, if any, is accurate on any date subsequent to the date set forth on the front of the document or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference, even though this prospectus and any accompanying prospectus supplement is delivered or securities are sold on a later date.

"Genocea," the "Company," "we," "us," "our" and similar names refer to Genocea Biosciences, Inc. unless we state otherwise or the context otherwise requires.

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SUMMARY

This summary highlights selected information contained elsewhere or incorporated by reference in this prospectus. The summary may not contain all the information that you should consider before investing in our common stock. You should read the entire prospectus carefully, including "Risk Factors" contained in this prospectus and the documents incorporated by reference herein, before making an investment decision.

Overview

We are a biopharmaceutical company that discovers and develops novel vaccines and immunotherapies to address diseases with significant unmet needs. We use our proprietary discovery platform, ATLAS, to rapidly design vaccines and immunotherapies that act, in part, through T cell (or cellular) immune responses, in contrast to approved vaccines and immunotherapies, which are designed to act primarily through B cell (or antibody) immune responses. We believe that by harnessing T cells we can develop first-in-class vaccines and immunotherapies to address diseases where T cells are central to the control of the disease.

We have two product candidates in Phase 2 clinical development: GEN-003, an immunotherapy for the treatment of genital herpes and GEN-004, a universal vaccine for the prevention of pneumococcal infections. We also have product candidates in pre-clinical development for diseases including genital herpes, chlamydia and malaria.

GEN-003 Phase 2 immunotherapy for genital herpes

Our lead program is GEN-003, a Phase 2 candidate therapeutic vaccine, or immunotherapy, that we are developing to treat genital herpes infections. Data from our double-blind, placebo-controlled, dose-escalating Phase 1/2a trial for GEN-003 represented the first reported instance of a therapeutic vaccine working against an infectious disease.

Final analysis of the data from the Phase 1/2a trial showed that, for the best performing 30µg dose group, there was a sustained reduction in the viral shedding rate. After completion of dosing for this group, the viral shedding rate fell by 52% versus baseline and, at six months after the final dose, the shedding rate remained at 40% below baseline. At 12 months, the viral shedding rate returned to baseline for this dose group. The reduction in the genital lesion rate after completion of the third dose was greatest for the 30µg dose group at 48%. After six months, the reduction from baseline in genital lesion rate for this dose group was 65% and, after 12 months, the genital lesion rate was 42% lower than baseline. GEN-003 was safe and well tolerated over the 12 months of this trial. We believe the six-month duration of reduced viral shedding and genital lesion rates may be clinically meaningful.

Having identified a dose that, according to company-sponsored market research, delivers clinically meaningful efficacy in magnitude and durability, we are now conducting a 310-subject Phase 2 dose optimization trial. The objective of this trial is to test six combinations of proteins and adjuvant, including the best-performing 30µg per protein / 50µg of adjuvant dose from the Phase 1/2a trial, to determine the optimal dose for future trials. This trial is fully enrolled and we expect to announce top-line data from this trial late in the second quarter of 2015. If GEN-003 successfully completes clinical development and is approved, we believe it would represent an important new treatment option for patients with genital herpes.

GEN-004 Phase 2 universal vaccine for the prevention of pneumococcal infections

We are also developing a second T cell-stimulating vaccine candidate, GEN-004, a potential universal *Streptococcus pneumoniae*, or pneumococcus, vaccine to protect against the leading cause of infectious disease mortality worldwide. GEN-004 is designed to stimulate T helper 17 (TH17) cells, a rare cell type that provides immunity at epithelial and mucosal surfaces, in the nasopharynx to prevent colonization by pneumococcus.

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In June 2014, we announced top-line data from a Phase 1 clinical trial for GEN-004. This trial met its safety, tolerability and immunogenicity goals including measurable increases in the blood of TH17 cells. We initiated a 98-subject Phase 2a trial in September 2014 to demonstrate that GEN-004 can reduce the frequency, magnitude or duration of colonization of pneumococcus in the nasopharynx in healthy adults. This trial is fully enrolled and we expect to announce top-line data from this trial in the fourth quarter of 2015.

ATLAS Platform

Vaccines represent a major healthcare success story, having eradicated or significantly reduced the global prevalence of many infectious diseases. To date, all approved vaccines have been developed primarily to elicit B cell responses. However, there remain many infections for which no effective vaccines or only partially effective vaccines exist. A major reason is that the organisms that cause these infections largely evade the antibody immune response generated by B cells, which can generally only address pathogens in the bloodstream. Such organisms may reside in host cells or mucosal surfaces of the nose and throat. To address these pathogens, vaccines targeting responses from the T cell arm of the immune system may present the solution.

We believe T cell target discovery has been particularly challenging for two reasons. First, the diversity of human T cell responses contrasts with the generally uniform B cell responses in humans. Second, the number of candidate targets for T cell responses can be exponentially greater than for B cell responses. These complexities represent fundamental barriers that traditional vaccine discovery tools, which rely largely on empirically selecting the potential targets from the proteins of a pathogen and iteratively testing them in animal models, have not been able to address.

We have designed the ATLAS platform to overcome these T cell target discovery challenges. We believe ATLAS represents the most comprehensive high throughput system for T cell vaccine and immunotherapy discovery in the biopharmaceutical industry. ATLAS is designed to mimic the T cell arm of the human immune system in a laboratory setting. Using ATLAS, we are able to measure T cell responses to the entire set of protein targets for a specific pathogen in blood samples from large, genetically diverse populations, allowing us to identify vaccine and immunotherapy targets associated with protective T cell responses to disease. By comparing antigens identified in individuals who naturally control their infection with those who do not, we can select the antigens that may have the best likelihood of inducing protective T cell immune responses.

We believe we are a leader in the field of T cell vaccine and immunotherapy discovery and development. Our management and scientific teams possess considerable experience in vaccine, immunotherapy and anti-infective research, manufacturing, clinical development and regulatory matters.

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Our Product Candidate Pipeline

The following table describes our current development programs:

Vaccine Candidate	Program	Stage of Development	Next Milestone	Anticipated Timeline
GEN-003	Genital herpes Therapeutic	Phase 2	Top-line data from Phase 2 dose optimization trial	Late second quarter of 2015
GEN-004	Pneumococcus Prophylaxis	Phase 2a	Top-line data from Phase 2a trial	Fourth quarter of 2015
GEN-001	Chlamydia Prophylaxis	Pre-clinical	File investigational new drug application (or IND)	2017
GEN-002	HSV-2 Prophylaxis	Pre-clinical	File IND	2017
GEN-005	Malaria Prophylaxis	Research	Initiate pre-clinical studies	Second half of 2015

Our Team

Our management and scientific teams possess considerable experience in vaccine and anti-infective research, manufacturing, clinical development and regulatory matters. We have also assembled a team of leading advisors, led by George Siber, M.D., to guide the further development of our programs. Previously, Dr. Siber was the Chief Scientific Officer of Wyeth Vaccines, where he led the development of several first-in-class vaccines including Prevnar. He is also an inventor of Respigam and Cytogam, antibodies to treat and protect against respiratory syncytial virus and cytomegalovirus, respectively. Dr. Siber is one of our directors and chairs our Scientific Advisory Board.

Our Strategy

Our objective is to be the leading T cell vaccine and immunotherapy company. Key components of our strategy are:

Continue to rapidly advance our lead vaccine candidate, GEN-003. GEN-003 is a potential first-in-class therapeutic vaccine candidate we are developing to treat genital herpes infections, for which we are currently conducting a Phase 2 trial to optimize the vaccine dose. Top-line data from this trial is expected late in the second quarter of 2015. We intend to commence a Phase 2b trial in the second half of 2015 to optimize the dosing regimen. We retain all rights to GEN-003 and plan to advance this program through regulatory approval and, if approved, commercialize this vaccine through a focused commercial effort in the United States. Outside the United States, we intend to evaluate partnerships for GEN-003 opportunistically.

Continue to rapidly advance GEN-004. Our second clinical-stage product candidate is GEN-004, a vaccine candidate designed to prevent infections caused by all strains of pneumococcus. We are currently conducting a Phase 2a clinical trial to seek to demonstrate that GEN-004 can reduce colonization of pneumococcus in the nasopharynx in healthy adults. Top-line data from this trial is expected in the fourth quarter of 2015. We believe this trial could provide the first evidence in humans that a T cell vaccine, with potential to become a universal vaccine, can reduce colonization by pneumococcus. We intend to commence a further Phase 1/2 trial of GEN-004 in toddlers in 2016. We retain all rights to this program, other than certain rights we have granted in developing countries, and intend to evaluate partnerships for GEN-004 opportunistically.

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Advance our discovery stage and non-clinical novel vaccine programs. We expect similarly to advance our novel non-clinical prophylactic vaccine and immunotherapy programs against chlamydia, HSV-2 and malaria through human proof of concept. We will seek partnerships opportunistically for late-stage development and commercialization of such programs.

Utilize ATLAS, our vaccine discovery platform, to develop additional T cell vaccine candidates. We intend to continue to use ATLAS to discover and advance novel T cell vaccines. Since we begin our vaccine candidate discovery process by profiling human populations exposed to a pathogen, and use these subjects' own cells to comprehensively screen the entire proteome of the pathogens, we believe we have a better chance of identifying vaccines likely to protect against pathogens of interest. We intend to opportunistically expand our pipeline using ATLAS to discover T cell vaccines against pathogens for which B cell vaccines are ineffective or non-existent. We will also continue to investigate, either alone or through partnerships, the applicability of ATLAS to cancer immunotherapies.

Corporate Information

We were incorporated in the state of Delaware in August 2006 as Genocea, Inc., and we subsequently changed our name to Genocea Biosciences, Inc. Our principal executive offices are located at Cambridge Discovery Park, 100 Acorn Park Drive, 5th Floor, Cambridge, Massachusetts 02140, and our telephone number is (617) 876-8191. Our Internet website is www.genocea.com. We have included our website address in this prospectus solely as an inactive textual reference. The information on, or that can be accessed through, our website is not part of this prospectus, and you should not rely on any such information in making the decision whether to purchase our common stock.

Genocea® and the Genocea logo are our registered trademarks. The other trademarks, trade names and service marks appearing in this prospectus are the property of their respective owners.

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RISK FACTORS

Investing in our securities involves a high degree of risk. See "Item 1A Risk Factors" in our most recent Annual Report on Form 10-K and in any subsequent Quarterly Report on Form 10-Q incorporated by reference in this prospectus, in any other documents we file with the SEC that are deemed incorporated by reference into this prospectus and the "Risk Factors" section in the applicable prospectus supplement for a discussion of the factors you should carefully consider before deciding to purchase our securities. Before you invest in our securities, you should carefully consider these risks as well as other information we include or incorporate by reference into this prospectus and the applicable prospectus supplement. The risks and uncertainties we have described are not the only ones facing our company. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our business operations. The occurrence of any of these risks might cause you to lose all or part of your investment in the offered securities. The discussion of risks includes or refers to forward-looking statements; you should read the explanation of the qualifications and limitations on such forward-looking statements discussed elsewhere in this prospectus.

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FORWARD-LOOKING STATEMENTS

This prospectus, any prospectus supplement and the other documents we have filed with the SEC that are incorporated herein by reference, contain forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. In particular, you should consider the numerous risks described in our Annual Report on Form 10-K for the year ended December 31, 2014 and any subsequent Quarterly Reports on Form 10-Q, each incorporated by reference in this prospectus, and in the "Risk Factors" section in the applicable prospectus supplement. See "Where You Can Find More Information."

Although we believe the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, level of activity, performance or achievements. You should not rely upon forward-looking statements as predictions of future events. Unless required by law, we will not undertake and we specifically disclaim any obligation to release publicly the result of any revisions which may be made to any forward-looking statements to reflect events or circumstances after the date of such statements or to reflect the occurrence of events, whether or not anticipated. In that respect, we wish to caution readers not to place undue reliance on any such forward-looking statements, which speak only as of the date they are made.

This prospectus and the other documents incorporated by reference herein include statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. Industry publications and third party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe these industry publications and third party research, surveys and studies are reliable, we have not independently verified such data.

These risks and uncertainties include, among other things:

- risks related to our ability to progress any product candidates in preclinical or clinical trials;
- risks related to the scope, rate and progress of our preclinical studies and clinical trials and other research and development activities;
- the uncertainty of clinical trial results and the fact that current results may not be predictive of future results, even if the data from preclinical studies or clinical trials is positive;
- risks that our product candidates may not prove to be safe and efficacious;
- the risk that we may not be able to enter into future collaborations with industry partners and the government and the terms, timing and success of any such collaboration;
- risks relating to the cost of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights;
- risks related to the competition for clinical resources and patient enrollment from drug candidates in development by other companies with greater resources and visibility;

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risks related to the rate of cash utilized by us in our business and the period for which existing cash will be able to fund such operation; and

risks related to our ability to obtain adequate financing in the future through product licensing, co-promotional arrangements, public or private equity or debt financing or otherwise; general business conditions; competition; business abilities and judgment of personnel; and the availability of qualified personnel.

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USE OF PROCEEDS

Except as otherwise provided in the applicable prospectus supplement, we intend to use the net proceeds we receive from our sale of the securities covered by this prospectus primarily for preclinical and clinical development of our lead product candidates, discovery, research and development of other product candidates and other corporate purposes. Additional information on the use of net proceeds we receive from the sale of securities covered by this prospectus may be set forth in the prospectus supplement relating to the specific offering.

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RATIO OF COMBINED FIXED CHARGES AND PREFERRED STOCK DIVIDENDS TO EARNINGS

The following table sets forth our historical ratios of earnings to fixed charges and preferred stock dividends for the periods indicated. You should read this table in conjunction with the financial statements and notes incorporated by reference in this prospectus.

	Year Ended December 31,				Three Months Ended
	2011	2012	2013	2014	March 31, 2015
Ratio of combined fixed charges and preferred stock dividends to earnings(1)					

(1) Earnings were inadequate to cover fixed charges and preferred dividends for the years ended December 31, 2011, 2012, 2013 and 2014 by $16.3 million, $15.1 million, $22.4 million and $35.5 million, respectively, and for the three months ended March 31, 2015, by $12.1 million.

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PLAN OF DISTRIBUTION

We may sell securities in any of the ways described below or in any combination:

- to or through underwriters or dealers;
- through one or more agents;
- directly to purchasers or to a single purchaser; or
- in "at the market offerings", within the meaning of Rule 415(a)(4) of the Securities Act of 1933, as amended (the "Securities Act") to or through a market maker or into an existing trading market, or an exchange or otherwise.

The distribution of the securities by us may be effected from time to time in one or more transactions:

- at a fixed price, or prices, which may be changed from time to time;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

Each prospectus supplement will describe the method of distribution of the securities and any applicable restrictions.

The prospectus supplement will describe the terms of the offering of the securities, including the following:

- the name or names of any underwriters, dealers or agents and the amounts of securities underwritten or purchased by each of them;
- the public offering price of the securities and the proceeds to us and any discounts, commissions or concessions allowed or reallowed or paid to dealers; and
- any securities exchanges on which the securities may be listed.

Any offering price and any discounts or concessions allowed or reallowed or paid to dealers will be specified in the applicable prospectus supplement and may be changed from time to time.

Only the agents or underwriters named in each prospectus supplement are agents or underwriters in connection with the securities being offered thereby.

We may authorize underwriters, dealers or other persons acting as our agents to solicit offers by certain institutions to purchase securities from us pursuant to delayed delivery contracts providing for payment and delivery on the date stated in each applicable prospectus supplement. Each contract will be for an amount not less than, and the aggregate amount of securities sold pursuant to such contracts shall not be less nor

more than, the respective amounts stated in each applicable prospectus supplement. Institutions with whom the contracts, when authorized, may be made include commercial and savings banks, insurance companies, pension funds, investment companies, educational and charitable institutions and other institutions, but shall in all cases be subject to our approval. Delayed delivery contracts will be subject only to those conditions set forth in each applicable prospectus supplement, and each prospectus supplement will set forth any commissions we pay for solicitation of these contracts.

Agents, underwriters and other third parties described above may be entitled to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, or to contribution from us with respect to payments which the agents, underwriters or other third parties may be required to

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make in respect thereof. Agents, underwriters and such other third parties may be customers of, engage in transactions with, or perform services for us in the ordinary course of business. We may also use underwriters or such other third parties with whom we have a material relationship. We will describe the nature of any such relationship in the applicable prospectus supplement.

One or more firms, referred to as "remarketing firms," may also offer or sell the securities, if a prospectus supplement so indicates, in connection with a remarketing arrangement upon their purchase. Remarketing firms will act as principals for their own accounts or as our agents. These remarketing firms will offer or sell the securities in accordance with the terms of the securities. Each prospectus supplement will identify and describe any remarketing firm and the terms of its agreement, if any, with us and will describe the remarketing firm's compensation. Remarketing firms may be deemed to be underwriters in connection with the securities they remarket. Remarketing firms may be entitled under agreements that may be entered into with us to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, and may be customers of, engage in transactions with or perform services for us in the ordinary course of business.

Certain underwriters may use this prospectus and any accompanying prospectus supplement for offers and sales related to market-making transactions in the securities. These underwriters may act as principal or agent in these transactions, and the sales will be made at prices related to prevailing market prices at the time of sale. Any underwriters involved in the sale of the securities may qualify as "underwriters" within the meaning of Section 2(a)(11) of the Securities Act. In addition, the underwriters' commissions, discounts or concessions may qualify as underwriters' compensation under the Securities Act and the rules of the Financial Industry Regulatory Authority.

Our common stock is listed on The NASDAQ Global Market. Underwriters may make a market in our common stock, but will not be obligated to do so and may discontinue any market making at any time without notice. We can make no assurance as to the development, maintenance or liquidity of any trading market for the securities.

Certain persons participating in an offering may engage in overallotment, stabilizing transactions, short covering transactions and penalty bids in accordance with rules and regulations under the Securities Exchange Act of 1934, as amended (the "Exchange Act"). Overallotment 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. Short covering transactions involve purchases of the securities 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 short 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.

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DESCRIPTION OF COMMON STOCK

The following summary of the terms of our common stock does not purport to be complete and is qualified in its entirety by reference to our fifth amended and restated certificate of incorporation and amended and restated by-laws, both of which are on file with the SEC as exhibits to previous filings, and the applicable provisions of the Delaware General Corporation Law. We refer in this section to our fifth amended and restated certificate of incorporation as our certificate of incorporation, and we refer to our amended and restated by-laws as our by-laws.

General

Our authorized capital stock consists of 175,000,000 shares of our common stock, par value $0.001 per share. As of March 31, 2015, we had 24,137,395 shares of common stock outstanding.

Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. An election of directors by our stockholders shall be determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Holders of common stock are entitled to receive any dividends as may be declared by our board of directors, subject to any preferential dividend rights of outstanding preferred stock.

In the event of our liquidation, dissolution or winding up, the holders of common stock are entitled to receive proportionately all assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any outstanding preferred stock. Holders of common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of 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 and issue in the future.

Delaware Anti-Takeover Law and Certain Charter and Bylaw Provisions

Section 203 of the Delaware General Corporation Law

We are subject to the provisions of Section 203 of the Delaware General Corporation Law. In general, Section 203 prohibits a publicly-held Delaware corporation from engaging in a "business combination" with an "interested stockholder" for a three-year period following the time that this stockholder becomes an interested stockholder, unless the business combination is approved in a prescribed manner. A "business combination" includes, among other things, a merger, asset or stock sale or other transaction resulting in a financial benefit to the interested stockholder. An "interested stockholder" is a person who, together with affiliates and associates, owns, or did own within three years prior to the determination of interested stockholder status, 15% or more of the corporation's voting stock.

Under Section 203, a business combination between a corporation and an interested stockholder is prohibited unless it satisfies one of the following conditions: before the stockholder became interested, the board of directors approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder; 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 voting stock outstanding, shares owned by persons who are directors and also officers, and employee stock plans, in some instances; or at or after the time the stockholder became interested, the business combination was approved by the board of directors of the corporation and authorized at an annual or special meeting of the stockholders by the affirmative vote of at least two-thirds of the outstanding voting stock which is not owned by the interested stockholder.

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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 by-laws resulting from a stockholders' amendment approved by at least a majority of the outstanding voting shares. We have not opted out of these provisions. As a result, mergers or other takeover or change in control attempts of us may be discouraged or prevented.

Anti-Takeover Effects of Our Certificate of Incorporation and Our By-Laws

Our certificate of incorporation and by-laws contain certain provisions that are intended to enhance the likelihood of continuity and stability in the composition of the board of directors and which may have the effect of delaying, deferring or preventing a future takeover or change in control of the company unless such takeover or change in control is approved by the board of directors.

These provisions include:

Classified Board. Our certificate of incorporation provides that our board of directors is divided into three classes of directors, with the classes as nearly equal in number as possible. As a result, approximately one-third of our board of directors will be elected each year. The classification of directors will have the effect of making it more difficult for stockholders to change the composition of our board. Our certificate of incorporation also provides that, subject to any rights of holders of preferred stock to elect additional directors under specified circumstances, the number of directors will be fixed exclusively pursuant to a resolution adopted by our board of directors. Our board of directors currently consists of six members.

Action by Written Consent; Special Meetings of Stockholders. Our certificate of incorporation provides that stockholder action can be taken only at an annual or special meeting of stockholders and cannot be taken by written consent in lieu of a meeting. Our certificate of incorporation and the by-laws also provide that, except as otherwise required by law, special meetings of the stockholders can be called only by or at the direction of the board of directors pursuant to a resolution adopted by a majority of the total number of directors. Except as described above, stockholders are not permitted to call a special meeting or to require the board of directors to call a special meeting.

Removal of Directors. Our certificate of incorporation provides that our directors may be removed only for cause by the affirmative vote of at least 75% of the voting power of our outstanding shares of capital stock, voting together as a single class. This requirement of a supermajority vote to remove directors could enable a minority of our stockholders to prevent a change in the composition of our board.

Advance Notice Procedures. Our by-laws establish an advance notice procedure for stockholder proposals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to the board of directors. Stockholders at an annual meeting are only be able to consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of the board of directors or by a stockholder who was a stockholder of record on the record date for the meeting, who is entitled to vote at the meeting and who has given our Secretary timely written notice, in proper form, of the stockholder's intention to bring that business before the meeting. Although the by-laws do not give the board of directors the power to approve or disapprove stockholder nominations of candidates or proposals regarding other business to be conducted at a special or annual meeting, the by-laws may have the effect of precluding the conduct of certain business at a meeting if the proper procedures are not followed or may discourage or deter a potential acquirer from conducting a solicitation of proxies to elect its own slate of directors or otherwise attempting to obtain control of the company.

Super Majority Approval Requirements. The Delaware General Corporation Law generally provides that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend

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a corporation's certificate of incorporation or by-laws, unless either a corporation's certificate of incorporation or by-laws requires a greater percentage. Our certificate of incorporation and by-laws provide that the affirmative vote of holders of at least 75% of the total votes eligible to be cast in the election of directors is required to amend, alter, change or repeal the by-laws. This requirement of a supermajority vote to approve amendments to our by-laws could enable a minority of our stockholders to exercise veto power over any such amendments.

Authorized but Unissued Shares. Our authorized but unissued shares of common stock and preferred stock are available for future issuance without stockholder approval. These additional shares may be utilized for a variety of corporate purposes, including future public offerings to raise additional capital, corporate acquisitions and employee benefit plans. The existence of authorized but unissued shares of common stock and preferred stock could render more difficult or discourage an attempt to obtain control of a majority of our common stock by means of a proxy contest, tender offer, merger or otherwise.

Exclusive Forum. Our certificate of incorporation provides that, subject to limited exceptions, the state or federal courts located in the State of Delaware are the sole and exclusive forum for (i) any derivative action or proceeding brought on our behalf, (ii) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders, (iii) any action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law, our certificate of incorporation or our by-laws, or (iv) any other action asserting a claim against us that is governed by the internal affairs doctrine. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our certificate of incorporation described above. Although we believe these provisions benefit us by providing increased consistency in the application of Delaware law for the specified types of actions and proceedings, the provisions may have the effect of discouraging lawsuits against our directors and officers. The enforceability of similar choice of forum provisions in other companies' certificates of incorporation has been challenged in legal proceedings, and it is possible that, in connection with one or more actions or proceedings described above, a court could find the choice of forum provisions contained in our certificate of incorporation to be inapplicable or unenforceable.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A. The transfer agent and registrar's address is 144 Fernwood Ave, Edison, New Jersey 08837.

Listing

Our common stock is listed on The NASDAQ Global Market under the symbol "GNCA."

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DESCRIPTION OF PREFERRED STOCK

Under the terms of our certificate of incorporation, our board of directors is authorized to issue up to 25,000,000 shares of our preferred stock, par value $0.001 per share, in one or more series without stockholder approval. Our board of directors has the discretion to determine the rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, of each series of preferred stock. No shares of preferred stock are currently outstanding. It is not possible to state the actual effect of the issuance of any shares of preferred stock upon the rights of the holders of common stock until the board of directors determines the specific rights of the holders of preferred stock. However, effects of the issuance of preferred stock include restricting dividends on common stock, diluting the voting power of common stock, impairing the liquidation rights of common stock, and making it more difficult for a third party to acquire us, which could have the effect of discouraging a third party from acquiring, or deterring a third party from paying a premium to acquire, a majority of our outstanding voting stock.

If we offer a specific class or series of preferred stock under this prospectus, we will describe the terms of the preferred stock in the prospectus supplement for such offering and will file a copy of the certificate establishing the terms of the preferred stock with the SEC. To the extent required, this description will include:

the title and stated value;

the number of shares offered, the liquidation preference per share and the purchase price;

the dividend rate(s), period(s) and/or payment date(s), or method(s) of calculation for such dividends;

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

the procedures for any auction and remarketing, if any;

the provisions for a sinking fund, if any;

the provisions for redemption, if applicable;

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

whether the preferred stock will be convertible into our common stock, and, if applicable, the conversion price (or how it will be calculated) and conversion period;

voting rights, if any, of the preferred stock;

a discussion of any material U.S. federal income tax considerations applicable to the preferred stock;

the relative ranking and preferences of the preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of the affairs of the Company; and

any material limitations on issuance of any class or series of preferred stock ranking senior to or on a parity with the series of preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of the Company.

The preferred stock offered by this prospectus, when issued, will not have, or be subject to, any preemptive or similar rights.

Transfer Agent and Registrar

The transfer agent and registrar for any series or class of preferred stock will be set forth in each applicable prospectus supplement.

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DESCRIPTION OF WARRANTS

We may issue warrants to purchase shares of our common stock or preferred stock in one or more series together with other securities or separately, as described in each applicable prospectus supplement. Below is a description of certain general terms and provisions of the warrants that we may offer. Particular terms of the warrants will be described in the applicable warrant agreements and the applicable prospectus supplement for the warrants.

The applicable prospectus supplement will contain, where applicable, the following terms of and other information relating to the warrants:

- the specific designation and aggregate number of, and the price at which we will issue, the warrants;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- the designation, amount and terms of the securities purchasable upon exercise of the warrants;
- if applicable, the exercise price for shares of our common stock and the number of shares of common stock to be received upon exercise of the warrants;
- if applicable, the exercise price for shares of our preferred stock, the number of shares of preferred stock to be received upon exercise, and a description of that class or series of our preferred stock;
- the date on which the right to exercise the warrants will begin and the date on which that right will expire or, if the warrants may not be continuously exercised throughout that period, the specific date or dates on which the warrants may be exercised;
- whether the warrants will be issued in fully registered form or bearer form, in definitive or global form or in any combination of these forms, although, in any case, the form of a warrant included in a unit will correspond to the form of the unit and of any security included in that unit;
- any applicable material U.S. federal income tax consequences;
- the identity of the warrant agent for the warrants and of any other depositaries, execution or paying agents, transfer agents, registrars or other agents;
- the proposed listing, if any, of the warrants or any securities purchasable upon exercise of the warrants on any securities exchange;
- if applicable, the date from and after which the warrants and the common stock and/or preferred stock will be separately transferable;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;

information with respect to book-entry procedures, if any;

the anti-dilution provisions of the warrants, if any;

any redemption or call provisions;

whether the warrants are to be sold separately or with other securities as parts of units; and

any additional terms of the warrants, including terms, procedures and limitations relating to the exchange and exercise of the warrants.

Transfer Agent and Registrar

The transfer agent and registrar for any warrants will be set forth in the applicable prospectus supplement.

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DESCRIPTION OF UNITS

We may issue units consisting of any combination of the other types of securities offered under this prospectus in one or more series. We may evidence each series of units by unit certificates that we will issue under a separate agreement. We may enter into unit agreements with a unit agent. Each unit agent will be a bank or trust company that we select. We will indicate the name and address of the unit agent in the applicable prospectus supplement relating to a particular series of units.

The following description, together with the additional information included in any applicable prospectus supplement, summarizes the general features of the units that we may offer under this prospectus. You should read any prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of units being offered, as well as the complete unit agreements that contain the terms of the units. Specific unit agreements will contain additional important terms and provisions and we will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from another report that we file with the SEC, the form of each unit agreement relating to units offered under this prospectus.

If we offer any units, certain terms of that series of units will be described in the applicable prospectus supplement, including, without limitation, the following, as applicable:

the title of the series of units;

identification and description of the separate constituent securities comprising the units;

the price or prices at which the units will be issued;

the date, if any, on and after which the constituent securities comprising the units will be separately transferable;

a discussion of certain United States federal income tax considerations applicable to the units; and

any other terms of the units and their constituent securities.

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WHERE YOU CAN FIND MORE INFORMATION

We have filed a registration statement on Form S-3 with the SEC for the securities offered by this prospectus. This prospectus does not include all of the information contained in the registration statement. You should refer to the registration statement and its exhibits for additional information.

We are required to file annual and quarterly reports, current reports, proxy statements, and other information with the SEC. We make these documents publicly available, free of charge, on our website at www.genocea.com as soon as reasonably practicable after filing such documents with the SEC. The information contained on our website is not part of this prospectus. You can read our SEC filings, including the registration statement, on the SEC's website at http://www.sec.gov. You also may read and copy any document we file with the SEC at its public reference facility at:

Public Reference Room
100 F Street N.E.
Washington, DC 20549.

Please call the SEC at 1-800-732-0330 for further information on the operation of the public reference facilities.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" into this prospectus the information 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, and information in documents that we file later with the SEC will automatically update and supersede information in this prospectus. We incorporate by reference into this prospectus the documents listed below and any future filings made by us with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act, except for information "furnished" under Items 2.02, 7.01 or 9.01 on Form 8-K or other information "furnished" to the SEC which is not deemed filed and not incorporated in this prospectus, until the termination of the offering of securities described in the applicable prospectus supplement. We hereby incorporate by reference the following documents:

Our Annual Report on Form 10-K for the year ended December 31, 2014, as filed with the SEC on February 27, 2015;

The information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2014 from our definitive proxy statement on Schedule 14A, as filed with the SEC on April 16, 2015;

Our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2015, as filed with the SEC on May 8, 2015;

Our Current Reports on Form 8-K filed with the SEC on February 27, 2015 and March 12, 2015; and

Description of our common stock contained in our Registration Statement on Form 8-A, as filed with the SEC on January 30, 2014, including any amendment or report filed for the purpose of updating such description.

Any statement contained in a document incorporated or deemed to be incorporated by reference in this prospectus will be deemed modified, superseded or replaced for purposes of this prospectus to the extent that a statement contained in this prospectus modifies, supersedes or replaces such statement.

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You may request a copy of these filings, at no cost, by writing or telephoning us at the following address:

Investor Relations
100 Acorn Park Drive, 5th Floor,
Cambridge, Massachusetts 02140,
(617) 876-8191
email address: ir@genocea.com

Copies of these filings are also available, without charge, on the SEC's website at www.sec.gov and on our website at www.genocea.com as soon as reasonably practicable after they are filed electronically with the SEC. The information contained on our website is not a part of this prospectus.

LEGAL MATTERS

The validity of the issuance of the securities offered pursuant to this prospectus will be passed upon for us by Ropes & Gray LLP, Boston, Massachusetts. The validity of any securities will be passed upon for any underwriters or agents by counsel that we will name in the applicable prospectus supplement.

EXPERTS

The financial statements of Genocea Biosciences, Inc. appearing in Genocea Biosciences, Inc.'s Annual Report (Form 10-K) for the year ended December 31, 2014, have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon, included therein, and incorporated herein by reference. Such financial statements are incorporated herein by reference in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

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3,850,000 Shares

Common Stock

PROSPECTUS SUPPLEMENT

Joint Book-Running Managers

Cowen and Company

Piper Jaffray

Stifel

Co-Manager

Needham & Company