NAVIDEA BIOPHARMACEUTICALS, INC.
Form 10-K
March 23, 2016

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2015

or

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

Commission file number 001-35076

NAVIDEA BIOPHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	31-1080091
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
5600 Blazer Parkway, Suite 200, Dublin, Ohio	43017-7550
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code (614) 793-7500

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

Common Stock, par value $.001 per share	NYSE MKT
(Title of Class)	(Name of Each Exchange on Which Registered)

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

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

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

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes x No o

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. o

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

Large accelerated filer o	Accelerated filer x
Non-accelerated filer o	Smaller reporting company o

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

The aggregate market value of shares of common stock held by non-affiliates of the registrant on June 30, 2015 was $239,805,940.

The number of shares of common stock outstanding on March 1, 2016 was 155,566,583.

DOCUMENTS INCORPORATED BY REFERENCE

None.

The Private Securities Litigation Reform Act of 1995 (the Act) provides a safe harbor for forward-looking statements made by or on behalf of the Company. Statements in this document which relate to other than strictly historical facts, such as statements about the Company's plans and strategies, expectations for future financial performance, new and existing products and technologies, anticipated clinical and regulatory pathways, the ability to obtain, and timing of, regulatory approvals of the Company's products, the timing and anticipated results of commercialization efforts, and anticipated markets for the Company's products, are forward-looking statements within the meaning of the Act. The words "believe," "expect," "anticipate," "estimate," "project," and similar expressions identify forward-looking statements that speak only as of the date hereof. Investors are cautioned that such statements involve risks and uncertainties that could cause actual results to differ materially from historical or anticipated results due to many factors including, but not limited to, the Company's continuing operating losses, uncertainty of regulatory approvals for and market acceptance of its products, reliance on third party manufacturers, accumulated deficit, future capital needs, uncertainty of capital funding, dependence on limited product line and distribution channels, competition, limited marketing and manufacturing experience, risks of development of new products, and other risks set forth below under Item 1A, "Risk Factors." The Company undertakes no obligation to publicly update or revise any forward-looking statements.

PART I

Item 1. Business

Development of the Business

Navidea Biopharmaceuticals, Inc. (Navidea, the Company, or we), a Delaware corporation (NYSE MKT: NAVB), is a biopharmaceutical company focused on the development and commercialization of precision immunodiagnostic agents and immunotherapeutics. Navidea is developing multiple precision-targeted products based on our Manocept™ platform to help identify the sites and pathways of undetected disease and enable better diagnostic accuracy, clinical decision-making, targeted treatment and, ultimately, patient care.

Navidea's Manocept platform is predicated on the ability to specifically target the CD206 mannose receptor expressed on activated macrophages. The Manocept platform serves as the molecular backbone of Lymphoseek® (technetium Tc 99m tilmanocept) injection, the first product developed by Navidea based on the platform. Lymphoseek is a novel, state-of-the-art, receptor-targeted, small-molecule radiopharmaceutical used in the evaluation of lymphatic basins that may have cancer involvement in patients. Lymphoseek is designed for the precise identification of lymph nodes that drain from a primary tumor, which have the highest probability of harboring cancer. Lymphoseek is approved by the U.S. Food and Drug Administration (FDA) for use in solid tumor cancers where lymphatic mapping is a component of surgical management and for guiding sentinel lymph node biopsy in patients with clinically node negative breast cancer, melanoma or squamous cell carcinoma of the oral cavity. Lymphoseek has also received European approval in imaging and intraoperative detection of sentinel lymph nodes in patients with melanoma, breast cancer or localized squamous cell carcinoma of the oral cavity.

Building on the success of Lymphoseek, the flexible and versatile Manocept platform acts as an engine for the design of purpose-built molecules offering the potential to be utilized across a range of diagnostic modalities, including single photon emission computed tomography (SPECT), positron emission tomography (PET), intra-operative and/or optical-fluorescence detection in a variety of disease states.

Recent preclinical data generated by the Company in studies using tilmanocept linked to a therapeutic agent also suggest that tilmanocept's binding affinity to CD206 receptors demonstrates the potential for this technology to be useful in treating diseases linked to the over-activation of macrophages. This includes various cancers as well as autoimmune, infectious, cardiovascular, and central nervous system diseases. Our efforts in this area were further supported by the January 2015 formation of Macrophage Therapeutics, Inc., a majority-owned subsidiary that was

formed specifically to further explore therapeutic applications for the Manocept platform.

Our focus on development of our proprietary Manocept platform technology further supports the 2014 decision by the Company's Board of Directors to reduce our support for, while seeking to partner or out-license, our two neurological development programs, NAV4694 and NAV5001. The NAV5001 sublicense was terminated in April 2015.

Other than Lymphoseek, none of the Company's drug product candidates have been approved for sale in any market.

A Brief Look at Our History

We were originally incorporated in Ohio in 1983 and reincorporated in Delaware in 1988. From inception until January 2012, we operated under the name Neoprobe Corporation. In January 2012, we changed our name to Navidea Biopharmaceuticals, Inc. in connection with both the sale of our medical device business and our strategic repositioning as a precision medicines company focused on "NAVigating IDEAs" that result in the development and commercialization of precision diagnostic and therapeutic pharmaceuticals.

Since our inception, the majority of our efforts and resources have been devoted to the research and clinical development of radiopharmaceutical technologies primarily related to the intraoperative diagnosis and treatment of cancers. From the late 1990's through 2011, we also devoted substantial effort towards the development and commercialization of medical devices, including a line of handheld gamma detection devices which was sold in 2011 and a line of blood flow measurement devices which we operated from 2001 through 2009.

From our inception through August 2011, we manufactured a line of gamma radiation detection medical devices called the neoprobe® GDS system (the GDS Business). We sold the GDS Business to Devicor Medical Products, Inc. (Devicor) in August 2011. In exchange for the assets of the GDS Business, Devicor made net cash payments to us totaling $30.3 million, assumed certain liabilities of the Company associated with the GDS Business, and agreed to make royalty payments to us of up to an aggregate maximum amount of $20 million based on the net revenue attributable to the GDS Business through 2017. Based on the 2015 GDS Business revenue, we earned royalty payments of $1.2 million which we expect to receive in March 2016. We did not earn or receive any such royalty payments prior to 2015.

Following the sale of the GDS business and the subsequent strategic repositioning as a precision medicines company, the Company in-licensed the two neuro-tracer product candidates, NAV4694 and NAV5001. The Company progressed the development of both product candidates over the course of 2012 through 2014, moving both into Phase 3 clinical trials. However, in May 2014, the Navidea Board announced that, based on its belief that the public markets were not giving appropriate value to its Phase 3 pipeline products and were likely penalizing the Company for allocating resources to these programs, the Company would be restructuring its development efforts to focus on cost effective development of the Manocept platform while it sought development partners for NAV4694 and NAV5001. In April 2015, the Company entered into an agreement with Alseres Pharmaceuticals, Inc. (Alseres) to terminate the NAV5001 sub-license agreement. The Company is currently engaged in discussions related to the potential partnering or divestiture of NAV4694.

In December 2014, we announced the formation of a new business unit, Macrophage Therapeutics, to further explore therapeutic applications for the Manocept platform, which was incorporated as Macrophage Therapeutics, Inc. in January 2015.

Our Technology and Product Candidates

Our primary development efforts over the last few years have been focused on diagnostic products including our now-approved Lymphoseek product, as well as other diagnostic and therapeutic line extensions based on our Manocept platform, while we have sought to partner or divest our two neuro-imaging product candidates. Efforts to partner or divest NAV4694 are still active, while the in-license of NAV5001 we had with Alseres was terminated in April 2015.

Navidea remains committed to realizing the full potential of Lymphoseek. In mid-2015, we deployed our own field sales force and began implementing a new strategy to accelerate the strong year-over-year growth of this product. The Company believes that the resources being devoted to drive Lymphoseek sales will lead to positive cash flows and profitability. We are focused on expanding the market for Lymphoseek in all relevant markets.

The Company also continues working to establish new sources of non-dilutive funding, including collaborations and grant funding that can augment the balance sheet as the Company works to reduce spending to levels that can be increasingly offset by growing Lymphoseek revenue. In particular, substantial progress on the Manocept platform has resulted in several promising opportunities, including our R-NAV, LLC venture which began in July 2014, the formation of Macrophage Therapeutics, Inc. in January 2015, and Macrophage Therapeutics' research collaboration agreement with BIND Therapeutics, Inc. executed in June 2015.

Lymphoseek – Regulatory Background

Lymphoseek is a lymph node targeting radiopharmaceutical agent intended for use in intraoperative lymphatic mapping procedures and lymphoscintigraphy employed in the overall diagnostic assessment of certain solid tumor cancers. Lymphoseek has the potential to provide oncology surgeons with information to identify key predictive lymph nodes that may harbor cancer and to help avoid the unnecessary removal of non-cancerous lymph nodes and the surrounding tissue in patients with a variety of solid tumor cancers. Lymphoseek was approved and indicated for use in lymphatic mapping for breast cancer and melanoma by the FDA in March 2013. In June 2014, the FDA approved a supplemental New Drug Application (sNDA) for the expanded use of Lymphoseek indicated for guiding sentinel lymph node biopsy in head and neck cancer patients with squamous cell carcinoma of the oral cavity. In September 2014, the FDA granted Orphan Drug Designation for use in sentinel lymph node detection in patients with cancer of the head and neck. This designation provides for a seven-year market exclusivity period in this indication as well as certain incentives, including federal grants, tax credits and a waiver of filing fees. In October 2014, the FDA approved a second sNDA for lymphatic mapping in solid tumors and added sentinel lymph node detection for breast cancer and melanoma to the approved indications. The FDA also allowed expanded utilization of Lymphoseek with or without scintigraphic imaging, known as lymphoscintigraphy, to enable pre-operative imaging and mapping of lymph nodes to facilitate node localization during surgical procedures. Lymphoseek is now the first and only FDA-approved radiopharmaceutical agent for sentinel lymph node detection and is the only FDA-approved agent for

lymphatic mapping of solid tumors. Additional trials, including trials in anal/rectal, endometrial, and cervical cancers, and others in various stages of execution, planning or consideration, are anticipated to provide additional data to potentially support expansion of the Lymphoseek opportunity.

We submitted our Marketing Authorization Application (MAA) for Lymphoseek to the European Medicines Agency (EMA) in December 2012. In September 2014, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending marketing authorization for Lymphoseek for use in the EU in imaging and intraoperative detection of sentinel lymph nodes draining a primary tumor in adult patients with breast cancer, melanoma, or localized squamous cell carcinoma of the oral cavity. The CHMP's positive opinion was reviewed by the European Commission (EC), which has the authority to approve medicinal products for use in the 28 countries of the EU and generally follows the recommendations of the CHMP. The EC granted marketing authorization for Lymphoseek in the EU in November 2014. Our partner, SpePharm AG, is currently performing the customary pre-launch market access activities to support commercial launch in the EU later in 2016. Concurrently, we are completing manufacturing validation activities on a finished drug product contract manufacturing facility to support the Company’s supply chain, primarily in Europe.

Lymphoseek - Clinical Data and Licensing Background

In January 2015, we announced that an analysis comparing sentinel lymph node (SLN) biopsy procedures using Lymphoseek (TcTM) + vital blue dye (VBD) to filtered [99mTc] sulfur colloid (fTcSC) + VBD in breast cancer patients was published in the Annals of Surgical Oncology. Results demonstrated that (i) Lymphoseek patients had significantly fewer SLNs removed per procedure (mean TcTM: 1.85 vs. fTcSC: 3.24, $p < 0.0001$); (ii) proportionally fewer nodes were necessary to detect cancer spread; and (iii) nodes removed using Lymphoseek held greater predictive value for diagnosing the spread of breast cancer to lymph nodes. The study, “Comparison of [99mTc]Tilmanocept and Filtered [99mTc]Sulfur Colloid for Identification of SLNs in Breast Cancer Patients,” authored by Anne Wallace, M.D., et. al., at the UC San Diego School of Medicine was published in the January print issue of the journal Annals of Surgical Oncology.

In February 2015, we announced the peer-reviewed publication of results from a Phase 3 clinical trial of Lymphoseek in patients with certain head and neck cancer in the journal Annals of Surgical Oncology. The trial assessed the performance of Lymphoseek-guided sentinel node biopsy against the standard of care, nodal pathology, in planned elective neck dissection. Results demonstrated that Lymphoseek met the primary efficacy endpoint of accurately identifying sentinel lymph nodes in subjects with node-negative squamous cell carcinoma of the oral cavity, as compared to the removal of all lymph nodes during multiple level nodal dissection surgery of the head and neck. Pathology assessment of lymph nodes from the multiple-level nodal dissection surgery is considered the “gold standard” to determine the presence and extent of cancer spread. The study, “[99mTc]Tilmanocept Accurately Detects Sentinel Lymph Nodes and Predicts Pathology Status in Patients with Oral Squamous Cell Carcinoma of the Head and Neck: Results of a Phase III Multi-Institutional Trial” was published as an Online First article in the journal Annals of Surgical Oncology. Data from this study were previously presented in part at the 2013 Society of Nuclear Medicine and Molecular Imaging Annual Meeting (Vancouver, British Columbia), at the 2013 American College of Surgeons Clinical Congress (Washington, DC), and at the 6th European Congress on Head and Neck Oncology-2014 (Liverpool, UK).

In June 2015, results of an investigator-initiated, comparative study of Lymphoseek versus fTcSC measuring injection site pain in patients with breast cancer undergoing lymphoscintigraphy were presented at the 2015 Society of Nuclear Medicine and Molecular Imaging conference. The results of the trial, led by Anne Wallace, M.D., professor of surgery at University of California, San Diego (UCSD) School of Medicine, highlighted that fTcSC caused statistically significant greater levels of pain after injection compared to Lymphoseek. The randomized, double-blind clinical trial compared post-injection site pain using fTcSC versus Lymphoseek in 52 [(27) fTcSC and (25)

Lymphoseek] breast cancer patients undergoing lymphoscintigraphy. Pain was evaluated with a visual analogue scale and short form McGill Pain Questionnaire at 1, 2, 3, 4, 5, 15 and 30 minutes post-injection. Analysis of the data indicates baseline pain scores were similar between groups. At one minute post-injection, patients receiving fTcSC experienced a mean change in pain of 16.8mm (standard deviation (SD) 19.5) compared to 0.2mm (SD 7.3) in the Lymphoseek group (p =0.0002). Overall, patients receiving Lymphoseek experienced statistically significant less change in pain scores compared to patients receiving fTcSC at 1-3 minutes post-injection.

In July 2015, we announced the peer-reviewed publication of data verifying the Lymphoseek CD206-binding mechanism of action in the Journal of Immunology. Strong evidence-based studies demonstrate macrophages are the major target cell and identify CD206, the mannose receptor, as the tilmanocept-binding receptor. CD206 is highly expressed on the surface of tissue macrophages that are known to reside in the sentinel lymph nodes (SLNs) draining a primary tumor.

In August 2015, we announced the publication of the results from an investigator-initiated, comparative study of Lymphoseek versus filtered Tc-99m Sulfur Colloid (fTcSC) measuring injection site pain in patients with breast cancer undergoing lymphoscintigraphy. The paper, titled “Comparison of Post-injection Site Pain Between Technetium Sulfur Colloid and Technetium Tilmanocept in Breast Cancer Patients Undergoing Sentinel Lymph Node Biopsy,” was published online in the Annals of Surgical Oncology and indicated, with patient-reported data, a statistically significant reduction in the level of post-injection associated pain using Lymphoseek

compared with use of an fTcSC tracer. The publication included results of the randomized, double-blind clinical trial comparing post-injection site pain using fTcSC versus Lymphoseek in 52 [(27) fTcSC and (25) Lymphoseek] breast cancer patients undergoing lymphoscintigraphy. Pain was evaluated with a visual analogue scale and short form McGill Pain Questionnaire at 1, 2, 3, 4, 5, 15 and 30 minutes post-injection. Analysis of the data indicated baseline pain scores were similar between groups. At one minute post-injection, patients receiving fTcSC experienced a mean change in pain of 16.8mm (standard deviation (SD) 19.5) compared to 0.2mm (SD 7.3) in the Lymphoseek group (p =0.0002). Overall, patients receiving Lymphoseek experienced statistically significant less change in pain scores compared to patients receiving fTcSC at 1-3 minutes post-injection.

In December 2015, we announced that results from an investigator-initiated imaging study demonstrated Lymphoseek reduced imaging time by more than 50% in SLN biopsy procedures in malignant melanoma compared to Tc99m sulfur colloid (SC). This finding suggests hospitals and oncology treatment teams can achieve greater patient throughput and workflow efficiencies utilizing Lymphoseek. Results of the study, conducted at the Thomas Jefferson University Hospitals and led by Charles M. Intenzo, M.D., Professor of Radiology, Director, Nuclear Medicine and Molecular Imaging in the Department of Radiology, were presented at the Radiological Society of North America Annual Meeting (RSNA 2015) in Chicago, Illinois. A total of 34 consecutive patients with malignant melanoma underwent SLN mapping with Lymphoseek. Patients received the Lymphoseek dose in 4 intradermal administrations around the tumor site. Images were acquired at intervals up to 40 minutes after injection, which is the department's standard-of-care protocol used for SC procedures. This site's previous experience showed that SC injections required 40 to 45 minutes after injection for visualization of all lymph nodes in patients with malignant melanoma. Using Lymphoseek, the results show that in all 34 patients, all lymph nodes seen in the final 40-minute image were identified in the 20-minute image, providing rapid and stable localization and identification of the sentinel nodes. The study concludes that in malignant melanoma, SLN mapping with Lymphoseek involves a total imaging time of 20 minutes which is one-half of the time required for SC. From a clinical perspective, the authors conclude that utilizing Lymphoseek is more time-efficient than SC by facilitating patient throughput and expediting subsequent transport to the operating room.

Also in December 2015, we announced that results from an investigator-initiated retrospective analysis demonstrated Lymphoseek was successful in lymph node identification rate, node-positivity rate, and number of total nodes evaluated in SLN biopsy procedures in clinically node-negative breast cancer patients undergoing neoadjuvant chemotherapy (NAT) compared to patients undergoing initial surgical treatment. These findings suggest that Lymphoseek offers breast surgeons the confidence to specifically identify and remove sentinel lymph nodes in this patient population. Results of the study conducted at the University of California, San Diego, School of Medicine, led by Anne Wallace M.D., Professor of Surgery, and Jonathan Unkart, M.D., Department of Surgery, UC San Diego Health, were presented at the San Antonio Breast Cancer Conference in San Antonio, Texas. The aim of the study was to compare identification rate, node-positivity rate and total number of nodes evaluated during SLN biopsy with Lymphoseek and VBD in clinically node-negative patients receiving neoadjuvant endocrine or chemotherapy versus initial surgical treatment. A retrospective review of patients undergoing SLN biopsy with Lymphoseek plus VBD from May 2013-2015 at UCSD was conducted. Of the 417 total SLN cases identified, 72 (17.2%) cases were in patients who had received NAT (61- chemo, 11- endocrine). The SLN identification rate was 100% in both groups (p=1.0). Overall, there were 68 (16.3%) cases of SLN-positivity, 14 (19.4%) in the NAT group versus 54 (15.7%) in the non-NAT group (p= 0.54). The median number of identified nodes was 3 in both groups. In the a zero-truncated negative binomial count model, age, surgeon and evaluating pathologist were significant predictors of the total number of SLNs evaluated. The use of NAT did not significantly affect the number of SLNs evaluated. These findings show Lymphoseek's usefulness in the complicated NAT population and that the outcomes are not different from the standard breast cancer population. This analysis provides compelling evidence that Lymphoseek was successfully used for SLN biopsy in the breast cancer NAT population and could potentially reduce the necessity for unnecessary and morbid axillary dissections, and improve the quality of life for patients.

In January 2016, we announced that the first pediatric patient was enrolled in a clinical study comparing Lymphoseek and VBD in a pediatric population of patients with melanoma, rhabdomyosarcoma, or other solid tumors. The study is designed to investigate how Lymphoseek compares with VBD in identifying lymph nodes as well as evaluate safety and tolerability in the pediatric population. Lymphoseek is currently approved for adult use only. Enrollment is currently planned at approximately six sites throughout the U.S. The first patient was enrolled by Jennifer Aldrink, M.D., Assistant Professor of Clinical Surgery at The Ohio State University College of Medicine and Director of Surgical Oncology, Division of Pediatric Surgery at Nationwide Children's Hospital in Columbus, Ohio. Primary goals of this prospective, open-label, multicenter study are to evaluate safety and tolerability of Lymphoseek in this subject population and determine the concordance of in vivo detection rates of Lymphoseek and of VBD in tissue excised and histologically confirmed as lymph nodes. In addition, the study will measure other efficacy signals including assessment of the identified lymph node(s) to confirm: the presence/absence of tumor metastases; agent localization per tumor type; degree of localization (nodes per subject both intraoperatively and with preoperative SPECT/CT); reverse concordance parameters; change of subject stage based on histopathology and descriptive assessment on change in treatment plan; and number of lymph nodes detected with Lymphoseek intraoperatively compared with preoperative SPECT/CT imaging.

In February 2016, we announced enrollment of the first patient in a clinical study evaluating Lymphoseek in women with known cervical cancer. The study, funded by a Fast Track grant from the National Institutes of Health (NIH), will assess the use of Lymphoseek in SLN biopsy during cervical cancer surgery in support of the existing Lymphoseek label in lymphatic mapping.

Enrollment is currently planned in up to six sites throughout the U.S. The first patient was enrolled by Michael M. Frumovitz, M.D., M.P.H., Associate Professor, Department of Gynecologic Oncology and Reproductive Medicine, principal investigator at The University of Texas MD Anderson Cancer Center. This multi-center, prospective, open-label study intends to enroll up to 40 women with International Federation of Gynecology and Obstetrics IA2-IIA1 staging. Subjects will receive a single dose of Lymphoseek administered peritumorally approximately 1-2 hours before surgery. The results will report per-patient false negative rates and compare the pathology status of Lymphoseek-identified sentinel lymph nodes relative to the pathology status of non-sentinel lymph nodes in nodal staging of patients. Additionally, the study will report sensitivity, negative predictive value, and accuracy.

Manocept Platform - Diagnostics and Therapeutics Background

Navidea's Manocept platform is predicated on the ability to specifically target the CD206 mannose receptor expressed on activated macrophages. Activated macrophages play important roles in many disease states and are an emerging target in many diseases where diagnostic uncertainty exists. This flexible and versatile platform serves as an engine for purpose-built molecules that may significantly impact patient care by providing enhanced diagnostic accuracy, clinical decision-making, and target-specific treatment. This disease-targeted drug platform provides the capability to utilize a breadth of diagnostic modalities, including SPECT, PET, intra-operative and/or optical-fluorescence detection, as well as delivery of therapeutic compounds that target macrophages, and their role in a variety of immune- and inflammation-based disorders. The Company's FDA-approved sentinel node/lymphatic mapping agent, Lymphoseek, is representative of the ability to successfully exploit this mechanism to develop powerful new products.

Impairment of the macrophage-driven disease mechanisms is an area of increasing focus in medicine. The number of people affected by all the inflammatory diseases combined is estimated at more than 40 million in the United States and perhaps 700 million worldwide, making macrophage-mediated diseases an area of remarkable clinical importance. There are many recognized disorders having macrophage involvement, including rheumatoid arthritis (RA), atherosclerosis/vulnerable plaque, Crohn's disease, systemic lupus erythematosis, Kaposi's sarcoma (KS), and others that span clinical areas in oncology, autoimmunity, infectious diseases, cardiology, central nervous system (CNS) diseases, and inflammation. Data from studies using agents from the Manocept platform in RA, KS and tuberculosis (TB) were published in a special supplement, Nature Outlook: Medical Imaging, in Nature's October 31, 2013 issue. The supplement included a White Paper by Navidea entitled "Innovations in receptor-targeted precision imaging at Navidea: Diagnosis up close and personal," focused on the Manocept platform.

Manocept Platform - Diagnostics Clinical Data

In February 2014, data utilizing compounds from our Manocept platform in models of RA were presented by representatives from The Ohio State University at a Keystone Symposia on Molecular Cell Biology of Macrophages in Human Disease. The studies demonstrate the ability of fluorescent Cy3-tilmanocept to identify and localize to disease-state macrophages when administered intravenously, enabling detection of immune-mediated arthritis in affected joints in vivo in mice. Results were confirmed using histopathology. The data highlighted the identification of immune-mediated inflammation seen in arthritic joints of arthritis-affected mice but not in control mice or un-affected joints within arthritis-affected mice. The imaging results in this study showed preferential localization of macrophages by Cy3-tilmanocept in affected joints with little to no localization in unaffected joints.

In April 2014, collaborators from the University of California, San Francisco presented results at the 2014 American Association for Cancer Research conference, highlighting the potential utility of imaging agents derived from the Manocept platform in identifying affected tissues and lymph nodes in patients with KS. The investigators concluded that, based on the results obtained, labeled imaging agents from the CD206-targeting Manocept platform provide potential avenues to enhance diagnosis and staging in this disorder.

In July 2014, Navidea announced that it formed a joint enterprise with Essex Woodlands-backed Rheumco, LLC, to develop and commercialize radiolabeled diagnostic and therapeutic products for rheumatologic and arthritic diseases. The joint enterprise, called R-NAV, LLC (R-NAV), will combine Navidea's proprietary Manocept CD206 macrophage targeting platform and Rheumco's proprietary Tin-117m radioisotope technology to focus on leveraging the platforms across several indications with high unmet medical need.

Also in July 2014, the Company completed a license agreement with UCSD for the exclusive world-wide rights in all diagnostic and therapeutic uses of tilmanocept. The license agreement is effective until the third anniversary of the expiration date of the longest-lived underlying patent. Under the terms of the license agreement, UCSD has granted Navidea the exclusive rights to make, use, sell, offer for sale and import licensed products for all diagnostic and therapeutic uses as defined in the agreement and to practice the defined licensed methods during the term of the agreement. Navidea may also sublicense the patent rights, subject to certain sublicense terms as defined in the agreement. In consideration for the license rights, Navidea agreed to pay UCSD a license issue fee of $25,000 and license maintenance fees of $25,000 per year. We also agreed to make payments to UCSD upon successfully reaching certain clinical, regulatory and cumulative sales milestones, and a royalty on net sales of licensed products subject to a $25,000 minimum annual royalty. Navidea also agreed to reimburse UCSD for all patent-related costs and to meet certain diligence targets.

In June 2015, results from several pre-clinical Manocept studies in RA were presented at the EULAR 2015 European Congress of Rheumatology. The results of the studies, led by Wael Jarjour, M.D. and Thomas J. Rosol, D.V.M., Ph.D., of The Ohio State University Wexner Medical Center and College of Veterinary Medicine, respectively, highlighted the potential of CD206-targeting Manocept constructs to detect immune-mediated inflammation in RA which could be used diagnostically, to monitor therapeutic efficacy, or as a potential therapeutic platform. The presentation showed results from synovial fluid and tissue acquired from RA patients for comparison to normal frozen archival tissue and synovial tissue procured from patients with osteoarthritis (OA). Tissues were probed with Manocept-Cy3, DAPI nuclear stain, and anti CD206-cyanine. Mononuclear cells were isolated from RA synovial fluid and analyzed by flow cytometry. Results demonstrated that archival synovial tissue and synovial fluid obtained from patients diagnosed with RA contain a significant population of macrophages that express high levels of the CD206 receptor. It was shown that these macrophages strongly co-localize Manocept-Cy3 and CD206 receptors. The degree of macrophage infiltration in tissue from healthy or osteoarthritic patients was significantly lower than in RA tissues. Additionally, in an in-vivo animal study, arthritis was induced in mice and was followed with intravenous injection of Manocept-Cy3 and epi-fluorescent imaging. Imaging results indicated that Manocept can be detected in inflamed joints in an in vivo animal model of RA.

In July 2015, imaging results from the Manocept clinical trial in KS and other preclinical studies were presented at the 18th International Workshop on Kaposi's Sarcoma Herpesvirus (KSHV) and Related Agents. The clinical imaging study, using Tc 99m tilmanocept in both HIV+ and HIV- patients suggests that KS tumor lesions, both cutaneous and suspected extra-cutaneous sites, can be easily visualized and mapped, demonstrating that this technique may potentially provide a means for routine patient assessment. The results also demonstrate that use of Manocept represents a potential therapeutic pathway for targeting tumor-associated macrophages (TAMs). Manocept agents are designed to target CD206, which is highly expressed on TAMs and the KS tumor itself. As a potential therapeutic, Manocept could be used as a precision vehicle to deliver payloads to tumor sites throughout the body. Five Human Herpes Virus8 positive (HHV8+) patients (4 HIV+, 1HIV-) were enrolled in the NAV3-12 study. Patients received a single subcutaneous injection of Tc 99m tilmanocept in the region of a cutaneous KS lesion and imaging was performed at 1, 4 and 24 hours post-injection to visualize localization of tilmanocept. Results represented by whole body SPECT/CT imaging scans from study patients were presented. Collectively, the scans show localization of tilmanocept specifically in KS and detected multiple cutaneous lesions in the extremities, as well as extra-cutaneous localization found in the nasopharynx, lymph nodes and brain. Results also indicate that KS lesions are anatomically linked in chains by and within the lymph ducts. The study concludes that both HIV+ and HIV- patients have pan-tumor expression of CD206, strongly suggests tilmanocept crosses the blood-brain barrier and that a Manocept-drug conjugate may have the potential as a therapeutic with high target effect and low off-target concerns. The data from these studies also suggest a novel theory on the genesis of KS in which KS arises from an HHV8 infected macrophage type cell and its interaction with the lymphatic system. This interaction provides the means for access of the KS through CD206 receptor for diagnosis, evaluation, and potential therapy using the Manocept platform.

In July 2015, we received a notice of award for a Phase 1 Small Business Innovation Research (SBIR) grant providing $322,000 from the National Heart Lung and Blood Institute, NIH. The study, currently ongoing in collaboration with Massachusetts General Hospital and Harvard Medical School, will examine the ability of Tc 99m tilmanocept to localize in high-risk atherosclerotic plaques. These specific plaques are rich in CD206 expressing macrophages and are at high risk for near term rupture resulting in myocardial infarctions, sudden cardiac death and strokes. The consequences of atherosclerosis and the cardiovascular disease that atherosclerosis causes, while severe in all populations of people, are particularly concentrated in HIV+ patients. Recently, it has been observed that CD206 expressing macrophages densely populate vulnerable plaques or thin cap fibroatheromas but not other kinds (i.e., calcified plaques) of atherosclerotic plaques. A primary goal for this grant involves an approved clinical investigation of up to 18 individuals with and without aortic and high risk coronary atherosclerotic plaques and with and without HIV infection to determine the feasibility of Tc 99m tilmanocept to image high risk plaque by SPECT/CT. Contrast

with NaF18 is a parallel evaluation. Results have the potential to provide evidence of the potential of Tc 99m tilmanocept to accumulate in high risk morphology plaques, the ability to make preliminary comparisons of aortic Tc 99m tilmanocept uptake by SPECT/CT in each group, and to evaluate the ability of Tc 99m tilmanocept to identify the same aortic atherosclerotic plaques that are identified by contrast enhanced coronary computed tomography angiography and/or PET/CT.

Also in July 2015, we received an initial notice of award for a Fast Track SBIR grant providing for up to $1.7 million from the NIH's National Institute of Arthritis and Musculoskeletal and Skin Diseases, to fund preclinical animal studies and a Phase 1/2 human clinical study examining the ability of Tc 99m tilmanocept to identify skeletal joints that are inflamed due to RA. RA is a chronic, progressive, systemic autoimmune disease characterized by inflammation of numerous skeletal joints. If not treated successfully, RA can lead to disability, disfigurement and premature death. The funds for this Fast Track grant will be released in two parts, which together have the potential to provide a total of $1.7 million in resources over two and a half years to achieve the specific aims and objectives of the grant. The first part will provide $225,000 to support preclinical animal studies and to support activities needed to prepare for the Phase 1/2 clinical study. The second part of the award will support the Phase 1/2 study, the results from which are expected to confirm the safety and effectiveness of Tc 99m tilmanocept to identify skeletal joint inflammation due to RA.

In September 2015, we received an initial notice of award for a Fast Track SBIR grant providing for up to $1.8 million from the NIH’s National Cancer Institute to fund preclinical studies examining the safety of intravenous (IV) injection of Tc99m tilmanocept, a Manocept platform product, followed by a clinical study providing the initial evaluation of the safety and efficacy of SPECT imaging

studies with IV Tc99m tilmanocept to identify and quantify both skin- and organ-associated KS lesions in human patients. The grant is awarded in two parts with the potential for total grant money of up to $1.8 million over two and a half years. The first six-month funding segment of $300,000, which has already been awarded, is expected to enable Navidea to secure necessary collaborations and Institutional Review Board approvals. The second funding segment could provide for up to an additional $1.5 million to be used to accrue participants, perform the Phase 1/2 study and perform data analyses to confirm the safety and effectiveness of intravenously administered Tc99m tilmanocept.

Over the course of the last few years, management has provided periodic updates regarding the status of the NAV1800 development program we previously referred to as the RIGS® (radioimmunguided surgery) program. NAV1800 was originally intended to use a monoclonal antibody as an aid in identifying TAG-72, a specific factor associated with a primary tumor, ascertaining tumor margins, or determining the extent and location of occult and metastatic tumor in patients with solid tumor cancers, such as colorectal cancer, ovarian cancer, or endometrial cancer. The detection of clinically occult tumor was originally intended to provide the surgeon with a more accurate assessment of the extent and location of disease, and therefore impact the surgical and therapeutic management of the patient.

Over the last few years, our commercial evaluation of new clinical data has caused us to question the viability of the monoclonal antibody initiative as it was originally envisioned. During the same time period, we learned significantly more about tilmanocept, the underlying Manocept backbone, and the potential utility of tilmanocept in identifying TAMs, and their consequent potential utility in identifying multifocal tumor disease itself. To that end, we petitioned the NIH to repurpose the $1.5 million grant we were previously awarded towards the study of TAMs in colorectal cancer, and subsequently received confirmation of the acceptance of this repurposing. This repurposed grant now supports a Manocept-based diagnostic approach in patients with anal/rectal cancer and possibly colon cancer. We recognize this repurposing represents a major refocusing of the original NAV1800 initiative, but we are confident that this change represents the best course of action at this time towards benefiting patients afflicted with colorectal cancer and is one which is consistent with the excitement we are seeing on many fronts related to our work on the Manocept platform. However, we cannot assure you that if further clinical trials for this product proceed, that they will be successful, that the product will achieve regulatory approval, or if approved, that it will achieve market acceptance. See Risk Factors.

Macrophage Therapeutics Background

In December 2014, the Company formed a new business unit, Macrophage Therapeutics, to further explore therapeutic applications for the Manocept platform. In January 2015, Navidea incorporated the business unit as Macrophage Therapeutics, Inc. (MT), initially a wholly-owned subsidiary of Navidea.

In December 2014, MT hosted a conference where data were presented using the Manocept platform compound, tilmanocept, that was generated by Navidea and independent academic collaborators with expertise in the HIV/AIDS, cancer, TB, RA and cardiovascular disease therapeutic areas. The technical presentations highlighted tilmanocept's ability to target activated macrophages implicated in the natural history of numerous diseases.

In February 2015, Navidea announced the appointment of leading experts to a newly formed scientific advisory board (SAB) to serve as a strategic resource to MT as MT looks to develop therapeutic applications for Navidea's Manocept platform. The inaugural SAB consortium is comprised of world-renowned scientists and clinicians in the areas of oncology, immunology, autoimmune diseases and macrophage biology. The SAB will serve as an ongoing resource to provide counsel and guidance pertaining to the research, development, and clinical use of our Manocept technology in therapeutic applications.

In March 2015, MT entered into a Securities Purchase Agreement to sell up to 50 shares of its Series A Convertible Preferred Stock (MT Preferred Stock) and warrants to purchase up to an additional 1,500 common shares of

Macrophage Therapeutics, Inc. (MT Common Stock) to Platinum-Montaur Life Sciences LLC, an affiliate of Platinum Management (NY) LLC, Platinum Partners Value Arbitrage Fund L.P., Platinum Partners Liquid Opportunity Master Fund L.P., Platinum Liquid Opportunity Management (NY) LLC, and Montsant Partners LLC (collectively, Platinum) and Dr. Michael Goldberg, one of our directors and CEO of Macrophage Therapeutics, Inc. (collectively, the Investors); the agreed purchase price was $50,000 per unit. On March 13, 2015, Navidea announced that definitive agreements with the Investors had been signed for the sale of the first 10 shares of MT Preferred Stock and warrants to purchase 300 shares of MT Common Stock to the Investors, with gross proceeds to MT of $500,000. Under the agreement, 40% of the MT Preferred Stock and warrants are committed to be purchased by Dr. Goldberg, and the balance by Platinum. The full 50 shares of MT Preferred Stock and warrants that may be sold under the agreement are convertible into and exercisable for MT Common Stock representing an aggregate 1% interest on a fully converted and exercised basis. Navidea retains ownership of the remainder of MT Common Stock.

In addition, Navidea entered into a Securities Exchange Agreement with the Investors providing them an option to exchange their MT Preferred Stock for our common stock in the event that MT has not completed a public offering with gross proceeds to MT of at least $50 million by the second anniversary of the closing of the initial sale of MT Preferred Stock, at an exchange rate per share obtained by dividing $50,000 by the greater of (i) 80% of the twenty-day volume weighted average price per share of our common stock on the second anniversary of the initial closing or (ii) $3.00. To the extent that the Investors do not timely exercise their exchange right, MT

has the right to redeem their MT Preferred Stock for a price equal to $58,320 per share. Navidea also granted MT an exclusive license for certain therapeutic applications of the Manocept technology.

In June 2015, BIND Therapeutics, Inc. (BIND), an early clinical-stage nanomedicine company developing targeted and programmable therapeutics called Accurins™, and MT entered into a research collaboration to engineer Accurins with the Manocept targeting platform. This agreement was renewed in February 2016 to extend the agreement through February 2017. Disease-associated macrophages generally play a pro-tumoral role and are immunosuppressive, preventing the immune system from mounting an attack on tumor cells. Based on the expression of CD206 mannose receptors on disease-associated macrophages, BIND and MT plan to consider joint research programs that may be capable of concentrating various therapeutic payloads to the tumor microenvironment.

In September 2015, MT announced that it had developed preliminary processes for producing the first two therapeutic Manocept immunoconstructs, MT-1001, designed to specifically target and kill activated CD206+ macrophages and MT-2001, designed to inhibit the inflammatory activity of activated CD206+ macrophages. These constructs are the result of the activities of Navidea's clinical development and research group. MT-1001 and MT-2001 were developed from the Manocept platform technology and the efforts of Navidea's development team and contain a similar chemical scaffold and targeting moieties designed to selectively target CD206+ macrophages. A payload of a therapeutic molecule is conjugated to each immunoconstruct through a linkage that will release the molecule within the targeted tissue: MT-1001 has doxorubicin, an anthracycline antitumor antibiotic, conjugated to the Manocept backbone and MT-2001 has a potent anti-inflammatory agent conjugated to it. MT has contracted with an independent facility to produce sufficient quantities of MT-1001 and MT-2001 along with the concomitant analytical standards, to provide material for planned preclinical animal studies.

Macrophage Therapeutics Clinical Data

In March 2015, Navidea and MT announced that data from an ongoing human study indicated that the Manocept technology platform has the ability to safely cross the blood brain barrier without losing its ability to deliver its payload to the intended target. Based on these data and on the advice of the Company's SAB, MT hopes to expand the SAB to include members with specific expertise in CNS diseases. The blood brain barrier has proven to be a significant obstacle to treating many diseases of the central nervous system. In an imaging study using the Manocept targeted delivery system, foci on the other side of the blood brain barrier were observed that strongly and specifically localized tilmanocept. Many of the leading diseases of the central nervous system such as Alzheimer's and Parkinson's diseases as well as autoimmune CNS diseases such as multiple sclerosis and ALS have pathologies that can in part be attributed to over-active macrophages, the target for Manocept delivery technology.

In July 2015, Navidea and MT announced that preclinical results in KS demonstrated that a cytotoxic drug, doxorubicin, linked to Manocept was targeted to and dose-dependently taken up in CD206+ KS tumor cells and TAMs and caused apoptotic death of the KS tumor cells and TAMs. The results were presented at the 18th International Workshop on KSHV and Related Agents by Michael S. McGrath, M.D., Ph.D., Professor, Departments of Laboratory Medicine, Pathology, and Medicine at the University of California, San Francisco (UCSF). The study also shows that Cy3-Manocept and a Cy3-Manocept-doxorubicin conjugate quantitatively permitted the evaluation of tumor burden, tissue uptake of Manocept and tumor response to therapy in vitro and ex vivo, supporting the potential for the Manocept platform to be used not only diagnostically but as a precision targeted molecule to deliver payloads to tumor sites throughout the body. In summary, the data presented include evidence that:

- KS tissue based cells take up Cy3-Manocept or Cy3-Manocept-doxorubicin into both KS tumor cells and TAMs.
- Manocept conjugate uptake is dose and time dependent in CD206+ macrophages.
- Cy3-Manocept and Cy3-Manocept-doxorubicin bind to CD206 positive macrophages equivalently indicating that the linkage of a drug conjugate did not lessen the CD206 binding ability.

- Manocept-doxorubicin killed CD206 expressing macrophages. After 24 hours, Cy3-Manocept-doxorubicin killed 70% of CD206 positive macrophages in tissue cultures. Doxorubicin alone showed no toxicity.
- KS organ culture treated with Manocept-doxorubicin resulted in the loss of macrophages and induced programmed tumor cell death and apoptosis in KS HHV8+ spindle cells, and showed anti-HIV activity in HIV infected macrophage cultures.

Navidea and MT continue to evaluate emerging data in other disease states to define areas of focus, development pathways and partnering options to capitalize on the Manocept platform, including ongoing studies in KS and RA. The immune-inflammatory process is remarkably complex and tightly regulated with indicators that initiate, maintain and shut down the process. Macrophages are immune cells that play a critical role in the initiation, maintenance, and resolution of inflammation. They are activated and deactivated in the inflammatory process. Because macrophages may promote dysregulation that accelerates or enhances disease progression, diagnostic and therapeutic interventions that target macrophages may open new avenues for controlling inflammatory diseases. We cannot assure you that further evaluation or development will be successful, that any Manocept platform product candidate will ultimately achieve regulatory approval, or if approved, the extent to which it will achieve market acceptance. See Risk Factors.

NAV4694 (Candidate for Out-License)

NAV4694 is a fluorine-18 (F-18) labeled PET imaging agent being developed as an aid in the imaging and evaluation of patients with signs or symptoms of Alzheimer's disease (AD) and mild cognitive impairment (MCI). NAV4694 binds to beta-amyloid deposits in the brain that can then be imaged in PET scans. Amyloid plaque pathology is a required feature of AD and the presence of amyloid pathology is a supportive feature for diagnosis of probable AD. Patients who are negative for amyloid pathology do not have AD. NAV4694 has been studied in rigorous pre-clinical studies and clinical trials in humans. Clinical studies through Phase 3 have included subjects with MCI, suspected AD patients, and healthy volunteers. Results suggest that NAV4694 has the potential ability to image patients quickly and safely with high sensitivity and specificity.

In May 2014, the Board of Directors made the decision to refocus the Company's resources to better align the funding of our pipeline programs with the expected growth in Lymphoseek revenue. This realignment primarily involved reducing our near-term support for our neurological product candidates, including NAV4694, as we sought a development partner or partners for these programs. The Company is currently engaged in discussions related to the potential partnering or divestiture of NAV4694. We continue to have active interest from potential partners or acquirers; however, our negotiations have experienced delays due in large part to litigation brought by one of the potential partners (see Item 3 – Legal Proceedings). The Company believes the suit is without merit and has filed a motion to dismiss the action. While it is not possible to determine with any degree of certainty the ultimate outcome of this legal proceeding, including making a determination of liability, we believe that we have meritorious defenses with respect to the claims asserted against us and intend to vigorously defend our position.

NAV5001 (In-License Terminated)

NAV5001 is an iodine-123 (I-123) labeled SPECT imaging agent being developed as an aid in the diagnosis of Parkinson's disease (PD) and other movement disorders, with potential use as a diagnostic aid in dementia. The agent binds to the dopamine transporter (DAT) on the cell surface of dopaminergic neurons in the striatum and substantia nigra regions of the brain. Loss of these neurons is a hallmark of PD. In addition to its potential use as an aid in the differential diagnosis of PD and movement disorders, NAV5001 may also be useful in the diagnosis of Dementia with Lewy Bodies, one of the most common forms of dementia after AD.

In May 2014, the Board of Directors made the decision to refocus the Company's resources to better align the funding of our pipeline programs with the expected growth in Lymphoseek revenue. This realignment primarily involved reducing our near-term support for our neurological product candidates, including NAV5001.

In April 2015, the Company entered into an agreement with Alseres to terminate the sub-license agreement dated July 31, 2012 for research, development and commercialization of NAV5001. Under the terms of this agreement, Navidea transferred all regulatory, clinical and manufacturing-related data related to NAV5001 to Alseres. Alseres agreed to reimburse Navidea for any incurred maintenance costs of the contract manufacturer retroactive to March 1, 2015. In addition, Navidea has supplied clinical support services for NAV5001 on a cost-plus reimbursement basis. However, to this point, Alseres has been unsuccessful in raising the funds necessary to restart the program and reimburse Navidea. As a result, we have taken steps to end our obligations under the agreement and notified Alseres that we consider them in breach of the agreement. We are in the process of trying to recover the funds we expended complying with our obligations under the termination agreement.

Market Overviews

Lymphoseek - Cancer Market Overview

Cancer is the second leading cause of death in the U.S. and Western Europe. The American Cancer Society (ACS) estimates that cancer will cause over 596,000 deaths in 2016 in the U.S. alone. The Agency for Healthcare Research and Quality (AHRQ) has estimated that the direct medical costs for cancer in the U.S. for 2013 were $74.8 billion. Additionally, the ACS estimates that approximately 1.7 million new cancer cases will be diagnosed in the U.S. during 2016. For the types of cancer to which our oncology agents may be applicable (breast, melanoma, head and neck, prostate, lung, colorectal, gastrointestinal and gynecologic), the ACS has estimated that over 1.1 million new cases will occur in the U.S. in 2016.

Currently, the application of intraoperative lymphatic mapping (ILM) is most established in breast cancer. Breast cancer is the second leading cause of death from cancer among all women in the U.S. The probability of developing breast cancer generally increases with age, rising from about 1.9% in women under age 49 to 6.7% in women age 70 or older. According to the ACS, over 247,000 new cases of breast cancer are expected to be diagnosed during 2016 in the U.S. alone. The incidence rate for breast cancer appears to be stable. Thus, we believe that the aging of the population, combined with improved education and awareness of breast cancer and diagnostic methods, will continue to lead to an increased number of breast cancer surgical diagnostic procedures.

The use of ILM is also common in melanoma. The ACS estimates that approximately 76,000 new cases of melanoma will be diagnosed in the U.S. during 2016. In addition to breast cancer and melanoma, we believe that our oncology products may have utility in other cancer types with another 809,000 new cases expected during 2016 in the U.S.

If the potential of Lymphoseek as a radioactive tracing agent is ultimately realized, it may address not only the breast and melanoma markets on a procedural basis, but also assist in the clinical evaluation and staging of solid tumor cancers and expanding lymph node mapping to other solid tumor cancers such as prostate, gastric, colon, head and neck, gynecologic, and non-small cell lung. Lymphoseek is approved by the U.S. FDA for use in solid tumor cancers where lymphatic mapping is a component of surgical management and for guiding sentinel lymph node biopsy in patients with clinically node negative breast cancer, melanoma or squamous cell carcinoma of the oral cavity. Lymphoseek has also received European approval in imaging and intraoperative detection of sentinel lymph nodes in patients with melanoma, breast cancer or localized squamous cell carcinoma of the oral cavity.

Manocept Diagnostics and Macrophage Therapeutics Market Overview

Impairment of the macrophage-driven disease mechanism is an area of increasing focus in medicine. The number of people affected by all the inflammatory diseases combined is estimated at more than 40 million in the United States and perhaps 700 million worldwide, making these macrophage-mediated diseases an area of remarkable clinical importance. There are many recognized disorders having macrophage involvement, including RA, atherosclerosis/vulnerable plaque, Crohn's disease, TB, systemic lupus erythematosis, KS, and others that span clinical areas in oncology, autoimmunity, infectious diseases, cardiology, and inflammation. Data from studies using agents from the Manocept platform in RA, KS and TB were published in a special supplement, Nature Outlook: Medical Imaging, in Nature's October 31, 2013 issue. The supplement included a White Paper by Navidea entitled "Innovations in receptor-targeted precision imaging at Navidea: Diagnosis up close and personal," focused on the Manocept platform. While Navidea's development of the Manocept platform still in relatively early stage, below is a table summarizing potential target markets in which Manocept may have potential diagnostic or therapeutic applications:

Macrophage-Associated Diseases for CD206 Targeting (thousands)

	Incidence		Prevalence					
Disease	Kaposi's Sarcoma	Tuberculosis	Multiple Sclerosis	Crohn's Disease	Systemic Lupus Erythematosus	Rheumatoid Arthritis	Neuro-degenerative Diseases	Diabetes	Athero-sclerosis
Worldwide	50	8,700	1,800	3,800	27,100	60,000	33,000	122,000	480,000

NAV4694 - Alzheimer's Disease Market Overview

The Alzheimer's Association (AA) estimates that more than 5.3 million Americans had AD in 2015. On a global basis, Alzheimer's Disease International estimated in 2015 that there were 46.8 million people living with dementia. AA estimates that total costs for AD care was approximately $226 billion in 2015 and is expected to rise to more than $1 trillion by 2050. AA also estimates that there are over 15 million AD and dementia caregivers providing 17.9 billion hours of unpaid care valued at $217.7 billion. AD is the sixth-leading cause of death in the country and the only cause of death among the top 10 in the U.S. that cannot be prevented, cured or even slowed. Based on mortality data from 2000-2013, deaths from AD have risen 71 percent while deaths attributed to the number one cause of death, heart disease, decreased 14 percent during the same period. In February 2013, the American Academy of Neurology reported in the online issue of Neurology that the number of people with AD may triple by 2050.

Marketing and Distribution

We believe the most preferable and likely distribution partners for Lymphoseek would be entities with established radiopharmaceutical distribution channels, although it is possible that other entities with more traditional oncology or neurological pharmaceutical portfolios may also have interest.

During the fourth quarter of 2007, we executed an agreement with Cardinal Health Inc.'s (Cardinal) Nuclear Pharmacy Services division for the exclusive distribution of Lymphoseek in the U.S. The agreement is for a term of five years from the date of FDA marketing clearance, March 13, 2013. Under the terms of this agreement, Navidea receives a significant share of the revenue from each patient dose of Lymphoseek sold. In addition, Navidea will receive up to $3 million in payments upon the achievement of certain sales milestones by Cardinal Health. We cannot assure you that we will be able to maintain a successful relationship with Cardinal Health, on terms acceptable to the Company, or at all.

In May 2013 the Company announced the commercial launch of Lymphoseek in the U.S. through a distribution agreement with Cardinal. In addition to distributing Lymphoseek to hospitals, Cardinal augments product promotion to nuclear medicine professionals. The Navidea commercial team is responsible for designing and driving Lymphoseek promotional activities and conducting medical education programs tailored to the oncology treatment team, including surgeons and nuclear medicine physicians. Although it is early after the most recent FDA label expansion, we believe we are seeing positive signs in measures of success we believe are critical to the success of our new commercial strategy and deployment.

With respect to Lymphoseek commercialization in Europe, we are aiming to deploy a specialty pharmaceutical strategy to commercialization that would be supportive of premium product positioning and reinforce Lymphoseek's clinical value proposition, as opposed to a commodity or a generics positioning approach. Unlike the U.S., where institutions typically rely on radiopharmaceutical products which are compounded and delivered by specialized radiopharmacy distributors such as Cardinal, institutions in Europe predominantly purchase non-radiolabeled material and compound the radioactive product on-site. In March 2015, we entered into an exclusive sublicense agreement for the commercialization and distribution of Lymphoseek 250 microgram kit for radiopharmaceutical preparation (tilmanocept) in the European Union with SpePharm AG (an affiliate of Norgine BV), a European specialist pharmaceutical company with an extensive pan-European presence. Under the terms of the exclusive license agreement, Navidea will supply Lymphoseek product to SpePharm; however, Navidea will transfer responsibility for regulatory maintenance of the Lymphoseek Marketing Authorization to SpePharm. SpePharm will also be responsible for pricing, reimbursement, sales, marketing, medical affairs, and regulatory activities. In connection with entering into the agreement, Navidea is entitled to an upfront payment of $2 million, milestones totaling up to an additional $5 million, and royalties on European net sales. The initial territory covered by the agreement includes all 28 member states of the European Economic Community with the option to expand into additional geographical areas. SpePharm is currently performing the customary pre-launch market access activities to support commercial launch in the EU later in 2016. Concurrently, we are completing manufacturing validation activities on a finished drug product contract manufacturing facility to support the Company’s supply chain, primarily in Europe.

In August 2014, Navidea entered into an exclusive agreement with a wholly-owned subsidiary of Hainan Sinotau Pharmaceutical Co., Ltd. (Sinotau), a pharmaceutical organization with a broad China focus in oncology and other therapeutic areas, who will develop and commercialize Lymphoseek in China. In exchange, Navidea will earn revenue based on unit sales to Sinotau, a royalty based on Sinotau’s sales of Lymphoseek and up to $2.5 million in milestone payments from Sinotau, including a $300,000 non-refundable upfront payment. As part of the agreement, Sinotau is responsible for costs and conduct of clinical studies and regulatory applications to obtain Lymphoseek approval by the China Food and Drug Administration (CFDA). Upon approval, Sinotau will be responsible for all Lymphoseek sales, marketing, market access and medical affairs activities in China and excluding Hong Kong, Macau and Taiwan. Navidea and Sinotau will jointly support certain pre-market planning activities with a joint commitment on clinical and market development programs pending CFDA approval. In addition to the $300,000 upfront payment, Navidea is eligible for $700,000 in milestone payments up to and through product approval, and an additional $1.5 million in sales milestones.

The Company also has distribution arrangements covering other global markets such as Canada, Taiwan, Puerto Rico, and select medical centers in the Middle East. Lymphoseek is in various stages of approval in these territories and sales to this point in these markets, if any, have not been material. However, we believe that with international partnerships to complement our position in the U.S. and EU, we will help establish Lymphoseek as a global leader in lymphatic mapping, as we are aware of no other company which has this global geographic range. We cannot assure you that Lymphoseek will achieve regulatory approval in any market outside the U.S. or EU, or if approved, that it will achieve market acceptance in any market. We also cannot assure you that we will be successful in securing collaborative partners for other global markets or radiopharmaceutical products, or that we will be able to negotiate acceptable terms for such arrangements. See Risk Factors.

Manufacturing

We currently use and expect to continue to be dependent upon contract manufacturers to manufacture each of our product candidates. We have established a quality control and quality assurance program, including a set of standard operating procedures and specifications with the goal that our products and product candidates are manufactured in accordance with current good manufacturing practices (cGMP) and other applicable domestic and international regulations. We will need to invest in additional manufacturing and supply chain resources, and may seek to enter

into additional collaborative arrangements with other parties that have established manufacturing capabilities. It is likely that we will continue to rely on third-party manufacturers for our development and commercial products on a contract basis.

Lymphoseek Manufacturing

Reliable Biopharmaceutical Corporation (Reliable) produces the drug substance and OSO BioPharmaceuticals Manufacturing, LLC (OsoBio) performs final product manufacturing including final drug formulation, lyophilization (freeze-drying) and packaging processes for Lymphoseek to be sold in the U.S. Gipharma S.r.l. (Gipharma) will perform final product manufacturing for reduced-mass vials to be sold in the EU. Once packaged, the vialed drug can then be shipped to a hospital or regional commercial radiopharmacy where it will be made radioactive (radiolabeled) with 99m Tc to become the final form of Lymphoseek to be administered to a patient. All three organizations have assisted Navidea in the preparation of the chemistry, manufacturing and control (CMC) sections of our submissions to the FDA and the EMA. Reliable, OsoBio and Gipharma are registered manufacturers with the FDA and the EMA.

In November 2009, we completed a Manufacture and Supply Agreement with Reliable for the manufacture of the bulk drug substance with an initial term of 10 years. In September 2013, we entered into a Manufacturing Services Agreement with OsoBio for contract

pharmaceutical development, manufacturing, packaging and analytical services for Lymphoseek. The current agreement with OsoBio runs through December 2016, and automatically renews for additional two-year periods. Also in September 2013, we completed a Service and Supply Master Agreement with Gipharma for process development, manufacturing and packaging of reduced-mass vials for sale in the EU. The agreement with Gipharma has an initial term of three years and automatically renews for additional one-year periods. We cannot assure you that we will be successful in completing future agreements for the supply of Lymphoseek on terms acceptable to the Company, or at all.

NAV4694 Manufacturing

Supplies of NAV4694 used in clinical development through Phase 2b were manufactured by AstraZeneca through various arrangements. In May 2012, we executed an agreement with Molecular NeuroImaging, LLC (MNI) to produce and distribute NAV4694 to imaging centers within a specified geographic region. In October 2012, we completed an agreement with Spectron mrc, LLC (Spectron) to produce NAV4694 for use at certain clinical trial sites. In August 2013, we entered into a Manufacturing Services Agreement with PETNET Solutions, Inc. (PETNET) for the manufacture and distribution of NAV4694 with an initial term of 3 years. Under the terms of the agreement, PETNET will manufacture NAV4694 clinical trial material at select U.S. radiopharmacies, with the possibility of expanding into additional PETNET locations in the future. Navidea has continued to incur costs related to maintaining our NAV4694 manufacturing sites while seeking to partner or out-license the product, and we expect to continue to incur such costs while we complete our partnering/divestiture activities.

Summary

We cannot assure you that we will be successful in securing and/or maintaining the necessary manufacturing, supply and/or radiolabeling capabilities for our product candidates in clinical development. If and when established, we also cannot assure you that we will be able to maintain agreements or other purchasing arrangements with our subcontractors on terms acceptable to us, or that our subcontractors will be able to meet our production requirements on a timely basis, at the required levels of performance and quality, including compliance with FDA cGMP requirements. In the event that any of our subcontractors are unable or unwilling to meet our production requirements, we cannot assure you that an alternate source of supply could be established without significant interruption in product supply or without significant adverse impact to product availability or cost. Any significant supply interruption or yield problems that we or our subcontractors experience would have a material adverse effect on our ability to manufacture our products and, therefore, a material adverse effect on our business, financial condition, and results of operations until a new source of supply is qualified. See Risk Factors.

Competition

Competition in the pharmaceutical and biotechnology industries is intense. We face competition from a variety of companies focused on developing oncology and neurology diagnostic drugs. We compete with large pharmaceutical and other specialized biotechnology companies. We also face competition from universities and other non-profit research organizations. Many emerging medical product companies have corporate partnership arrangements with large, established companies to support the research, development, and commercialization of products that may be competitive with our products. In addition, a number of large established companies are developing proprietary technologies or have enhanced their capabilities by entering into arrangements with or acquiring companies with technologies applicable to the detection or treatment of cancer and other diseases targeted by our product candidates. Smaller companies may also prove to be significant competitors, particularly through collaborative arrangements with large pharmaceutical and established biotechnology companies. Many of these competitors have products that have been approved or are in development and operate large, well-funded research and development programs. Many of our existing or potential competitors have substantially greater financial, research and

development, regulatory, marketing, and production resources than we have. Other companies may develop and introduce products and processes competitive with or superior to ours.

We expect to encounter significant competition for our pharmaceutical products. Companies that complete clinical trials, obtain required regulatory approvals and commence commercial sales of their products before us may achieve a significant competitive advantage if their products work through a similar mechanism as our products and if the approved indications are similar. A number of biotechnology and pharmaceutical companies are developing new products for the treatment of the same diseases being targeted by us. In some instances, such products have already entered late-stage clinical trials or received FDA approval and may be marketed for some period prior to the approval of our products.

We believe that our ability to compete successfully will be based on our ability to create and maintain scientifically advanced “best-in-class” technology, develop proprietary products, attract and retain scientific personnel, obtain patent or other protection for our products, obtain required regulatory approvals and manufacture and successfully market our products, either alone or through third parties. We expect that competition among products cleared for marketing will be based on, among other things, product efficacy, safety, reliability, availability, price, and patent position. See Risk Factors.

Lymphoseek Competition

Surgeons who practice the lymphatic mapping procedure for which Lymphoseek is intended currently use other radiopharmaceuticals such as a sulfur colloid compound in the U.S., and other colloidal compounds in other markets. In addition, some surgeons still use vital blue dyes to assist in the visual identification of the draining lymphatic tissue around a primary tumor. In the U.S., sulfur colloid is manufactured by Pharmalucence, a subsidiary of Sun Pharmaceutical Industries Ltd. Sulfur colloid had been used "off-label" in the U.S. for ILM until July 2011, when it was approved by the FDA for use in lymphatic mapping in breast cancer patients based on a statistical meta-analysis of published literature that compared the use of sulfur colloid with that of the vital blue dyes. The product label for sulfur colloid was expanded to cover lymphatic mapping in melanoma in August 2012, again on the basis of a meta-analysis of published literature. In the EU and certain Pacific Rim markets, there are other colloidal-based compounds with various levels of approved labeling for use in lymphatic mapping, although a number of countries still employ the use of products used "off-label."

NAV4694 Competition

Several potential competitive [^{18}F] products have been approved for use as biomarkers to aid in detection of AD. Developed through Eli Lilly's wholly-owned Avid Radiopharmaceuticals (Avid), florbetapir, now known as Amyvid, received FDA approval to market in April 2012. Florbetapir also received marketing authorization in the EU in January 2013. In addition to fluorbetapir, there are two other beta-amyloid imaging agents available: florbetaben from Piramal Enterprises, Imaging Division, and flutemetamol from GE Healthcare. In October 2013, the FDA approved flutemetamol, under the name VizamylTM, for adults being evaluated for AD and dementia with PET brain imaging. Florbetaben, now called NeuraceqTM, received EMA approval for use in PET imaging of the brain to estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline from the EMA in February 2014 and from the FDA in March 2014.

Patents and Proprietary Rights

The patent position of biotechnology, including our company, generally is highly uncertain and may involve complex legal and factual questions. Potential competitors may have filed applications, or may have been issued patents, or may obtain additional patents and proprietary rights relating to products or processes in the same area of technology as that used by the Company. The scope and validity of these patents and applications, the extent to which we may be required to obtain licenses thereunder or under other proprietary rights, and the cost and availability of licenses are uncertain. We cannot assure you that our patent applications or those licensed to us will result in additional patents being issued or that any of our patents or those licensed to us will afford protection against competitors with similar technology; nor can we assure you that any of these patents will not be designed around by others or that others will not obtain patents that we would need to license or design around.

We also rely upon unpatented trade secrets. We cannot assure you that others will not independently develop substantially equivalent proprietary information and techniques, or otherwise gain access to our trade secrets, or disclose such technology, or that we can meaningfully protect our rights to our unpatented trade secrets.

We require our employees, consultants, advisers, and suppliers to execute a confidentiality agreement upon the commencement of an employment, consulting or manufacturing relationship with us. The agreement provides that all confidential information developed by or made known to the individual during the course of the relationship will be kept confidential and not disclosed to third parties except in specified circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual will be the exclusive property of our company. We cannot assure you, however, that these agreements will provide meaningful protection for our trade secrets in the event of an unauthorized use or disclosure of such information. We also employ a variety of security measures to

preserve the confidentiality of our trade secrets and to limit access by unauthorized persons. We cannot assure you, however, that these measures will be adequate to protect our trade secrets from unauthorized access or disclosure. See Risk Factors.

Manocept/Lymphoseek Intellectual Property

Lymphoseek, as well as certain aspects of intellectual property underlying the Manocept platform, is under exclusive worldwide license from the Regents of the University of California. The license grants Navidea the commercialization rights to Lymphoseek for diagnostic imaging and intraoperative detection applications.

Lymphoseek, including the Manocept backbone composition and methods of use, is the subject of multiple patent families totaling 26 patents and patent applications in the United States and certain major foreign markets. The patents and patent applications held by the Regents of the University of California have been licensed exclusively to Navidea for all diagnostic and therapeutic uses worldwide.

The first composition of matter patent covering Manocept was issued in the United States in June 2002. This patent will expire in May 2020, but a request for patent term extension has been filed to further extend the life of this patent. The claims of the composition of matter patent covering Manocept have been allowed in the EU and issued in the majority of major-market EU

countries in 2005. These patents will expire in 2020, but a request for supplemental protection certificates are in process to further extend the life of these patents. The composition of matter patent has also been issued in Japan. This patent will expire in 2020.

We have filed additional patent applications in the U.S. and certain major foreign markets related to manufacturing processes for Lymphoseek and Manocept, the first of which was issued in the U.S. in 2013. These patents and/or applications will expire between 2029 and 2032. We have filed further patent applications jointly with The Ohio State Innovation Foundation related to CD206 expressing cell-related disorders. These patents and/or applications will expire between 2034 and 2035. We have filed further patent applications related to 2-heteroaryl substituted benzofurans. These patents and/or applications will expire between 2036 and 2037.

We will also rely on trademark protection for products that we expect to commercialize and have registered or are in the process of registering the marks Lymphoseek®, Manocept™, and the Lymphoseek logo™ in the U.S. and other markets.

NAV4694 Intellectual Property

NAV4694 is being developed under an exclusive worldwide license from AstraZeneca. The NAV4694 license grants Navidea commercialization rights to the fluorine-18 labeled biomarker for use as an aid in the diagnosis of AD. NAV4694 is the subject of 3 issued patents in the U.S. and 29 patents issued or pending in 13 foreign jurisdictions covering the [^{18}F]NAV4694 drug substance and the NAV4694 precursor. These patents and/or applications will expire between 2028 and 2029.

Government Regulation

The research, development, testing, manufacture, labeling, promotion, advertising, distribution and marketing, among other things, of our products are extensively regulated by governmental authorities in the United States and other countries. In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, Public Health Service Act, and their implementing regulations. Failure to comply with applicable U.S. requirements may subject us to administrative or judicial sanctions, such as FDA refusal to approve pending new drug applications or supplemental applications, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions and/or criminal prosecution. We also may be subject to regulation under the Occupational Safety and Health Act, the Atomic Energy Act, the Toxic Substances Control Act, the Export Control Act and other present and future laws of general application as well as those specifically related to radiopharmaceuticals.

Most aspects of our business are subject to some degree of government regulation in the countries in which we conduct our operations. As a developer, manufacturer and marketer of medical products, we are subject to extensive regulation by, among other governmental entities, the FDA and the corresponding state, local and foreign regulatory bodies in jurisdictions in which our products are intended to be sold. These regulations govern the introduction of new products, the observance of certain standards with respect to the manufacture, quality, safety, efficacy and labeling of such products, the maintenance of certain records, the tracking of such products, performance surveillance and other matters.

Failure to comply with applicable federal, state, local or foreign laws or regulations could subject us to enforcement action, including product seizures, recalls, withdrawal of marketing clearances, and civil and criminal penalties, any one or more of which could have a material adverse effect on our business. We believe that we are in substantial compliance with such governmental regulations. However, federal, state, local and foreign laws and regulations regarding the manufacture and sale of radiopharmaceuticals are subject to future changes. We cannot assure you that such changes will not have a material adverse effect on our company.

For some products, and in some countries, government regulation is significant and, in general, there is a trend toward more stringent regulation. In recent years, the FDA and certain foreign regulatory bodies have pursued a more rigorous enforcement program to ensure that regulated businesses like ours comply with applicable laws and regulations. We devote significant time, effort and expense addressing the extensive governmental regulatory requirements applicable to our business. To date, we have not received a noncompliance notification or warning letter from the FDA or any other regulatory bodies of alleged deficiencies in our compliance with the relevant requirements, nor have we recalled or issued safety alerts on any of our products. However, we cannot assure you that a warning letter, recall or safety alert, if it occurred, would not have a material adverse effect on our company. See Risk Factors.

In the early- to mid-1990s, the review time by the FDA to clear medical products for commercial release lengthened and the number of marketing clearances decreased. In response to public and congressional concern, the FDA Modernization Act of 1997 (the 1997 Act) was adopted with the intent of bringing better definition to the clearance process for new medical products. While the FDA review times have improved since passage of the 1997 Act, we cannot assure you that the FDA review processes will not delay our Company's introduction of new products in the U.S. in the future. In addition, many foreign countries have adopted more stringent regulatory requirements that also have added to the delays and uncertainties associated with the development and release of new products, as well as the clinical and regulatory costs of supporting such releases. It is possible that delays in receipt of, or failure to receive, any necessary clearance for our new product offerings could have a material adverse effect on our business, financial condition or results of operations. See Risk Factors.

The U.S. Drug Approval Process

None of our drugs may be marketed in the U.S. until such drug has received FDA approval. The steps required before a drug may be marketed in the U.S. include:

- preclinical laboratory tests, animal studies and formulation studies;
- submission to the FDA of an Investigational New Drug (IND) application for human clinical testing, which must become effective before human clinical trials may begin;
- adequate and well-controlled human clinical trials to establish the safety and efficacy of the investigational product for each indication;
- submission to the FDA of a New Drug Application (NDA);
- satisfactory completion of FDA inspections of the manufacturing and clinical facilities at which the drug is produced, tested, and/or distributed to assess compliance with cGMPs and current good clinical practices (cGCP) standards; and
- FDA review and approval of the NDA.

Preclinical tests include laboratory evaluation of product chemistry, toxicity and formulation, as well as animal studies. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND, which must become effective before human clinical trials may begin. An IND will automatically become effective 30 days after receipt by the FDA unless, before that time, the FDA raises concerns or questions about issues such as the conduct of the trials as outlined in the IND. In such a case, the IND sponsor and the FDA must resolve any outstanding FDA concerns or questions before clinical trials can proceed. We cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin.

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators. Clinical trials are conducted under protocols detailing the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. Each protocol must be submitted to the FDA as part of the IND.

Clinical trials typically are conducted in three sequential phases, but the phases may overlap or be combined. The study protocol and informed consent information for study subjects in clinical trials must also be approved by an institutional review board at each institution where the trials will be conducted. Study subjects must sign an informed consent form before participating in a clinical trial. Phase 1 usually involves the initial introduction of the investigational product into people to evaluate its short-term safety, dosage tolerance, metabolism, pharmacokinetics and pharmacologic actions, and, if possible, to gain an early indication of its effectiveness. Phase 2 usually involves trials in a limited subject population to (i) evaluate dosage tolerance and appropriate dosage, (ii) identify possible adverse effects and safety risks, and (iii) evaluate preliminarily the efficacy of the product candidate for specific indications. Phase 3 trials usually further evaluate clinical efficacy and further test its safety by using the product candidate in its final form in an expanded subject population. There can be no assurance that Phase 1, Phase 2 or Phase 3 testing will be completed successfully within any specified period of time, if at all. Furthermore, we or the FDA may suspend clinical trials at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk.

The FDA and the IND sponsor may agree in writing on the design and size of clinical studies intended to form the primary basis of an effectiveness claim in an NDA application. This process is known as a Special Protocol Assessment (SPA). These agreements may not be changed after the clinical studies begin, except in limited circumstances. The existence of a SPA, however, does not assure approval of a product candidate.

Assuming successful completion of the required clinical testing, the results of the preclinical studies and of the clinical studies, together with other detailed information, including information on the manufacturing quality and composition of the investigational product, are submitted to the FDA in the form of an NDA requesting approval to market the product for one or more indications. The testing and approval process requires substantial time, effort and financial resources. Submission of an NDA requires payment of a substantial review user fee to the FDA. Before approving a NDA, the FDA usually will inspect the facility or the facilities where the product is manufactured, tested and distributed and will not approve the product unless cGMP compliance is satisfactory. If the FDA evaluates the NDA and the manufacturing facilities as acceptable, the FDA may issue an approval letter or a complete response letter. A complete response letter outlines conditions that must be met in order to secure final approval of the NDA. When and if those conditions have been met to the FDA's satisfaction, the FDA will issue an approval letter. The approval letter authorizes commercial marketing of the drug for specific indications. As a condition of approval, the FDA may require post-marketing testing and surveillance to monitor the product's safety or efficacy, or impose other post-approval commitment conditions.

The NDA for Lymphoseek was submitted with the intention for use in intraoperative lymphatic mapping across a broad range of cancers. As a part of their review, the FDA examined the pre-clinical, clinical and CMC data supporting our application, and, as is also typical of such reviews, conducted site audits of our facilities and those of the sites where the referenced clinical trials were performed, as well as of contract suppliers and third party vendors being used in the manufacturing and quality assessment processes

for Lymphoseek. Lymphoseek was approved and indicated for use in lymphatic mapping for breast cancer and melanoma by the FDA in March 2013. In June 2014, the FDA approved a sNDA for the expanded use of Lymphoseek indicated for guiding sentinel lymph node biopsy in head and neck cancer patients with squamous cell carcinoma of the oral cavity. In October 2014, the FDA approved a second sNDA for lymphatic mapping in solid tumors and added sentinel lymph node detection for breast cancer and melanoma to the approved indications. The FDA also allowed expanded utilization of Lymphoseek with or without scintigraphic imaging, known as lymphoscintigraphy, to enable pre-operative imaging and mapping of lymph nodes to facilitate node localization during surgical procedures. Additional trials, including an ongoing trial in colorectal cancer, and others in various stages of execution, planning or consideration, are anticipated to provide additional data to potentially support expansion of the Lymphoseek opportunity. We cannot assure you that Lymphoseek will achieve regulatory approval in any market outside the U.S. or EU, or if approved, that it will achieve market acceptance in any market. See Risk Factors.

The FDA has various programs, including fast track, priority review and accelerated approval, which are intended to expedite or simplify the process of reviewing drugs and/or provide for approval on the basis of surrogate endpoints. Generally, drugs that may be eligible for one or more of these programs are those for serious or life threatening conditions, those with the potential to address unmet medical needs and those that provide meaningful benefit over existing treatments. We cannot assure you that any of our drug candidates will qualify for any of these programs, or that, if a drug candidate does qualify, the review time will be reduced or the product will be approved.

After approval, certain changes to the approved product, such as adding new indications, making certain manufacturing changes or making certain additional labeling claims, are subject to further FDA review and approval. Obtaining approval for a new indication generally requires that additional clinical studies be conducted.

U.S. Post-Approval Requirements

Holders of an approved NDA are required to: (i) conduct pharmacovigilance and report certain adverse reactions to the FDA, (ii) comply with certain requirements concerning advertising and promotional labeling for their products, and (iii) continue to have quality control and manufacturing procedures conform to cGMP. The FDA periodically inspects the sponsor’s records related to safety reporting and/or manufacturing and distribution facilities; this latter effort includes assessment of compliance with cGMP. Accordingly, manufacturers must continue to expend time, money and effort in the area of production, quality control and distribution to maintain cGMP compliance. We use and will continue to use third-party manufacturers to produce our products in clinical and commercial quantities, and future FDA inspections may identify compliance issues at our facilities or at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of problems with a product after approval may result in restrictions on a product, manufacturer or holder of an approved NDA, including withdrawal of the product from the market.

Marketing of prescription drugs is also subject to significant regulation through federal and state agencies tasked with consumer protection and prevention of medical fraud, waste and abuse. We must comply with restrictions on off-label use promotion, anti-kickback, ongoing clinical trial registration, and limitations on gifts and payments to physicians.

Non-U.S. Regulation

Before our products can be marketed outside of the United States, they are subject to regulatory approval similar to that required in the U.S., although the requirements governing the conduct of clinical trials, including additional clinical trials that may be required, product licensing, pricing and reimbursement vary widely from country to country. No action can be taken to market any product in a country until an appropriate application has been approved by the regulatory authorities in that country. The current approval process varies from country to country, and the

time spent in gaining approval varies from that required for FDA approval. In certain countries, the sales price of a product must also be approved. The pricing review period often begins after market approval is granted. Even if a product is approved by a regulatory authority, satisfactory prices may not be approved for such product.

In Europe, marketing authorizations may be submitted at a centralized, a decentralized or national level. The centralized procedure is mandatory for the approval of biotechnology products and provides for the grant of a single marketing authorization that is valid in all EU member states. As of January 1995, a mutual recognition procedure is available at the request of the applicant for all medicinal products that are not subject to the centralized procedure.

We submitted our MAA for Lymphoseek to the EMA in December 2012. In September 2014, the CHMP adopted a positive opinion recommending marketing authorization for Lymphoseek for use in the EU in imaging and intraoperative detection of sentinel lymph nodes draining a primary tumor in adult patients with breast cancer, melanoma, or localized squamous cell carcinoma of the oral cavity. The CHMP's positive opinion was reviewed by the EC, which has the authority to approve medicinal products for use in the 28 countries of the EU and generally follows the recommendations of the CHMP. The EC granted marketing authorization for Lymphoseek in the EU in November 2014.

While we are unable to predict the extent to which our business may be affected by future regulatory developments, we believe that our substantial experience dealing with governmental regulatory requirements and restrictions on our operations throughout the world, and our development of new and improved products, should enable us to compete effectively within this environment.

Regulation Specific to Radiopharmaceuticals

Our radiolabeled targeting agents and biologic products, if developed, would require a regulatory license to market from the FDA and from comparable agencies in foreign countries. The process of obtaining regulatory licenses and approvals is costly and time consuming, and we have encountered significant impediments and delays related to our previously proposed biologic products.

The process of completing pre-clinical and clinical testing, manufacturing validation and submission of a marketing application to the appropriate regulatory bodies usually takes a number of years and requires the expenditure of substantial resources, and we cannot assure you that any approval will be granted on a timely basis, if at all. Additionally, the length of time it takes for the various regulatory bodies to evaluate an application for marketing approval varies considerably, as does the amount of preclinical and clinical data required to demonstrate the safety and efficacy of a specific product. The regulatory bodies may require additional clinical studies that may take several years to perform. The length of the review period may vary widely depending upon the nature and indications of the proposed product and whether the regulatory body has any further questions or requests any additional data. Also, the regulatory bodies require post-marketing reporting and surveillance programs (pharmacovigilance) to monitor the side effects of the products. We cannot assure you that any of our potential drug or biologic products will be approved by the regulatory bodies or approved on a timely or accelerated basis, or that any approvals received will not subsequently be revoked or modified.

The Nuclear Regulatory Commission (NRC) oversees medical uses of nuclear material through licensing, inspection, and enforcement programs. The NRC issues medical use licenses to medical facilities and authorized physician users, develops guidance and regulations for use by licensees, and maintains a committee of medical experts to obtain advice about the use of byproduct materials in medicine. The NRC (or the responsible Agreement State) also regulates the manufacture and distribution of these products. The FDA oversees the good practices in the manufacturing of radiopharmaceuticals, medical devices, and radiation-producing x-ray machines and accelerators. The states regulate the practices of medicine and pharmacy and administer programs associated with radiation-producing x-ray machines and accelerators. We cannot assure you that we will be able to obtain all necessary licenses and permits and be able to comply with all applicable laws. The failure to obtain such licenses and permits or to comply with applicable laws would have a materially adverse effect on our business, financial condition, and results of operations.

Corporate Information

Our executive offices are located at 5600 Blazer Parkway, Suite 200, Dublin, OH 43017. Our telephone number is (614) 793-7500. “Navidea”, the Navidea logo, “Lymphoseek” and “RIGS” are trademarks of Navidea Biopharmaceuticals, Inc. or its subsidiaries in the U.S. and/or other countries. Other trademarks or service marks appearing in this report may be trademarks or service marks of other owners.

The address for our website is http://www.navidea.com. We make available free of charge on our website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings pursuant to Section 13(a) or 15(d) of the Exchange Act, and amendments to such filings, as soon as reasonably practicable after each is electronically filed with, or furnished to, the SEC.

Financial Statements

Our consolidated financial statements and the related notes, including revenues, income (loss), total assets and other financial measures are set forth at pages F-1 through F-31 of this Form 10-K.

Research and Development

We spent approximately $12.8 million, $16.8 million and $23.7 million on research and development activities in the years ended December 31, 2015, 2014 and 2013, respectively.

Employees

As of February 29, 2016, we had 51 full-time and 6 part-time employees. We consider our relations with our employees to be good.

Item 1A. Risk Factors

An investment in our common stock is highly speculative, involves a high degree of risk, and should be made only by investors who can afford a complete loss. You should carefully consider the following risk factors, together with the other information in this Form 10-K, including our financial statements and the related notes, before you decide to buy our common stock. Our most significant risks and uncertainties are described below; however, they are not the only risks we face. If any of the following risks actually occur, our business, financial condition, or results of operations could be materially adversely affected, the trading of our common stock could decline, and you may lose all or part of your investment therein.

If we do not achieve commercial success with our approved product, Lymphoseek, or if we do not successfully develop any additional product candidates into marketable products, we may be unable to generate significant revenue or become profitable.

Our near-term financial success depends in large part on Lymphoseek achieving commercial success in the U.S. and, pending approval in other markets, on achievement of commercial success in those markets as well. Lymphoseek was approved and indicated for use in lymphatic mapping for breast cancer and melanoma by the FDA in March 2013. In June 2014, the FDA approved a sNDA for the expanded use of Lymphoseek indicated for guiding sentinel lymph node biopsy in head and neck cancer patients with squamous cell carcinoma of the oral cavity. In October 2014, the FDA approved a second sNDA for lymphatic mapping in solid tumors and added sentinel lymph node detection for breast cancer and melanoma to the approved indications. The FDA also allowed expanded utilization of Lymphoseek with or without scintigraphic imaging, known as lymphoscintigraphy, to enable pre-operative imaging and mapping of lymph nodes to facilitate node localization during surgical procedures. Additional trials, including an ongoing trial in colorectal cancer, and others in various stages of execution, planning or consideration, are anticipated to provide additional data to potentially support expansion of the Lymphoseek opportunity. We began generating revenues from product sales of Lymphoseek in the second quarter of 2013.

We submitted our MAA for Lymphoseek to the EMA in December 2012. In September 2014, the CHMP adopted a positive opinion recommending marketing authorizations for Lymphoseek for use in the EU in imaging and intraoperative detection of sentinel lymph nodes draining a primary tumor in adult patients with breast cancer, melanoma, or localized squamous cell carcinoma of the oral cavity. The CHMP's positive opinion was reviewed by the EC, which granted marketing authorization for Lymphoseek in the EU in November 2014. We announced an exclusive EU distribution partnership for Lymphoseek with SpePharm AG, a subsidiary of Norgine B.V., in March 2015, and we expect to commence marketing of Lymphoseek in the EU in late 2016.

Notwithstanding these marketing approvals, we cannot assure you that Lymphoseek will achieve commercial success in the U.S. or any other global market, that we will realize sales at levels necessary for us to achieve sales milestone payments, or that revenue from Lymphoseek will lead to us becoming profitable.

Additional diagnostic and therapeutic applications of the Manocept platform, including diagnosis of other solid cancers, rheumatoid arthritis and cardiovascular disease, are in various stages of pre-clinical and clinical development. Regulatory approval of label expansions for Lymphoseek or additional Manocept-based product candidates may not be successful, or if successful, may not result in increased sales. Additional clinical testing for products based on our Manocept platform or other product candidates may not be successful and, even if they are, we may not be successful in developing any of them into a commercial product which will provide sufficient revenue to make us profitable.

We have announced that we are seeking to partner or sub-license our NAV4694 candidate, which is designed to enable PET imaging of beta-amyloid deposits in the brain, believed to correlate with the presence of AD. While

discussions with a potential licensee have progressed, our pending litigation with Sinotau Pharmaceuticals has prevented completion of a licensing transaction. See Item 3 – Legal Proceedings. Pending resolution of the Sinotau litigation, we are incurring significant costs to continue clinical evaluation of this product candidate to preserve it for eventual sub-licensing.

Many companies in the pharmaceutical industry suffer significant setbacks in advanced clinical trials even after reporting promising results in earlier trials. Even if our Lymphoseek and Manocept trials are viewed as successful, we may not get regulatory approval for expansion of the label for Lymphoseek or marketing of any Manocept product candidate. Our Manocept product candidates will be successful only if:

- they are developed to a stage that will enable us to commercialize them or sell related marketing rights to pharmaceutical companies;
- we are able to commercialize them in clinical development or sell the marketing rights to third parties; and
- upon being developed, they are approved by the regulatory authorities.

We are dependent on the achievement of a number of these goals in order to generate future revenues. The failure to generate such revenues may preclude us from continuing our research and development of these and other product candidates.

We cannot guarantee that we will obtain regulatory approval to manufacture or market our unapproved drug candidates and our approval to market our products or anticipated commercial launch may be delayed as a result of the regulatory review process.

Obtaining regulatory approval to market drugs to diagnose or treat cancer and other diseases is expensive, difficult and risky. Preclinical and clinical data as well as information related to the CMC processes of drug production can be interpreted in different ways which could delay, limit or preclude regulatory approval. Negative or inconclusive results, adverse medical events during a clinical trial, or issues related to CMC processes could also delay, limit or prevent regulatory approval. Even if we receive regulatory clearance to market a particular product candidate, the approval could be conditioned on us conducting additional costly post-approval studies or could limit the indicated uses included in our labeling.

We may be unable to complete partnering or divestiture activities related to NAV4694 at a reasonable price, on a timely basis, or at all.

We have announced that we are seeking to partner or sub-license our NAV4694 candidate, which is designed to enable PET imaging of beta-amyloid deposits in the brain, believed to correlate with the presence of AD. While discussions with a potential licensee have progressed, our pending litigation with Sinotau Pharmaceuticals has prevented completion of a licensing transaction. See Item 3 – Legal Proceedings. Pending resolution of the Sinotau litigation, we continue to incur costs to maintain our ability to support future clinical evaluation of this product candidate to preserve it for eventual sub-licensing.

Our pharmaceutical products will remain subject to ongoing regulatory review following the receipt of marketing approval. If we fail to comply with continuing regulations, we could lose these approvals and the sale of our products could be suspended.

Approved products may later cause adverse effects that limit or prevent their widespread use, force us to withdraw it from the market or impede or delay our ability to obtain regulatory approvals in additional countries. In addition, any contract manufacturer we use in the process of producing a product and its facilities will continue to be subject to FDA review and periodic inspections to ensure adherence to applicable regulations. After receiving marketing clearance, the manufacturing, labeling, packaging, adverse event reporting, storage, advertising, promotion and record-keeping related to the product will remain subject to extensive regulatory requirements. We may be slow to adapt, or we may never adapt, to changes in existing regulatory requirements or adoption of new regulatory requirements.

If we fail to comply with the regulatory requirements of the FDA and other applicable U.S. and foreign regulatory authorities or previously unknown problems with our products, manufacturers or manufacturing processes are discovered, we could be subject to administrative or judicially imposed sanctions, including:

- restrictions on the products, manufacturers or manufacturing processes;
- warning letters;
- civil or criminal penalties;
- fines;
- injunctions;
- product seizures or detentions;
- import bans;
- voluntary or mandatory product recalls and publicity requirements;
- suspension or withdrawal of regulatory approvals;
- total or partial suspension of production; and

- refusal to approve pending applications for marketing approval of new drugs or supplements to approved applications.

Even if our drug candidates are successful in clinical trials, we may not be able to successfully commercialize them.

We have dedicated and will continue to dedicate substantially all of our resources to the research and development of our Lymphoseek and Manocept technologies and related compounds. Lymphoseek is now approved for use in lymphatic mapping in solid tumors and in sentinel lymph node detection for breast cancer and melanoma in the U.S. Lymphoseek has also been approved for use in imaging and intraoperative detection of sentinel lymph nodes draining a primary tumor in adult patients with breast cancer, melanoma, or localized squamous cell carcinoma of the oral cavity in the EU. However, our other compounds currently are in research or development and have not received marketing approval.

There are many difficulties and uncertainties inherent in pharmaceutical research and development (R&D) and the introduction of new products. A high rate of failure is inherent in new drug discovery and development. The process to bring a drug from the discovery phase to regulatory approval can take 12 to 15 years or longer and cost more than $1 billion. Failure can occur at any point in the process, including late in the process after substantial investment. As a result, most research programs will not generate financial returns. New product candidates that appear promising in development may fail to reach the market or may have only limited commercial success. Delays and uncertainties in the regulatory approval processes in the US and in other countries can result in delays in product launches and lost market opportunities. Consequently, it is very difficult to predict which products will ultimately be approved. Due to the risks and uncertainties involved in the R&D process, we cannot reliably estimate the nature, timing, completion dates, and costs of the efforts necessary to complete the development of our R&D projects, nor can we reliably estimate the future potential revenue that will be generated from a successful R&D project.

Prior to commercialization, each product candidate requires significant research, development and preclinical testing and extensive clinical investigation before submission of any regulatory application for marketing approval. The development of radiopharmaceutical technologies and compounds, including those we are currently developing, is unpredictable and subject to numerous risks. Potential products that appear to be promising at early stages of development may not reach the market for a number of reasons including that they may:

- be found ineffective or cause harmful side effects during preclinical testing or clinical trials;
- fail to receive necessary regulatory approvals;
- be difficult to manufacture on a scale necessary for commercialization;
- be uneconomical to produce;
- fail to achieve market acceptance; or
- be precluded from commercialization by proprietary rights of third parties.

The occurrence of any of these events could adversely affect the commercialization of our product candidates. Products, if introduced, may not be successfully marketed and/or may not achieve customer acceptance. If we fail to commercialize products or if our future products do not achieve significant market acceptance, we will not likely generate significant revenues or become profitable.

Clinical trials for our product candidates will be lengthy and expensive and their outcome is uncertain.

Before obtaining regulatory approval for the commercial sale of any product candidates, we must demonstrate through preclinical testing and clinical trials that our product candidates are safe and effective for use in humans. Conducting clinical trials is a time consuming, expensive and uncertain process and may take years to complete.

With respect to Lymphoseek, we expect to support a number of efforts in various indications, whether internally sponsored or under investigator-sponsored studies, to provide additional data to support expansion of the Lymphoseek opportunity. We also expect to sponsor efforts to explore the Manocept platform, whether in potential diagnostic uses or investigation of uses related to Macrophage Therapeutics.

We continually assess our clinical trial plans and may, from time to time, initiate additional clinical trials to support our overall strategic development objectives. Historically, the results from preclinical testing and early clinical trials often do not predict the results obtained in later clinical trials. Frequently, drugs that have shown promising results in preclinical or early clinical trials subsequently fail to establish sufficient safety and efficacy data necessary to obtain regulatory approval. At any time during the clinical trials, we, the participating institutions, the FDA or the EMA might delay or halt any clinical trials for our product candidates for various reasons, including:

- ineffectiveness of the product candidate;
- discovery of unacceptable toxicities or side effects;

- development of disease resistance or other physiological factors;
- delays in patient enrollment; or
- other reasons that are internal to the businesses of our potential collaborative partners, which reasons they may not share with us.

While we have achieved some level of success in our clinical trials for Lymphoseek as indicated by the FDA and EMA approvals, the results of some of these clinical trials that have not been yet reviewed by the FDA or other regulatory bodies, as well as pending and future trials for these and other product candidates that we may develop or acquire, are subject to review and interpretation by various regulatory bodies during the regulatory review process and may ultimately fail to demonstrate the safety or effectiveness of our

product candidates to the extent necessary to obtain regulatory approval, or that commercialization of our product candidates is worthwhile. Any failure or substantial delay in successfully completing clinical trials and obtaining regulatory approval for our product candidates could materially harm our business.

We extensively outsource our clinical trial activities and usually perform only a small portion of the start-up activities in-house. We rely on independent third-party contract research organizations (CROs) to perform most of our clinical studies, including document preparation, site identification, screening and preparation, pre-study visits, training, post-study audits and statistical analysis. Many important aspects of the services performed for us by the CROs are out of our direct control. If there is any dispute or disruption in our relationship with our CROs, our clinical trials may be delayed. Moreover, in our regulatory submissions, we rely on the quality and validity of the clinical work performed by third-party CROs. If any of our CROs' processes, methodologies or results were determined to be invalid or inadequate, our own clinical data and results and related regulatory approvals could be adversely impacted.

If we fail to establish and maintain collaborations or if our partners do not perform, we may be unable to develop and commercialize our product candidates.

We have entered into collaborative arrangements with third parties to develop and/or commercialize product candidates and are currently seeking additional collaborations. Such collaborations might be necessary in order for us to fund our research and development activities and third-party manufacturing arrangements, seek and obtain regulatory approvals and successfully commercialize our existing and future product candidates. If we fail to enter into collaborative arrangements or fail to maintain our existing collaborative arrangements, the number of product candidates from which we could receive future revenues would decline.

Our dependence on collaborative arrangements with third parties will subject us to a number of risks that could harm our ability to develop and commercialize products including that:

- collaborative arrangements may not be on terms favorable to us;
- disagreements with partners or regulatory compliance issues may result in delays in the development and marketing of products, termination of our collaboration agreements or time consuming and expensive legal action;
- we cannot control the amount and timing of resources partners devote to product candidates or their prioritization of product candidates and partners may not allocate sufficient funds or resources to the development, promotion or marketing of our products, or may not perform their obligations as expected;
- partners may choose to develop, independently or with other companies, alternative products or treatments. including products or treatments which compete with ours;
- agreements with partners may expire or be terminated without renewal, or partners may breach collaboration agreements with us;
- business combinations or significant changes in a partner's business strategy might adversely affect that partner's willingness or ability to complete its obligations to us; and
- the terms and conditions of the relevant agreements may no longer be suitable.

The occurrence of any of these events could adversely affect the development or commercialization of our products.

If users of our products are unable to obtain adequate reimbursement from third-party payers, or if new restrictive legislation is adopted, market acceptance of our products may be limited and we may not achieve anticipated revenues.

Our ability to commercialize our products will depend in part on the extent to which appropriate reimbursement levels for the cost of our products and related treatment are obtained by governmental authorities, private health insurers and other organizations such as health maintenance organizations (HMOs). Generally, in Europe and other countries outside the U.S., the government-sponsored healthcare system is the primary payer of patients' healthcare

costs. Third-party payers are increasingly challenging the prices charged for medical care. Also, the trend toward managed health care in the United States and the concurrent growth of organizations such as HMOs which could control or significantly influence the purchase of health care services and products, as well as legislative proposals to further reform health care or reduce government insurance programs, may all result in lower prices for our products if approved for commercialization. The cost containment measures that health care payers and providers are instituting and the effect of any health care reform could materially harm our ability to sell our products at a profit.

In August 2013, we announced that the CMS had issued a HCPCS “C Code” for Lymphoseek. The cost pass-through provisions supporting this C Code extended through December 31, 2015. Lymphoseek has also been granted a permanent “A Code” effective January 1, 2014. Following the expiration of the pass-through C Code, the cost of Lymphoseek must be absorbed by the institution as a part of the bundled procedural code for the surgical procedure in which Lymphoseek is used. Although we have not as of the date of

this report seen a negative impact of this change in reimbursement on Lymphoseek sales, we cannot assure you that the change in reimbursement will not adversely affect the rate of grown in sales of the product.

We may be unable to establish or contract for the pharmaceutical manufacturing capabilities necessary to develop and commercialize our potential products.

We are in the process of establishing third-party clinical manufacturing capabilities for our compounds under development. We intend to rely on third-party contract manufacturers to produce sufficiently large quantities of drug materials that are and will be needed for clinical trials and commercialization of our potential products. Third-party manufacturers may not be able to meet our needs with respect to timing, quantity or quality of materials.

We have a supply agreement with Reliable to manufacture the drug substance for our Lymphoseek product and a manufacturing agreement with OsoBio for the finishing and vialing of our Lymphoseek product. These are single-source relationships, and we are actively looking to add other supply and manufacturing relationships. However, if we are unable to contract for a sufficient supply of needed materials on acceptable terms, or if we should encounter delays or difficulties in our relationships with manufacturers, revenues from Lymphoseek may be adversely impacted. In addition, clinical trials for our other product candidates may be delayed, thereby delaying the submission of product candidates for regulatory approval and the market introduction and subsequent commercialization of our potential products, and for approved products, any such delays, interruptions or other difficulties may render us unable to supply sufficient quantities to meet demand. Any such delays or interruptions may lower our revenues and potential profitability.

We and any third-party manufacturers that we may use must continually adhere to cGMPs and regulations enforced by the FDA through its facilities inspection program and/or foreign regulatory authorities where our products will be tested and/or marketed. If our facilities or the facilities of third-party manufacturers cannot pass a pre-approval plant inspection, the FDA and/or foreign regulatory authorities will not grant approval to market our product candidates. In complying with these regulations and foreign regulatory requirements, we and any of our third-party manufacturers will be obligated to expend time, money and effort on production, record-keeping and quality control to assure that our potential products meet applicable specifications and other requirements. The FDA and other regulatory authorities may take action against a contract manufacturer who violates cGMPs.

Our product supply and related patient access could be negatively impacted by, among other things: (i) product seizures or recalls or forced closings of manufacturing plants; (ii) disruption in supply chain continuity including from natural or man-made disasters at a critical supplier, as well as our failure or the failure of any of our suppliers to comply with cGMPs and other applicable regulations or quality assurance guidelines that could lead to manufacturing shutdowns, product shortages or delays in product manufacturing; (iii) manufacturing, quality assurance/quality control, supply problems or governmental approval delays; (iv) the failure of a sole source or single source supplier to provide us with the necessary raw materials, supplies or finished goods within a reasonable timeframe; (v) the failure of a third-party manufacturer to supply us with bulk active or finished product on time; and (vi) other manufacturing or distribution issues, including limits to manufacturing capacity due to regulatory requirements, and changes in the types of products produced, physical limitations or other business interruptions.

We may lose out to larger or better-established competitors.

The biotech and pharmaceutical industries are intensely competitive. Many of our competitors have significantly greater financial, technical, manufacturing, marketing and distribution resources as well as greater experience in the industry than we have. The particular medical conditions our product lines address can also be addressed by other medical procedures or drugs. Many of these alternatives are widely accepted by physicians and have a long history of use.

To remain competitive, we must continue to launch new products and technologies. To accomplish this, we commit substantial efforts, funds, and other resources to research and development. A high rate of failure is inherent in the research and development of new products and technologies. We must make ongoing substantial expenditures without any assurance that our efforts will be commercially successful. Failure can occur at any point in the process, including after significant funds have been invested. Promising new product candidates may fail to reach the market or may only have limited commercial success because of efficacy or safety concerns, failure to achieve positive clinical outcomes, inability to obtain necessary regulatory approvals, limited scope of approved uses, excessive costs to manufacture, the failure to establish or maintain intellectual property rights, or infringement of the intellectual property rights of others. Even if we successfully develop new products or enhancements or new generations of our existing products, they may be quickly rendered obsolete by changing customer preferences, changing industry standards, or competitors' innovations. Innovations may not be accepted quickly in the marketplace because of, among other things, entrenched patterns of clinical practice or uncertainty over third-party reimbursement. We cannot state with certainty when or whether any of our products under development will be launched, whether we will be able to develop, license, or otherwise acquire compounds or products, or whether any products will be commercially successful. Failure to launch successful new products or new indications for existing products may cause our products to become obsolete, causing our revenues and operating results to suffer.

Physicians may use our competitors' products and/or our products may not be competitive with other technologies. Lymphoseek is expected to continue to compete against sulfur colloid in the U.S. and other colloidal agents in other global markets.

If our competitors are successful in establishing and maintaining market share for their products, our sales and revenues may not occur at the rate we anticipate. In addition, our current and potential competitors may establish cooperative relationships with larger companies to gain access to greater research and development or marketing resources. Competition may result in price reductions, reduced gross margins and loss of market share.

Several pharmaceutical companies currently have product candidates in development that they expect to have a significant impact on the diagnosis and treatment of AD in coming years. The prospects for these product candidates could have a significant impact, either positive or negative, on our ability to sub-license our NAV4694 product candidate.

We may be exposed to product liability claims for our product candidates and products that we are able to commercialize.

The testing, manufacturing, marketing and use of our commercial products, as well as product candidates in development, involve substantial risk of product liability claims. These claims may be made directly by consumers, healthcare providers, pharmaceutical companies or others. In recent years, coverage and availability of cost-effective product liability insurance has decreased, so we may be unable to maintain sufficient coverage for product liabilities that may arise. In addition, the cost to defend lawsuits or pay damages for product liability claims may exceed our coverage. If we are unable to maintain adequate coverage or if claims exceed our coverage, our financial condition and our ability to clinically test our product candidates and market our products will be adversely impacted. In addition, negative publicity associated with any claims, regardless of their merit, may decrease the future demand for our products and impair our financial condition.

The administration of drugs in humans, whether in clinical studies or commercially, carries the inherent risk of product liability claims whether or not the drugs are actually the cause of an injury. Our products or product candidates may cause, or may appear to have caused, injury or dangerous drug interactions, and we may not learn about or understand those effects until the product or product candidate has been administered to patients for a prolonged period of time. We may be subject from time to time to lawsuits based on product liability and related claims, and we cannot predict the eventual outcome of any future litigation. We may not be successful in defending ourselves in the litigation and, as a result, our business could be materially harmed. These lawsuits may result in large judgments or settlements against us, any of which could have a negative effect on our financial condition and business if in excess of our insurance coverage. Additionally, lawsuits can be expensive to defend, whether or not they have merit, and the defense of these actions may divert the attention of our management and other resources that would otherwise be engaged in managing our business.

As a result of a number of factors, product liability insurance has become less available while the cost has increased significantly. We currently carry product liability insurance that our management believes is appropriate given the risks that we face. We will continually assess the cost and availability of insurance; however, there can be no guarantee that insurance coverage will be obtained or, if obtained, will be sufficient to fully cover product liabilities that may arise.

If any of our license agreements for intellectual property underlying Lymphoseek, our Manocept platform, or any other products or potential products are terminated, we may lose the right to develop or market that product.

We have licensed intellectual property, including patents and patent applications relating to the underlying intellectual property for Lymphoseek and our Manocept platform. We may also enter into other license agreements or acquire other product candidates. The potential success of our product development programs depend on our ability to maintain rights under these licenses, including our ability to achieve development or commercialization milestones contained in the licenses. Under certain circumstances, the licensors have the power to terminate their agreements with us if we fail to meet our obligations under these licenses. We may not be able to meet our obligations under these licenses. If we default under any license agreement, we may lose our right to market and sell any products based on the licensed technology.

We may not have sufficient legal protection against infringement or loss of our intellectual property, and we may lose rights or protection related to our intellectual property if diligence requirements are not met, or at the expiry of underlying patents.

Our success depends, in part, on our ability to secure and maintain patent protection for our products and product candidates, to preserve our trade secrets, and to operate without infringing on the proprietary rights of third parties. While we seek to protect our proprietary positions by filing United States and foreign patent applications for our important inventions and improvements, domestic and foreign patent offices may not issue these patents. Third parties may challenge, invalidate, or circumvent our patents or patent applications in the future. Competitors, many of which have significantly more resources than we have and have made substantial investments in competing technologies, may apply for and obtain patents that will prevent, limit, or interfere with our ability to make, use, or sell our products either in the United States or abroad.

Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are or may be developing products. As the biotechnology and pharmaceutical industry expands and more patents are issued, the risk increases that we will be subject to claims that our products or product candidates, or their use, infringe the rights of others. In the United States, most patent applications are secret for a period of 18 months after filing, and in foreign countries, patent applications are secret for varying periods of time after filing. Publications of discoveries tend to significantly lag the actual discoveries and the filing of related patent applications. Third parties may have already filed applications for patents for products or processes that will make our products obsolete, limit our patents, invalidate our patent applications or create a risk of infringement claims.

Under recent changes to U.S. patent law, the U.S. has moved to a "first to file" system of patent approval, as opposed to the former "first to invent" system. As a consequence, delays in filing patent applications for new product candidates or discoveries could result in the loss of patentability if there is an intervening patent application with similar claims filed by a third party, even if we or our collaborators were the first to invent.

We or our suppliers may be exposed to, or threatened with, future litigation by third parties having patent or other intellectual property rights alleging that our products, product candidates and/or technologies infringe their intellectual property rights or that the process of manufacturing our products or any of their respective component materials, or the component materials themselves, or the use of our products, product candidates or technologies, infringe their intellectual property rights. If one of these patents was found to cover our products, product candidates, technologies or their uses, or any of the underlying manufacturing processes or components, we could be required to pay damages and could be unable to commercialize our products or use our technologies or methods unless we are able to obtain a license to the patent or intellectual property right. A license may not be available to us in a timely manner or on acceptable terms, if at all. In addition, during litigation, a patent holder could obtain a preliminary injunction or other equitable remedy that could prohibit us from making, using or selling our products, technologies or methods.

Our currently held and licensed patents expire over the next one to sixteen years. Expiration of the patents underlying our technology, in the absence of extensions or other trade secret or intellectual property protection, may have a material and adverse effect on us.

In addition, it may be necessary for us to enforce patents under which we have rights, or to determine the scope, validity and unenforceability of other parties' proprietary rights, which may affect our rights. There can be no assurance that our patents would be held valid by a court or administrative body or that an alleged infringer would be found to be infringing. The uncertainty resulting from the mere institution and continuation of any patent related litigation or interference proceeding could have a material and adverse effect on us.

We typically require our employees, consultants, advisers and suppliers to execute confidentiality and assignment of invention agreements in connection with their employment, consulting, advisory, or supply relationships with us. They may breach these agreements and we may not obtain an adequate remedy for breach. Further, third parties may gain unauthorized access to our trade secrets or independently develop or acquire the same or equivalent information.

Agencies of the United States government conducted some of the research activities that led to the development of antibody technology that some of our proposed antibody-based surgical cancer detection products use. When the United States government participates in research activities, it retains rights that include the right to use the technology for governmental purposes under a royalty-free license, as well as rights to use and disclose technical data that could preclude us from asserting trade secret rights in that data and software.

We and our collaborators may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on all of our product candidates and products, when and if we have any, in every jurisdiction would be prohibitively expensive. Competitors may use our technologies in jurisdictions where we or our licensors have not obtained patent protection to develop their own products. These products may compete with our products, when and if we have any, and may not be covered by any of our or our licensors' patent claims or other intellectual property rights.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States, and many companies have encountered significant problems in protecting and defending such rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to biotechnology and/or pharmaceuticals, which could make it difficult for us to stop the infringement of our patents. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business.

The intellectual property protection for our product candidates depends on third parties.

With respect to Lymphoseek and Manocept, and NAV4694, we have exclusively licensed certain issued patents and pending patent applications covering the respective technologies underlying these product candidates and their commercialization and use and we

have licensed certain issued patents and pending patent applications directed to product compositions and chemical modifications used in product candidates for commercialization, and the use and the manufacturing thereof.

The patents and pending patent applications underlying our licenses do not cover all potential product candidates, modifications and uses. In the case of patents and patent applications licensed from UCSD, we did not have any control over the filing of the patents and patent applications before the effective date of the Lymphoseek license, and have had limited control over the filing and prosecution of these patents and patent applications after the effective date of the Lymphoseek license. In the case of patents and patent applications licensed from AstraZeneca, we have limited control over the filing, prosecution or enforcement of these patents or patent applications. We cannot be certain that such prosecution efforts have been or will be conducted in compliance with applicable laws and regulations or will result in valid and enforceable patents. We also cannot be assured that our licensors or their respective licensing partners will agree to enforce any such patent rights at our request or devote sufficient efforts to attain a desirable result. Any failure by our licensors or any of their respective licensing partners to properly protect the intellectual property rights relating to our product candidates could have a material adverse effect on our financial condition and results of operation.

We may become involved in disputes with licensors or potential future collaborators over intellectual property ownership, and publications by our research collaborators and scientific advisors could impair our ability to obtain patent protection or protect our proprietary information, which, in either case, could have a significant effect on our business.

Inventions discovered under research, material transfer or other such collaborative agreements may become jointly owned by us and the other party to such agreements in some cases and the exclusive property of either party in other cases. Under some circumstances, it may be difficult to determine who owns a particular invention, or whether it is jointly owned, and disputes could arise regarding ownership of those inventions. These disputes could be costly and time consuming and an unfavorable outcome could have a significant adverse effect on our business if we were not able to protect our license rights to these inventions. In addition, our research collaborators and scientific advisors generally have contractual rights to publish our data and other proprietary information, subject to our prior review. Publications by our research collaborators and scientific advisors containing such information, either with our permission or in contravention of the terms of their agreements with us, may impair our ability to obtain patent protection or protect our proprietary information, which could significantly harm our business.

Security breaches and other disruptions could compromise our information and expose us to liability, which would cause our business and reputation to suffer.

In the ordinary course of our business, we collect and store sensitive data, including intellectual property, our proprietary business information and that of our suppliers and business partners, and personally identifiable information of employees and clinical trial subjects, in our data centers and on our networks. The secure maintenance and transmission of this information is critical to our operations and business strategy. Despite our security measures, our information technology and infrastructure may be vulnerable to attacks by hackers or breached due to employee error, malfeasance or other disruptions. Any such breach could compromise our networks and the information stored there could be accessed, publicly disclosed, lost or stolen. Any such access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, and regulatory penalties, disrupt our operations, and damage our reputation, which could adversely affect our business, revenues and competitive position.

Failure to comply with domestic and international privacy and security laws can result in the imposition of significant civil and criminal penalties. The costs of compliance with these laws, including protecting electronically stored information from cyber-attacks, and potential liability associated with failure to do so could adversely affect our

business, financial condition and results of operations. We are subject to various domestic and international privacy and security regulations, including but not limited to The Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA mandates, among other things, the adoption of uniform standards for the electronic exchange of information in common healthcare transactions, as well as standards relating to the privacy and security of individually identifiable health information, which require the adoption of administrative, physical and technical safeguards to protect such information. In addition, many states have enacted comparable laws addressing the privacy and security of health information, some of which are more stringent than HIPAA.

We do not currently carry cyber risk insurance.

We are subject to domestic and foreign anticorruption laws, the violation of which could expose us to liability, and cause our business and reputation to suffer.

We are subject to the U.S. Foreign Corrupt Practices Act and similar anti-corruption laws in other jurisdictions. These laws generally prohibit companies and their intermediaries from engaging in bribery or making other prohibited payments to government officials for the purpose of obtaining or retaining business, and some have record keeping requirements. The failure to comply with these laws could result in substantial criminal and/or monetary penalties. We operate in jurisdictions that have experienced corruption, bribery,

pay-offs and other similar practices from time-to-time and, in certain circumstances, such practices may be local custom. We have implemented internal control policies and procedures that mandate compliance with these anti-corruption laws. However, we cannot be certain that these policies and procedures will protect us against liability. There can be no assurance that our employees or other agents will not engage in such conduct for which we might be held responsible. If our employees or agents are found to have engaged in such practices, we could suffer severe criminal or civil penalties and other consequences that could have a material adverse effect on our business, financial position, results of operations and/or cash flow, and the market value of our common stock could decline.

Our international operations expose us to economic, legal, regulatory and currency risks.

Our operations extend to countries outside the United States, and are subject to the risks inherent in conducting business globally and under the laws, regulations, and customs of various jurisdictions. These risks include, but are not limited to: (i) compliance with a variety of national and local laws of countries in which we do business, including but not limited to restrictions on the import and export of certain intermediates, drugs, and technologies, (ii) compliance with a variety of US laws including, but not limited to, the Iran Threat Reduction and Syria Human Rights Act of 2012; and rules relating to the use of certain “conflict minerals” under Section 1502 of the Dodd-Frank Wall Street Reform and Consumer Protection Act, (iii) changes in laws, regulations, and practices affecting the pharmaceutical industry and the health care system, including but not limited to imports, exports, manufacturing, quality, cost, pricing, reimbursement, approval, inspection, and delivery of health care, (iv) fluctuations in exchange rates for transactions conducted in currencies other than the functional currency, (v) adverse changes in the economies in which we or our partners and suppliers operate as a result of a slowdown in overall growth, a change in government or economic policies, or financial, political, or social change or instability in such countries that affects the markets in which we operate, particularly emerging markets, (vi) differing local product preferences and product requirements, (vii) changes in employment laws, wage increases, or rising inflation in the countries in which we or our partners and suppliers operate, (viii) supply disruptions, and increases in energy and transportation costs, (ix) natural disasters, including droughts, floods, and earthquakes in the countries in which we operate, (x) local disturbances, terrorist attacks, riots, social disruption, or regional hostilities in the countries in which we or our partners and suppliers operate and (xi) government uncertainty, including as a result of new or changed laws and regulations. We also face the risk that some of our competitors have more experience with operations in such countries or with international operations generally and may be able to manage unexpected crises more easily. Furthermore, whether due to language, cultural or other differences, public and other statements that we make may be misinterpreted, misconstrued, or taken out of context in different jurisdictions. Moreover, the internal political stability of, or the relationship between, any country or countries where we conduct business operations may deteriorate. Changes in a country’s political stability or the state of relations between any such countries are difficult to predict and could adversely affect our operations, profitability and/or adversely impact our ability to do business there. The occurrence of any of the above risks could have a material adverse effect on our business, financial position, results of operations and/or cash flow, and could cause the market value of our common stock to decline.

We may have difficulty raising additional capital, which could deprive us of necessary resources to pursue our business plans.

We expect to devote significant capital resources to fund research and development, to maintain existing and secure new manufacturing resources, and to acquire new product candidates. In order to support the initiatives envisioned in our business plan, we will likely need to raise additional funds through the sale of assets, public or private debt or equity financing, collaborative relationships or other arrangements. Our ability to raise additional financing depends on many factors beyond our control, including the state of capital markets, the market price of our common stock and the development or prospects for development of competitive technology by others. Sufficient additional financing may not be available to us or may be available only on terms that would result in further dilution to the current owners of our common stock.

Our future expenditures on our programs are subject to many uncertainties, including whether our product candidates will be developed or commercialized with a partner or independently. Our future capital requirements will depend on, and could increase significantly as a result of, many factors, including:

- the costs of seeking regulatory approval for our product candidates, including any nonclinical testing or bioequivalence or clinical studies, process development, scale-up and other manufacturing and stability activities, or other work required to achieve such approval, as well as the timing of such activities and approval;
- the extent to which we invest in or acquire new technologies, product candidates, products or businesses and the development requirements with respect to any acquired programs;
- the scope, prioritization and number of development and/or commercialization programs we pursue and the rate of progress and costs with respect to such programs;
- the costs related to developing, acquiring and/or contracting for sales, marketing and distribution capabilities and regulatory compliance capabilities, if we commercialize any of our product candidates for which we obtain regulatory approval without a partner;

- the timing and terms of any collaborative, licensing and other strategic arrangements that we may establish;
- the extent to which we will need to expand our workforce to pursue our business plan, and the costs involved in recruiting, training and incentivizing new employees;
- the effect of competing technological and market developments; and
- the cost involved in establishing, enforcing or defending patent claims and other intellectual property rights.

We believe that we currently have access to limited financial resources with which to fund our operations and those of our subsidiaries for the foreseeable future, including the proceeds of grants, cash flow generated from sales of Lymphoseek, and the Platinum line of credit. Given our recent low stock price and covenants in the Securities Exchange Agreement under which we issued our Series LL warrants, we may have only limited ability to raise equity financing, and our access to debt capital is limited by the terms of our indebtedness to Capital Royalty Partners II L.P. These constraints may adversely affect our ability to develop our product candidates or expand the labeling for Lymphoseek, as well as the timing of those efforts. If our current funds become inadequate, we may not be able to obtain sufficient additional funding for such activities, on satisfactory terms, if at all. If we are unsuccessful in raising additional capital, or the terms of raising such capital are unacceptable, we may have to modify our business plan and/or significantly curtail our planned development activities, acquisition of new product candidates and other operations.

There may be future sales or other dilution of our equity, which may adversely affect the market price of shares of our common stock.

Our existing warrants or other securities convertible into or exchangeable for our common stock, or securities we may issue in the future, may contain adjustment provisions that could increase the number of shares issuable upon exercise, conversion or exchange, as the case may be, and decrease the exercise, conversion or exchange price. The market price of our shares of common stock could decline as a result of sales of a large number of shares of our common stock or other securities in the market, the triggering of any such adjustment provisions or the perception that such sales could occur in the future.

Our indebtedness imposes significant restrictions on us, and a default could materially adversely affect our operations and financial condition.

All of our material assets, except our intellectual property, have been pledged as collateral for our borrowings under the Term Loan Agreement (the CRG Loan Agreement) with Capital Royalty Partners II L.P. (CRG).

In addition to the security interest in our assets, the CRG Loan Agreement carries covenants that impose significant requirements on us, including, among others, requirements that we:

- pay all principal, interest and other charges on the outstanding balance of the borrowed funds when due;
- meet certain annual EBITDA or revenue targets ($22.5 million of revenue from Lymphoseek sales in 2016) as defined in the CRG Loan Agreement;
- maintain liquidity of at least $5 million during the term of the CRG Loan Agreement;
- provide certain financial information and reports to CRG in a timely manner; and
- indemnify CRG against certain liabilities.

Additionally, with certain exceptions, the CRG Loan Agreement prohibits us from:

- making any material dispositions of our assets, except for permitted dispositions;
- making any changes in our business or business locations;
- entering into any merger or consolidation without CRG’s consent;
- acquiring or making investments in any other person other than permitted investments;
- incurring any indebtedness, other than permitted indebtedness;

- granting or permitting liens against our assets, other than permitted liens;
- declaring or paying any dividends or making any other distributions; or
- entering into any material transaction with any affiliate, other than in the ordinary course of business.

The events of default under the CRG Loan Agreement also include a failure of Platinum to perform its funding obligations under the Platinum Loan Agreement (as defined below) at any time as to which the Company had negative EBITDA for the most recent fiscal

quarter, as a result either of Platinum's repudiation of its obligations under the Platinum Loan Agreement, or the occurrence of an insolvency event with respect to Platinum. The events of default also include a change of control with respect to the Company. Our ability to comply with these provisions may be affected by changes in our business condition or results of our operations, or other events beyond our control. The breach of any of these covenants would result in a default under the CRG Loan Agreement.

We call to your attention that we did not achieve the 2015 annual Lymphoseek sales revenue target of $11 million initially established under the CRG Loan Agreement, but in December 2015 CRG agreed to a reduction of that target to $10 million and we were able to meet that reduced target with Lymphoseek sales revenue of $10.3 million, thereby complying with the covenant. We also call to your attention that as of the time of filing this report, it appears likely that we will need to draw on the Platinum line of credit in order to maintain compliance with the $5 million liquidity covenant of the CRG Loan Agreement beginning in the second quarter of 2016. In the event Platinum does not honor the draw request, our inability to meet the liquidity covenant would be an event of default under the CRG Loan Agreement. In addition, if we are unable to reach the 2016 annual Lymphoseek sales revenue target of $22.5 million, this would also be an event of default under the CRG Loan Agreement; however, potential shortfalls to this revenue covenant are curable by the Company depositing 2.5 times the amount of the shortfall in a bank account controlled by CRG. Our ability to comply with these covenants may be affected by changes in our business condition or results of operations, or other events beyond our control. An event of default would entitle CRG to accelerate the maturity of our indebtedness, increase the interest rate to the default rate of 18% per annum, and invoke other remedies available to it under the loan agreement and the related security agreement, including sale of the assets securing the debt, which could raise substantial doubt about the Company's ability to continue as a going concern. See Management's Discussion and Analysis of Financial Conditions and Results of Operations – Liquidity and Capital Resources.

In addition, our Loan Agreement with Platinum (the Platinum Loan Agreement) carries standard non-financial covenants typical for commercial loan agreements, many of which are similar to those contained in the CRG Loan Agreement, that impose significant requirements on us. Our ability to comply with these provisions may be affected by changes in our business condition or results of our operations, or other events beyond our control. The breach of any of these covenants would result in a default under the Platinum Loan Agreement, permitting Platinum to terminate our ability to obtain additional draws under the Platinum Loan Agreement and accelerate the maturity of the debt, subject to the limitations of the Subordination Agreement with CRG. Such actions by Platinum could materially adversely affect our operations, results of operations and financial condition, including causing us to substantially curtail our product development activities.

Platinum may exercise its conversion right, and that could dilute your ownership and the net tangible book value per share of our common stock.

Platinum may exercise the right to convert all or any portion of the unpaid principal or unpaid interest (the Conversion Amount) accrued on any draw advanced by Platinum under the Platinum Loan Agreement into shares of Navidea's common stock, provided that our common stock is trading above $2.53 per share. Platinum may also exercise a conversion right on the amount of any mandatory repayment due following the Company achieving $2,000,000 in cumulative revenues from sales or licensing of Lymphoseek, provided that our common stock is trading above $2.53 per share, if the Company is prohibited from making such repayment under the terms of the Subordination Agreement between Platinum, CRG and the Company. If Platinum exercises any or all of its conversion rights, the percentage ownership of our current stockholders will be reduced. The issuance of additional common stock may also result in dilution in the net tangible book value per share of our common stock.

Shares of common stock are equity securities and are subordinate to our existing and future indebtedness and preferred stock.

Shares of our common stock are common equity interests. This means that our common stock ranks junior to any preferred stock that we may issue in the future, to our indebtedness and to all creditor claims and other non-equity claims against us and our assets available to satisfy claims on us, including claims in a bankruptcy or similar proceeding. Our existing indebtedness restricts payment of dividends on our common stock, and future indebtedness and preferred stock may restrict payments of dividends on our common stock.

Additionally, unlike indebtedness, where principal and interest customarily are payable on specified due dates, in the case of our common stock, (i) dividends are payable only when and if declared by our Board of Directors or a duly authorized committee of our Board of Directors, and (ii) as a corporation, we are restricted to making dividend payments and redemption payments out of legally available assets. We have never paid a dividend on our common stock and have no current intention to pay dividends in the future. Furthermore, our common stock places no restrictions on our business or operations or on our ability to incur indebtedness or engage in any transactions, subject only to the voting rights available to shareholders generally.

The continuing contentious federal budget negotiations may have an impact on our business and financial condition in ways that we currently cannot predict, and may further limit our ability to raise additional funds.

The continuing federal budget disputes not only may adversely affect financial markets, but could also delay or reduce research grant funding and adversely affect operations of government agencies that regulate us, including the FDA, potentially causing delays in obtaining key regulatory approvals.

Our failure to maintain continued compliance with the listing requirements of the NYSE MKT exchange could result in the delisting of our common stock.

Our common stock has been listed on the NYSE MKT since February 2011. The rules of NYSE MKT provide that shares be delisted from trading in the event the financial condition and/or operating results of the Company appear to be unsatisfactory, the extent of public distribution or the aggregate market value of the common stock has become so reduced as to make further dealings on the NYSE MKT inadvisable, the Company has sold or otherwise disposed of its principal operating assets, or has ceased to be an operating company, or the Company has failed to comply with its listing agreements with the Exchange. For example, the NYSE MKT may consider suspending trading in, or removing the listing of, securities of an issuer that has stockholders' equity of less than $6.0 million if such issuer has sustained losses from continuing operations and/or net losses in its five most recent fiscal years. As of December 31, 2015, the Company had a stockholders' deficit of approximately $53.8 million. Even if an issuer has a stockholders' deficit, the NYSE MKT will not normally consider removing from the list securities of an issuer that fails to meet these requirements if the issuer has (1) total value of market capitalization of at least $50,000,000; or total assets and revenue of $50,000,000 each in its last fiscal year, or in two of its last three fiscal years; and (2) the issuer has at least 1,100,000 shares publicly held, a market value of publicly held shares of at least $15,000,000 and 400 round lot shareholders. Based on the number of outstanding shares of our common stock, recent trading price of that stock, and number of round lot holders, we believe that we meet these exception criteria and that our common stock will not be delisted as a result of our failure to meet the minimum stockholders' equity requirement for continued listing. We cannot assure you that the Company will continue to meet these and other requirements necessary to maintain the listing of our common stock on the NYSE MKT. For example, we may determine to grow our organization or product pipeline or pursue development or other activities at levels or on timelines that reduces our stockholders' equity below the level required to maintain compliance with NYSE MKT continued listing standards.

The NYSE MKT Company Guide also provides that the Exchange may suspend or remove from listing any common stock selling for a substantial period of time at a low price per share, if the issuer shall fail to effect a reverse split of such shares within a reasonable time after being notified that the Exchange deems such action to be appropriate under all the circumstances. The Company's common stock has recently traded for a price as low as $0.75 per share, and if the low trading price persists, there is a risk that the Exchange may require the Company to effect a reverse split of its common stock in order to maintain its NYSE MKT listing, and that the shares will be delisted if such action is not taken to the satisfaction of the NYSE MKT.

The delisting of our common stock from the NYSE MKT likely would reduce the trading volume and liquidity in our common stock and may lead to decreases in the trading price of our common stock. The delisting of our common stock may also materially impair our stockholders' ability to buy and sell shares of our common stock. In addition, the delisting of our common stock could significantly impair our ability to raise capital, which is critical to the execution of our current business strategy.

The price of our common stock has been highly volatile due to several factors that will continue to affect the price of our stock.

Our common stock traded as low as $0.75 per share and as high as $2.50 per share during the 12-month period ended February 29, 2016. The market price of our common stock has been and is expected to continue to be highly volatile. Factors, including announcements of technological innovations by us or other companies, regulatory matters, new or existing products or procedures, concerns about our financial position, operating results, litigation, government regulation, developments or disputes relating to agreements, patents or proprietary rights, may have a significant impact on the market price of our stock. In addition, potential dilutive effects of future sales of shares of common stock by the Company and by stockholders, and subsequent sale of common stock by the holders of warrants and options could have an adverse effect on the market price of our shares.

Some additional factors which could lead to the volatility of our common stock include:

- market perceptions of our ability to meet the revenue and liquidity covenants contained in the CRG Loan Agreement;
- price and volume fluctuations in the stock market at large or of companies in our industry which do not relate to our operating performance;
- changes in securities analysts' estimates of our financial performance or deviations in our business and the trading price of our common stock from the estimates of securities analysts;
- FDA or international regulatory actions and regulatory developments in the U.S. and foreign countries;

- financing arrangements we may enter that require the issuance of a significant number of shares in relation to the number of shares currently outstanding;
- public concern as to the safety of products that we or others develop;
- activities of short sellers in our stock; and
- fluctuations in market demand for and supply of our products.

The realization of any of the foregoing could have a dramatic and adverse impact on the market price of our common stock. In addition, class action litigation has often been instituted against companies whose securities have experienced substantial decline in market price. Moreover, regulatory entities often undertake investigations of investor transactions in securities that experience volatility following an announcement of a significant event or condition. Any such litigation brought against us or any such investigation involving our investors could result in substantial costs and a diversion of management's attention and resources, which could hurt our business, operating results and financial condition.

An investor's ability to trade our common stock may be limited by trading volume.

During the 12-month period beginning on March 1, 2015 and ending on February 29, 2016, the average daily trading volume for our common stock on the NYSE MKT was approximately 600,000 shares. We cannot assure you that this trading volume will be consistently maintained in the future.

The market price of our common stock may be adversely affected by market conditions affecting the stock markets in general, including price and trading fluctuations on the NYSE MKT exchange.

The market price of our common stock may be adversely affected by market conditions affecting the stock markets in general, including price and trading fluctuations on the NYSE MKT. These conditions may result in (i) volatility in the level of, and fluctuations in, the market prices of stocks generally and, in turn, our shares of common stock, and (ii) sales of substantial amounts of our common stock in the market, in each case that could be unrelated or disproportionate to changes in our operating performance.

Because we do not expect to pay dividends on our common stock in the foreseeable future, stockholders will only benefit from owning common stock if it appreciates.

We have paid no cash dividends on any of our common stock to date, and we currently intend to retain our future earnings, if any, to fund the development and growth of our business. As a result, with respect to our common stock, we do not expect to pay any cash dividends in the foreseeable future, and payment of cash dividends, if any, will also depend on our financial condition, results of operations, capital requirements and other factors and will be at the discretion of our Board of Directors. Furthermore, we are subject to various laws and regulations that may restrict our ability to pay dividends and we may in the future become subject to contractual restrictions on, or prohibitions against, the payment of dividends. Due to our intent to retain any future earnings rather than pay cash dividends on our common stock and applicable laws, regulations and contractual obligations that may restrict our ability to pay dividends on our common stock, the success of your investment in our common stock will likely depend entirely upon any future appreciation and there is no guarantee that our common stock will appreciate in value.

We may have difficulty attracting and retaining qualified personnel and our business may suffer if we do not.

Our business has experienced a number of successes and faced several challenges in recent years that have resulted in several significant changes in our strategy and business plan, including the shifting of resources to support our current development initiatives. Our management will need to remain flexible to support our business model over the next few years. However, losing members of the Navidea management team could have an adverse effect on our operations. Our success depends on our ability to attract and retain technical and management personnel with

expertise and experience in the pharmaceutical industry, and the acquisition of additional product candidates may require us to acquire additional highly qualified personnel. The competition for qualified personnel in the biotechnology industry is intense and we may not be successful in hiring or retaining the requisite personnel. If we are unable to attract and retain qualified technical and management personnel, we will suffer diminished chances of future success.

We may be adversely affected if our controls over external financial reporting fail or are circumvented.

We regularly review and update our internal controls, disclosure controls and procedures, and corporate governance policies. In addition, we are required under the Sarbanes Oxley Act of 2002 to report annually on our internal control over financial reporting. If it were to be determined that our internal control over financial reporting is not effective, such shortcoming could have an adverse effect on our business and financial results and the price of our common stock could be negatively affected. This reporting

requirement could also make it more difficult or more costly for us to obtain certain types of insurance, including director and officer liability insurance, and we may be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. Any system of internal controls, however well designed and operated, is based in part on certain assumptions and can provide only reasonable, not absolute, assurances that the objectives of the system are met. Any failure or circumvention of the controls and procedures or failure to comply with regulation concerning control and procedures could have a material effect on our business, results of operation and financial condition. Any of these events could result in an adverse reaction in the financial marketplace due to a loss of investor confidence in the reliability of our financial statements, which ultimately could negatively affect the market price of our shares, increase the volatility of our stock price and adversely affect our ability to raise additional funding. The effect of these events could also make it more difficult for us to attract and retain qualified persons to serve on our Board of Directors and our Board committees and as executive officers.

We call to your attention that our management's evaluation of the effectiveness of the Company's internal controls over financial reporting as of December 31, 2015 concluded that our controls were not effective, due to a material weakness resulting from the failure of officers of our subsidiary, Macrophage Therapeutics, Inc., to provide accurate and timely information to the Company. However, notwithstanding this material weakness, management has concluded that the consolidated financial statements included in this Report fairly present, in all material respects, the Company's consolidated financial position, results of operations and cash flows for the periods presented therein, in conformity with accounting principles generally accepted in the United States of America. Although the Company is taking steps to remediate the material weakness, there can be no assurance that similar incidents can be prevented in the future if the internal controls are not followed by officers of the Company or our subsidiaries. See Controls and Procedures—Disclosure Controls and Procedures.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

We currently lease approximately 25,000 square feet of office space at 5600 Blazer Parkway, Dublin, Ohio, as our principal offices. The current lease term expires in October 2022, at a monthly base rent of approximately $25,000 during 2016. We must also pay a pro-rata portion of the operating expenses and real estate taxes of the building. We believe this facility is in good condition.

Item 3. Legal Proceedings

Section 16(b) Action

On August 12, 2015, a shareholder of the Company filed an action in the United States District Court for the Southern District of New York against two funds managed by Platinum alleging violations of Section 16(b) of the Securities Exchange Act in connection with purchases and sales of the Company's common stock by the Platinum funds, and seeking disgorgement of the short-swing profits realized by the funds. The Company is a nominal defendant in the action, no relief is sought against the Company, and a portion of any amount awarded to the plaintiff by judgment or settlement of the action will likely accrue to the benefit of the Company. Platinum has moved to dismiss the action, and a decision on the motion to dismiss is expected shortly following oral argument, currently scheduled for March 30, 2016.

Sinotau Litigation

On August 31, 2015, Sinotau Pharmaceutical Group (Sinotau) filed a suit for damages, specific performance and injunctive relief against the Company in the United States District Court for the District of Massachusetts alleging breach of a letter of intent for licensing to Sinotau of the Company's NAV4694 product candidate and technology. The Company believes the suit is without merit and has filed a motion to dismiss the action. While it is not possible to determine with any degree of certainty the ultimate outcome of this legal proceeding, including making a determination of liability, we believe that we have meritorious defenses with respect to the claims asserted against us and intend to vigorously defend our position.

Item 4. Mine Safety Disclosure

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Our common stock trades on the NYSE MKT exchange under the trading symbol NAVB. Prior to our name change from Neoprobe Corporation to Navidea Biopharmaceuticals, Inc. on January 5, 2012, our common stock was traded on the NYSE MKT under the trading symbol NEOP. The prices set forth below reflect the quarterly high and low sales prices for shares of our common stock during the last two fiscal years.

	High	Low
Fiscal Year 2015:		
First Quarter	$1.96	$1.55
Second Quarter	1.67	1.22
Third Quarter	2.50	1.28
Fourth Quarter	2.40	1.32
Fiscal Year 2014:		
First Quarter	$2.12	$1.62
Second Quarter	1.99	1.29
Third Quarter	1.53	1.20
Fourth Quarter	2.02	0.97

As of March 1, 2016, we had approximately 650 holders of common stock of record.

We have not paid any dividends on our common stock and do not anticipate paying cash dividends on our common stock in the foreseeable future. We intend to retain any earnings to finance the growth of our business. We cannot assure you that we will ever pay cash dividends. Whether we pay cash dividends in the future will be at the discretion of our Board of Directors and will depend upon our financial condition, results of operations, capital requirements and any other factors that the Board of Directors decides are relevant. See Management's Discussion and Analysis of Financial Condition and Results of Operations.

During the three-month period ended December 31, 2015, we issued 18,501 shares of our common stock to our Board of Directors as payment of their second and third quarter 2015 retainers. The issuance of these securities was exempt from registration under Section 4(2) of the Securities Act and Regulation D promulgated thereunder.

There were no repurchases of our common stock during the three-month period ended December 31, 2015.

Stock Performance Graph

The following graph compares the cumulative total return on a $100 investment in each of the common stock of the Company, the Russell 3000, and the NASDAQ Biotechnology Index for the period from December 31, 2010 through December 31, 2015. This graph assumes an investment in the Company's common stock and the indices of $100 on December 31, 2010 and that any dividends were reinvested.

COMPARISON OF 5 YEAR CUMULATIVE TOTAL RETURN*

Among Navidea Biopharmaceuticals, the Russell 3000 Index, and the NASDAQ Biotechnology Index

*$100 invested on 12/31/2010 in stock or index, including reinvestment of dividends.

	Cumulative Total Return as of December 31,					
	2010	2011	2012	2013	2014	2015
Navidea Biopharmaceuticals	100.00	127.18	137.38	100.49	91.75	64.56
Russell 3000	100.00	99.08	112.93	147.87	163.33	160.92
NASDAQ Biotechnology	100.00	111.81	147.48	244.24	327.52	364.93

Item 6. Selected Financial Data

The following summary financial data are derived from our consolidated financial statements that have been audited by our independent registered public accounting firm. These data are qualified in their entirety by, and should be read in conjunction with, our Consolidated Financial Statements and Notes thereto included elsewhere in this Form 10-K as well as Management's Discussion and Analysis of Financial Condition and Results of Operations. Summary financial data for 2015 and 2011 reflect the disposition of our gamma detection device business in August 2011 and the reclassification of certain related items to discontinued operations.

(Amounts in thousands, except per share data)	Years Ended December 31,				
	2015	2014	2013	2012	2011
Statement of Operations Data:					
Revenue	$13,249	$6,275	$1,131	$79	$598
Cost of goods sold	1,755	1,586	333	—	—
Research and development expenses	12,788	16,780	23,710	16,890	15,154
Selling, general and administrative expenses	17,257	15,542	15,526	11,178	9,548
Loss from operations	(18,551)	(27,633)	(38,438)	(27,989)	(24,104)
Other expenses, net	(10,208)	(8,094)	(4,261)	(1,168)	(943)
Benefit from income taxes	436	—	—	—	7,880
Loss from continuing operations	(28,323)	(35,727)	(42,699)	(29,157)	(17,167)
Discontinued operations, net of tax effect	759	—	—	—	22,780
Net (loss) income	(27,564)	(35,727)	(42,699)	(29,157)	5,613
Less loss attributable to noncontrolling interest	(1)	—	—	—	—
Deemed dividend	(46)	—	—	—	—
Preferred stock dividends	—	—	—	(43)	(100)
(Loss) income attributable to common stockholders	$(27,609)	$(35,727)	$(42,699)	$(29,200)	$