NAVIDEA BIOPHARMACEUTICALS, INC.
Form 10-K
March 18, 2013

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, 2012

or

¨ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE EXCHANGE ACT

For the transition period from to _____ to _____

Commission file number H01-35076

NAVIDEA BIOPHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)

Delaware (State or other jurisdiction of incorporation or organization)	31-1080091 (I.R.S. Employer Identification No.)
425 Metro Place North, Suite 450, Dublin, Ohio (Address of principal executive offices)	43017-1367 (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 ¨ 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 ¨ No x

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.

Yes x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate 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 ¨

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.

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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 ¨	Accelerated filer x
Non-accelerated filer ¨	Smaller reporting company ¨

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12-b-2 of the Act.)

Yes ¨ No x

The aggregate market value of shares of common stock held by non-affiliates of the registrant on June 30, 2012 was $355,918,124.

The number of shares of common stock outstanding on March 1, 2013 was 117,610,966.

DOCUMENTS INCORPORATED BY REFERENCE

None.

References in this report to Navidea Biopharmaceuticals, Navidea, the Company, we, our and us refer to Navidea Biopharmaceuticals, Inc. and its subsidiaries on a consolidated basis. In January 2012, we changed our name to Navidea Biopharmaceuticals, Inc. from Neoprobe Corporation. Navidea was chosen as the new name to reflect the Company's dedication to "NAVigating IDEAs" that translate cutting edge innovation and precision diagnostics technology into novel products to advance patient care. Historical references within this Annual Report on Form 10-K to Neoprobe Corporation have therefore generally been revised to refer to our new name.

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., a Delaware corporation, is a biopharmaceutical company focused on the development and commercialization of precision diagnostics and radiopharmaceutical agents. Our Company's core mission is to bring the next generation of precision radiopharmaceutical agents to market so doctors and patients can readily access, and benefit from, cutting-edge diagnostic science.

For patients and physicians, we aspire to provide innovative diagnostic imaging agents to improve patient care for serious diseases. For our shareholders, we aim to deliver superior growth through our focus on our innovative

diagnostics platforms and products and efficient business processes. For our employees, we provide a culture focused on the direct impact our efforts can have on patients and an innovative development environment enabling new breakthrough products.

Navidea's current radiopharmaceutical development programs include:

- Lymphoseek® (technetium Tc 99m tilmanocept) Injection is a novel, receptor-targeted, small-molecule, radiopharmaceutical designed for use in lymphatic mapping procedures that are performed to help stage certain solid tumors. Lymphoseek is intended to help identify the lymph nodes that drain from a primary tumor, which have the highest probability of harboring cancer. Lymphoseek was approved for use in lymphatic mapping for breast cancer and melanoma by the U.S. Food and Drug Administration (FDA) on March 13, 2013. Additional trials, two of which are already ongoing in head and neck cancer and colorectal cancer, are anticipated to provide support for expanding the utilization of Lymphoseek into multiple other cancer types.
- NAV4694 is an F-18 radiolabeled positron emission tomography (PET) imaging agent being developed as an aid in the diagnosis of patients with signs or symptoms of cognitive impairment such as Alzheimer's disease (AD).

- NAV5001 is an Iodine-123 radiolabeled single photon emission computed tomography (SPECT) imaging agent being developed as an aid in the diagnosis of Parkinson's disease (PD) and other movement disorders, with potential additional use as a diagnostic aid in dementia.
- RIGScan™ is a radiolabeled monoclonal antibody being developed as a diagnostic aid for use during surgery to help surgeons locate occult or metastatic cancer, with a primary focus on colorectal cancer.

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 diagnostics company focused on "NAVigating IDEAS" that result in the development and commercialization of precision diagnostic 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 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). From October 1999 through July 2010, the GDS products were marketed throughout most of the world through a distribution arrangement with Ethicon Endo-Surgery, Inc. (EES), a Johnson & Johnson company. From July 2010 through August 2011, the neoprobe GDS system products were marketed through a distribution arrangement with Devicor Medical Products, Inc. (Devicor), a successor to EES. During the fiscal years ended December 31, 2011 and 2010, we derived revenue from the sale of our GDS system products of $7.6 million and $10.0 million, respectively. Of those amounts, $7.4 million and $9.8 million, respectively, were derived from the sale of our GDS system products in the United States, and $166,000 and $182,000, respectively, were derived from the sale of our GDS system products in foreign countries.

In July 2010, Devicor acquired EES's breast biopsy business, including an assignment of the distribution agreement with Navidea. Shortly after this acquisition, Devicor approached us regarding its interest in acquiring the GDS Business. After careful consideration of Devicor's proposal and in-depth discussion regarding the changes this transaction would have on our strategy and focus, the Company's Board of Directors authorized the sale of the GDS Business to Devicor (the Asset Sale) and we executed an Asset Purchase Agreement (APA) with Devicor in May 2011. Our stockholders approved the Asset Sale at our Annual Meeting of Stockholders on August 15, 2011, and the Asset Sale closed on August 17, 2011, consistent with the terms of the APA. Under the terms of the APA, we sold the assets and assigned certain liabilities that were primarily related to the GDS Business. 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 over the course of the next six fiscal years.

The cornerstone of our current business was established in 2001 when we restarted our pharmaceutical development by entering into a worldwide license agreement for Lymphoseek with the Regents of the University of California through their San Diego affiliate (UCSD). In 2004, we initiated our first corporate-sponsored clinical trial of Lymphoseek. Our business strategy is focused on advancing Navidea as a leader in the area of precision diagnostics, a field aimed at helping physicians deliver the right treatment to the right patient at the right time.

Our Technology and Product Candidates

We have a deep understanding of and experience in translating precision diagnostics technology, particularly in the area of radiopharmaceuticals, into novel products to advance patient care. Innovative precision diagnostic agents hold the potential to improve diagnostic accuracy, clinical decision-making and patient care. Navidea's pipeline includes clinical-stage radiopharmaceutical agents used to identify the presence and status of disease to achieve these objectives.

Lymphoseek – The First and Only FDA-Approved Receptor-Targeted Radiopharmaceutical Lymphatic Mapping Agent

Lymphoseek is a lymph node targeting radiopharmaceutical agent intended for use in intraoperative lymphatic mapping (ILM) 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 on March 13, 2013. Additional trials, two of which are already ongoing in head and neck cancer and colorectal cancer, are anticipated to provide support for expanding the utilization of Lymphoseek into multiple other cancer types.

The Lymph System: Infection Fighter and Cancer Conduit

The lymph system is a critical component of the body's immune system. Comprised of a complex network of organs, nodes, ducts and vessels, the lymph system transports lymph – a fluid rich in white blood cells, known as lymphocytes – from tissues into the bloodstream. The key components of the lymph system are lymph nodes – small anatomic structures that contain disease-fighting lymphocytes, filter lymph of bacteria and cancer cells, and signal infection in response to heightened levels of pathogens.

The lymph system is also a common pathway for cancer to spread, or metastasize. In fact, malignant cells will often infiltrate lymph nodes as an initial step of the metastatic process. An assessment of the degree of lymph node involvement is instrumental to staging cancer, enabling suitable treatment regimens and offering more accurate prognosis. Studies in a broad range of malignancies demonstrate that the greater the extent of lymph node involvement, the poorer the likely outcome.

ILM: Targeting High-Risk Nodes

Until the 1990s, cancer patients would often undergo extensive surgeries involving the removal and biopsy of large numbers of lymph nodes to assess disease progress. Studies subsequently showed that as many as 80 percent of node dissections ultimately revealed no sign of cancer, exposing patients to significant pain, morbidity, debilitating adverse effects and long recovery times for little benefit.

Over the last two decades, ILM, using injected dyes or radiopharmaceutical agents, has become a widely accepted, less invasive technique to identify potentially cancerous lymph nodes. Upon injection, these tracing agents follow the natural drainage path from the primary tumor into the first tier of surrounding lymph nodes. The initial nodes in this pathway – key predictive nodes called sentinel nodes that are most likely to harbor cancer – are of critical importance in gauging the degree of infiltration. If this initial node or nodes show no sign of cancer cells, there is a high likelihood that lymph nodes further along the continuum are cancer-free. If the sentinel node is positive for disease, a more comprehensive resection of nodes may be warranted. Regardless, a patient can be more accurately staged in light of knowledge that cancer has moved from the primary tumor site into the lymphatic system.

Lymphoseek: Tracing the Path to an ILM Advance

ILM has become the cancer-staging procedure of choice for oncology surgeons because it helps them focus on key predictive lymph nodes and reduce patient exposure to unnecessary surgical complications. Lymphoseek is a radiolabeled diagnostic for detection of the key predictive lymph nodes draining the tumor region. Lymphoseek is purposely-designed to accumulate in lymphatic tissue by specifically binding to mannose binding receptor (MBR; CD206) proteins present on the surface of immune cells. Lymphoseek is a macromolecule consisting of multiple units of diethylene triamine pentaacetic acid (DTPA) and mannose, each synthetically attached to a 10 kDa dextran backbone. The mannose acts as a ligand for the receptor, and the DTPA serves as a chelating agent for labeling with the radio-isotope Technetium Tc 99m.

In clinical studies, Lymphoseek has demonstrated significant benefits over an approved comparator agent, vital blue dye (VBD). In Navidea's Phase 3 clinical studies of Lymphoseek, it detected over 97 percent of positive nodes identified by VBD. Conversely, VBD missed 31 percent of the overall nodes identified by Lymphoseek. More importantly, VBD missed 21 percent of nodes identified by Lymphoseek that were subsequently confirmed as containing cancer, whereas Lymphoseek missed less than 1 percent of these cancer-positive nodes, representing a greater than twenty-fold reduction in the rate at which cancer-positive lymph nodes were missed. Importantly, this resulted in 9.2% of subjects in our Phase 3 clinical studies being up-staged by the use of Lymphoseek in cases that would have been under-staged using VBD alone.

In the U.S., ILM employs a non-standard, Technetium 99mTc-labeled radiopharmaceutical agent known as sulfur-colloid (TcSC) which was recently approved by the FDA based on a literature review for use in ILM for breast cancer and melanoma. In contrast, Lymphoseek was studied in two well-controlled, prospective Phase 3 trials which compared Lymphoseek to VBD, the same color agent utilized in the literature-based FDA assessment of TcSC.

An abstract reviewing a meta-analysis of Phase 3 clinical trials for ILM of lymph nodes in breast cancer, compared to standard of care techniques including colloid agents, was published in conjunction with the 2012 Annual Meeting of the American Society of Clinical Oncology (ASCO). The abstract entitled, *"The novel receptor targeted (CD206) 99mTc-labeled tilmanocept versus the currently employed Tc99m-sulfur colloid in intraoperative lymphatic mapping (ILM) on key performance metrics in breast cancer"* was published in the *Journal of Clinical Oncology Online 2012; e21066*.

Assessment by meta-analysis and pooled analysis methods have been completed comparing Lymphoseek alone to TcSC plus VBD used together in subjects with breast cancer, employing the data provided in the FDA's approval of TcSC. Two endpoints were evaluated; the *Localization Rate,* which is the percentage of subjects with one or more radio-detected (Lymphoseek) or radio-detected and/or blue dye-positive (TcSC/VBD) nodes and the *Degree of Localization,* which is the number of nodes detected per subject. Both of these metrics help define the potential for an imaging agent's performance in ILM and the potential identification of metastasis to lymph nodes. The Localization

Rate for TcSC/VBD was 94%. The Localization Rate for Lymphoseek was statistically significantly greater at 99.91% by meta-analysis and 98.65% by pooled analysis ($p<0.0001$ and $p<0.008$, respectively). The Degree of Localization derived from the publication database for TcSC/VBD was 1.6 nodes per subject and for Lymphoseek it was 2.08 per subject by meta-analysis and 2.16 per subject by pooled analysis ($p<0.0001$ and $p<0.0001$, respectively). The analysis concluded that, in breast cancer, Lymphoseek provided significantly greater performance over the current ILM standard of care techniques in the key metrics of lymph node localization and identification of the number of lymph nodes found per subject.

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In June 2012, we published data developed from Phase 3 trials of Lymphoseek demonstrating important performance characteristics of Lymphoseek compared to a commercially available radiolabeled colloid used in intra-operative lymphatic mapping. The analysis evaluated the performance of Lymphoseek to a meta-analysis of published data for 99m-Tc-labeled nanocolloid human serum albumin (Nanocoll®), commercially available and considered a standard of care in Europe. Data for Nanocoll were derived from a meta-analysis of published literature that reported on the outcomes of localization rate (the proportion of subjects with at least one localized lymph node), and degree of localization (the average number of localized nodes relative to the subject population). Data for Lymphoseek were derived from a meta-analysis of two completed Lymphoseek Phase 3 clinical trials. Lymphoseek demonstrated a localization rate of 99.9% whereas Nanocoll showed a 95.9% localization rate. The degree of Lymphoseek localization was 2.16 (CI 1.99-2.36), whereas the colloid standard of care showed 1.67 (CI 0.94-0.98). The differences between Lymphoseek and Nanocoll in both of these parameters were statistically significant ($p < 0.0001$). The study, *"The efficacy of Tilmanocept in sentinel lymph node mapping and identification in breast cancer patients: a comparative review and meta-analysis of the 99m-Tc-labeled nanocolloid human serum albumin standard of care,"* can be found in the online edition of the peer-reviewed journal *Clinical and Experimental Metastasis [DOI 10.1007/s10585-012-9497-x]*. In September 2012, we announced the presentation of related data at the European Society of Surgical Oncology annual meeting.

We believe Lymphoseek's unique properties in ILM and lymphoscintigraphy may offer several potential advantages over agents currently used in ILM, including:

- Improved presence in key predictive lymph nodes (distinct mechanism of action allows for effective identification of key tumor-draining lymph nodes)
- More rapid clearance of the injection site (detectable in lymph nodes within 10 minutes and up to 30 hours)
- Reduced patient trauma, morbidity and injection pain
- Faster nuclear medicine imaging – reduced nuclear medicine downtime (detectable in lymph nodes within 10 minutes and up to 30 hours)
- Enhanced operating room efficiency; reduced operating room idle time (ILM can be performed from 15 minutes up to 15 hours post-injection)
- Enhanced hospital and healthcare plan reimbursement

Expansion of ILM for staging of colon, prostate, gastric, lung and other cancers

The application of ILM to solid tumor cancer management has been most widely developed in the breast cancer and melanoma indications. Numerous clinical studies, involving thousands of patients, published in peer-reviewed medical journals as far back as *Oncology* (January 1999) and *The Journal of The American College of Surgeons* (December 2000), have indicated sentinel lymph node biopsy (SLNB) is approximately 95% accurate in predicting the presence or absence of disease spread in melanoma and breast cancers. Consequently, it is estimated that more than 80% of breast cancer patients who would otherwise have undergone full axillary lymph node dissections (ALND), involving the removal of as many as 20 - 30 lymph nodes, might be spared this radical surgical procedure and concomitant morbidity if the sentinel node was found to be free of cancer.

Although ILM has found its greatest acceptance in breast cancer and melanoma, we believe that Lymphoseek may be instrumental in extending ILM into other solid tumor cancers such as prostate, gastric, colon, head and neck, and non-small cell lung. Investigations in these other cancer types have thus far met with mixed levels of success due in part, we believe, to limitations associated with currently available radioactive tracing agents. We believe our development of Lymphoseek may positively impact the effectiveness of ILM in such expanded applications.

Lymphoseek Clinical Development

The initial pre-clinical evaluations of Lymphoseek were completed by UCSD in 2001. Since that time, Navidea, in cooperation with UCSD, has completed or initiated five Phase 1 clinical trials, one multi-center Phase 2 trial and three multi-center Phase 3 trials involving Lymphoseek. Two comprehensive Phase 3 studies have been completed in subjects with breast cancer and melanoma. These pivotal Phase 3 results have been presented at scientific conferences of a number of the world's leading oncology associations and nuclear medicine societies, including the American Society of Clinical Oncology and the Society for Nuclear Medicine. Earlier-phase studies conducted at UCSD through grants from the Susan B. Komen Breast Cancer Research Foundation have been published in leading medical journals including Journal of Nuclear Medicine and Annals of Surgical Oncology. Clinical research continues with a Phase 3 trial involving subjects with head and neck squamous cell carcinoma.

Lymphoseek development has involved feedback from the FDA at a number of stages along the development pathway. In early 2005, the UCSD physician Investigational New Drug (IND) application was transferred to Navidea and we assumed full clinical and commercial responsibility for the development of Lymphoseek. Additional non-clinical testing was successfully completed in late 2005. None of the non-clinical studies revealed any toxicity issues associated with the drug. To provide commercially-produced Lymphoseek needed for clinical study, Navidea engaged Reliable Biopharmaceutical Corporation (Reliable) to manufacture the drug substance and OSO BioPharmaceuticals Manufacturing LLC (OsoBio, formerly Cardinal Health PTS) for commercial manufacturing of the final drug product.

We completed a successful Phase 2 clinical study of Lymphoseek in 80 subjects in June 2007 and announced positive results later that year. Localization of Lymphoseek to lymphoid tissue was confirmed by pathology in over 99% of the lymph node tissue samples removed during the Phase 2 trial. We held an end of Phase 2 meeting with the FDA during late October 2007. Results of the study were published in the February 2011 online edition of the *Annals of Surgical Oncology*.

From 2008 to March 2009, we undertook and completed a Phase 3 clinical study in subjects with either breast cancer or melanoma (NEO3-05), an open label trial of node-negative subjects designed to evaluate the safety and the accuracy of Lymphoseek in identifying the lymph nodes draining from the subject's primary tumor site. The primary efficacy objective of the study was a statistically acceptable concordance rate between the identification of lymph nodes with VBD and Lymphoseek. In addition, a secondary endpoint of the study was to pathologically examine lymph nodes identified by either VBD or Lymphoseek to determine if cancer was present in the lymph nodes.

In June 2009, we initiated a Phase 3 trial in subjects with head and neck squamous cell carcinoma on the head or in the mouth (NEO3-06). The NEO3-06 study was designed to expand the potential labeling for Lymphoseek to other cancer types and include a sentinel lymph node targeting claim.

In March 2010, Navidea met with the FDA to review the clinical outcomes of the NEO3-05 Phase 3 trial. The meeting included a review of the efficacy and safety results of the study and Navidea's plans for the submission of a New Drug Application (NDA) for Lymphoseek based on the results of NEO3-05 and other previously completed clinical studies. In July 2010, Navidea initiated enrollment in another Phase 3 clinical evaluation of Lymphoseek in subjects with either breast cancer or melanoma (NEO3-09) accruing subjects primarily for purposes of augmenting the safety population and supporting expanded product labeling claims. Based on guidance received in the March 2010 meeting, we planned to file data related to the NEO3-09 trial as part of a planned major amendment to the primary NDA.

In October 2010, Navidea met with the FDA for a pre-NDA assessment for Lymphoseek. As a result of the pre-NDA assessment, the FDA requested that data from both the completed NEO3-05 study and the NEO3-09 study then in progress be included in the Company's primary NDA for Lymphoseek rather than submitting the NEO3-09 study safety data as a planned major amendment to the ongoing NDA review, as initially intended. The pre-NDA

assessment resulted in no modification to the NEO3-09 trial design or endpoints or to any of the other previously agreed-to clinical or regulatory components of the Lymphoseek NDA.

Upon completion of the NEO3-09 study in early 2011, Navidea submitted the NDA for Lymphoseek in August 2011, and was notified of acceptance of the NDA by the FDA in October 2011. The Lymphoseek NDA submission was based on the clinical results of the NEO3-05 and NEO3-09 Phase 3 clinical studies and other completed clinical and non-clinical evaluations. The safety database submitted with the NDA included data from over five hundred subjects and identified no significant drug-related adverse events.

In October 2012, we announced peer-reviewed publication of results of Lymphoseek from Phase 3 Clinical Trials in Melanoma in the *Annals of Surgical Oncology*. In the trials, a total of 154 subjects with melanoma from 15 centers received Lymphoseek followed by VBD and then underwent sentinel lymph node mapping. Lymph nodes that demonstrated Lymphoseek uptake and/or the presence of blue dye were removed and examined for the presence of tumor. Of the 235 blue-dyed lymph nodes removed from the 154 subjects, 232 (98.7%) demonstrated Lymphoseek uptake ($p<0.001$). The performance of Lymphoseek in intraoperative lymph node identification was also assessed. Of the 154 subjects injected with both Lymphoseek and VBD who underwent surgical removal of the lymph nodes, 150 subjects (97.4%) had at least one radioactive node due to Lymphoseek uptake, and 138 subjects (89.6%) had at least one blue node. This difference was statistically significant ($p<0.002$). Melanoma-containing lymph nodes were detected in 34 (22.1%) subjects; Lymphoseek identified all 45 melanoma-positive lymph nodes found in the 34 subjects. Four of these 34 node-positive subjects were detected exclusively by Lymphoseek. Blue dye detected 36 of the 45 melanoma-positive lymph nodes, but no melanoma-positive lymph nodes were detected exclusively by blue dye.

Clinical research continues with an ongoing Phase 3 trial involving subjects with head and neck squamous cell carcinoma (NEO3-06). The NEO3-06 clinical study was designed to provide evidence of Lymphoseek performance in a third cancer type and to potentially expand the product label for Lymphoseek. In January 2013, we announced that we had accrued sufficient subjects in our NEO3-06 study in subjects with head and neck cancer to enable us to conduct a pre-planned interim analysis. This Phase 3 trial of Lymphoseek is designed to demonstrate the performance of Lymphoseek in identifying sentinel lymph nodes in subjects with squamous cell carcinoma on the head or in the mouth. The interim analysis will compare the pathological analysis of the sentinel lymph nodes localized using Lymphoseek with that of all the lymph nodes removed during a full nodal dissection surgery of the head and neck. This full dissection surgery is considered the gold standard for determining the presence and extent of cancer and staging of the disease in such subjects. A total of 83 subjects who underwent pre-planned, full dissection surgery were enrolled to the interim analysis point. Results from three investigators participating in the NEO3-06 trial representing approximately half of the enrolled subjects were presented at major scientific conferences during 2012, all of which noted a 0% false negative rate in the subjects. Results from the full interim statistical analysis and reporting of the findings will be available upon completion of full site and data audits planned for later in 2013.

Following the FDA's acceptance of our Lymphoseek NDA filing in October 2011, the FDA established a Prescription Drug User Fee Act (PDUFA) date for Lymphoseek of June 10, 2012. In April 2012, the FDA notified us that the Agency had elected to modify the PDUFA date for Lymphoseek by 90 days to September 10, 2012 from the initial PDUFA date of June 10, 2012. On September 10, 2012, we received a complete response letter (CRL) from the FDA. The decision was focused on deficiencies in current Good Manufacturing Practices (cGMP) identified by the FDA during their pre-approval site inspections of third-party contract manufacturing facilities, and was not related to the efficacy or safety data filed within the Lymphoseek NDA. On October 30, 2012, we resubmitted our NDA in response to the CRL. Following the FDA's acceptance of our Lymphoseek NDA resubmission, the FDA established a new PDUFA date for Lymphoseek of April 30, 2013. Lymphoseek was subsequently approved and indicated for use in lymphatic mapping procedures in breast cancer and melanoma by the FDA on March 13, 2013.

Navidea was advised in February 2012 by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) that the Committee had adopted the advice of the Scientific Advice Working Party (SAWP)

regarding the Lymphoseek development program and determined that Lymphoseek is eligible for a Marketing Authorization Application (MAA) submission based on clinical data accumulated from completed pivotal studies and supporting clinical literature. We submitted our MAA for Lymphoseek to the EMA in December 2012.

We cannot assure you that Lymphoseek will achieve regulatory approval in the EU or any market outside the U.S. or if approved, that it will achieve market acceptance in any market. See Risk Factors.

NAV4694 – Precision Imaging Agent to Aid in Diagnosis of Alzheimer's Disease

In December 2011, we executed a license agreement with AstraZeneca AB for NAV694, a proprietary compound that is primarily intended for use in diagnosing AD and other central nervous system disorders. The license agreement is effective until the later of the tenth anniversary of the first commercial sale of NAV4694 or the expiration of the underlying patents. Under the terms of the license agreement, AstraZeneca granted us an exclusive worldwide royalty-bearing license for NAV4694 with the right to grant sublicenses. In consideration for the license rights, we paid AstraZeneca a license issue fee of $5.0 million upon execution of the agreement. We also agreed to pay AstraZeneca up to $6.5 million in contingent milestone payments based on the achievement of certain clinical development and regulatory filing milestones, and up to $11.0 million in contingent milestone payments due following receipt of certain regulatory approvals and the initiation of commercial sales of the licensed product. In addition, we agreed to pay AstraZeneca a royalty on net sales of licensed and sublicensed products.

NAV4694 is a Fluorine-18 labeled precision radiopharmaceutical candidate for use in the imaging and evaluation of patients with signs or symptoms of cognitive impairment such as AD. 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.

Based on the data accumulated to date, NAV4694 appears to have better sensitivity and specificity in detecting beta-amyloid than other agents in development. Due to its high affinity for amyloid, improved contrast, and enhanced uptake in the amyloid-target regions of interest in the brain compared with low uptake in white matter background, better signal-to-noise ratios have been observed. Greater contrast may enable the ability to detect smaller amounts of amyloid and earlier identification of disease, as well as the opportunity to detect smaller changes in amyloid levels and monitor disease progression over time.

Beta-Amyloid Imaging for Alzheimer's Disease

Alzheimer's disease is a progressive and fatal neurodegenerative disease which affects a person's memory and ability to learn, reason, communicate and carry out daily activities. Increasing age is the greatest risk factor for AD and there is no prevention or cure. The World Health Organization estimates that AD affects over 24 million people worldwide. Currently in the U.S. alone, there are over 5 million Alzheimer's patients and according to Alzheimer's Association (AA) estimates, as many as 16 million Americans could have the disease by 2050. Among the brain changes evident in the development of AD is the accumulation of the protein beta-amyloid outside nerve cells (neurons) in the brain. Somewhere around 100 experimental therapies aimed at slowing or stopping the progression of AD are now undergoing clinical evaluation. Regardless of causative associations, beta-amyloid levels continue to be viewed as a reliable marker of AD.

There is a need for improvements in testing and diagnosis for AD. While there is an accepted diagnostic process for assessing dementia, the only currently definitive diagnosis for AD is a post-mortem analysis of brain tissue. A positive finding of plaques and tangles in the brain upon autopsy leads to this definitive diagnosis, which is too late to benefit the patient. For this reason, the AD and imaging communities have been interested in an effective biomarker of AD which could facilitate earlier definitive diagnosis.

Alzheimer's disease imaging agents are potentially powerful tools aiding in the diagnosis of AD as well as the evaluation of new drugs aiming to modify amyloid plaque levels and alter disease progression. The prototype agent in this diagnostic quest was identified almost a decade ago at the University of Pittsburgh. This imaging agent targets the deposits of amyloid plaque which are a hallmark of AD pathology. This agent, frequently referred to as Pittsburgh B, or PIB, is a radiolabeled small molecule utilized with PET imaging. As such, the PIB tracer provided strong image resolution and was able to distinguish significant amyloid burdens in the brains of AD patients as opposed to the relative absence of amyloid in subjects without AD. Unfortunately, PIB uses C-11, a very short-lived radio-isotope, and thus cannot be readily commercialized.

Other PET amyloid tracers are currently moving through the drug development process. Like PIB, these compounds are also high-resolution PET tracers, but utilize an F-18 isotope, which permits broader effective distribution.

These agents constitute a major step forward, but each has potential limitations. Navidea's NAV4694 appears to have several important advantages including clean images with less white matter uptake for identification of lower levels of amyloid and earlier detection; images that are easier to read and interpret; and images that can be acquired more quickly.

NAV4694 Clinical Development

NAV4694 has been studied in rigorous pre-clinical studies and several clinical trials in humans. Clinical studies through Phase 2 have included 140 subjects to date, both 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. We are currently supporting a Phase 2 trial that we initiated in September 2012, primarily to expand the safety database for the compound. We also expect to initiate a Phase 2b trial in subjects with mild cognitive impairment in early 2013, as well as a Phase 3 autopsy-based trial in the first half of 2013, to support registration in the U.S. and the EU. We cannot assure you, however, that further clinical trials for this product will be successful, that it will achieve regulatory approval, or if approved, that it will achieve market acceptance. See Risk Factors.

NAV5001

In January 2012, we executed an option agreement with Alseres Pharmaceuticals, Inc. (Alseres) to sublicense NAV5001. Under the terms of the option agreement, Navidea paid Alseres an option fee of $500,000 for the exclusive right to negotiate a definitive sublicense agreement by June 30, 2012. In order to perform thorough due diligence, Navidea extended the option period from June 30, 2012, to July 31, 2012. On July 31, 2012, we entered into an agreement to sublicense NAV5001 from Alseres. Under the terms of the sublicense agreement, Alseres granted Navidea an exclusive, worldwide sublicense to research, develop and commercialize NAV5001. The final terms of the agreement required Navidea to make a one-time sublicense execution payment to Alseres equal to (i) $175,000 in cash and (ii) 300,000 shares of our common stock. The sublicense agreement also provides for contingent milestone payments of up to $2.9 million, $2.5 million of which will principally occur at the time of product registration or upon commercial sales, and the issuance of up to an additional 1.15 million shares of Navidea common stock, 950,000 shares of which are issuable at the time of product registration or upon commercial sales. In addition, the sublicense terms anticipate royalties on annual net sales of the approved product which are consistent with industry-standard terms and certain sublicense extension fees, payable in cash and shares of common stock, in the event certain diligence milestones are not met.

NAV5001 is a patented, novel, Iodine-123 labeled small molecule radiopharmaceutical used with SPECT imaging to identify the status of specific regions in the brains of patients suspected of having PD. 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.

NAV5001 has been administered to over 600 subjects to date. Results from clinical trials have demonstrated that NAV5001 has high affinity for DAT and rapid kinetics which enable the generation of clean images quickly, beginning within about 20 minutes after injection, while other agents typically have waiting periods from 4 to 24 hours before imaging can occur. 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 (DLB), one of the most common forms of dementia after AD. We expect to initiate a Phase 2b trial in subjects with DLB in the first half of 2013, as well as a Phase 3 trial in subjects with PD in the second half of 2013. We cannot assure you, however, that further clinical trials for this product will be successful, that it will achieve regulatory approval, or if approved, that it will achieve market acceptance. See Risk Factors.

RIGScan

RadioImmunoGuided Surgery (RIGS®) is a technique to provide diagnostic information during cancer surgery. RIGS is intended to enable a surgeon to identify and delineate occult or metastatic cancerous tissue "targeted" through the use of RIGScan, a radiolabeled, cancer-specific targeting antibody. RIGScan is administered prior to surgery and is identified by pre-operative imaging or during surgery with a gamma detection probe, thereby assisting a surgeon in identifying the location of cancerous tissues. Before surgery, a cancer patient is injected with the antibody which circulates throughout the patient's body and binds specifically to cancer cell antigens or receptors. Concentrations of the antibody within affected tissue are then detected using imaging methods prior to surgery or a gamma probe during surgery to direct the surgeon to targeted tissue for removal.

Our RIGScan technology is a radiolabeled murine monoclonal antibody that serves as the biologic targeting agent for intraoperative detection of occult or metastatic cancer. The antibody localizes or binds to tumor antigen called TAG-72 expressed on solid tumor cancers. RIGScan is intended to be used in conjunction with other diagnostic methods for the detection of the extent and location of occult tumor and tumor metastases in patients with such cancers, potentially including colorectal cancer, ovarian cancer, prostate cancer and other cancers of epithelial origin. The detection of clinically occult tumor is intended to provide the surgeon with a more accurate assessment of the extent of disease, and therefore may impact the surgical and therapeutic management of the patient.

RIGScan Clinical Development

The RIGScan approach has been studied in several clinical trials, including Phase 3 studies. Results from certain of these studies have been published in leading cancer journals including *Clinical Cancer Research, Annals of Surgical Oncology* and *Diseases of the Colon and Rectum*. In 1996, Navidea submitted applications to the EMA and the FDA for marketing approval of RIGScan for the detection of metastatic colorectal cancer based primarily on results of a single Phase 3 clinical trial, NEO2-14, but the FDA declined approval, indicating that, in addition to identifying additional pathology-confirmed disease, the clinical studies of RIGScan needed to demonstrate clinical utility in enhancing patient outcomes, an endpoint which the completed studies were not designed to address. Navidea withdrew its application to the EMA in November 1997.

To resume RIGScan development, we filed a new investigational new drug (IND) request with the FDA in late 2010. We held a pre-IND meeting with the FDA in February 2011 to define the basic chemistry, manufacturing and control (CMC) requirements needed to resume clinical development efforts on RIGScan. The FDA provided guidance regarding enhancing our manufacturing platform, including process improvements to increase manufacturing efficiency and the quality of the underlying biologic antibody and potentially transitioning from a murine-based antibody to a human-based antibody. In August 2011, we also held a meeting with the SAWP of the EMA and received similar guidance. With this collective guidance, we have transitioned from a murine antibody to a humanized antibody. In September 2012, we were awarded a grant from the National Institutes of Health (NIH) to further the

development of RIGScan. The first phase of the grant, which has been awarded, is for $315,000; the second phase of the grant, which requires that we meet certain conditions, primarily investigational review board approval, will be for an additional $1.2 million. We have focused on manufacturing the humanized antibody with the aim of completing the necessary manufacturing steps to support the start of clinical development; however, as the scope and required resources for the RIGScan program, particularly in light of other development opportunities such as Lymphoseek, NAV4694, NAV5001, or other agents continues to be assessed, the timing and scope of our plans for RIGScan may be further affected.

RIGScan is a biologic drug that has not been produced for several years. We have completed the initial steps in assessing the materials required for future clinical testing. We will need to establish robust manufacturing and radiolabeling capabilities for the antibody in order to meet the regulatory needs for the RIGScan product. We cannot assure you that further clinical development will be successful, that the FDA or the EMA will clear RIGScan for marketing, or that it will be successfully introduced or achieve market acceptance. See Risk Factors.

Market Overviews

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 580,000 deaths in 2013 in the U.S. alone. The NIH has estimated the overall annual costs for cancer for the U.S. for 2007 at $226.8 billion: $103.8 billion for direct medical costs and $123.0 billion for indirect mortality. 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 nearly 1.3 million new cases will occur in the U.S. in 2013. An analysis of Globocan 2008 estimates for these same cancer types indicates an annual incidence rate for these cancer types in excess of 7.2 million cases outside the U.S.

Currently, the application of 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 0.5% in women under age 40 to 6.7% in women age 70 or older. While the incidence rate for breast cancer appears to be decreasing, the overall number of new cases of breast cancer is still increasing. According to the ACS, over 232,000 new cases of invasive breast cancer are expected to be diagnosed during 2013 in the U.S. alone. 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. While many breast cancer patients are treated in large cancer centers or university hospitals, regional and/or community hospitals continue to treat the majority of breast cancer patients.

The use of ILM is also common in melanoma. The ACS estimates that approximately 77,000 new cases of melanoma will be diagnosed in the U.S. during 2013. In addition to breast cancer and melanoma, we believe that our oncology products may have utility in other cancer types with another 1 million new cases expected during 2013 in the U.S.

If the potential of Lymphoseek as a radioactive tracing agent is ultimately realized, it may address not only the current 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, and non-small cell lung.. However, we cannot assure you that Lymphoseek will be cleared to market for cancers other than breast or melanoma, or if cleared to market for other cancer types, that it will achieve significant revenue. See Risk Factors.

Alzheimer’s Disease Market Overview

The AA estimates that more than 5.4 million Americans had AD in 2012. On a global basis, Alzheimer's Disease International estimated in 2010 that there were 36 million people living with dementia. AA estimates that total costs for AD care will be approximately $200 billion in 2012. AA also estimates that there are over 15 million AD and dementia caregivers providing 17.4 billion hours of unpaid care valued at over $210 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 2000-2008, death rates have declined for most major diseases while deaths from AD have risen 66 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.

While there are several approved therapies for the treatment of AD, there is significant interest in the development of disease-modifying therapeutics that could slow or reverse progression of the disease. In fact, studies with cholinesterase inhibitors and experimental AD therapies suggest therapeutic intervention is likely to have a bigger impact on disease progression when dosed in patients with early-stage disease than in patients with advanced disease.

For many patients, simply slowing the progression from mild cognitive impairment associated with early-stage disease to advanced AD could have a material impact on quality of life and medical burden for the healthcare system. Delaying the onset of AD by five years could reduce the disease prevalence by 50% during the next few decades and, according to estimates from AA, reduce annual healthcare expenditures by more than $50 billion.

While early detection is the goal of AD staging, there are no validated biomarkers for the onset of symptomatic disease. All AD patients have beta-amyloid plaque deposits in the brain. Currently, detection of the early-stages of AD is based largely on assessing the patient's history of increasing cognitive impairment with some patients also receiving testing by an experimental PET scan to confirm the presence of amyloid plaque. The interest in accurate imaging agent biomarkers for the detection of beta-amyloid has grown significantly in recent years as physicians are attempting to identify methods for detecting amyloid earlier.

Parkinson’s Disease Market Overview

Parkinson’s disease, following AD, is the second-most common neurodegenerative disorder in the United States. The Parkinson’s Disease Foundation (PDF) estimates that up to 10 million people worldwide are living with PD, including 1 million people in the U.S. Approximately 60,000 new cases of PD are diagnosed in the U.S. each year. The Centers for Disease Control rated complications from PD as the 14th leading cause of death in the U.S. and as with AD, there is no cure.

A recent article conservatively estimates that the combined direct and indirect cost of PD exceeds $14.4 billion per year. There are approved therapies for the treatment of PD symptoms but these treatments often become ineffectual as the disease progresses and none have been approved to modify, slow or reverse the disease progression. The burden of this chronic condition is projected to grow substantially over the next few decades as the size of the elderly population grows. Such projections are driving the need for innovative new treatments to prevent, delay onset, or alleviate symptoms of PD. Slowing Parkinson's progression by 50% would reduce health care costs for PD patients by 35%, representing a dramatic reduction in cost of care even when spread over a longer expected survival and positively impacting the patient quality of life.

PD is commonly misdiagnosed or completely missed in clinical evaluations as symptoms are often attributed to the normal aging process. Essential tremor and other similar conditions including DLB, AD, multiple system atrophy, progressive supranuclear palsy, and normal pressure hydrocephalus are also common sources of confusion in PD diagnosis. Collectively, there are over 25 million people in the U.S. and Europe with some type of movement disorder, comprising a large differential diagnosis population. Current diagnostic guidelines are limited since they characterize PD by the presence of motor symptoms. Error rates using clinical diagnostic methods have been reported to be high. Research has shown the importance of who is undertaking a potential PD diagnosis by showing data that nearly half (47%) of PD diagnoses are incorrect when performed in the primary care setting, and specialists whose expertise is not specific movement disorders have an error rate of approximately 25%, while movement disorder specialists are

mistaken in only 6% to 8% of cases.

The interest by the medical community in using imaging as an aid in diagnosing neurological conditions is growing. In PD, people lose dopamine-producing cells in a part of the brain associated with movement. Loss of these cells is the hallmark of PD. Current neuroimaging agents in combination with SPECT imaging are able to aid physicians in their diagnosis by visualizing this area of the brain to show the degree of loss of these motor neurons.

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. Examples of entities with established regional and/or global radiopharmaceutical distribution networks include Cardinal Health, Covidien/Mallinckrodt GE Healthcare, IBA Molecular, Advanced Accelerator Applications, Eckert & Zeigler AG, Lantheus Medical Imaging and Bracco Imaging.

During the fourth quarter of 2007, we executed an agreement with Cardinal Health's 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 will receive 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.

We are in various stages of discussion with potential marketing and distribution partners in the EU and other world markets; however, we do not currently have distribution agreements covering Lymphoseek in any areas of the world other than the U.S. We currently have no distribution agreements for NAV4694, NAV5001 or RIGScan. In addition, it should be noted that the distribution model we have established with Cardinal Health in the U.S. for Lymphoseek may not necessarily be applicable to other markets or even our other potential radiopharmaceutical candidates due to differences in regional distribution infrastructure, regulation and medical practice patterns. We 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.

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 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

In preparation for the commencement of a multi-center clinical evaluation of Lymphoseek, Navidea engaged manufacturing organizations to produce drug used in Phase 2 and Phase 3 trials, and they are expected to be used in the ongoing Phase 3 clinical work. Reliable has produced the drug substance and OsoBio has performed final product manufacturing including final drug formulation, lyophilization (freeze-drying) and packaging processes. Once packaged, the vialed drug can then be shipped to a hospital or regional commercial radiopharmacy where it will be made radioactive (radiolabeled) with technetium-99m (^{99m}Tc) to become the final form of Lymphoseek to be administered to a patient. The commercial manufacturing processes at Reliable and OsoBio are being concurrently validated in parallel with the approval and commercial launch of Lymphoseek. Both organizations have assisted Navidea in the preparation of the CMC sections of our submissions to the FDA and the EMA. Both Reliable and

OsoBio are registered manufacturers with the FDA and/or 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. At this point, drug product produced by OsoBio has been manufactured under clinical development agreements. A commercial supply agreement with OsoBio is in process. We cannot assure you that we will be successful in reaching a commercial supply agreement with OsoBio on terms satisfactory to us, or at all.

NAV4694 Manufacturing

Supplies of NAV4694 used in clinical development through Phase 2b were manufactured by AstraZeneca through various arrangements. As a part of the technology transfer process related to our license of NAV4694, we are in the process of identifying and contracting with third party manufacturers and radiolabeling contractors necessary to build an integrated supply chain to produce the drug product for use in further clinical studies as well as for subsequent commercial use. We are producing drug substance, and are developing a commercial drug product kit, along with a commercial radiolabeling process and building a network of partners for the manufacture and distribution of NAV4694. We cannot assure you that we will be successful in executing agreements for the supply of NAV4694 on terms acceptable to the Company, or at all.

NAV5001 Manufacturing

Supplies of NAV5001 used in clinical development through Phase 3 were manufactured by Alseres under an agreement they had in place with Nordion, Inc. (Nordion), a Canadian corporation and well-recognized manufacturer of ^{123}I and nuclear medicine labeled imaging agents. As a part of the technology transfer process related to our sublicense of NAV5001, we have begun the process of identifying potential manufacturers and have initiated preliminary negotiations to produce the drug product for use in further clinical studies as well as for subsequent commercial use. We cannot assure you that we will be successful in completing a supply agreement on terms acceptable to the Company, or at all.

RIGScan Manufacturing

During the third quarter of 2009, we announced that we had executed a Biopharmaceutical Development and Supply Agreement for RIGScan with Laureate Biopharmaceutical Services, Inc. We will need to re-establish radiolabeling capabilities for the antibody in order to meet the regulatory needs for the RIGScan product. We cannot assure you that we will be successful in completing the necessary development or supply agreements to support RIGScan development or commercialization on terms acceptable to the Company, or at all.

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. See Risk Factors.

We expect to encounter significant competition for the principal pharmaceutical products we plan to develop. 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 will continue to seek licenses for technologies related to our field of interest and may face competition with respect to such efforts. 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.

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, many surgeons 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. 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 or are in development for use as biomarkers to aid in detection of AD. Developed through Eli Lilly’s wholly-owned Avid Radiopharmaceuticals (Avid), florbetapir was reviewed in January 2011 by the FDA Peripheral and Central Nervous System Drugs Advisory Committee, which voted 16-0 in favor of recommending that this drug be approved for use. However, the recommendation was contingent on a training program as there was significant variability in interpretation among readers of images generated by this agent. In March 2011, Avid received an FDA complete response letter primarily focused on the need to establish a reader training program to ensure reader accuracy and consistency of interpretations of existing

florbetapir scans. In April 2012, Avid received FDA approval to market florbetapir. Florbetapir also received marketing authorization in the EU in January 2013.

In addition to fluorbetipir, there are two other beta-amyloid imaging agents in late stage development: florbetaben from Piramal Enterprises, Imaging Division, who acquired a molecular imaging research and development portfolio from Bayer Pharma AG in April 2012, and flutemetamol from GE Healthcare. Both have completed Phase 3 trials. Data from the Phase 3 study of florbetaben was presented in April 2012. The study was designed to evaluate the power of florbetaben to identify whether a suspected AD patient has cerebral beta-amyloid deposits. The data were verified by histological verification in a postmortem autopsy. GE Healthcare is developing another PIB derivative, flutemetamol, for similar application. NDA and MAA submissions for flutemetamol have been accepted by the FDA and EMA, respectively. The NDA and MAA submissions were based on data from a series of clinical trials, including Phase 3 brain autopsy and biopsy studies which showed high sensitivity and specificity for visual image reads as well as strong concordance between [^{18}F]flutemetamol PET images and beta amyloid brain pathology. Data from these studies were presented at the Alzheimer's Association International Conference 2012 in Vancouver and the American Academy of Neurology's 64th Annual Meeting in New Orleans. The filing also includes data from a recently completed [^{18}F]flutemetamol PET image reader training validation study, results of which will be presented at a scientific forum in coming months.

NAV5001 Competition

In July 2000,GE Healthcare received EMA approval to market DaTscan™(Ioflupane ^{123}I Injection), a radiopharmaceutical agent intended for use with SPECT imaging for the detection of dopamine transporters in the brains of adult patients with suspected Parkinsonian syndromes, in the EU. DaTscan was developed to help physicians evaluate neurodegenerative movement disorders, such as idiopathic (of unknown cause) PD. In July 2006, GE Healthcare received expanded approval for DaTscan for use in DLB. For patients with dementia, DaTscan has been successfully used in Europe to separate Alzheimer's disease from DLB. This has important implications in determining which medications can be safely used to treat the dementia. GE Healthcare received FDA approval to market DaTscan in the U.S. in January 2011.

RIGScan Competition

We do not believe there are any intraoperative diagnostic radiopharmaceuticals directly competitive with RIGScan that would be used in the colorectal cancer application at which RIGScan is initially targeted. There are other radiopharmaceuticals that are used as preoperative imaging agents; however, we are unaware of any that could be used as a real-time diagnostic aid during surgery such as RIGScan.

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 our 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.

Lymphoseek Intellectual Property

Lymphoseek is being developed under exclusive worldwide license from the Regents of the University of California through their UCSD affiliate. The UCSD license grants Navidea the commercialization rights to Lymphoseek for diagnostic imaging and intraoperative detection applications.

Lymphoseek is also the subject of patents and patent applications in the United States and certain major foreign markets. The patents and patent applications are held by The Regents of the University of California and have been licensed exclusively to Navidea for lymphatic tissue imaging and intraoperative detection worldwide. The first composition of matter patent covering Lymphoseek was issued in the United States in June 2002. The claims of the composition of matter patent covering Lymphoseek have been allowed in the EU and issued in the majority of EU countries in 2005. The composition of matter patent has also been issued in Japan. We have filed additional patent applications in the U.S. related to manufacturing processes for Lymphoseek. We will also rely on trademark protection for products that we expect to commercialize and have registered the mark Lymphoseek® in the U.S. and other markets.

NAV4694 Intellectual Property

NAV4694 is being developed under exclusive worldwide license from AstraZeneca. The NAV4694 license grants Navidea commercialization rights to the F-18 labeled biomarker for use as an aid in the diagnosis of AD. NAV4694 is the subject of 2 issued patents and 1 patent pending in the U.S. and 9 issued patents and 57 patents pending in 31 foreign jurisdictions. In addition, the [^{18}F]NAV4694 drug substance and NAV4694 Precursor 214 are the subjects of 2 issued patents and 1 patent pending in the U.S. and 9 issued patents and 57 patents pending in 31 foreign jurisdictions.

NAV5001 Intellectual Property

NAV5001 is being developed under an exclusive sublicense from Alseres. The NAV5001 sublicense grants Navidea commercialization rights to the Iodine-123 labeled biomarker for use as an aid in the diagnosis of PD and other movement disorders, with potential use as a diagnostic aid in dementia. NAV5001 is the subject of 3 issued patents and 1 patent pending in the U.S., 1 issued patent in Europe, and 9 patents pending in 3 foreign jurisdictions.

RIGScan Intellectual Property

We continue to support proprietary protection for the products related to RIGS in major global markets such as the U.S. and the EU, which although not currently integral to our near-term business plans, may be important to a potential RIGS development partner. Composition of matter patents have been issued in the U.S. and EU that cover the antibodies used in clinical studies. The most recent of these patents was issued in 2004 and additional patent applications are pending. We have a license to these patents through the NIH; however, our license is subject to ongoing diligence requirements and we could lose these license rights if we don’t diligently pursue commercialization of the patented technology. Additionally, statutory exclusivity exists for biologics upon approval in the U.S. for 12 years. In the EU, data exclusivity extends for 10 years following marketing authorization.

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 (FDCA), Public Health Service Act (PHSA), 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 Environmental Protection 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 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 IND 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 an 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 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. On September 10, 2012, we received a CRL from the FDA, denying our initial application for approval of Lymphoseek. The decision was focused on deficiencies in cGMP identified by the FDA during their pre-approval site inspections of third-party contract manufacturing facilities, and was not related to the efficacy or safety data filed within the Lymphoseek NDA. We worked diligently with our advisors, contract manufacturers and the FDA to address the third party cGMP manufacturing deficiencies noted in the FDA's September CRL. On October 30, 2012, we resubmitted our NDA in response to the CRL. The FDA accepted the resubmission and established a new PDUFA date of April 30, 2013. Lymphoseek was approved and indicated for use in lymphatic mapping for breast cancer and melanoma by the FDA on March 13, 2013. Additional trials, two of which are already ongoing in head and neck cancer and colorectal cancer, are anticipated to provide support for expanding the utilization of Lymphoseek into multiple other cancer types. We cannot assure you that Lymphoseek will achieve regulatory approval in the EU or any market outside the U.S., 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 drugs will qualify for any of these programs, or that, if a drug 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.

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 cannot assure you that the chosen regulatory strategy will secure regulatory approvals on a timely basis or at all.

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, or our manufacturer of the radiolabeled antibodies, must obtain a specific license from the NRC (or the responsible Agreement State) to manufacture and distribute radiolabeled antibodies, as well as comply with all applicable regulations. We must also comply with Department of Transportation regulations on the labeling and packaging requirements for shipment of radiolabeled antibodies to licensed clinics, and must comply with federal, state, and local governmental laws regarding the disposal of radioactive waste. 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 425 Metro Place North, Suite 450, Dublin, Ohio 43017. Our telephone number is (614) 793-7500. “Navidea”, the Navidea logo, “Lymphoseek”, “RIGS” and “RIGScan” 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-26 of this Form 10-K.

Research and Development

We spent approximately $16.9 million, $15.2 million and $8.9 million on research and development activities in the years ended December 31, 2012, 2011 and 2010, respectively.

Employees

As of March 1, 2013, we had 47 full-time and 9 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 report, 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 or if we do not successfully develop our product candidates into marketable products, we may be unable to generate significant revenue or become profitable.

We divested the neoprobe GDS line of gamma detection medical devices in August 2011. Through that time, sales of gamma detection devices represented our primary source of revenue. As a result, 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 on March 13, 2013. Additional trials, two of which are already ongoing in head and neck cancer and colorectal cancer, are anticipated to provide support for expanding the utilization of Lymphoseek into multiple other cancer types. We expect to begin generating revenues from product sales of Lymphoseek in the second quarter of 2013. As we generate revenues from Lymphoseek, it is possible we will ultimately receive payments related to the achievement of certain sales milestones by our marketing partner in the U.S. However, 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.

In addition, NAV4694, NAV5001 and RIGScan are in various stages of clinical development. Regulatory approval for additional indications for Lymphoseek may not be successful, or if successful, may not result in increased sales. Additional clinical trials for NAV4694, NAV5001, RIGScan, 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.

Many companies in the pharmaceutical industry suffer significant setbacks in advanced clinical trials even after reporting promising results in earlier trials. Even if our trials are viewed as successful, we may not get regulatory approval. Our 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 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 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.

Our radiopharmaceutical 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.

With the historical exception of our discontinued medical device businesses, we have dedicated and will continue to dedicate substantially all of our resources to the research and development of our radiopharmaceutical technologies and related compounds. With the exception of Lymphoseek, now approved for use in lymphatic mapping in breast cancer and melanoma in the U.S., all of our compounds currently are in research or development or regulatory review and have not received marketing approval.

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.

If we are not successful in licensing or acquiring additional drug candidates or technologies to expand our product pipeline, our future product portfolio and potential profitability could be harmed.

One component of our business strategy is to in-license drug compounds developed by other pharmaceutical and biotechnology companies or academic research laboratories. All of our product candidates in clinical development are in-licensed from third parties, consisting of Lymphoseek, NAV4694, NAV5001 and RIGScan. We may not successfully acquire additional drug candidates or technologies to expand our product pipeline. The number of such candidates and technologies is limited. Competition among large pharmaceutical companies and biopharmaceutical companies for promising drug candidates and technologies is intense because such companies generally desire to expand their product pipelines through purchase or in-licensing. If we fail to expand our product pipeline, our potential future revenues may be adversely affected.

Clinical trials for our radiopharmaceutical 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. During 2011, we successfully completed a second Phase 3 clinical trial in subjects with breast cancer or melanoma for our most advanced radiopharmaceutical product candidate, Lymphoseek. These Phase 3 clinical trials served as the basis for the approval of Lymphoseek in March 2013.

Clinical research of Lymphoseek continues with an ongoing third Phase 3 trial involving subjects with head and neck squamous cell carcinoma (NEO3-06). The NEO3-06 clinical study was designed to provide evidence of Lymphoseek performance in a third cancer type and to potentially expand the product label for Lymphoseek. In January 2013, we announced that we had accrued sufficient subjects in our NEO3-06 study in patients with head and neck cancer to enable us to conduct a pre-planned interim analysis. This Phase 3 trial of Lymphoseek was designed to demonstrate the performance of Lymphoseek in identifying sentinel lymph nodes in subjects with squamous cell carcinoma on the head or in the mouth. The interim analysis will compare the pathological analysis of the sentinel lymph nodes localized using Lymphoseek with that of all the lymph nodes removed during a full nodal dissection surgery of the head and neck. This full dissection surgery is considered the gold standard for determining the presence and extent of cancer and staging of the disease in such patients. A total of 83 subjects who underwent pre-planned, full dissection surgery were enrolled and represent the interim analysis cohort. Results from the interim statistical analysis and reporting of the findings are expected to be available upon completion of full site and data audits planned for later in 2013.

With respect to NAV4694, AstraZeneca has completed clinical development through a Phase 2a level. During the third quarter of 2012, we commenced our clinical development through some additional Phase 2 testing, mainly intended to expand the safety population, and we intend to commence Phase 2b testing in patients with mild cognitive impairment and autopsy-based Phase 3 testing of NAV4694 in 2013, but these plans could also experience complications and delays.

With respect to NAV5001, Alseres had previously completed five clinical trials in over 600 subjects. Alseres received a Phase 3 SPA from the FDA for NAV5001 in 2009. We have held preliminary discussions with the FDA regarding the SPA and expect to update the SPA over the coming months.

In August 2011, we held a meeting regarding RIGScan with the SAWP of the EMA and received similar guidance as we received from the FDA, as well as the suggestion that we consider use of a humanized version of the RIGS antibody. With this collective guidance, we have changed our development plans from a murine-based antibody to a humanized antibody on our development and regulatory timelines. As the scope and required resources for other

development opportunities such as for NAV4694 and/or NAV5001 continues to be assessed, the timing and scope of our development and commercialization plan for RIGScan may be continue to be affected.

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 recent FDA approval, and our licensing partners have also achieved successful outcomes from earlier trials of NAV4694 and NAV5001, 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 expect to enter 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). 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.

While we expect a “pass-through” reimbursement code related to Lymphoseek’s designation as a new chemical entity to be established by the U.S. Center for Medicaid and Medicare Services (CMS) in the months following FDA approval on March 13, 2013, there can be no assurance that such pass-through code will be received from CMS, and if not received, that the cost of Lymphoseek will be absorbed by healthcare providers. In addition, there can be no assurance that, even if a pass-through code is obtained, following the expiration of such code (generally two to three years following approval), we will be successful in establishing a separate permanent code for reimbursement of

Lymphoseek and therefore the cost of Lymphoseek may be need to be absorbed by the institution as a part of the bundled procedural code for the surgical procedure in which Lymphoseek is used. If this is the case, our expectations of the pricing we expect to achieve for Lymphoseek and the related potential revenue may be significantly diminished.

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 commercial manufacturing capabilities on a third-party contract basis for our Lymphoseek product and clinical manufacturing capabilities for our other radiopharmaceutical compounds. 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 we currently use OsoBio for the finishing and vialing of our Lymphoseek product. 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, our clinical trials 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.

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

The biotechnology industry is intensely competitive. Some of our competitors have significantly greater financial, technical, manufacturing, marketing and distribution resources as well as greater experience in the pharmaceutical 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. Physicians may use our competitors' products and/or our products may not be competitive with other technologies. Lymphoseek is expected to compete against sulfur colloid in the U.S. and other colloidal agents in other global markets. NAV4694 is expected to compete against florbetapir, a first-generation beta-amyloid imaging agent which Eli Lilly received approval for in 2012. We are also aware of two additional first-generation beta-amyloid imaging agents in late stages of development by two other large pharmaceutical companies. In addition, NAV5001 if approved, is expected to compete against a product marketed by GE Healthcare. 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.

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, NAV4694, NAV5001 or RIGScan, 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 intellectual property for Lymphoseek, NAV4694, NAV5001 and RIGScan. 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 to our licensed intellectual property if diligence requirements are not met.

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.

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, including AstraZeneca and Alseres, 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, NAV4694, NAV5001 and RIGScan, 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 AstraZeneca, we have limited control over the filing, prosecution or enforcement of these patents or patent applications. 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. We also have limited rights to enforce patents and patent applications licensed from AstraZeneca and Alseres. 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 AstraZeneca, UCSD, Alseres, the NIH 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 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 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 have access to sufficient financial resources with which to fund our operations and those of our subsidiaries for the foreseeable future. However, certain events or actions may shorten the period through which our current operating funds will sustain us, including, without limitation, if we decide to grow our organization in pursuit of development or commercialization activities for our current or newly acquired or developed product candidates, if we incur unexpected expenses, or if Lymphoseek does not generate our expected levels of sales and cash flow. We may also acquire new technologies, product candidates and/or products and the cost to acquire, develop and/or commercialize such new technologies, product candidates and/or products may shorten the period through which our current operating funds will sustain us. 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.

Our ability to raise capital may be limited by applicable laws and regulations.

Our ability to raise additional capital through the sale and issuance of our equity securities may be limited by, among other things, current Securities and Exchange Commission (Commission) and NYSE MKT rules and regulations. Our capital raising plans include primary offerings of equity securities using a "shelf" registration on Form S-3, which typically enables an issuer to raise additional capital on a more timely and cost effective basis than through other means, such as registration of a securities offering under a Form S-1 registration statement. Under current Commission rules and regulations, to be eligible to use a Form S-3 registration statement for primary offerings without restriction as to the amount of securities to be sold and issued, an issuer must, among other requirements, have outstanding common equity with a market value of at least $75 million held by non-affiliates. Although we currently have outstanding common equity with a market value of significantly more than $75 million held by non-affiliates, if we file a "shelf" Form S-3 registration statement at a time when the aggregate market value of our common stock held by non-affiliates, or public float, is less than $75 million (calculated as set forth in Form S-3 and Commission rules and regulations), the amount we could raise through primary offerings of our securities in any 12-month period using the Form S-3 registration statement may be limited to an aggregate of one-third of our public float. Moreover, the market value of all securities sold by us under a Form S-3 registration statement during the prior 12 months may be subtracted from that amount to determine the amount we can then raise under the Form S-3 registration statement. The Commission's rules and regulations require that we periodically re-evaluate the value of our public float. If, at a re-evaluation date, our public float is less than $75 million, the amount we could raise through primary offerings of our securities in any 12-month period using a Form S-3 registration statement would be subject to the one-third of public float limitation described above.

In addition, under current Commission rules and regulations, if our public float is less than $75 million or if we seek to register a resale offering (i.e., an offering of our securities by persons other than us), we must, among other requirements, maintain our listing with the NYSE MKT or have our common stock listed and registered on another national securities exchange in order to be eligible to use a Form S-3 registration statement for any primary or resale offering. Alternative means of raising capital through sales of our securities, including through the use of a Form S-1 registration statement, may be more costly and time-consuming.

Currently, our common stock is listed on the NYSE MKT. The NYSE MKT will review the appropriateness of continued listing of any issuer that falls below the exchange's continued listing standards. For additional information regarding this risk, see the risk factor below titled "Our failure to maintain continued compliance with the listing requirements of the NYSE MKT exchange could result in the delisting of our common stock." If our common stock were delisted from the NYSE MKT, our ability to raise capital on terms and conditions we deem acceptable, if at all, may be materially impaired.

Our ability to timely raise sufficient additional capital also may be limited by the NYSE MKT's requirements relating to stockholder approval for transactions involving the issuance of our common stock or securities convertible into our common stock. For instance, the NYSE MKT requires that we obtain stockholder approval of any transaction involving the sale, issuance or potential issuance by us of our common stock (or securities convertible into our

common stock) at a price less than the greater of book or market value, which (together with sales by our officers, directors and principal stockholders) equals 20% or more of our presently outstanding common stock, unless the transaction is considered a “public offering” by the NYSE MKT staff. Based on our outstanding common stock as of February 28, 2013 and the average closing price of $3.11 over the thirty trading days preceding February 28, 2013, we could not raise more than approximately $70 million without stockholder approval, unless the transaction is deemed a public offering or does not involve the sale, issuance or potential issuance by us of our common stock (or securities convertible into our common stock) at a price less than the greater of book or market value. However, certain prior sales by us may be aggregated with any offering we may propose in the near-term, further limiting the amount we could raise in any future offering that is not considered a public offering by the NYSE MKT staff and would involve the sale, issuance or potential issuance by us of our common stock (or securities convertible into our common stock) at a price less than the greater of book or market value. The NYSE MKT will also require stockholder approval if the issuance or potential issuance of additional shares will be considered by the exchange staff to result in a change of control of Navidea.

Obtaining stockholder approval is a costly and time-consuming process. If we are required to obtain stockholder approval, we would expect to spend substantial additional money and resources. In addition, seeking stockholder approval would delay our receipt of otherwise available capital, which may materially and adversely affect our ability to execute our current business strategy, and there is no guarantee our stockholders ultimately would approve a proposed transaction. A public offering under the NYSE MKT rules typically involves broadly announcing the proposed transaction, which often has the effect of depressing the issuer's stock price. Accordingly, the price at which we could sell our securities in a public offering may be less and the dilution existing stockholders experience may in turn be greater than if we were able to raise capital through other means.

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 and future preferred stock, warrants or other securities convertible into or exchangeable for our common stock 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 or preferred stock could decline as a result of sales of a large number of shares of our common stock or preferred stock or similar 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 Loan and Security Agreement with Hercules Technology II, LP (Hercules).

In addition to the security interest in our assets, the Loan and Security Agreement carries substantial 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;
- we keep reserved out of our authorized shares of common stock sufficient shares to satisfy our obligation to issue shares on conversion of the debt and the exercise of the warrants issued in connection with the Loan and Security Agreement;
- we provide certain financial information and reports to Hercules in a timely manner; and
- we indemnify Hercules against certain liabilities.

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

- amending our organizational or governing agreements and documents, entering into any merger or consolidation, dissolving the Company or liquidating its assets, or acquiring all or any substantial part of the business or assets of any other person;
- incurring any indebtedness, capital leases, or contingent obligations outside the ordinary course of business or without prior written approval;
- granting or permitting liens against or security interests in our assets;
- acquiring or making investments in any other person other than permitted investments;
- making any material dispositions of our assets outside the ordinary course of business; or
- declaring or paying any dividends or making any other distributions.

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 Loan and Security Agreement, permitting Hercules to accelerate the maturity of the debt and to sell the assets securing it. Such actions by Hercules could materially adversely affect our operations, results of operations and financial condition, including causing us to substantially curtail our product development activities.

Due to the extension of the PDUFA date for Lymphoseek to September 10, 2012, we did not receive FDA approval of Lymphoseek by the June 30, 2012 deadline established in the Loan and Security Agreement with Hercules, and therefore expect that additional loan proceeds of up to $3 million thereunder will not be available to us under the current terms.

In addition, our Loan Agreement with Platinum-Montaur Life Sciences, LLC (Montaur) carries covenants typical for commercial loan agreements, and similar to those contained in the Hercules Loan and Security 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 Loan Agreement, permitting Montaur to terminate our ability to obtain additional draws under the Loan Agreement and accelerate the maturity of the debt. Such actions by Montaur could materially adversely affect our operations, results of operations and financial condition, including causing us to substantially curtail our product development activities.

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 our outstanding shares of Series B Preferred Stock and 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 and preferred stock restrict 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 global financial crisis and continuing federal budget deadlock 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 ongoing credit crisis and related turmoil in the global financial system has had and may continue to have an impact on our business and our financial condition. We may face significant challenges if conditions in the financial markets do not improve or continue to worsen. In particular, our ability to access the capital markets and raise funds required for our operations may be severely restricted at a time when we would like, or need, to do so which could have an adverse effect on our ability to meet our current and future funding requirements and on our flexibility to react to changing economic and business conditions. The continuing federal budget deadlock 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, 2012, the Company had a stockholders' deficit of approximately $1.4 million. However, 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 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 $2.14 per share and as high as $4.77 per share during the 12-month period ended February 28, 2013. 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:

- 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.

Historically, the trading volume for our common stock has been relatively limited. The average daily trading volume for our common stock on the OTC Bulletin Board for the 12-month period ended January 31, 2011 was approximately 194,000 shares. Following the listing of our common stock on the NYSE MKT on February 10, 2011, trading in our common stock has been more active. During the 12-month period beginning on March 1, 2012 and ending on February 28, 2013, the average daily trading volume for our common stock on the NYSE MKT was approximately 850,000 shares. We cannot, however, 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.

If we make any acquisitions, we will incur a variety of costs and may never realize the anticipated benefits.

If appropriate opportunities become available, we may attempt to acquire businesses and assets that we believe are a strategic fit with our business. While we periodically are engaged in discussions regarding potential business or product acquisitions, we currently have no binding agreements to consummate any material acquisitions. If we pursue any such transaction, the process of negotiating the acquisition and integrating an acquired business and assets may result in operating difficulties and expenditures and may require significant management attention that would otherwise be available for ongoing development of our business whether or not any such transaction is ever consummated. Moreover, we may never realize the anticipated benefits of any acquisition. Future acquisitions could result in potentially dilutive issuances of equity securities, the incurrence of debt, contingent liabilities and/or amortization expenses related to goodwill and other intangible assets which could harm our business, financial condition, operating results and prospects and the trading price of our securities.

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.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

We currently lease approximately 15,000 square feet of office space at 425 Metro Place North, Dublin, Ohio, as our principal offices. The current lease term expires October 31, 2013, at a monthly base rent of approximately $12,000 during 2013. We must also pay a pro-rata portion of the operating expenses and real estate taxes of the building. We also lease approximately 4,000 square feet of office space at 10 New England Business Center Drive, Andover, Massachusetts, primarily for our business development and commercialization departments. The current lease term expires March 2014, at a monthly base rent of approximately $6,400 during 2013. We must also pay a pro-rata portion of the electricity cost of the building. We believe both facilities are in good condition, but that we may need to expand our leased space related to our radiopharmaceutical development activities depending on the level of activities performed internally versus by third parties.

Item 3. Legal Proceedings

None.

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. Prior to being listed on the NYSE MKT beginning February 10, 2011, our common stock was traded on the OTC Bulletin Board under the trading symbol NEOP.OB. The prices set forth below reflect the quarterly high, low and closing sales prices for shares of our common stock during the last two fiscal years as reported by Reuters Limited. These quotations reflect inter-dealer prices, without retail markup, markdown or commission, and may not represent actual transactions.

	High	Low
Fiscal Year 2012:		
First Quarter	$3.55	$2.60
Second Quarter	3.79	2.60
Third Quarter	4.77	2.28
Fourth Quarter	2.98	2.14
Fiscal Year 2011:		
First Quarter	$4.71	$2.00
Second Quarter	5.48	3.05
Third Quarter	3.60	1.62
Fourth Quarter	3.18	2.05

As of March 1, 2013, we had approximately 701 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, 2012, Platinum Montaur Life Sciences, LLC (Montaur) exercised 6,000,000 Series W warrants in exchange for issuance of 6,000,000 shares of our common stock, resulting in gross

proceeds of $1,920,000. The issuance of the shares was exempt from registration under Sections 4(2) of the Securities Act and Regulation D promulgated thereunder.

Also during the three-month period ended December 31, 2012, 1,000 shares of the Series C Convertible Preferred Stock automatically converted into 3,226,000 shares of our common stock. The issuance of the shares was exempt from registration under Sections 4(2) of the Securities Act and Regulation D promulgated thereunder.

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, 2007 through December 31, 2012. This graph assumes an investment in the Company's common stock and the indices of $100 on December 31, 2007 and that all dividends were reinvested.

	Cumulative Total Return as of December 31,					
	2007	2008	2009	2010	2011	2012
Navidea Biopharmaceuticals	$100.00	$199.30	$426.57	$720.28	$916.08	$989.51
Russell 3000	100.00	62.69	80.46	94.08	95.05	110.65
NASDAQ Biotechnology	100.00	93.40	103.19	113.89	129.12	163.33

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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 2012 and prior periods 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,				
	2012	2011	2010	2009	2008
Statement of Operations Data:					
Revenue	$79	$598	$617	$—	$—
Research and development expenses	16,890	15,154	8,941	4,380	3,756
Selling, general and administrative expenses	11,178	9,548	4,353	3,028	2,936
Loss from operations	(27,989)	(24,104)	(12,677)	(7,408)	(6,692)
Other expenses, net	(1,168)	(943)	(43,567)	(35,891)	(2,124)
Benefit from income taxes	—	7,880	2,135	1,256	1,241
Loss from continuing operations	(29,157)	(17,167)	(54,109)	(42,043)	(7,575)
Discontinued operations, net of tax effect	—	22,780	4,144	2,437	2,409
Net (loss) income	(29,157)	5,613	(49,965)	(39,606)	(5,166)
Preferred stock dividends	(43)	(100)	(8,207)	(240)	—
(Loss) income attributable to common stockholders	$(29,200)	$5,513	$(58,172)	$(39,846)	$(5,166)
(Loss) income per common share (basic and diluted):					
Continuing operations	$(0.29)	$(0.17)	$(0.77)	$(0.57)	$(0.12)
Discontinued operations	$—	$0.23	$0.05	$0.03	$0.04
(Loss) income attributable to common stockholders	$(0.29)	$0.06	$(0.72)	$(0.54)	$(0.08)
Shares used in computing (loss) income per common share: [1]					
Basic and diluted	99,060	90,509	80,726	73,772	68,594

	As of December 31,				
	2012	2011	2010	2009	2008
Balance Sheet Data:					
Total assets	$11,972	$31,194	$10,863	$9,018	$9,619
Long-term obligations	7,187	6,714	2,787	13,485	7,323
Accumulated deficit	(274,558)	(245,357)	(250,870)	(192,699)	(148,840)

(1) Basic earnings (loss) per share is calculated by dividing net income (loss) attributable to common stockholders by the weighted-average number of common shares and, except for periods with a loss from operations, participating securities outstanding during the period. Diluted earnings (loss) per share reflects additional common shares that would have been outstanding if dilutive potential common shares had been issued. Potential common shares that may be issued by the Company include convertible securities, options and warrants.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

The following discussion should be read together with our Consolidated Financial Statements and the Notes related to those statements, as well as the other financial information included in this Form 10-K. Some of our discussion is forward-looking and involves risks and uncertainties. For information regarding risk factors that could have a material adverse effect on our business, refer to Item 1A of this Form 10-K, Risk Factors.

The Company

Navidea Biopharmaceuticals, Inc. (Navidea, the Company, or we), a Delaware corporation, is a biopharmaceutical company focused on the development and commercialization of precision diagnostics and radiopharmaceutical agents. We have one approved product in the U.S., Lymphoseek® (technetium Tc 99m tilmanocept) Injection, a novel, receptor-targeted, small-molecule radiopharmaceutical, indicated for use in lymphatic mapping for breast cancer and melanoma. Lymphoseek is designed to identify the lymph nodes that drain from a primary tumor, which have the highest probability of harboring cancer. Additional investigational trials in other solid tumor cancers are anticipated to provide support for expanding the utilization of Lymphoseek into multiple other cancer types. We are currently developing three other radiopharmaceutical agent platforms. NAV4694, is an F-18 radiolabeled positron emission tomography (PET) imaging agent being developed as an aid in the diagnosis of patients with signs or symptoms of cognitive impairment such as Alzheimer's disease (AD). NAV5001, is an Iodine-123 radiolabeled single photon emission computed tomography (SPECT) imaging agent being developed as an aid in the diagnosis of Parkinson's disease (PD) and other movement disorders, with potential additional use as a diagnostic aid in dementia. RIGScan™, is a radiolabeled monoclonal antibody being developed as a diagnostic aid for use during surgery to help surgeons locate occult or metastatic cancer, with a primary focus on colorectal cancer. All of these investigational drug products are still in development and must be cleared for marketing by the appropriate regulatory authorities before they can be sold in any markets.

Executive Summary