NAVIDEA BIOPHARMACEUTICALS, INC.
Form 10-K
March 14, 2014

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

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

For the fiscal year ended December 31, 2013

or

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

For the transition period from to to

Commission file number 001-35076

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

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

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 ý

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 ý 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 ý 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. ¨

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

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

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

The aggregate market value of shares of common stock held by non-affiliates of the registrant on June 30, 2013 was $315,338,908.

The number of shares of common stock outstanding on February 28, 2014 was 149,702,543.

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 products and programs include:

- Lymphoseek® (technetium Tc 99m tilmanocept) Injection is a novel, receptor-targeted, small-molecule radiopharmaceutical used in lymphatic mapping procedures that are performed to help evaluate patients with 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. It was approved by the U.S. Food and Drug Administration (FDA) in March 2013, and launched commercially in the United States in May 2013.
- Navidea's Manocept™ platform is predicated on the ability to specifically target the CD206 mannose receptor expressed on macrophages. This flexible and versatile platform acts as an engine for the design of purpose-built molecules offering the potential to be utilized across a range of diagnostic modalities, including single photon emission

computed tomography (SPECT), positron emission tomography (PET), intra-operative and/or optical-fluorescence detection in a variety of disease states.

- NAV4694 is a Fluorine-18 (F-18) radiolabeled PET imaging agent being developed as an aid in the diagnosis of patients with signs or symptoms of Alzheimer's disease (AD) and mild cognitive impairment (MCI).
- NAV5001 is an Iodine-123 (I-123) radiolabeled SPECT imaging agent being developed as an aid in the diagnosis of Parkinson's disease (PD) and other movement disorders, with potential use as a diagnostic aid in dementia.
- NAV1800 (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, and from July 2010 through August 2011 through a distribution arrangement with Devicor Medical Products, Inc. (Devicor).

We executed an Asset Purchase Agreement (APA) for the sale of the GDS Business (the Asset Sale) 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. To date, we have not received any such royalty payments.

Our Technology and Product Candidates

We focus on precision diagnostics technology, particularly in the area of radiopharmaceuticals. Innovative precision diagnostic agents hold the potential to improve diagnostic accuracy, clinical decision-making and patient care. Navidea's pipeline includes our commercial product, clinical-stage radiopharmaceutical agents, and a platform technology, all 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

In 2001, we entered 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. 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 in March 2013. Additional trials, one in head and neck cancer (NEO3-06) which is the focus of a supplemental New Drug Application (sNDA) that

now has a Prescription Drug User Fee Act (PDUFA) target date of June 16, 2014, an ongoing trial in colorectal cancer, and other planned investigator-sponsored trials, are anticipated to provide additional support for the potential expansion of Lymphoseek utilization into multiple other cancer types. A second sNDA aimed at expanding the Lymphoseek label to support more flexible utilization practices for Lymphoseek in lymphatic mapping and lymphoscintigraphy imaging has a PDUFA target date of October 16, 2014.

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 (WBCs) – from tissues into the bloodstream. The key components of the lymph system are lymph nodes – small anatomic structures that contain disease-fighting WBCs, 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, intraoperative lymphatic mapping (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 the initial node or nodes show no sign of cancer cells, there is a high likelihood that lymph nodes further along the chain 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 proteins (MBR; CD206) present on the surface of immune cells. Lymphoseek is a macromolecule consisting of multiple units of diethylene triamine pentaacetic acid (DTPA) and mannose, 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 Phase 3 clinical studies NEO3-05 and NEO3-09 in subjects with breast cancer or melanoma, Lymphoseek demonstrated highly effective lymph node identification and significant benefits over an approved comparator agent, vital blue dye (VBD). Importantly, Lymphoseek missed significantly less cancer-positive lymph nodes, resulting in nearly 10% of subjects in these Phase 3 clinical studies being up-staged by the use of Lymphoseek who would have been under-staged using VBD alone.

In clinical study NEO3-06 in head and neck squamous cell carcinoma, the primary endpoint was based on the number of subjects with cancer-positive lymph nodes following a multiple level lymph node dissection. Among the total of 83

subjects evaluated in the trial, Lymphoseek accurately identified 38 of 39 subjects who had pathology-positive lymph nodes, for an overall false negative rate (FNR) of 2.56%, which was statistically significant (p=0.0205), meeting the statistical threshold for success of the primary endpoint of the study.

In the U.S., ILM has also historically employed a non-standard, Technetium 99mTc-labeled radiopharmaceutical agent known as sulfur-colloid (TcSC), often used in place of, or in addition to, VBD. 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 Lymphoseek provided significantly greater performance in breast cancer patients 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. 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.

Similar meta-analyses have been performed with Lymphoseek melanoma and head and neck cancer data from the Phase 3 studies NEO3-05, NEO3-09, and NEO3-06 to compare Lymphoseek's performance against TcSC performance. Pooled data from melanoma patients enrolled in NEO3-05 and NEO3-09 was compared to published retrospective and prospective data for melanoma ILM with TcSC submitted for U.S. regulatory review. Through this analysis, Lymphoseek was shown to identify at least one hot SLN in 98% of patients, whereas TcSC identified at least one hot SLN in 96.4%, a difference that was statistically significant ($p=0.0014$). Lymphoseek also identified more hot nodes per patient than TcSC: 2.38 vs 1.70 ($p<0.0001$).

In head and neck cancer, Lymphoseek's performance in the NEO3-06 study was compared to the performance of TcSC as published in the American College of Surgeons Oncology Group (ACOSOG) study Z-0360. The FNR for TcSC was 0.10 (95% CI=0.027,0.231) compared to an FNR for Lymphoseek of 0.03 (95% CI=0.001,0.138), a difference that was statistically significant ($p<0.0006$). The accuracy for TcSC was 0.97 (95% CI=0.928,0.992) versus an accuracy for Lymphoseek of 0.99 (95% CI=0.934,1.000), again a difference that was statistically significant ($p<0.0161$). Based on these meta-analyses of clinical data, Lymphoseek provided statistically significantly better performance than TcSC in the key metrics of FNR and accuracy in head/neck squamous cell carcinoma.

In June 2012, we published data developed from the NEO3-05 and NEO3-09 Phase 3 trials of Lymphoseek demonstrating important performance characteristics of Lymphoseek compared to a European commercially available radiolabeled colloid used in intra-operative lymphatic mapping. The analysis evaluated the performance of Lymphoseek in breast cancer patients 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 on Nanocoll's performance in breast cancer patients 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). 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 ($p < 0.0001$). In September 2012, we announced the presentation of related data at the European Society of Surgical Oncology annual meeting. 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].

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

- Improved detection of 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, involving the removal of as many as 20 to 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. Application to head and neck cancer is a focus of our sNDA under review at FDA with the PDUFA target date of June 16, 2014.

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 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. A third Phase 3 trial involving subjects with head and neck squamous cell carcinoma was completed in 2013.

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) 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 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 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 two Phase 3 clinical trials of Lymphoseek in melanoma in the Annals of Surgical Oncology showing strong lymph node identification properties.

Lymphoseek was approved and indicated for use in lymphatic mapping procedures in breast cancer and melanoma by the FDA in March 2013.

Clinical research continued with a Phase 3 trial involving subjects with head and neck squamous cell carcinoma (NEO3-06) which was initiated in June 2009. The NEO3-06 clinical study was designed to demonstrate the performance of Lymphoseek in head and neck cancer as well as to potentially expand the product label for Lymphoseek as a SLNB agent after the initial marketing clearance for the product. 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 to enable us to conduct a pre-planned interim analysis. The interim analysis compared the pathological analysis of the sentinel lymph nodes localized using Lymphoseek with that of all the lymph nodes removed during a multiple level nodal dissection surgery of the head and neck. This multiple level nodal 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.

In April 2013, the Company announced top-line results from the NEO3-06 clinical study. Results of the interim analysis demonstrated that Lymphoseek met the primary efficacy endpoint of accurately identifying sentinel lymph nodes (SLNs) in subjects with squamous cell carcinoma of the head, neck or mouth, as compared to the removal of all lymph nodes during multiple level nodal dissection surgery of the head and neck. The primary endpoint for the NEO3-06 trial was based on the number of subjects with pathology-positive lymph nodes (that is, lymph nodes found to harbor cancer) following a multiple level lymph node dissection and required a minimum of 38 subjects whose lymph nodes contained pathology-confirmed disease. The FNR of 2.56% was statistically significant and met the statistical threshold for success of the primary endpoint. FNR is the rate of occurrence of negative test results in subjects known to have metastatic disease in the lymph nodes, for which the individual is being tested. These findings indicate that Lymphoseek accurately identified SLNs in these trial subjects, and is likely to be predictive of overall node pathology status. On the basis of the strong safety and efficacy data observed in the interim analysis, an assessment of subject risk:benefit in the trial, and a consideration of potential benefit to head and neck cancer patients at large, the independent Data Safety Monitoring Committee (DSMC) for the NEO3-06 trial recommended terminating enrollment and closing the study. Subsequently, based on results from the NEO3-06 study, results from other studies already completed, the recommendation of the independent DSMC, and a constructive meeting with the

FDA on our findings, we officially closed the NEO3-06 study.

In September 2013, results from the NEO3-06 study conducted at The Ohio State University Comprehensive Cancer Center - James Cancer Hospital & Solove Research Institute were published in the peer-reviewed journal, JAMA Otolaryngology Head and Neck Surgery, a publication of the American Medical Association. The publication, “Use of a Novel Receptor-Targeted (CD206) Radiotracer, 99m-Tc-Tilmanocept, and SPECT/CT for Sentinel Lymph Node Detection in Oral Cavity Squamous Cell Carcinoma: Initial Institutional Report in an Ongoing Phase 3 Study,” describes the experience at one of the clinical trial sites that participated in NE03-06. The results, published independently by this single clinical trial site in our larger Phase 3 NE03-06 study, corroborate data for the ability of Lymphoseek to identify sentinel lymph nodes in head and neck squamous cell carcinoma.

In October 2013, we announced additional results from the fully completed NEO3-06 study indicating that Lymphoseek also met all other pre-specified study endpoints, including sensitivity, negative predictive value (NPV) and overall accuracy relative to the pathology status of non-SLNs. Lymphoseek demonstrated a sensitivity rate of 97.6%, a NPV of 97.8%, and overall accuracy of 98.8%. No differences were observed in the ability of Lymphoseek to detect SLNs between same-day or subsequent-day surgery following Lymphoseek injection.

Moreover, multiple level nodal dissection of patients in the trial with cancer-positive lymph nodes led to an average removal of 38 lymph nodes per patient, whereas Lymphoseek on average led to the identification of approximately 4 lymph nodes. This reduction in potential lymph node removal could lead to a substantial reduction in potential morbidity for patients with head and neck cancer undergoing sentinel lymph node biopsy, as well as potentially enabling reductions in the time and cost of surgery.

In December 2013, the FDA granted fast track designation to Lymphoseek for sentinel lymph node detection in patients with head and neck cancer and we submitted a sNDA with the FDA seeking approval for the marketing and sale of Lymphoseek for the same indication. In assessing the application, the FDA chose to separate the filing into two applications based on the proposed labeling extensions requested and the scope of information provided. The first sNDA, aimed at Lymphoseek's use as a sentinel lymph node detection agent in patients with head and neck cancer, was accepted for review by the FDA in February 2014, and was granted a priority review. Under PDUFA, the FDA has set a target review date for the first Lymphoseek sNDA in June 2014. In March 2014, the FDA accepted for review the second sNDA to support a broader and more flexible use of Lymphoseek in imaging and lymphatic mapping procedures, including lymphoscintigraphy and other optimization capabilities. Under PDUFA, the FDA has set a target review date for the second sNDA in October 2014.

We are currently pursuing registration of Lymphoseek in the European Union (EU). In February 2012, Navidea was advised 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. In December 2013, the EMA provided updated feedback on the MAA as it continued its review. The updated feedback was limited to supplemental product specification data and the NEO3-06 Phase 3 study in head and neck cancer. Based on the cumulative feedback to date, we anticipate the CHMP could take up consideration of the MAA early in 2014. A positive opinion for approval would enable commercialization in the EU subsequent to European Commission (EC) adoption of the CHMP opinion and pricing determinations on a country-by-country basis in each member state, a process which could take several months. However, 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.

Manocept Platform

Navidea's Manocept platform is predicated on the ability to specifically target the CD206 mannose receptor expressed on macrophages. Macrophages play important roles in many disease states and are an emerging target in many diseases where diagnostic uncertainty exists. This flexible and versatile platform acts as an engine for purpose-built molecules that may enhance diagnostic accuracy, clinical decision-making and ultimately patient care, while offering the potential to utilize a breadth of diagnostic modalities, including SPECT, PET, intra-operative and/or optical-fluorescence detection. The Company's FDA-approved precision diagnostic lymphatic mapping agent, Lymphoseek, is representative of the ability to successfully exploit this mechanism to develop powerful new diagnostic agents.

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In September 2013, we presented collaborative data at the Cancer Advance Conference at Harvard Medical School from the proof-of-principle imaging studies using Cy3-tilmanocept, a fluorescent-labeled agent derived from the Manocept platform, utilizing the technical principles underlying Lymphoseek. Data presented at the conference establish the feasibility of using Manocept compounds to bind to the CD206 mannose receptor and target macrophage inflammatory cells, an approach that may enable the design of novel immune cell-targeted agents for diagnosis and disease staging. These studies focused on establishing the ability of fluorescent Cy3-tilmanocept to target macrophages in two disease states which are representative of a broader set of disorders which involve macrophages: Kaposi's Sarcoma (KS) and tuberculosis (TB), both outside the current lymphatic mapping application. These data support the expansion of the Manocept platform into potential new indications in disorders that are mediated by, or associated with, macrophages utilizing immune-cell targeting to address unmet diagnostic needs in this emerging area. Other recognized disorders having macrophage involvement include not only KS and TB, but also rheumatoid arthritis (RA), Systemic Lupus Erythematosis, atherosclerosis/vulnerable plaque, Crohn's disease and others that span clinical areas in oncology, autoimmunity, infectious diseases, cardiology, and inflammation. These data were published in a special supplement, Nature Outlook: Medical Imaging, in the October 31, 2013 issue of Nature. The supplement included a White Paper entitled Innovations in receptor-targeted precision imaging at Navidea: Diagnosis up close and personal. The online edition also includes several peer-reviewed articles published previously by Nature Publishing Group that reinforce the principle of CD206 mannose receptor targeting using Manocept compounds to identify macrophages.

In November 2013, we announced our collaboration with investigators at the University of California, San Francisco (USCF), on a clinical study to evaluate, for the first time, the use and performance of technetium–labeled tilmanocept in patients with KS. The investigator–initiated study will evaluate HIV patients with various stages of KS who will be administered 99mTc-tilmanocept and assessed by SPECT imaging for localization of KS lesions and possible identification of KS disease spread.

In February 2014, data utilizing compounds from our Manocept platform in models of RA were presented by Thomas Rosol, DVM, PhD, DACVP from The Ohio State University at a Keystone Symposia on Molecular Cell Biology of Macrophages in Human Disease held in Santa Fe, NM. The poster presentation, entitled "Imaging of macrophages in immune-mediated inflammatory disease and cartilage antibody-induced arthritis in mice using Cy3-tilmanocept" highlights research from Dr. Rosol and other Navidea collaborators at The Ohio State University. The studies demonstrate the ability of Cy3-tilmanocept to identify and localize to disease-state macrophages when administered intravenously, enabling detection of immune-mediated arthritis in affected joints in vivo in mice. Results were confirmed using histopathology. The data highlighted the identification of immune-mediated inflammation seen in arthritic elbows and knees of arthritis-affected mice but not in control mice or un-affected joints within arthritic mice. The imaging results in this study showed preferential localization of macrophages by Cy3-tilmanocept in affected joints with little to no localization in unaffected joints. As the mannose receptor is a key portal for imaging pathological states of macrophage-associated inflammation, the Manocept-derived molecules are potentially potent tools for addressing unmet needs in this area such as identifying, staging, assessing disease activity and monitoring therapeutic efficacy.

The Company continues to evaluate emerging data in other disease states to define areas of focus, development pathways and partnering options to capitalize on the Manocept platform. We cannot assure you that further evaluation or development will be successful, that any Manocept platform product candidate will ultimately achieve regulatory approval, or if approved, the extent to which it will achieve market acceptance. See Risk Factors.

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

In December 2011, we executed a license agreement with AstraZeneca AB for NAV4694, 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 AD and potentially also MCI. NAV4694 binds to beta-amyloid deposits in the brain that can then be imaged in PET scans. Amyloid plaque pathology is a required feature of AD and the presence of amyloid pathology is a supportive feature for diagnosis of probable AD. Patients who are negative for amyloid pathology do not have AD.

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.

Although these other agents constitute a step forward, each has potential limitations. Navidea's NAV4694 tracer appears to have several important advantages, including the ability to generate clean images with less white matter uptake to enable identification of lower levels of amyloid, making the images easier to read and interpret and potentially facilitating earlier detection of disease.

NAV4694 Clinical Development

NAV4694 has been studied in rigorous pre-clinical studies and clinical trials in humans. Clinical studies through Phase 3 have included over 180 subjects to date and have included subjects with mild cognitive impairment (MCI), suspected AD patients, and healthy volunteers. Results suggest that NAV4694 has the potential ability to image patients quickly and safely with high sensitivity and specificity. We recently completed US enrollment in a Phase 2 trial that we initiated in September 2012, primarily to understand the diagnostic performance of NAV4694 and to

expand the safety database for the compound. We also initiated a Phase 2b trial in subjects with MCI 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.

In July 2013 at the Alzheimer's Association International Conference (AAIC), it was announced that the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) plans to switch to NAV4694 for use in its comprehensive research initiative in Alzheimer’s disease and MCI from a PET imaging agent for ß-amyloid detection that for many has remained the accepted benchmark standard for studies investigating Alzheimer’s disease and differential diagnoses of dementia. Recently published results from a head-to-head study that directly compared NAV4694 to the accepted standard agent PiB demonstrated that NAV4694 displayed nearly identical imaging characteristics, and is accessible and affordable and can be reliably interpreted in a variety of clinical settings.

Also at the 2013 AAIC, researchers at the McGill Centre for Studies in Aging, Douglas Research Institute, and Montreal Neurological Institute presented results of a post-mortem brain tissue study comparing performance characteristics of NAV4694 to this accepted standard PiB, concluding that NAV4694 better differentiated amyloid deposition associated with AD in post-mortem brains.

In August 2013, we signed an agreement with Siemens PETNET Solutions that grants PETNET Solutions the right to manufacture NAV4694 for our clinical trials. Under the terms of the agreement, PETNET Solutions will initially manufacture NAV4694 clinical trial material at select U.S. radiopharmacies, with the possibility of expanding into additional Siemens' PETNET Solutions locations in the future.

Also in August 2013, we were awarded a Small Business Innovation Research (SBIR) grant from the National Institute on Aging (NIA) of the National Institutes of Health (NIH) in connection with our Phase 3 clinical program for NAV4694 as an aid in the differential diagnosis of Alzheimer's disease. The SBIR grant has the potential to provide up to $1.8 million in support, if fully funded, through the conclusion of the Phase 3 clinical study. Funding of $259,000 for the approved first stage of the grant is intended to provide support for initiation activities of the Phase 3 clinical program. Funding of the second stage of the grant is contingent upon meeting specific aims related to the first stage of the grant such as institutional review board approval of the Phase 3 protocol, clinical site contracting and investigator training.

In September 2013, we were awarded an additional SBIR grant from the NIA of the NIH in connection with the evaluation of NAV4694 as a diagnostic imaging agent that may aid physicians in identifying those individuals with MCI who are at greatest risk of progressing to AD. The grant has the potential to provide up to $2.3 million in support, if fully funded, through the conclusion of the clinical study. Funding of $152,000 for the approved first stage of the grant is intended to provide support for initiation activities of the clinical trial program. Funding of the second stage of the grant is contingent upon meeting specific aims related to the first stage of the grant such as clinical site contracting, investigator training and institutional review board approvals.
In February 2014, we announced that NAV4694 produced highly differentiated images in the first cohort of subjects enrolled in our Phase 2b PET imaging study of subjects with MCI. The subjects were enrolled and evaluated at the Alzheimer's Disease Center at Quincy Medical Center, Quincy, MA. The results indicate that NAV4694 produced high-quality diagnostic images that segregated MCI subjects into two discrete groups, either amyloid-positive or amyloid-negative. The image evaluation was performed on twelve subjects meeting pre-defined inclusion/exclusion criteria for emerging, or early-stage, cognitive impairment. NAV4694 scans were assessed by two independent readers using a 3-point visual scale. Image interpretation used the Company's proprietary visual-read algorithm. All twelve MCI subjects segregated into either amyloid-positive or amyloid-negative categories. The technical quality of the scans was good and both raters were in complete agreement on the 3-point scale, with 8 scans highly positive for ß-amyloid and 4 scans negative. There were no intermediate ratings or ambiguous cases despite the early-stage characterization of the subjects' cognitive impairment status. The scans were easy to read and the readers noted that the high gray matter relative to white matter signal made image interpretation very straight forward. To date, the product candidate appears to be safe and well-tolerated. Results are expected to be presented at an upcoming scientific conference on AD. We cannot assure you, however, that further clinical trials for this product will be successful, that the product 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, which was extended to July 31, 2012, to complete due diligence. 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 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 approximately 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 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 initiated a Phase 2b program in DLB in April 2013, commencing an investigator-initiated study. In December 2013, we announced that the first subject had been enrolled in a pivotal Phase 3 clinical trial to assess the safety and efficacy of NAV5001 as an aid in the differential diagnosis of Parkinsonian Syndromes from non-Parkinsonian tremor. This clinical study will focus on subjects with emerging symptoms in whom diagnostic uncertainty and unmet need are highest. Results from earlier trials using NAV5001 suggest that it may be an effective, well-tolerated imaging agent. The high affinity for DAT with resulting clear images can assist physicians in reaching an accurate diagnosis sooner, and the rapid kinetics with minimal time between injection and scanning and time in the SPECT scanner not only decrease patient exposure and but also facilitate increased efficiency with potential cost savings for the nuclear medicine facility. Reducing diagnostic uncertainty and error rates for patients with movement disorders who often exhibit similar clinical symptoms has the potential to afford great value, especially early in the initial clinical presentation, and may lead to improved clinical decision-making and patient management.

In August 2013, we reached agreement with the FDA for two special protocol assessments (SPAs) for the Company's pivotal Phase 3 program with NAV5001 as an aid in the differential diagnosis of Parkinsonian Syndromes from non-Parkinsonian tremor. The SPAs are written agreements between the Company, as the program's sponsor, and the FDA regarding the design, endpoints and statistical analysis for the two pivotal Phase 3 clinical trials to be used in support of a potential NAV5001 NDA. The Company is actively preparing for the initiation of the pivotal Phase 3 trials later this year. The international, open-label, pivotal NAV5001 Phase 3 program consists of two similar clinical trials that will run in parallel and enroll approximately 550 total subjects who exhibit early stage tremor. Each Phase 3 trial was the subject of a SPA with the FDA. The primary endpoint of both studies is to evaluate the relative diagnostic efficacy of the NAV5001 SPECT images compared with the diagnosis made by neurologists and that established by a consensus panel of three movement disorder specialists as the 'Standard of Truth.' In one study, each subject will undergo SPECT imaging with NAV5001 only. In the second study, subjects will undergo SPECT imaging with both NAV5001 and an alternative SPECT agent, ioflupane, in a cross-over comparison design. In December 2013 we enrolled our first subject for the studies. We cannot assure you, however, that further clinical trials for this product will be successful, that the product will achieve regulatory approval, or if approved, that it will achieve market acceptance. See Risk Factors.

NAV1800 (formerly RIGScan)

NAV1800 is a radiolabeled, cancer-specific targeting monoclonal antibody intended to enable identification of cancerous tissue and delineate tumor or occult or metastatic cancerous tissue. NAV1800 is administered to the patient and is potentially identified by imaging or, during surgery with a gamma detection probe, thereby assisting a surgeon in identifying the location of cancerous tissues.

Our NAV1800 technology is a radiolabeled monoclonal antibody that serves as the biologic targeting agent for detection of occult or metastatic cancer. The antibody localizes or binds to a tumor antigen called TAG-72 expressed on many solid tumor cancers. NAV1800 is intended to aid in identifying a primary tumor, ascertaining margins, or determining the extent and location of occult and metastatic tumor in patients with solid tumor cancers that express the TAG-72 antigen, such as colorectal cancer, ovarian cancer, prostate cancer, lung 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.

NAV1800 Clinical Development

The murine monoclonal antibody of NAV1800 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 NAV1800 for the detection of metastatic colorectal cancer based primarily on results of a single Phase 3 clinical trial, NEO2-14. The FDA declined approval, indicating that, in addition to identifying additional pathology-confirmed disease, the clinical studies of NAV1800 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 support resuming NAV1800 development, we filed a new IND request with the FDA in late 2010. In a pre-IND meeting with the FDA in February 2011, the FDA provided guidance regarding our manufacturing process, to increase manufacturing efficiency and the quality of the underlying biologic antibody and potentially transitioning from a murine-based monoclonal antibody to a human-based monoclonal antibody. In August 2011, we also held a meeting with the SAWP of the EMA and received similar guidance. With this collective guidance, we transitioned from a murine monoclonal antibody used in the previous studies noted above to a humanized monoclonal antibody.

In September 2012, we were awarded a grant from the NIH to further develop NAV1800. 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 completion of the first phase, development of a protocol, and institutional review board approval, will be for an additional $1.2 million.

We have focused over the last several years on manufacturing and quality of the humanized antibody with the aim of completing the necessary steps to support clinical development. Rigorous CMC evaluation must be completed as a pre-requisite to clinical trials to ensure the antibody is adequate for human study. NAV1800 is a biologic drug that has not been produced for several years. We will need to establish robust manufacturing and radiolabeling capabilities for the antibody in order to meet the regulatory needs for the NAV1800 product. Additional non-clinical studies could potentially be required by regulatory authorities. We cannot assure you, however, that if further clinical trials for this product proceed, that if they proceed that they will be successful, that the product will achieve regulatory approval, or if approved, that it will achieve market acceptance. See Risk Factors.

In November 2013, we initiated a collaboration with investigators at the University of Alabama at Birmingham (UAB) on a potential clinical study to evaluate the safety and efficacy of NAV1800 in cancer patients. The study is intended to evaluate up to 20 patients with colorectal cancer by administering NAV1800 and assessing by SPECT/CT imaging for the presence of liver metastasis, as well as evaluate other parameters of the performance of the radiolabeled antibody. Investigators at UAB have published extensively on the use of TAG-72 targeted monoclonal antibodies in the cancer setting. As the scope and required resources for the NAV1800 program continues to be assessed, particularly in light of other development opportunities such as Lymphoseek, NAV4694, NAV5001, our Manocept platform, or other agents, the timing and scope of our plans for NAV1800 may be further affected.

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 586,000 deaths in 2014 in the U.S. alone. The NIH has estimated the overall annual costs for cancer for the U.S. for 2009 at $216.6 billion: $86.6 billion for direct medical costs and $130.0 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 1.1 million new cases will occur in the U.S. in 2014.

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 1.9% in women under age 49 to 6.7% in women age 70 or older. While the incidence rate for breast cancer appears to be stable, the overall number of new cases of breast cancer is still increasing. According to the ACS, over 233,000 new cases of invasive breast cancer are expected to be diagnosed during 2014 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 76,000 new cases of melanoma will be diagnosed in the U.S. during 2014. In addition to breast cancer and melanoma, we believe that our oncology products may have utility in other cancer types with over another 1 million new cases expected during 2014 in the U.S. Additionally, the ACS estimates that approximately 1.7 million new cancer cases will be diagnosed in the U.S. during 2014.

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 5.2 million Americans had AD in 2013. On a global basis, Alzheimer's Disease International estimated in 2013 that there were 44.4 million people living with dementia. AA estimates that total costs for AD care was approximately $203 billion in 2013 and is expected to rise to $1.2 trillion by 2050. AA also estimates that there are over 15.4 million AD and dementia caregivers providing 17.5 billion hours of unpaid care valued at over $216.4 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 2000-2010, death rates have declined for most major diseases while deaths from AD have risen 68 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 MCI 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 imag