NAVIDEA BIOPHARMACEUTICALS, INC.
Form 10-K
March 15, 2019

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2018

or

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

For the transition period from to _____ to _____

Commission file number 001-35076

NAVIDEA BIOPHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	31-1080091

(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
4995 Bradenton Avenue, Suite 240, Dublin, Ohio	43017-3552
(Address of principal executive offices)	(Zip Code)

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

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

Common Stock, par value $.001 per share	NYSE American
(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

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

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 No

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted 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 such files). Yes 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, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of “large accelerated filer,” “accelerated filer,” “smaller reporting company,” and “emerging growth company” in Rule 12b-2 of the Exchange Act.

Large accelerated filer	Accelerated filer
Non-accelerated filer	Smaller reporting company
	Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

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

The aggregate market value of shares of common stock held by non-affiliates of the registrant on June 30, 2018 was $35,842,392.

The number of shares of common stock outstanding on March 1, 2019 was 200,690,700.

DOCUMENTS INCORPORATED BY REFERENCE

None.

The Private Securities Litigation Reform Act of 1995 (the "PSLRA") 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 PSLRA. The words "anticipate," "believe," "estimate," "expect," "future," "intend," "plan," "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, our history of operating losses and uncertainty of future profitability, accumulated deficit, future capital needs, the outcome of any pending litigation, uncertainty of capital funding, dependence on royalties and grant revenue, limited product line and distribution channels, competition, risks of development of new products, our ability to maintain effective control over financial reporting, our ability to comply with NYSE American continued listing standards, and other risks set forth below under Item 1A, "Risk Factors." The Company undertakes no obligation to publicly update or revise any forward-looking statements.

PART I

Item 1. Business

Development of the Business

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

Navidea's Manocept platform is predicated on the ability to specifically target the CD206 mannose receptor expressed on activated macrophages. The Manocept platform serves as the molecular backbone of Tc99m tilmanocept, the first product developed and commercialized by Navidea based on the platform.

On March 3, 2017, pursuant to an Asset Purchase Agreement dated November 23, 2016 (the "Purchase Agreement"), the Company completed its previously announced sale to Cardinal Health 414, LLC ("Cardinal Health 414") of its assets

used, held for use, or intended to be used in operating its business of developing, manufacturing and commercializing a product used for lymphatic mapping, lymph node biopsy, and the diagnosis of metastatic spread to lymph nodes for staging of cancer (the "Business"), including the Company's radioactive diagnostic agent marketed under the Lymphoseek® trademark for current approved indications by the U.S. Food and Drug Administration ("FDA") and similar indications approved by the FDA in the future (the "Product"), in Canada, Mexico and the United States (the "Territory") (giving effect to the License-Back described below and excluding certain assets specifically retained by the Company) (the "Asset Sale"). Such assets sold in the Asset Sale consist primarily of, without limitation, (i) intellectual property used in or reasonably necessary for the conduct of the Business, (ii) inventory of, and customer, distribution, and product manufacturing agreements related to, the Business, (iii) all product registrations related to the Product, including the new drug application approved by the FDA for the Product and all regulatory submissions in the United States that have been made with respect to the Product and all Health Canada regulatory submissions and, in each case, all files and records related thereto, (iv) all related clinical trials and clinical trial authorizations and all files and records related thereto, and (v) all rights, title and interest in and to the Product, as specified in the Purchase Agreement (the "Acquired Assets").

In connection with the closing of the Asset Sale, the Company entered into a License-Back Agreement (the "License-Back") with Cardinal Health 414. Pursuant to the License-Back, Cardinal Health 414 granted to the Company a sublicensable (subject to conditions) and royalty-free license to use certain intellectual property rights included in the Acquired Assets and owned by Cardinal Health 414 as of the closing of the Asset Sale to the extent necessary for the Company to (i) on an exclusive basis, subject to certain conditions, develop, manufacture, market, sell and distribute new pharmaceutical and other products that are not Competing Products (as defined in the License-Back), and (ii) on a non-exclusive basis, develop, manufacture, market, sell and distribute the Product throughout the world other than in the Territory. Subject to the Company's compliance with certain restrictions in the License-Back, the License-Back also restricts Cardinal Health 414 from using the intellectual property rights included in the Acquired Assets to develop, manufacture, market, sell, or distribute any product other than the Product or other product that (a) accumulates in lymphatic tissue or tumor-draining lymph nodes for the purpose of (1) lymphatic mapping or (2) identifying the existence, location or staging of cancer in a body, or (b) provides for or facilitates any test or procedure that is reasonably substitutable for any test or procedure provided for or facilitated by the Product. Pursuant to the License-Back and subject to rights under existing agreements, Cardinal Health 414 was given a right of first offer to market, sell and/or market any new products developed from the intellectual property rights licensed by Cardinal Health 414 to the Company by the License-Back.

As part of the Asset Sale, the Company and Cardinal Health 414 also entered into ancillary agreements providing for transitional services and other arrangements. The Company amended and restated its license agreement with The Regents of the University of California, San Diego ("UCSD") pursuant to which UCSD granted a license to the Company to exploit certain intellectual property rights owned by UCSD and, separately, Cardinal Health 414 entered into a license agreement with UCSD pursuant to which UCSD granted a license to Cardinal Health 414 to exploit certain intellectual property rights owned by UCSD for Cardinal Health 414 to sell the Product in the Territory.

Upon closing of the Asset Sale, the Supply and Distribution Agreement, dated November 15, 2007, as amended, between Cardinal Health 414 and the Company was terminated and, as a result, the provisions thereof are of no further force or effect (other than any indemnification, payment, notification or data sharing obligations which survive the termination).

Other than Tc99m tilmanocept, which the Company has a license to distribute outside of Canada, Mexico and the United States, none of the Company's drug product candidates have been approved for sale in any market.

Our business is focused on two primary types of drug products: (i) diagnostic substances, including Tc99m tilmanocept and other diagnostic applications of our Manocept platform and NAV4694, and (ii) therapeutic development programs, including therapeutic applications of our Manocept platform and all development programs undertaken by Macrophage Therapeutics, Inc. See Note 18 to the consolidated financial statements for more information about our business segments.

Our History

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

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

From our inception through August 2011, we manufactured a line of gamma radiation detection medical devices called the neoprobe® GDS system (the "GDS Business"). We sold the GDS Business to Devicor Medical Products, Inc. ("Devicor") in August 2011. Following the sale of the GDS business and the subsequent strategic repositioning as a precision medicines company, the Company in-licensed two neuro-tracer product candidates, NAV4694 and NAV5001. The Company progressed the development of both product candidates over the course of 2012 through 2014, moving both into Phase 3 clinical trials. However, in May 2014, the Navidea Board announced that the Company would restructure its development efforts to focus on cost effective development of the Manocept platform and divest its neuro-tracer product candidates. In April 2015, the Company entered into an agreement with Alseres Pharmaceuticals, Inc. ("Alseres") to terminate the NAV5001 sub-license agreement. In April 2018, the Company executed an agreement to provide Meilleur Technologies, Inc. ("Meilleur") worldwide rights to conduct research using NAV4694, as well as an exclusive license for the development and commercialization of NAV4694 in Australia, Canada, China, and Singapore. Meilleur also has an option to commercialize worldwide.

In December 2014, we announced the formation of a new business unit to further explore therapeutic applications for the Manocept platform, which was incorporated as Macrophage Therapeutics, Inc. ("MT") in January 2015 as a majority-owned subsidiary of Navidea. Navidea also granted MT an exclusive sublicense for certain therapeutic applications of the Manocept technology. MT has developed processes for producing the first two therapeutic Manocept immuno-constructs, MT-1002, designed to specifically target and kill activated CD206+ macrophages by delivering doxorubicin, and MT-2002, designed to inhibit the inflammatory activity of activated CD206+ macrophages by delivering a potent anti-inflammatory agent. MT has contracted with independent facilities to produce sufficient quantities of the MT-1002 and MT-2002 agents along with the concomitant analytical standards, to provide material for planned preclinical animal studies and future clinical trials.

In August 2018, the Company entered into an agreement (the "Agreement") with Dr. Michael Goldberg related to his resignation from his positions as an executive officer and a director of Navidea. Among other things, the Agreement provided that Dr. Goldberg would become Chief Executive Officer of MT, and that MT would redeem all of Dr. Goldberg's MT preferred stock and issue to Dr. Goldberg MT super voting common stock equal to 5% of the outstanding shares of MT, subject to execution of Definitive Agreements. As of the date of filing of this Annual Report on Form 10-K, the Definitive Agreements have not yet been signed.

On February 11, 2019, Dr. Goldberg represented to the MT Board that he had, without MT Board or shareholder approval, created a subsidiary of MT, transferred all of the assets of MT into the subsidiary, and then issued himself stock in the subsidiary. On February 19, 2019, Navidea notified MT that it was terminating the sublicense effective March 1, 2019 because MT became insolvent in violation of the sublicense agreement. On February 20, 2019, the Board of Directors of MT removed Dr. Goldberg as President and Chief Executive Officer of MT and from any other office of MT to which he may have been appointed or in which he was serving. Dr. Goldberg remains a member of the MT Board, together with Michael Rice and Dr. Claudine Bruck. Mr. Rice and Dr. Bruck remain members of the board of directors of Navidea. The MT Board then appointed Mr. Latkin to serve as President and Chief Executive Officer of MT.

On February 20, 2019, Navidea filed a complaint against Dr. Goldberg in the United States District Court for the Southern District of New York, alleging breach of the Agreement, as well as a breach of the covenant of good faith and fair dealing and to obtain a declaratory judgment that Navidea's performance under the Agreement is excused and that Navidea is entitled to terminate the Agreement as a result of Dr. Goldberg's actions. Also on February 20, 2019, MT initiated a suit against Dr. Goldberg in the Court of Chancery of the State of Delaware, alleging, among other things, breach of fiduciary duty as a director and officer of MT and conversion, and to obtain a declaratory judgment that the transactions Dr. Goldberg caused MT to enter into are void. On March 13, 2019, the Court of Chancery entered an order maintaining status quo, which provided, among other things, that MT's board of directors may authorize any act or transaction on behalf of the Company, and that without prior written authorization of the MT board, Dr. Goldberg shall not hold himself out as CEO of MT or purport to act or authorize any action on behalf of MT except as authorized by the MT board.

On March 7, 2019, Dr. Goldberg filed a complaint against Navidea and MT in the United States District Court for the Southern District of New York. The Complaint alleges a breach of contract claim against both Navidea and MT for failure to pay to Dr. Goldberg funds allegedly due to him under the Promissory Note, dated July 25, 2012, made by the Company in favor of Platinum-Montaur Life Sciences LLC (the "Platinum Note"). The Complaint further alleges a breach of contract claim against Navidea due to Navidea's failure to issue 23.5 million shares to Dr. Goldberg, to issue MT Super Voting Common Stock, by removing Dr. Greene from the MT Board of Directors, by appointing Mr. Rice and Dr. Bruck to the MT Board of Directors, and by terminating Dr. Goldberg as CEO of MT.

Our Technology and Product Candidates

Our primary development efforts over the last several years were focused on diagnostic products, including Lymphoseek which was sold to Cardinal Health 414 in March 2017. Our more recent initiatives have been focused exclusively on diagnostic and therapeutic line extensions based on our Manocept platform.

Manocept Platform - Diagnostics and Therapeutics Background

Navidea's Manocept platform is predicated on the ability to specifically target the CD206 mannose receptor expressed primarily on activated macrophages. This flexible and versatile platform serves as a molecular engine for purpose-built targeted imaging molecules that may significantly impact patient care by providing enhanced diagnostic accuracy, clinical decision-making, and target-specific treatment. This CD206-targeted drug platform is applicable to a range of diagnostic modalities, including single photon emission computed tomography ("SPECT"), positron emission tomography ("PET"), gamma-scanning (both imaging and topical) and intra-operative and/or optical-fluorescence detection, as well as delivery of therapeutic compounds that target macrophages, and their role in a variety of immune- and inflammation-involved diseases. The FDA-approved sentinel node/lymphatic mapping agent, Tc99m tilmanocept, is representative of the ability to successfully exploit this mechanism to develop powerful new products and to expand this technology into additional diagnostic and therapeutic applications.

Activated macrophages play important roles in many disease states and are an emerging target in many diseases where diagnostic uncertainty exists. Impairment of the macrophage-driven disease mechanisms is an area of increasing and proven focus in medicine. The number of people affected by all the inflammatory diseases combined is estimated at more than 40 million in the United States and up to 700 million worldwide, making macrophage-mediated diseases an area of remarkable clinical importance. There are many recognized disorders having macrophage involvement, including rheumatoid arthritis ("RA"), atherosclerosis/vulnerable plaque, nonalcoholic steatohepatitis ("NASH"), inflammatory bowel disease, systemic lupus erythematosus, Kaposi's sarcoma ("KS"), leishmaniosis, and others that span general clinical areas in oncology, autoimmunity, infectious diseases, cardiology, CNS diseases, and inflammation. For the near term, we have selected target diseases that may, if successfully developed, benefit from this technology.

Manocept Platform – Immuno-Diagnostics Clinical Data

Rheumatoid Arthritis

Two Tc99m tilmanocept dose escalation studies in RA have been completed. The first study was completed and included 18 subjects (nine with active disease and nine healthy subjects) dosed subcutaneously with 50 and 200 µg/2mCi Tc99m tilmanocept (ClinicalTrials.gov NCT02683421). The results of this study were presented at five international meetings, including Biotechnology Innovation Organization ("BIO"), Society of Nuclear Medicine and Molecular Imaging ("SNMMI"), and The American College of Rheumatology ("ACR"). In addition, based on completion of extensive preclinical dosing studies pursuant to our dialog with the FDA, we have completed a Phase 1/2 study involving intravenous ("IV") dosing of 39 subjects with IV-administered Tc99m tilmanocept (ClinicalTrials.gov NCT02865434). In conjunction with this study, we have completed pharmacokinetic, pharmacodynamics and radiation dosimetry phases in human subjects as well. The majority of the costs of these studies have been supported through a Small Business Innovation Research ("SBIR") grant (NIH/NIAMSD Grant 1 R44 AR067583-01A1). Results were presented at the June 2018 SNMMI meeting. These studies have been combined and submitted for peer review publication and full published results will follow.

Cardiovascular Disease ("CV")

In collaboration with researchers at Massachusetts General Hospital, Navidea has completed one and initiated a second clinical study evaluating Tc99m tilmanocept's ability to enable imaging of atherosclerotic plaques. Results of these studies provide strong preliminary evidence of the potential of Tc99m tilmanocept to accumulate specifically in and enable imaging of non-calcified atherosclerotic plaques. Non-calcified atherosclerotic plaques include plaques with morphologies indicating a high risk of rupture. Rupture of such plaques causes myocardial infarctions (heart attacks) and a significant portion of ischemic strokes. The studies compared aortic Tc99m tilmanocept uptake imaged by SPECT/CT in clinically asymptomatic subjects with intermediate Framingham Risk Scores ("FRS") who were infected with Human Immunodeficiency Virus ("HIV") as compared to healthy, uninfected, FRS and age-matched subjects. Tc99m tilmanocept SPECT/CT images were compared to aortic images of the same subjects obtained by

contrast enhanced coronary computed tomography angiography and/or [18F]NaF PET/CT.

A nine-subject study to evaluate diagnostic imaging of emerging atherosclerosis plaque with the Tc99m tilmanocept product dosed subcutaneously is complete (ClinicalTrials.gov NCT02542371). The results of this study were presented at two major international meetings (Conference on Retroviruses and Opportunistic Infections ("CROI") and SNMMI, 2017) and published in early release in the *Journal of Infectious Diseases* in January 2017 (published in the circulated version, *Journal of Infectious Diseases* (2017) **215** (8): 1264-1269), confirming that the Tc99m tilmanocept product can both quantitatively and qualitatively target non-calcified plaque in the aortic arch of Acquired Immunodeficiency Syndrome ("AIDS") patients (supported by NIH/NHLBI Grant 1 R43 HL127846-01).

We have also commenced a second Phase1/2 study in cooperation with Massachusetts General Hospital in subjects with HIV that expands the original study in both the scope of the drug administration as well as the diagnostic assessment of the subjects. This study will enroll up to 24 AIDS subjects and healthy controls in imaging non-calcified plaque using IV-administered Tc99m tilmanocept and will expand the initial investigation to the assessment of aortic plaque as well as carotid and coronary arteries. Initial images from this study are currently being evaluated.

Kaposi's Sarcoma

KS is a serious and potentially life-threatening illness, which in the United States occurs disproportionately in persons infected with HIV and in organ transplant patients. The prognosis for patients with treatment-resistant KS is poor with high probabilities for mortality and greatly diminished quality of life. We initiated and completed a study of KS in 2015 (ClinicalTrials.gov NCT022201420), and received additional funding from the National Institutes of Health ("NIH") in 2016 to continue diagnostic studies in this disease. The new support not only continues the imaging of the cutaneous form of this disease but expands this to imaging of visceral disease via IV administration of Tc99m tilmanocept (NIH/NCI 1 R44 CA192859-01A1; ClinicalTrials.gov NCT03157167). This now-escalated study includes a pathology/biopsy component as well as an imaging component to determine pathology concordance with image assessment. We received Institutional Review Board approval of the clinical protocol, we initiated a Phase 1/2 clinical study in KS in 2017, and the trial is currently ongoing.

Colorectal Cancer ("CRC") and Synchronous Liver Metastases

During the first quarter of 2017, we initiated an imaging study in subjects with CRC and liver metastases via IV administration of Tc99m tilmanocept. This study was supported through a SBIR grant (NIH/NCI 1 R44 CA1962783-01A1; ClinicalTrials.gov NCT03029988). The trial intended to enroll up to 12 subjects with dose modification. After an interim analysis of the first three completed subjects, a decision was made to not continue with the trial and the study is now closed. An initial presentation took place at SNMMI in June of 2018. An additional report has been submitted to the National Cancer Institute ("NCI") on the early results of this study.

Nonalcoholic Steatohepatitis

We have concluded a clinical study (ClinicalTrials.gov NCT03332940) that was originally designed to enroll 12 subjects with IV administration of Tc99m tilmanocept and an imaging comparator to identify and quantify the extent of NASH lesions in human patients. A semiquantitative evaluation of the images from the first six subjects indicated that imaging the remaining six subjects planned in the study may not sufficiently further our knowledge of Tc99m tilmanocept imaging in individuals with NASH to justify continuing the study using the current protocol. The study is now complete. Ongoing quantitative analyses of the images from the first six subjects will determine if future studies in subjects with NASH are likely to be productive. Initial results were presented at the NASH Summit in Boston in April 2018, and the results are available on Navidea's website.

Biomarker Application and Qualification

In November 2017, the Company commenced the qualification of the biomarker CD206 with the FDA Biomarker Section of The Center for Drug Evaluation and Research ("CDER"). As per FDA protocol, Navidea submitted a draft letter of intent ("LOI") to CDER prior to the November 2017 meeting. According to the CDER directive, "the Biomarker Qualification Program was established to support the CDER's work with external stakeholders to develop biomarkers that aid in the drug development process. Through the FDA's Biomarker Qualification Program, an entity may request regulatory qualification of a biomarker for a particular context of use ("COU") in drug development." Following the meeting with the FDA, and because of Navidea's data sets and the general external publication database, Navidea, in conjunction with FDA, is now reviewing the LOI with the FDA's recommended consultants. Navidea has revised the LOI draft strategy in order to expedite the application process. In March 2018, Navidea had a follow-up meeting with the FDA's assigned strategist, during which the potential to further narrow the LOI elements was reviewed. Navidea is continuing the process of finalizing the COU LOI and providing the background data sets for qualification review with the FDA/CDER. Additional meetings have taken place and the pursuit of this qualification is progressing well.

Macrophage Therapeutics Background

In December 2014, the Company formed a new business unit to further explore therapeutic applications for the Manocept platform. In January 2015, Navidea incorporated the business unit as MT, a majority-owned subsidiary of Navidea. MT has developed processes for producing the first two therapeutic Manocept immuno-constructs, MT-1002, designed to specifically target and kill activated CD206+ macrophages by delivering doxorubicin, and MT-2002, designed to inhibit the inflammatory activity of activated CD206+ macrophages by delivering a potent anti-inflammatory agent. MT has contracted with independent facilities to produce sufficient quantities of the MT-1002 and MT-2002 agents along with the concomitant analytical standards, to provide material for planned preclinical animal studies and future clinical trials.

See Notes 10 and 15 to the accompanying consolidated financial statements.

Manocept Platform – In-Vitro and Pre-Clinical Immunotherapeutics Data

MT has been set up to pursue the therapeutic drug delivery model. This model enables the Company to leverage its technology over many potential disease applications and with multiple partners simultaneously without significant capital outlays. To date, the Company has developed two lead families of therapeutic products. The MT-1000 class is designed to deplete activated macrophages via apoptosis. The MT-2000 class is designed to modulate activated macrophages from a classically activated phenotype to the alternatively activated phenotype. Both families have been tested in a number of disease models in rodents.

We have already reported on the peripheral infectious disease aspects of KS, including HIV and HHV8 (CROI, Boston 2016, and KS HHV8 Summit Miami 2015). As noted, we continue this work funded by the NIH/NIAID and NCI. The Company has completed preclinical studies employing both MT 1000-class and 2000-class therapeutic conjugates of Manocept. The positive results from these studies are indicative of Manocept's specific targeting supported by its strong binding affinity to CD206 receptors. This high degree of specificity is a foundation of the potential for this technology to be useful in treating diseases linked to the over-activation of macrophages. This includes various cancers as well as autoimmune, infectious, CV, and central nervous system ("CNS") diseases.

Kaposi's Sarcoma

The novel MT-1000 class constructs are designed to specifically deliver doxorubicin, a chemotoxin, which can kill KS tumor cells and their tumor-associated macrophages, potentially altering the course of cancer. We have received

additional funding to continue therapeutic studies in this disease with the goal of completing an investigational new drug ("IND") submission for a Manocept construct (MT-1000 class of compounds) consisting of tilmanocept linked to doxorubicin for the treatment of KS. The first part of the grant, now complete, supported analyses including *in vitro* and cell culture studies, to be followed by Parts 2 and 3 FDA-required preclinical animal testing studies. The information from these studies will be combined with other information in an IND application that will be submitted to the FDA requesting permission to begin testing the compound in selected KS subjects (supported by NIH/NCI 1 R44 CA206788-01).

Nonalcoholic Fatty Liver Disease ("NAFLD")

NAFLD is a spectrum of liver disorders and is defined by the presence of steatosis in more than 5% of hepatocytes with little or no alcohol consumption. NASH is the most extreme form of NAFLD. A major characteristic of NASH involves cells undergoing lipotoxicity, releasing endogenous signals prompting the accumulation of various macrophages to assess the damage. Studies have shown that levels of endogenous molecular inflammatory signals positively correlate with inflammation, hepatocyte ballooning, and other NAFLD symptoms. We have developed a molecular delivery technology capable of targeting disease-causing macrophages by selectively binding to the CD206 receptor. Selective binding and efficient delivery of this agent diminishes the potential of interfering more broadly with the normal function of the immune system.

We have completed five *in vivo* studies employing our MT-1002 and MT-2002 Manocept conjugates in a mouse model of NAFLD/NASH and liver fibrosis. The NALFD scores, which correlate to the agents' effectiveness, were significantly reduced, with all the activity related to inflammation and "ballooning" scores. Fibrosis decreased significantly when compared to the control in the later dosing arm of the study. Liver weights did not differ during any phase of the study between control and agent-treated groups, nor was there any evidence of damage to the roughly 30% of the liver made up of un-activated macrophages called Kupffer cells. MT-1002 and MT-2002 both significantly reduced key disease assessment parameters in the *in vivo* STAM™ NASH model. We believe these agents present themselves as potential clinically effective candidates for further evaluation. We continue to use this model to further assess the activity of our agents.

Other Immunotherapeutic Applications

We have completed an expanded series of predictive *in vitro* screening tests of the MT-1002 and MT-2002 therapeutic conjugates against the Zika and Dengue viruses, which included infectivity and viral replication inhibition effectiveness as well as dose finding studies and mechanisms of action, the latter based on conjugate structures. We have also completed a series of predictive *in vivo* screening tests of the MT-1002 and MT-2002 therapeutic conjugates against Leishmaniosis, which included host cell targeting and killing effectiveness as well as dose finding studies and mechanisms of action. A portion of the results from the *in vivo* Leishmaniosis study, completed in conjunction with the National Institute of Allergy and Infectious Diseases/NIH, was recently published in the *Journal of Experimental Medicine (*published in the circulated version *Journal of Experimental Medicine* 2018 Jan 2;215(1):357-375). The results from all evaluations were positive and have provided a basis for moving forward with additional *in vivo* testing of the selected conjugates. We have selected collaborators for these *in vivo* studies, which we expect will take place over the next four to six months. We will provide updates as information becomes available on future testing.

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, including ongoing studies in KS, RA and infectious diseases. The immuno-inflammatory process is remarkably complex and tightly regulated with indicators that initiate, maintain and shut down the process. Macrophages are immune cells that play a critical role in the initiation, maintenance, and resolution of inflammation. They are activated and deactivated in the inflammatory process. Because macrophages may promote dysregulation that accelerates or enhances disease progression, diagnostic and therapeutic interventions that target macrophages may open new avenues for controlling inflammatory diseases. There can be no assurance 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.

NAV4694 (Sublicensed)

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

In May 2014, the Board of Directors made the decision to refocus the Company's resources to better align the funding of our pipeline programs with the expected growth in Tc99m tilmanocept revenue. This realignment primarily

involved reducing our near-term support for our neurological product candidates, including NAV4694, as we sought a development partner or partners for these programs. In April 2018, the Company executed an agreement to provide Meilleur, a wholly-owned subsidiary of Cerveau Technologies, Inc. ("Cerveau"), worldwide rights to conduct research using NAV4694, as well as an exclusive license for the development and commercialization of NAV4694 in Australia, Canada, China, and Singapore. Meilleur also has an option to commercialize worldwide.

Market Overview

Tc99m Tilmanocept – Cancer Market Overview

Cancer is the second leading cause of death in the United States. The American Cancer Society ("ACS") estimates that cancer will cause over 600,000 deaths in 2019 in the United States alone. Additionally, the ACS estimates that approximately 1.7 million new cancer cases will be diagnosed in the United States during 2019. The Agency for Healthcare Research and Quality has estimated that the direct medical costs for cancer in the United States for 2015 were $80.2 billion. Cancer is also the second leading cause of death in Europe. The World Health Organization reports more than 3.7 million new cases and 1.9 million deaths in Europe each year.

Tc99m tilmanocept is approved by the FDA for use in solid tumor cancers where lymphatic mapping is a component of surgical management and for guiding sentinel lymph node biopsy in patients with clinically node negative breast cancer, head and neck cancer, melanoma or squamous cell carcinoma of the oral cavity. Tc99m tilmanocept has also received European approval in imaging and intraoperative detection of sentinel lymph nodes in patients with melanoma, breast cancer or localized squamous cell carcinoma of the oral cavity. If the potential of Tc99m tilmanocept as a radioactive tracing agent is ultimately realized, it may address not only the breast and melanoma markets on a procedural basis, but also assist in the clinical evaluation and staging of solid tumor cancers and expanding lymph node mapping to other solid tumor cancers such as prostate, gastric, colon, gynecologic, and non-small cell lung.

Manocept Diagnostics and Macrophage Therapeutics Market Overview

Impairment of the macrophage-driven disease mechanism is an area of increasing focus in medicine. There are many recognized disorders having macrophage involvement, including RA, atherosclerosis/vulnerable plaque, Crohn's disease, TB, systemic lupus erythematosus, KS, and others that span clinical areas in oncology, autoimmunity, infectious diseases, cardiology, and inflammation. The number of people affected by all the inflammatory diseases combined is estimated at more than 40 million in the United States, making these macrophage-mediated diseases an area of significant clinical importance. The Arthritis Foundation estimates that RA alone affects over 1.5 million people in the United States and as much as 1% of the worldwide population. Based on 2005 U.S. Medicare/Medicaid data, total annual societal costs of RA are estimated to be $39.2 billion. Data from studies using agents from the Manocept platform in RA, KS and TB were published in a special supplement, *Nature Outlook: Medical Imaging*, in *Nature's* October 31, 2013 issue. The supplement included a White Paper by Navidea entitled "*Innovations in receptor-targeted precision imaging at Navidea: Diagnosis up close and personal,*" focused on the Manocept platform.

NAV4694 - Alzheimer's Disease Market Overview

The Alzheimer's Association ("AA") estimates that more than 5.7 million Americans had AD in 2018. On a global basis, Alzheimer's Disease International estimated in 2015 that there were 46.8 million people living with dementia, and this number is believed to be close to 50 million people in 2017. This number is expected to almost double every 20 years, reaching 75 million in 2030 and over 130 million in 2050. AD is the sixth-leading cause of death in the U.S. and the only cause of death among the top 10 in the U.S. that cannot be prevented, cured or even slowed. Based on U.S. mortality data from 2000 to 2015, deaths from AD have risen 123 percent while deaths attributed to the number one cause of death, heart disease, decreased 11 percent during the same period. AA estimates that total costs for AD care was approximately $259.0 billion in 2017. AA also estimates that there are over 16 million AD and dementia caregivers providing 18.4 billion hours of unpaid care valued at over $232.0 billion.

Marketing and Distribution

In March 2017, Navidea completed the Asset Sale to Cardinal Health 414, as discussed previously under "Development of the Business." Pursuant to the Purchase Agreement, we sold all of our assets used, held for use, or intended to be used in operating the Business, including the Product, in the Territory. Upon closing of the Asset Sale, the Supply and Distribution Agreement between Cardinal Health 414 and the Company was terminated and Cardinal Health 414 has assumed responsibility for marketing Lymphoseek in the Territory.

Unlike the United States, where institutions typically rely on radiopharmaceutical products that are compounded and delivered by specialized radiopharmacy distributors such as Cardinal Health 414, institutions in Europe predominantly

purchase non-radiolabeled material and compound the radioactive product on-site. With respect to Tc99m tilmanocept commercialization in Europe, we have chosen a specialty pharmaceutical strategy that should be supportive of premium product positioning and reinforce Tc99m tilmanocept's clinical value proposition, as opposed to a commodity or a generics positioning approach. In March 2015, we entered into an exclusive sublicense agreement for the commercialization and distribution of a 50 microgram kit for radiopharmaceutical preparation (tilmanocept) in the European Union ("EU") with SpePharm AG (an affiliate of Norgine BV), a European specialist pharmaceutical company with an extensive pan-European presence. Under the terms of the exclusive license agreement, Navidea transferred responsibility for regulatory maintenance of the Tc99m tilmanocept Marketing Authorization to SpePharm in January 2017. SpePharm is also responsible for production, distribution, pricing, reimbursement, sales, marketing, medical affairs, and regulatory activities. In connection with entering into the agreement, Navidea received an upfront payment of $2.0 million, and is entitled to milestones totaling up to an additional $5.0 million and royalties on European net sales. The initial territory covered by the agreement includes all 28 member states of the European Economic Community with the option to expand into additional geographical areas. During the second quarter of 2017, SpePharm launched Tc99m tilmanocept in select EU markets, providing a number of early adopters with sample doses to provide exposure to the product. EU sales commenced during the third quarter of 2017.

In August 2014, Navidea entered into an exclusive agreement with Sinotau, a pharmaceutical organization with a broad China focus in oncology and other therapeutic areas, who will develop and commercialize Tc99m tilmanocept in China. In exchange, Navidea will earn revenue based on unit sales to Sinotau, royalties based on Sinotau's sales of Tc99m tilmanocept and milestone payments from Sinotau, including a $300,000 non-refundable upfront payment. As part of the agreement, Sinotau is responsible for costs and conduct of clinical studies and regulatory applications to obtain Tc99m tilmanocept approval by the China Food and Drug Administration ("CFDA"). Upon approval, Sinotau will be responsible for all Tc99m tilmanocept sales, marketing, market access and medical affairs activities in China and excluding Hong Kong, Macau and Taiwan. Navidea and Sinotau will jointly support certain pre-market planning activities with a joint commitment on clinical and market development programs pending CFDA approval.

In June 2017, Navidea entered into an exclusive license and distribution agreement with Sayre Therapeutics ("Sayre") for the development and commercialization of Tc99m tilmanocept in India. Sayre specializes in innovative treatments and medical devices commercialization in South Asia. Under the terms of the agreement, Navidea received a $100,000 upfront payment and is eligible to receive milestone payments and double-digit royalties associated with the sale of Tc99m tilmanocept in India. Tc99m tilmanocept has not yet received marketing approval in India.

Tc99m tilmanocept is in various stages of approval in other global markets and sales to this point in these markets, to the extent there were any, have not been material. However, we believe that with international partnerships to complement our positions in the EU, China and India, we will help establish Tc99m tilmanocept as a global leader in lymphatic mapping, as we are not aware of any other company that has a global geographic range. However, it is possible that Tc99m tilmanocept will never achieve regulatory approval in any market outside the United States or EU, or if approved, that it may not achieve market acceptance in any market. We may also experience difficulty in securing collaborative partners for other global markets or radiopharmaceutical products, or successfully negotiating acceptable terms for such arrangements. See Item 1A - “Risk Factors.”

Manufacturing

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

In November 2009, we completed a Manufacture and Supply Agreement with Reliable Biopharmaceutical Corporation (“Reliable”) for the manufacture of the bulk drug substance with an initial term of 10 years. In September 2013, we entered into a Manufacturing Services Agreement with OSO BioPharmaceuticals Manufacturing, LLC (“OsoBio”) for contract pharmaceutical development, manufacturing, packaging and analytical services for Tc99m tilmanocept. Also in September 2013, we completed a Service and Supply Master Agreement with Gipharma S.r.l. (“Gipharma”) for process development, manufacturing and packaging of 50-microgram vials for sale in the EU. Upon closing of the Asset Sale to Cardinal Health 414, our contracts with Reliable and OsoBio were transferred to Cardinal Health 414. Similarly, following the transfer of the Tc99m tilmanocept Marketing Authorization to SpePharm, our contract with Gipharma was transferred to SpePharm. We may not be successful in completing future agreements for the supply of Tc99m tilmanocept on terms acceptable to the Company, or at all. See Item 1A - “Risk Factors.”

Competition

Competition in the pharmaceutical and biotechnology industries is intense. We face competition from a variety of companies focused on developing oncology and neurology diagnostic drugs. We compete with large pharmaceutical and other specialized biotechnology companies. We also face competition from universities and other non-profit research organizations. Many emerging medical product companies have corporate partnership arrangements with large, established companies to support the research, development, and commercialization of products that may be

competitive with our products. In addition, a number of large established companies are developing proprietary technologies or have enhanced their capabilities by entering into arrangements with or acquiring companies with technologies applicable to the detection or treatment of cancer and other diseases targeted by our product candidates. Smaller companies may also prove to be significant competitors, particularly through collaborative arrangements with large pharmaceutical and established biotechnology companies. Many of these competitors have products that have been approved or are in development and operate large, well-funded research and development programs. Many of our existing or potential competitors have substantially greater financial, research and development, regulatory, marketing, and production resources than we have. Other companies may develop and introduce products and processes competitive with or superior to ours.

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

We believe that our ability to compete successfully will be based on our ability to create and maintain scientifically advanced “best-in-class” technology, develop proprietary products, attract and retain scientific personnel, obtain patent or other protection for our products, obtain required regulatory approvals and manufacture and successfully market our products, either alone or through third parties. We expect that competition among products cleared for marketing will be based on, among other things, product efficacy, safety, reliability, availability, price, and patent position. See Item 1A - “Risk Factors.”

Tc99m Tilmanocept Competition – Currently Approved Indications

Surgeons who practice the lymphatic mapping procedure for which Tc99m tilmanocept is intended currently use other radiopharmaceuticals such as a sulfur colloid or other colloidal compounds. In addition, some surgeons still use vital blue dyes to assist in the visual identification of the draining lymphatic tissue around a primary tumor. In the EU and certain Pacific Rim markets, there are colloidal-based compounds with various levels of approved labeling for use in lymphatic mapping, although a number of countries still employ products used “off-label.”

Rheumatoid Arthritis Competition

Currently, no single test is available to diagnose and monitor RA. Rather, a rheumatologist will make a diagnosis based on several procedures that may include a physical exam, blood tests, and/or imaging tests, among others. The Arthritis Foundation states that the goals of RA treatment are to relieve symptoms, stop inflammation, prevent joint and organ damage, improve physical function and well-being, and reduce long-term complications. Medications for the treatment of RA currently fall into two categories: drugs that ease symptoms, such as nonsteroidal anti-inflammatory drugs, and drugs that slow disease activity. Drugs that slow disease activity include corticosteroids, disease-modifying antirheumatic drugs, biologics, and Janus kinase inhibitors. Many of these drugs are produced and sold by large pharmaceutical companies, including AbbVie, Amgen, Bristol Meyers Squibb, Johnson & Johnson, Merck, Pfizer, and Roche, among others.

Patents and Proprietary Rights

The patent position of biotechnology companies, including Navidea, generally is highly uncertain and may involve complex legal and factual questions. Potential competitors may have filed applications, or may have been issued patents, or may obtain additional patents and proprietary rights relating to products or processes in the same area of technology as that used by the Company. The scope and validity of these patents and applications, the extent to which we may be required to obtain licenses thereunder or under other proprietary rights, and the cost and availability of licenses are uncertain. Our patent applications or those licensed to us may not result in additional patents being issued, and our patents or those licensed to us may not afford protection against competitors with similar technology; these patents may be designed around by others or others may obtain patents that we would need to license or design around.

We also rely upon unpatented trade secrets. Others may independently develop substantially equivalent proprietary information and techniques, or otherwise gain access to our trade secrets, or disclose such technology, or we may not be able to 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. However, these agreements may not 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. However, these measures may not be adequate to protect our trade secrets from unauthorized access or disclosure. See Item 1A - “Risk Factors.”

Tilmanocept Intellectual Property

Tilmanocept is under license from UCSD to Navidea for the exclusive world-wide rights in all diagnostic and therapeutic uses of tilmanocept, except for the diagnostic use of Tc99m tilmanocept in Canada, Mexico and the United States, which rights have been licensed directly to Cardinal Health 414 by UCSD in connection with the Asset Sale. Navidea maintains license rights to Tc99m tilmanocept in the rest of the world, as well as a license to the intellectual property underlying the Manocept platform.

Tc99m tilmanocept and related compositions, including the Manocept backbone composition and methods of use, are the subject of multiple patent families totaling 44 patents and patent applications in the United States and certain major foreign markets.

The first composition of matter patent covering tilmanocept was issued in the United States in June 2002, and will expire in May 2020, however Navidea has applied for a patent term extension under the Hatch Waxman Act that would extend the term by five years due to time lost in regulatory review. The claims of the composition of matter patent covering tilmanocept have been allowed in the EU and issued in the majority of major-market EU countries in 2004. These patents will expire in 2020, but a request for supplemental protection certificates are in process to further extend the life of these patents, and some have been granted, extending the patent term to 2025. The composition of matter patent has also been issued in Japan, which will expire in 2020.

Patent applications have been filed in the U.S. and certain major foreign markets related to manufacturing processes for tilmanocept, the first of which was issued in the U.S. in 2013. These patents and/or applications will expire between 2029 and 2034. Further patent applications have been filed by Navidea alone or with The Ohio State Innovation Foundation related to CD206 expressing cell-related disorders and diseases. These patents and/or applications would be expected to expire between 2034 and 2035. We have filed further patent applications related to 2-heteroaryl substituted benzofurans. These patents and/or applications will expire between 2036 and 2038.

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Government Regulation

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

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

Failure to comply with applicable federal, state, local or foreign laws or regulations could subject us to enforcement action, including product seizures, recalls, withdrawal of marketing clearances, and civil and criminal penalties, any one or more of which could have a material adverse effect on our business. We believe that we are in substantial compliance with such governmental regulations. However, federal, state, local and foreign laws and regulations regarding the manufacture and sale of radiopharmaceuticals are subject to future changes. Such changes may 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, a warning letter, recall or safety alert, if it occurred, could have a material adverse effect on our company. See Item 1A - “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, the FDA review processes could delay our Company's introduction of new products in the United States 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 Item 1A - “Risk Factors.”

The U.S. Drug Approval Process

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

preclinical laboratory tests, animal studies and formulation studies;

submission to the FDA of an IND application for human clinical testing, which must become effective before human clinical trials may begin;

adequate and well-controlled human clinical trials to establish the safety and efficacy of the investigational product for each indication;

submission to the FDA of a New Drug Application (“NDA”);

satisfactory completion of FDA inspections of the manufacturing and clinical facilities at which the drug is produced, tested, and/or distributed to assess compliance with cGMPs and current good clinical practices (“cGCP”) standards; and

FDA review and approval of the NDA.

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

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

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

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

Assuming successful completion of the required clinical testing, the results of the preclinical studies and of the clinical studies, together with other detailed information, including information on the manufacturing quality and composition of the investigational product, are submitted to the FDA in the form of an NDA requesting approval to market the product for one or more indications. The testing and approval process requires substantial time, effort and financial resources. Submission of an NDA requires payment of a substantial review user fee to the FDA. Before approving a NDA, the FDA usually will inspect the facility or the facilities where the product is manufactured, tested and distributed and will not approve the product unless cGMP compliance is satisfactory. If the FDA evaluates the NDA

and the manufacturing facilities as acceptable, the FDA may issue an approval letter or a complete response letter. A complete response letter outlines conditions that must be met in order to secure final approval of the NDA. When and if those conditions have been met to the FDA's satisfaction, the FDA will issue an approval letter. The approval letter authorizes commercial marketing of the drug for specific indications. As a condition of approval, the FDA may require post-marketing testing and surveillance to monitor the product's safety or efficacy, or impose other post-approval commitment conditions.

The 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. Our drug candidates may not qualify for any of these programs, or, if a drug candidate does qualify, the review time may not be reduced or the product may not be approved.

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

U.S. Post-Approval Requirements

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

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 United States, 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. A mutual recognition procedure is available at the request of the applicant for all medicinal products that are not subject to the centralized procedure.

The European Commission granted marketing authorization for Tc99m tilmanocept in the EU in November 2014, and a reduced-mass vial developed for the EU market was approved in September 2016.

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 any approval may not 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. Our potential drug or biologic products may not be approved by the regulatory bodies or may not be approved on a timely or accelerated basis, or any approvals received may 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 may not be able to obtain all necessary licenses and permits and we may not 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 4995 Bradenton Avenue, Suite 240, Dublin, OH 43017. Our telephone number is (614) 793-7500. "Navidea" and the Navidea logo are trademarks of Navidea Biopharmaceuticals, Inc. or its subsidiaries in the United States and/or other countries. Other trademarks or service marks appearing in this report may be trademarks or service marks of other owners.