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Navidea Biopharmaceuticals Submits Lymphoseek Marketing Authorization Application to European Medicines Agency

DUBLIN, Ohio--(BUSINESS WIRE)-- Navidea Biopharmaceuticals, Inc. (NYSE MKT: NAVB), a biopharmaceutical company focused on precision diagnostic radiopharmaceuticals, today announced that it has submitted a Marketing Authorization Application (MAA) for its investigational radiopharmaceutical Lymphoseek® (technetium Tc 99m tilmanocept) injection, a novel intraoperative lymphatic mapping (ILM) agent, to the European Medicines Agency (EMA).

“The submission of the Lymphoseek **MAA marks** a significant milestone for Navidea as we continue our global development and commercialization efforts for Lymphoseek. It is also important to note that, as part of the normal MAA filing process, the EMA required good manufacturing practices (GMP) pre-submission inspections at the Lymphoseek contract manufacturing facilities. These inspections were recently successfully completed by independent auditors from the European Union (EU), thereby enabling our MAA filing,” commented Dr. Mark Pykett, President and CEO of Navidea. “We are encouraged by these positive pre-submission manufacturing audits which we believe bode well for Lymphoseek’s ultimate commercialization. We are prepared to support the ongoing EMA approval process and to continue our pre-commercialization activities as we confidently anticipate U.S. approval of Lymphoseek in the coming months.”

Navidea is seeking marketing approval for Lymphoseek in the EU for use in ILM, a surgical oncology procedure in which lymph nodes draining the area around a tumor are identified and biopsied to determine if cancer has spread to the lymph nodes. The Lymphoseek MAA has proposed the use of the agent in general lymphatic mapping not restricted to any particular solid tumor type. According to the European Union’s FACT Public Health Programme Fighting Against Cancer, approximately 2.2 million new cases of solid tumor type cancers are expected to be diagnosed in the EU.[i]

Dr. Pykett added, “For patients and medical professionals, ILM is part of the standard of care in Europe for certain solid-tumor cancers, including breast cancer and melanoma and is actively being investigated in other cancer types such as head and neck cancer and prostate cancer. Lymphoseek is specifically designed to target key predictive lymph nodes through a receptor-based mechanism, which we believe may lead to enhanced diagnostic accuracy through rapid injection site clearance, stable target binding, lower false negative results, and better cancer staging of patients in ILM procedures while affording scheduling flexibility.”

About the Lymphoseek MAA Submission

The Marketing Authorization Application submission is supported by a comprehensive clinical program including the results from two Phase 3 studies of Lymphoseek, NEO3-05 and NEO3-09, performed in patients with either breast cancer or melanoma. The primary endpoint for both the NEO3-05 and NEO3-09 studies was the concordance (or the rate of agreement) on a lymph node count basis of Lymphoseek with vital blue dye. In both of the Phase 3 studies (NEO3-05, NEO3-09), the concordance of Lymphoseek to vital blue dye was highly statistically significant ($p<0.0001$).[ii] Lymphoseek met all primary and secondary endpoints across both studies. In addition, a meta-analysis and pooled-data comparison of results from Navidea's prospective Phase 3 clinical trials of Lymphoseek in patients with breast cancer and melanoma to European colloidal products was included in the MAA filing. The analysis evaluated the performance of Lymphoseek to a meta-analysis of historical, published data for 99m-Tc-labeled colloidal agents considered part of the standard of care in Europe. [iii]

In more than 500 subjects receiving Lymphoseek to date, including those studied as a part of the NEO3-05 and NEO3-09 studies, no drug-related serious adverse events or clinically significant drug-related adverse events have been reported.

U.S. regulatory status

Navidea is also seeking marketing approval of Lymphoseek in the United States. The U.S. Food and Drug Administration (FDA) has assigned the Lymphoseek New Drug Application (NDA) a Prescription Drug User Fee Act (PDUFA) goal date of April 30, 2013.

About Lymphoseek®

Lymphoseek® (technetium Tc 99m tilmanocept) Injection is a novel, receptor-targeted, small-molecule, investigational radiopharmaceutical used in lymphatic mapping procedures that are performed to help stage cancers such as 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.

Lymphatic mapping is a procedure in which lymph nodes that may contain tumor metastases are identified and biopsied to determine if cancer has spread beyond the primary tumor. Accurate staging of cancer is critical, as it guides therapy decisions and determines patient prognosis and risk of recurrence. According to the American Cancer Society, approximately 229,000 new cases of breast cancer and 76,000 new cases of melanoma are expected to be diagnosed in the United States in 2012.

About Lymphatic Mapping

Lymphatic mapping is a procedure designed to guide lymph node dissection and biopsy procedures. It consists of Intraoperative Lymphatic Mapping (ILM) often accompanied by lymphoscintigraphy. Lymphoscintigraphy is an imaging procedure routinely performed pre-operatively to provide guidance on the location of lymph nodes to be biopsied. ILM is a surgical procedure in which lymph nodes draining the area around a tumor are identified and biopsied to determine if cancer has spread to the lymph nodes. These nodes, commonly referred to as "Sentinel Lymph Nodes," are removed and analyzed for the presence of malignant cells. Lymphatic Mapping provides an accurate staging procedure that can help

ensure optimal surgical and therapeutic choices, including the avoidance of the morbidity of a complete lymph node dissection for patients in whom the Sentinel Lymph Nodes were found to be free of cancer.

About Navidea

Navidea Biopharmaceuticals, Inc. (NYSE MKT: NAVB) is a biopharmaceutical company focused on the development and commercialization of precision diagnostics and radiopharmaceutical agents. Navidea is actively developing four radiopharmaceutical agent platforms – Lymphoseek®, NAV4694, NAV5001 and RIGScan™ – to help identify the sites and pathways of undetected disease and enable better diagnostic accuracy, clinical decision-making and, ultimately, patient care. Navidea's strategy is to deliver superior growth and shareholder return by bringing to market novel radiopharmaceutical agents and advancing the Company's pipeline through selective acquisitions, global partnering and commercialization efforts. For more information, please visit www.navidea.com.

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 news release, 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, and 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 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, regulatory risks and other risks detailed in the Company's most recent Annual Report on Form 10-K and other Securities and Exchange Commission filings. The Company undertakes no obligation to publicly update or revise any forward-looking statements.

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[i] Coleman, MP, Alexe, DM, Albreht, T, McKee, M, eds. *Responding to the Challenge of Cancer in Europe*. Ljubljana, Slovenia: Institute of Public Health of the Republic of Slovenia, 2008. Project FACT – Fighting Against Cancer Today, funded by the European Union's Public Health Programme.

[ii] Sondak, VK, King, DW, Zager, JS, et al.Combined Analysis of Phase III Trials Evaluating [99mTc]Tilmanocept and Vital Blue Dye for Identification of Sentinel Lymph Nodes in Clinically Node-Negative Cutaneous Melanoma*, Ann Surg Oncog.* [DOI 10.1245/s10434-012-2612-z].

[iii] Tokin, CA, Cope, FO, Metz, WL, et al. 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, *Clinical and Experimental Metastasis.* October 2012, Volume 29, Issue 7, pp681-686. [DOI 10.1007/s10585-012-9497-x].

Navidea Biopharmaceuticals, Inc.
Brent Larson, 614-822-2330
Sr. VP & CFO

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