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# Lymphoseek® Results from Phase 3 Clinical Trial in Oral Cavity Cancer of the Head and Neck Published in *Annals of Surgical Oncology*

*– Lymphoseek Successful in Sentinel Lymph Node Identification Compared With Pathology Gold Standard –*

DUBLIN, Ohio--(BUSINESS WIRE)-- Navidea Biopharmaceuticals, Inc. (NYSE MKT:NAV), today announced the peer-reviewed publication of results from a Phase 3 clinical trial of Lymphoseek® (technetium 99m tilmanocept) injection in patients with certain head and neck cancer (squamous cell carcinoma of the oral cavity, NEO3-06; NCT00911326) in the journal *Annals of Surgical Oncology*. The trial assessed the performance of Lymphoseek-guided sentinel node biopsy against the standard of care, nodal pathology, in planned elective neck dissection (END). Results demonstrated that Lymphoseek met the primary efficacy endpoint of accurately identifying sentinel lymph nodes (SLNs) in subjects with node-negative squamous cell carcinoma of the oral cavity, as compared to the removal of all lymph nodes during multiple level nodal dissection surgery of the head and neck. Pathology assessment of lymph nodes from the multiple level nodal dissection surgery is considered the “gold standard” to determine the presence and extent of cancer spread.

"For many patients with head and neck cancer, especially oral tumors, the current standard of care involves removal and pathological examination of up to several dozen lymph nodes via formal open neck dissection in order to determine whether cancer has spread to the lymphatic system. This procedure, however, is quite invasive and carries potential for significant morbidity," said Amit Agrawal, M.D., an oncologic head and neck surgeon with The Ohio State University Comprehensive Cancer Center -- Arthur G. James Cancer Hospital and Richard J. Solove Research Institute in Columbus, Ohio. "Used in conjunction with sentinel node biopsy, targeted lymphatic mapping agents like tilmanocept may facilitate the diagnostic evaluation of these patients by determining whether lymphatic metastases has occurred, and thus afford more limited lymph node surgery in those patients whose sentinel nodes prove negative for cancer spread."

The study, "[<sup>99m</sup>TcTilmanocept Accurately Detects Sentinel Lymph Nodes and Predicts Pathology Status in Patients with Oral Squamous Cell Carcinoma of the Head and Neck: Results of a Phase III Multi-Institutional Trial](#)" was published as an *Online First* article in the journal *Annals of Surgical Oncology* [DOI 10.1245/s10434-015-4382-x]. Data from this study were previously presented in part at the 2013 Society of Nuclear Medicine and Molecular Imaging Annual Meeting (Vancouver, British Columbia), at the 2013 American College of Surgeons Clinical Congress (Washington, DC), and at the 6th European Congress on Head and Neck Oncology-2014, (Liverpool, UK).

“Lymphoseek-guided pre- and intraoperative SLN detection can considerably reduce the number of subjects with oral cancer that require neck dissection, thus leading to a substantial reduction in surgical trauma with potential subsequent morbidity. Lymphoseek was specifically designed to provide clinicians reliable and accurate location of sentinel lymph nodes to aid effective cancer staging and inform post-surgical treatment. Thus, thousands of patients with oral cavity cancers may benefit from a less invasive procedure with accurate diagnostic evaluation of their condition,” said Michael Tomblyn, M.D., Navidea’s Executive Medical Director. “We are pleased that the published results from our NEO3-06 Phase 3 clinical trial demonstrating its utility and safety in identifying SLNs are now available to the patient and medical community.”

Lymphoseek is a receptor-targeted imaging agent that was approved by the U.S. Food and Drug Administration (FDA) for guiding sentinel lymph node biopsy in patients with clinically node negative breast cancer, melanoma and squamous cell carcinoma of the oral cavity as well as for lymphatic mapping in patients with solid tumors for which this procedure is a component of intraoperative management. In these procedures, key lymph nodes adjacent to a primary tumor, that may contain tumor metastases, are identified and biopsied to determine if cancer has spread to these lymph nodes.

### **Phase 3 NEO3-06 Lymphoseek Clinical Trial Results**

Navidea’s Phase 3 clinical trial (NEO3-06) was a prospective, open-label, multicenter, within-patient study of Lymphoseek<sup>®</sup> (technetium Tc 99m tilmanocept) injection. It was designed to identify sentinel lymph nodes (SLNs) and determine the false-negative rate (FNR) associated with Lymphoseek-identified SLNs relative to the pathology status of lymph nodes of the neck in patients with clinically node-negative intraoral squamous cell carcinoma. The primary endpoint for the NEO3-06 trial was based on the number of subjects with pathology-positive lymph nodes (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. Of the more than 80 subjects enrolled in the NEO3-06 trial, 39 subjects were determined to have pathology-positive lymph nodes during surgery. Results demonstrated that Lymphoseek-guided sentinel node biopsy correctly identified 38 of these 39 subjects, for an overall FNR of 2.56%. This was statistically significant ( $p=0.0205$ ) against the pre-specified statistical threshold for success. These findings indicate that Lymphoseek accurately identified SLNs in these trial subjects, and is likely to be predictive of overall node pathology status of the neck. FNR is the rate of occurrence of negative test results in subjects known to have the disease for which the individual is being tested. Moreover, multiple level nodal dissection of patients in the trial led to an average removal of 38 lymph nodes per patient, whereas Lymphoseek-guided sentinel node biopsy on average led to the removal of approximately 4 lymph nodes, representing a reduction in potential morbidity for patients with SCC undergoing guided sentinel lymph node biopsy.

Secondary endpoints for the NEO3-06 trial included the determination of negative predictive value (NPV), overall accuracy of Lymphoseek relative to the pathology status of non-SLNs, and detection rate of SLNs by Lymphoseek. Lymphoseek demonstrated a NPV of 97.78% and overall accuracy of 98.80%, with an overall detection rate of SLNs in 97.6% of subjects. In this study, Lymphoseek performed similarly in its ability to detect SLNs between same-day or subsequent-day injection and surgery, and between anatomic tumor locations including floor-of-mouth tumors.

## **About Lymphoseek**

Lymphoseek<sup>®</sup> (technetium Tc 99m tilmanocept) injection is the first and only FDA-approved receptor-targeted lymphatic mapping agent. It is a novel, receptor-targeted, small-molecule radiopharmaceutical used in the evaluation of lymphatic basins that may have cancer involvement in patients. Lymphoseek is designed for the precise identification of lymph nodes that drain from a primary tumor, which have the highest probability of harboring cancer. Lymphoseek is approved by the U.S. Food and Drug Administration (FDA) for use in solid tumor cancers where lymphatic mapping is a component of surgical management and for guiding sentinel lymph node biopsy in patients with clinically node negative breast cancer, melanoma or squamous cell carcinoma of the oral cavity. Lymphoseek has also received European approval in imaging and intraoperative detection of sentinel lymph nodes in patients with melanoma, breast cancer or localized squamous cell carcinoma of the oral cavity.

Accurate diagnostic evaluation of cancer is critical, as it guides therapy decisions and determines patient prognosis and risk of recurrence. Overall in the U.S., solid tumor cancers may represent up to 1.2 million cases per year. The sentinel node label in the U.S. and Europe may address approximately 235,000 new cases of breast cancer, 76,000 new cases of melanoma and 45,000 new cases of head and neck/oral cancer in the U.S., and approximately 367,000 new cases of breast cancer, 83,000 new cases of melanoma and 55,000 new cases of head and neck/oral cancer diagnosed in Europe annually.

## **Lymphoseek Indication and Important Safety Information**

Lymphoseek is a radioactive diagnostic agent indicated with or without scintigraphic imaging for:

- Lymphatic mapping using a handheld gamma counter to locate lymph nodes draining a primary tumor site in patients with solid tumors for which this procedure is a component of intraoperative management.
- Guiding sentinel lymph node biopsy using a handheld gamma counter in patients with clinically node negative squamous cell carcinoma of the oral cavity, breast cancer or melanoma.

## **Important Safety Information**

In clinical trials with Lymphoseek, no serious hypersensitivity reactions were reported, however Lymphoseek may pose a risk of such reactions due to its chemical similarity to dextran. Serious hypersensitivity reactions have been associated with dextran and modified forms of dextran (such as iron dextran drugs).

Prior to the administration of Lymphoseek, patients should be asked about previous hypersensitivity reactions to drugs, in particular dextran and modified forms of dextran. Resuscitation equipment and trained personnel should be available at the time of Lymphoseek administration, and patients observed for signs or symptoms of hypersensitivity following injection.

Any radiation-emitting product may increase the risk for cancer. Adhere to dose recommendations and ensure safe handling to minimize the risk for excessive radiation

exposure to patients or health care workers.

In clinical trials, no patients experienced serious adverse reactions and the most common adverse reactions were injection site irritation and/or pain (<1%).

FULL LYMPHOSEEK PRESCRIBING INFORMATION CAN BE FOUND AT:  
[WWW.LYMPHOSEEK.COM](http://WWW.LYMPHOSEEK.COM)

### **About Navidea Biopharmaceuticals Inc.**

Navidea Biopharmaceuticals, Inc. (NYSE MKT:NAV) is a biopharmaceutical company focused on the development and commercialization of precision diagnostics, therapeutics and radiopharmaceutical agents. Navidea is developing multiple precision-targeted products and platforms including Manocept™, NAV4694, and NAV5001, to help identify the sites and pathways of undetected disease and enable better diagnostic accuracy, clinical decision-making, targeted treatment and, ultimately, patient care. Lymphoseek® (technetium Tc 99m tilmanocept) injection, Navidea's first commercial product from the Manocept platform, was approved by the FDA in March 2013 and by the EMA in November 2014. 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](http://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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