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RESEARCH**

APPLICATION NUMBER:

202207Orig1s000

MEDICAL REVIEW(S)

Division of Medical Imaging Products

Clinical Review Memorandum

NDA: 202207
Date Submitted: 10/30/2012, 11/28/2012
Sequence No: 0035 (SD 38), 0039 (SD 42)
Product: Lymphoseek
Applicant: Navidea Biopharmaceutical
Reviewer: Brenda Ye, M.D.

Regulatory Background

Navidea Biopharmaceutical resubmitted a New Drug Application (NDA) for Lymphoseek on 10/30/2012 to address deficiencies identified in facility inspections. Navidea further amended the submission on 11/28/2012 with a Clinical Safety Update. This review focuses on the Clinical Safety Update.

Review of Submission

There is one ongoing clinical trial of Lymphoseek – Study NEO3-06 in head and neck squamous cell carcinoma (HNSCC). Navidea has submitted safety updates from this ongoing NEO3-06 trial to the NDA 202207 at 120-day increments after submission of the original NDA:

- 120-day update (N=525 patients) on 12/8/2011 (Sequence 0009)
- 240-day update (N=531) on 3/22/2012 (Sequence 0018)
- 360-day update (N=542) on 7/26/2012 (Sequence 0026)
- 480-day update (N=551) on 11/28/2012 (Sequence 0039)

Since the 360-day update, nine additional NEO3-06 patients haven been injected with Lymphoseek (N=551). There has been no significant change in the overall safety profile of Lymphoseek.

Assessment and Plan

No significant changes in the product's safety profile.

With the Compliance issues (manufacturing facilities' inspections) having been resolved, this reviewer recommends approving the NDA 202207 for Lymphoseek as a radioactive diagnostic agent indicated for lymphatic mapping with a hand-held gamma counter to assist in the localization of lymph nodes draining a primary tumor site in patients with breast cancer or melanoma. Clinically relevant labeling issues have been all addressed during the previous review cycle.

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/s/

BRENDA Q YE
02/25/2013

ALEXANDER GOROVETS
02/26/2013

Clinical/Cross-Disciplinary Team Leader concurs with the recommendations of the clinical reviewer and acknowledges the resolution of the facilities inspection deficiencies as out lined in the CMC review.

Summary Review for Regulatory Action

Date	February 27, 2013
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	202207
Applicant Name	Navidea Biopharmaceuticals, Inc.
Date of Submission	Second cycle submission on 10/31/2012 First cycle submission on 08/10/2011
PDUFA Goal Date	April 30, 2013
Proprietary Name / Established (USAN) Name	Lymphoseek/technetium Tc 99m tilmanocept
Dosage Forms / Strength	A solution prepared in the nuclear pharmacy from the Kit for preparation of Lymphoseek/the dose is 50 mcg containing 92.5 MBq (b) (4) administered according to the planned lymphatic mapping technique (intradermal, subcutaneous or peritumoral); the volume injected varies with the mapping technique as described in the proposed labeling.
Proposed Indication(s)	(b) (4)
Action/Recommended Action:	Complete Response due to facility/manufacturing deficiencies

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Brenda Ye, MD
Statistical Review	& Jyoti Zalkikar, PhD
Pharmacology Toxicology Review	Olayinka Dina, PhD
CMC Review/OBP Review	Ravindra Kasliwal, PhD
Microbiology Review	John Metcalfe, PhD
Clinical Pharmacology Review	Christy John, PhD & Y. Gene Williams, PhD (TL)
DDMAC/DPP	James Dvorsky
DSI	Jong Hoon Lee, MD
CDTL Review	Alex Gorovets, MD
OSE/DMEPA	Jibril Abdus-Samad, PharmD & Todd Bridges, PharmD (TL)
Pediatric and Maternal Health	Jeanine Best, MSN and Upasana Bhatnagar, MD
Project Manager	Alberta Davis-Warren

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication renamed as DPP, Division of Professional Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
TL = Team Leader
CMC = chemistry, manufacturing and controls

1. Introduction:

This is a second cycle review for Lymphoseek, a diagnostic radiopharmaceutical. The first cycle review was completed with resolution of all issues except for facility inspectional items. Labeling and all clinical/statistical/clinical pharmacology/nonclinical toxicology matters were resolved during the first cycle. During this second cycle, the facility inspectional issues were resolved and the drug is now recommended for approval.

For ease of review within a single document, here I am largely reiterating comments from my original review. The only update pertains to the chemistry, manufacturing and control (CMC) section; here I cite the resolved facility inspection issues. The review team is also recommending that a pending Citizen's Petition (CP) be addressed prior to or at the time of the approval. The team has completed a consult pertaining to this CP, and the team has explicitly stated that the Lymphoseek approval is unrelated to the CP concern. Specifically, the CP expressed concern that FDA not approve drugs for sentinel lymph node detection unless certain criteria were met. Lymphoseek is not indicated for sentinel lymph node detection; hence, the CP concern does not apply to Lymphoseek.

Lymphoseek was shown in clinical studies to be useful in the intraoperative identification of lymph nodes among patients with breast cancer or melanoma. Lymphoseek contains radioactive technetium complexed with tilmanocept, a mannosylated dextran molecule. The mannose components are thought to facilitate binding to mannose receptors on macrophages and dendritic cells within lymph nodes. Following injection of Lymphoseek, a surgeon uses a gamma probe to detect the radioactive signal that identifies a Lymphoseek-tagged lymph node.

The applicant performed two phase 3 clinical studies that achieved the primary endpoints and secondary endpoints. The clinical and statistical staff verified that the applicant supplied sufficient evidence of Lymphoseek clinical safety and efficacy. Lymphoseek was shown in clinical studies to successfully localize to lymph nodes in a manner that facilitated surgical identification of the nodes.

Lymphoseek is to be supplied as a kit which contains five "powder" vials and five "diluent" vials. A kit contains sufficient drug to nominally expose ^(b)₍₄₎ patients and, because the diluent contains a preservative, one reconstituted vial may supply doses for up to ^(b)₍₄₎ patients. Lymphoseek is relatively complicated to reconstitute because the mass dose, reconstitution vial volume and the ultimate volume to be injected into a patient with a syringe(s) need to be considered during the drug's preparation.

Considerable review effort was expended in refining the prescribing information to clearly describe the reconstitution directions.

2. Background:

The localization of lymph nodes has assumed an important role in the surgical care of patients with melanoma and breast cancer because removal of lymph nodes can help assess the extent of metastatic disease. Importantly, the sponsor's proposed indication related to the relatively non-specific localization of lymph nodes; not the more specific indication for "sentinel lymph node detection." The Lymphoseek application signaled the important difference between the non-specific structural-type indication the company was seeking (lymph node localization) in contrast to the more specific indication of sentinel lymph localization. Both indications are clinically important but have different clinical implications.

- The non-specific lymph node localization indication sought by Navidea is in line with use of the drug by surgeons who are attempting to ensure they have identified all lymph nodes draining a melanoma or breast cancer to use this information in a manner that may alter the surgical resection procedure.
- The more specific sentinel lymph node indication (which the sponsor was not seeking) relates to the identification of the "first" lymph node(s) draining a primary cancer such that the absence of cancer within this "first" lymph node may negate the need for excision of other lymph nodes.

These are important indication/usage distinctions and the sponsor's proposed labeling makes no claims relevant to the use of the drug in sentinel lymph node detection. Currently, two drugs are approved for use in lymph node mapping, isosulfan blue and sulfur colloid. Isosulfan blue is also sometimes referred to as a "vital blue dye" or "blue dye."

The applicant's clinical development program was typical for lymph node mapping agents in that two phase 3 clinical studies examined the extent to which Lymphoseek and another tracer ("blue dye") were detected within lymph nodes excised from patients who were undergoing surgical procedures aimed at complete lymph node excision (based on palpation, visual examination or detection of the tracer within nodes).

A pre-NDA meeting was held in which the applicant described the success of the phase 3 clinical studies and their plan to seek a lymph node mapping indication. The applicant currently has an on-going phase 3 study (b) (4)

3. Chemistry, Manufacturing and Controls:

The Chemistry review was performed mainly by Dr. Ravindra Kasliwal who reviewed the applicant's supplied manufacturing information as well as the information contained

within several referenced drug master files. Based upon information supplied in this second cycle submission, Dr. Kasliwal confirms that all manufacturing issues have been resolved. Facility inspectional issues have also been resolved. Dr. Kasliwal has not identified a need for post-marketing studies.

I concur with Dr. Kasliwal's observations and conclusion.

4. Nonclinical Pharmacology/Toxicology:

I concur with the conclusions reached by the Dr. Olayinka Dina who found the supplied nonclinical pharmacology/toxicology data supportive of the drug's approval. In vitro binding assays showed the drug product bound specifically to mannose binding receptors on the surface of human macrophages. Safety pharmacology studies in beagle dogs showed that intravenous doses of the drug caused no toxicity even at doses substantially in excess of those proposed for clinical use (564-fold higher). Pharmacokinetic studies of subcutaneous dosing in dogs, rabbits and rats showed rapid systemic absorption of the drug (into the blood within 4 minutes of injection) from the injection site with predominant excretion of the drug via urine. Lymph node localization of the drug was identified in the popliteal node ipsilateral to a subcutaneous injection site; localization was not detected in the contralateral popliteal node.

Single dose toxicology studies in rats, rabbits and dogs as well as repeat dose toxicology studies in rats and dogs all showed no toxicity (with the no adverse effect level cited as the maximum administered dose). Genetic toxicology studies were negative in the in vitro bacterial reverse mutation, in vitro mouse lymphoma and in vivo bone marrow micronucleus assays. Carcinogenicity studies were not performed and the sponsor submitted a waiver for reproductive and developmental toxicology studies. The waiver was granted, as shown in Dr. Paul Brown's supervisory memorandum.

Local irritation studies in rabbits showed the drug produced no injection site histopathology; no specific toxicology studies were performed for impurities due to the known tolerability nature of the impurities (b)(4) and their low concentrations.

5. Clinical Pharmacology/Biopharmaceutics:

I have read the review performed by Dr. Christy John and I concur with his recommendations to approve the "same day" surgery dose of Lymphoseek (b)(4)

Dr. John described the proposed Lymphoseek dose as a "micro-dose" with low systemic exposure. He noted that immunogenicity tests were not performed but he did not regard

immunogenicity as a concern (Lymphatic mapping is likely to be rarely, if ever, performed more than one time in a patient).

Dr. John further noted that in dose-ranging clinical studies, injection site clearance rates were similar across all Lymphoseek doses (4 to 200 mcg) with a mean elimination rate constant in the range of 0.222 to 0.396/hr , resulting in a drug half-life at the injection site of 1.75 to 3.05 hours. The amount of the accumulated radioactive dose in the liver, kidney, and bladder reached a maximum 1 hour post administration of Lymphoseek and was approximately 1% to 2% injected dose in each tissue.

6. Clinical Microbiology:

Dr. John Metcalfe completed the review of the applicant’s microbiology-related information; he detected no deficiencies and I concur with his findings. No post-marketing studies were proposed.

7. Clinical/Statistical-Efficacy:

Dr. Brenda Ye performed the primary clinical review and Dr. Alex Gorovets performed the Cross Discipline Team Leader review. Dr. Satish Misra performed the statistical review. I have read the reviews and concur with the findings.

The applicant performed two phase 3 clinical studies that succeeded upon their study objectives and verified the ability of Lymphoseek to provide clinically useful information. In both phase 3 studies, patients with breast cancer or melanoma had injection of Lymphoseek and blue dye (“tracers”). Subsequently, surgeons performed intraoperative lymph node resection, removing all visible, palpable or tracer-identified lymph nodes. Both phase 3 studies achieved the primary endpoints of showing “concordance” with blue dye.

Perhaps the most notable finding from Dr. Misra and Ye’s review was that the clinical data were

(b) (4)



The following comments are an excerpt from the proposed labeling that succinctly summarizes the ability of Lymphoseek to tag lymph nodes and allows a comparison to the blue dye tracer.

Lymphoseek safety and efficacy were assessed in two open-label, multicenter, single arm, within-subject active comparator trials of patients with melanoma or breast cancer. Prior to the nodal mapping procedure, the patients had no nodal or metastatic disease by

standard tumor staging criteria. Diagnostic efficacy was determined by the number of histology-confirmed lymph nodes detected by Lymphoseek. Lymphoseek (50 mcg; 0.5) was injected into patients at least 15 minutes prior to the scheduled surgery, and blue dye was injected shortly prior to initiation of the surgery. Intraoperative lymphatic mapping was performed using a handheld gamma detection probe followed by excision of lymph nodes identified by Lymphoseek, blue dye or the surgeon’s visual and palpation examination. The resected lymph nodes were sent for histopathology evaluation.

In Study One, of 179 patients who received Lymphoseek, 94 (53%) had known or suspected breast cancer and 85 (48%) had known or suspected melanoma. The median age was 59 years (range 20 to 90 years) and most (72%) were women.

In Study Two, of 153 patients who received Lymphoseek, 77 (50%) had known or suspected breast cancer and 76 (50%) had known or suspected melanoma. The median age was 61 years (range 26 to 88 years) and most (68%) were women.

Approximately 94% of patients from the two studies underwent preoperative lymphoscintigraphy to help identify nodal basins and to facilitate intraoperative identification of lymph nodes. (b) (4)

Efficacy analyses were based upon comparisons of the number and proportion of resected lymph nodes that contained a lymph node tracer (Lymphoseek and/or blue dye) or neither tracer. Evaluable lymph nodes were resected from 138 Study One patients and 150 Study Two patients who received Lymphoseek at the dose of 0.5 mCi in 50 mcg administered 15 minutes to 15 hours prior to surgery. Table 9 shows the distribution of resected lymph nodes by the presence or absence of a tracer. Most of the resected lymph nodes were identified by either Lymphoseek (LS) or blue dye (BD) or both.

Table 1. Resected Lymph Nodes and Content of Lymphoseek (LS) and/or Blue Dye (BD)

Study	T	Nodes n	BD Present n (%); 95% CI	LS Present n (%); 95% CI	Only BD Present, n (%); 95% CI	Only LS Present, n (%); 95% CI	Neither BD nor LS Present, n (%); 95% CI
One	M	155	99 (64%) (56 - 71%)	145 (94%) (89 - 97%)	1 (1%) (0 - 4%)	47 (30%) (23 - 38%)	9 (6%) (3 - 11%)
	B	154	108 (70%) (62 - 77 %)	146 (95%) (90 - 98%)	7 (5%) (2 - 9%)	45 (29%) (22 - 37%)	1 (1%) (0 - 4%)
Two	M	196	115 (59%) (51 - 66%)	196 (100%) (98 - 100%)	0 (0 - 2%)	81 (41%) (34 - 49%)	0 (0 - 2%)
	B	180	112 (62%) (55 - 69%)	180 100%) (98 - 100%)	0 (0 - .2%)	68 (38%) (31- 45%)	0 (0 - 2%)

T = tumor; M = melanoma; B = breast cancer; The percents may not add to 100% due to rounding. 95% Confidence Intervals are based on Exact Binomial and represent the spread in the individual estimates.

8. Safety:

Based upon the exposure of 531 patients to Lymphoseek, the most notable safety findings pertain to the radiation risks implicit for radiopharmaceuticals as well as the *potential* for a hypersensitivity reaction (especially considering the dextran-nature of the Lymphoseek active moiety. Clinical studies identified only mild injection site pain/discomfort (in less than 1% of patients) as adverse reactions. No hypersensitivity reactions were detected.

Post-marketing Requirements (PMR): none

Post-marketing Commitments (PMC): none

9. Advisory Committee Meeting:

This application was not reviewed at an Advisory Committee because the clinical data presented no unique concerns and the nature of the proposed indication is similar to currently approved products. Advisory Consultation was not necessary due to the lack of any unsettled clinical or statistical matters. The main issues during the review pertained to manufacturing and facility information.

10. Pediatrics:

Based upon the proposed indication, Ms. Jeanine Best documented that the applicant has been granted a full waiver for pediatric studies under the PREA expectation because melanoma and breast cancer are considered “adult indications” such that clinical studies would be impossible or impracticable in the pediatric population.

11. Other Relevant Regulatory Issues:

Dr. Lee’s review documents no notable deficiencies from inspection of the clinical data obtained from clinical sites involved in the phase 3 studies. Five good clinical practice inspections were performed; four clinical sites and the sponsor site.

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/s/

RAFEL D RIEVES
02/27/2013

Office Director Decisional Memo for Regulatory Action

Date	September 7, 2012
From	Charles J. Ganley, MD
Subject	Office Director Summary Review
NDA/BLA #	202207
Applicant Name	Navidea Biopharmaceuticals, Inc.
Date of Submission	August 10, 2011
PDUFA Goal Date	September 10, 2012
Proprietary Name / Established (USAN) Name	Lymphoseek/technetium Tc 99m tilmanocept
Dosage Forms / Strength	A solution prepared in the nuclear pharmacy from the Kit for preparation of Lymphoseek/the dose is 50 mcg containing 92.5 MBq (b) (4) administered according to the planned lymphatic mapping technique (intradermal, subcutaneous or peritumoral); the volume injected varies with the mapping technique as described in the proposed labeling.
Proposed Indication(s)	(b) (4)
Action:	Complete Response due to facility/manufacturing deficiencies

Summary

Lymphoseek is a diagnostic radiopharmaceutical developed to assist in the localization of lymph nodes draining a primary tumor site in patients with breast cancer or melanoma. After pre-operative injection, the intra-operative localization of lymph nodes is performed by a handheld gamma detection probe. The sponsor conducted two phase 3 clinical studies in patients with a diagnosis of breast cancer or melanoma to support the effectiveness of the agent in detecting lymph nodes. The ability to detect lymph nodes was based on a relative comparison to currently approved products. Manufacturing related issues led to a three month extension of the review clock when the sponsor submitted additional manufacturing information. The application, however, cannot be approved at this time because the manufacturing issues have not been completely resolved.

A citizen petition was submitted by MSMB Capital Management LLC, a hedge fund investment firm, requesting that the application not be approved because they did not provide a sufficient database to obtain a sentinel node claim. MSMB was a short seller of Navidea¹ stock. This petition will be denied whenever the application is ready for approval. The sponsor in this application was not seeking a sentinel node indication and so it is not relevant to the current application.

Clinical Review

- There were two clinical studies (NE03-05 and NE03-09) conducted in patients with melanoma or breast cancer. Patients received an injection either on the day of surgery or the day before surgery. Both Lymphoseek and blue dye were injected in patients.

¹ Formerly named Neoprobe

- In study NE03-05, 195 patients were enrolled. Dr. Ye reports that, 475 lymph nodes were harvested from 176 patients. 38 patients underwent next day surgery after injection. These patients received 1 mCi of Lymphoseek 12 – 30 hours prior to surgery. The remainder of the patients received the injection (.5 mCi) on the same day, 15 minutes to 12 hours prior to surgery. There is insufficient data to support the injection of Lymphoseek the day prior to surgery.
- In study NE03-09, 163 patients enrolled. All but two patients received the injection on the same day as surgery (30 minutes – 15 hours prior). The patients who had “next day” surgery received a Lymphoseek dose of 2 mCi.
- The FDA analysis focused on the ability of Lymphoseek to identify lymph nodes (the truth standard was lymph node histology). Greater than 99% of the tissue samples identified by Lymphoseek were confirmed to be lymph nodes by histology in both studies (see table 5 and 6 in Dr. Ye’s clinical review).
- Of the lymph nodes that were blue dye positive, Dr. Ye reports that 3.6% and 0% (NE03-05 and NE03-09) were Lymphoseek negative. Lymphoseek was likely to detect the lymph nodes that were also detected by blue dye.
- Of the lymph nodes that were blue dye negative, Dr. Ye also notes that 24.7% and 37.5% (NE03-05 and NE03-09) were Lymphoseek positive. Lymphoseek was able to detect more lymph nodes than blue dye.
- There is no analysis of the number of lymph nodes identified as a function of time after injection. The analysis was a concordance analysis that compared Lymphoseek to blue dye. There was no difference in concordance. The clinical review team can determine whether more lymph nodes can be detected as a function of time after injection. Because the applicant is receiving a complete response there is no need to complete that analysis prior to the action letter. I am assuming that there will not be sufficient data to adequately assess this because the average number of lymph nodes per person is between 2 to 3.

Pediatric Waiver Request

A complete pediatric waiver is recommended.

Pharm Tox

- DTPA-mannosyl-dextran has specific binding interaction with mannose binding receptors expressed on the surface of human lymphocytic system derived macrophages with a high binding affinity.
- There are no pharm tox issues. Carcinogenicity and developmental and reproductive toxicity studies have not been conducted with Technetium TC 99m Tilmanocept.
- Genotoxicity studies were negative in the in vitro bacterial reverse mutation, in vitro L5178Y/TK+/- mouse lymphoma and in the in vivo bone micronucleus assays.
- Single dose and repeat dose toxicity studies in rats and dogs showed no evidence of toxicity.
- Antigenicity studies conducted in guinea pigs did not induce any anaphylactic reaction with doses up to 280 ug/kg.
- Two in vivo safety studies conducted in beagle dogs to evaluate the cardiovascular pharmacology effect showed no adverse effects.

CMC/Micro

- Lymphoseek is a macromolecule that consists of multiple units of diethylenetriaminepentaacetic acid (DTPA) and mannose attached to a dextran core. The DTPA chelates to Tc 99m and the mannose binds with receptors in the lymph nodes.
- The drug product is provided as a kit containing a sterile lyophilized preparation of Tilmanocept 0.25 mg and co-packaged with a sterile buffer saline diluent. Technetium Tc 99m obtained from a commercially available generator is added at the testing site.

- The drug product and diluent are manufactured by (b) (4). There are no microbiology deficiencies identified.
- The Kit for the preparation of Lymphoseek (technetium Tc99m tilmanocept) injection should be granted a 12 month expiration dating period. This date may be extended based on testing of the first three conformance batches at room temperature.
- The radiolabeled Lymphoseek (technetium Tc99m tilmanocept) injection should be granted a 6 hour expiration dating period.
- The sponsor makes the following commitments:
 - The applicant commits to provide a statistical analysis of the potency data (for Tilmanocept Powder vial) generated using the new method (SAM3404AR) to determine if the specification can be (b) (4) of the labeled amount. The evaluation and justification for the potency specification will be provided in the first annual report.
 - The applicant commits to test for stability the first three production conformance / validation batches according to the post approval stability protocol. Applicant also commits to test for stability not less than one batch produced during each subsequent year of manufacture according to the post approval stability protocol.
 - The applicant commits to providing the validation report by 31-Dec-2012 for the HPLC impurities method for tilmanocept bulk drug substance.
- Inspection of two of the contract manufacturers resulted in withhold recommendations and it the reason that a complete response letter will be issued. Both (b) (4), the manufacturer of the active pharmaceutical ingredient, and (b) (4), the manufacturer of the final finished dose preparation, had deficiencies during the inspection. I have reviewed the basis for the withhold recommendations made by the Division of Good Manufacturing Practice Assessment and agree with the recommendations. Specific deficiencies are not discussed in this memo because contract manufacturers are involved. The deficiencies have been discussed with the contract manufacturers by FDA.

Clinical Pharmacology

There are no outstanding clinical pharmacology issues.

Labeling

There are no outstanding labeling issues.

Recommendation

Complete Response

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/s/

CHARLES J GANLEY
09/07/2012

Division of Medical Imaging Products

Clinical Review Memorandum

NDA: 202207
Date Submitted: 08/10/2011
Product: Lymphoseek
Sponsor: Neoprobe Corp. (later acquired by Navidea Biopharmaceutical)
Reviewer: Brenda Ye, M.D.

Neoprobe Corp. submitted a New Drug Application (NDA) for Lymphoseek on Aug 10, 2011. This review addendum addresses expectations in ethics and Good Clinical Practices (GCP) of the NDA.

1. Compliance with Good Clinical Practices

The Applicant stated in the Clinical Study Reports of NEO3-05 and NE03-09, the two phase 3 clinical studies, that the studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirements. The protocol and the informed consent documents were approved by an IRB/IEC. Each patient signed and dated an informed consent document.

2. Financial Disclosures

In Lymphoseek's clinical development program, there are (b) (4) investigators who received "any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria": (b) (6)

Schedule of financial involvement:

Description	Amount	Date
(b) (6)	\$48,000.00	2005-2007
(b) (6)	\$54,000.00	2005-2007
(b) (6)	\$7,500.00	February 7, 2005
(b) (6)	\$10,000.00	February 23, 2005
(b) (6)	\$10,000.00	October 26, 2005
(b) (6)	\$20,000.00	September 14, 2007
(b) (6)	\$10,000.00	July 7, 2009
(b) (6)	\$4,414.10	March 27, 2010
(b) (6)	\$4,414.10	March 27, 2010



None of the disbursements were prospectively planned with regard to the clinical trials conducted at (b) (6) and other healthcare facilities under Neoprobe's sponsorship. The disbursements had no bearing on the outcome of any particular study conducted at

(b) (6)

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/s/

BRENDA Q YE
08/27/2012

ALEXANDER GOROVETS
08/27/2012

Summary Review for Regulatory Action

Date	August 26, 2012
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	202207
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1. Introduction:

Lymphoseek is a diagnostic radiopharmaceutical that was shown in clinical studies to be useful in the intraoperative identification of lymph nodes among patients with breast cancer or melanoma. Lymphoseek contains radioactive technetium complexed with tilmanocept, a mannosylated dextran molecule. The mannose components are thought to facilitate binding to mannose receptors on macrophages and dendritic cells within lymph nodes. Following injection of Lymphoseek, a surgeon uses a gamma probe to detect the radioactive signal that identifies a Lymphoseek-tagged lymph node.

I recommend a Complete Response letter issuance for this application due to the inability to verify that the applicant has sufficient control of the Lymphoseek manufacturing process, as evidenced by deficiencies noted on FDA inspection of contract manufacturing facilities. The chemistry reviewer (Dr. Kasliwal) has also identified some manufacturing information deficiencies and at the time of this review document generation, Dr. Kasliwal is completing his review of the applicant's recently submitted attempt at resolution of these manufacturing deficiencies. At a minimum, a Complete Response letter is anticipated to describe the facility deficiencies. Notably, the review clock was extended by a Major Amendment that followed the applicant's submission of additional manufacturing information.

Also at the time of this document generation, we have supplied the applicant with FDA edits upon the proposed labeling (both prescribing information and container labels). We are awaiting the applicant's response to these labeling proposals. If labeling concerns are not resolved then we anticipate that labeling deficiencies may also form a component of a Complete Response letter.

The applicant performed two phase 3 clinical studies that achieved the primary endpoints and secondary endpoints. The clinical and statistical staff verified that the applicant supplied sufficient evidence of Lymphoseek clinical safety and efficacy. Lymphoseek was shown in clinical studies to successfully localize to lymph nodes in a manner that facilitated surgical identification of the nodes.

Lymphoseek is to be supplied as a kit which contains five "powder" vials and five "diluent" vials. A kit contains sufficient drug to nominally expose (b) (4) patients and, because the diluent contains a preservative, one reconstituted vial may supply doses for up to (b) (4) patients. Lymphoseek is relatively complicated to reconstitute because the mass dose, reconstitution vial volume and the ultimate volume to be injected into a patient with a syringe(s) need to be considered during the drug's preparation.

Considerable review effort was expended in refining the prescribing information to clearly describe the reconstitution directions.

2. Background:

The localization of lymph nodes has assumed an important role in the surgical care of patients with melanoma and breast cancer because removal of lymph nodes can help assess the extent of metastatic disease. Importantly, the sponsor's proposed indication related to the relatively non-specific localization of lymph nodes; not the more specific indication for "sentinel lymph node detection." The Lymphoseek application signaled the important difference between the non-specific structural-type indication the company was seeking (lymph node localization) in contrast to the more specific indication of sentinel lymph localization. Both indications are clinically important but have different clinical implications.

- The non-specific lymph node localization indication sought by Navidea is in line with use of the drug by surgeons who are attempting to ensure they have identified all lymph nodes draining a melanoma or breast cancer to use this information in a manner that may alter the surgical resection procedure.
- The more specific sentinel lymph node indication (which the sponsor was not seeking) relates to the identification of the "first" lymph node(s) draining a primary cancer such that the absence of cancer within this "first" lymph node may negate the need for excision of other lymph nodes.

These are important indication/usage distinctions and the sponsor's proposed labeling makes no claims relevant to the use of the drug in sentinel lymph node detection. Currently, two drugs are approved for use in lymph node mapping, isosulfan blue and sulfur colloid. Isosulfan blue is also sometimes referred to as a "vital blue dye" or "blue dye."

The applicant's clinical development program was typical for lymph node mapping agents in that two phase 3 clinical studies examined the extent to which Lymphoseek and another tracer ("blue dye") were detected within lymph nodes excised from patients who were undergoing surgical procedures aimed at complete lymph node excision (based on palpation, visual examination or detection of the tracer within nodes).

A pre-NDA meeting was held in which the applicant described the success of the phase 3 clinical studies and their plan to seek a lymph node mapping indication. The applicant currently has an on-going phase 3 study (b) (4)

3. Chemistry, Manufacturing and Controls:

The Chemistry review was performed mainly by Dr. Ravindra Kasliwal who reviewed the applicant's supplied manufacturing information as well as the information contained

within several referenced drug master files. Dr. Kasliwal found the supplied manufacturing information was insufficient to support the approval and he listed several deficiencies within his review (such as the need for updated radiochemical purity specification and pH specifications); at the time of this summary document generation, Dr. Kasliwal is completing a review of the sponsor's very recently submitted response to his findings. Nonetheless, inspection of two of the contracted manufacturing facilities ((b) (4) —responsible for the active pharmaceutical ingredient; and (b) (4) —responsible for the final finished dose preparation) disclosed deficiencies that cannot be resolved during this review cycle and will necessitate a Complete Response letter to the applicant. A follow-up inspection of one of the manufacturing facilities (b) (4) is necessary to verify the firm's updated manufacturing procedures—the firm was not ready for re-inspection prior to the action due date; another manufacturing firm ((b) (4) is currently investigating why an unapproved manufacturing batch record appeared within a review of the firm's records. This investigation remains incomplete at the time of the action due date.

Dr. Kasliwal currently envisions the need for post-marketing studies once the applicant resolves the manufacturing/facility deficiencies. He cited a need for 12 month long term and six month accelerated stability studies; he also cited a need for the applicant to develop a method to quantitate (b) (4) in the drug product and to use this method as a drug release specification and also as a component of the stability program.

I concur with the reviewer's findings and note that the facility inspectional issues appear to represent the main unresolved deficiency. During the review period, Dr. Kasliwal provided the applicant notice of deficiencies and the applicant rushed to resolve these deficiencies, necessitating Dr. Kasliwal to continue reviewing information beyond the typical review document generation time line.

4. Nonclinical Pharmacology/Toxicology:

I concur with the conclusions reached by the Dr. Olayinka Dina who found the supplied nonclinical pharmacology/toxicology data supportive of the drug's approval. In vitro binding assays showed the drug product bound specifically to mannose binding receptors on the surface of human macrophages. Safety pharmacology studies in beagle dogs showed that intravenous doses of the drug caused no toxicity even at doses substantially in excess of those proposed for clinical use (564-fold higher). Pharmacokinetic studies of subcutaneous dosing in dogs, rabbits and rats showed rapid systemic absorption of the drug (into the blood within 4 minutes of injection) from the injection site with predominant excretion of the drug via urine. Lymph node localization of the drug was identified in the popliteal node ipsilateral to a subcutaneous injection site; localization was not detected in the contralateral popliteal node.

Single dose toxicology studies in rats, rabbits and dogs as well as repeat dose toxicology studies in rats and dogs all showed no toxicity (with the no adverse effect level cited as the maximum administered dose). Genetic toxicology studies were negative in the in vitro bacterial reverse mutation, in vitro mouse lymphoma and in vivo bone marrow

micronucleus assays. Carcinogenicity studies were not performed and the sponsor submitted a waiver for reproductive and developmental toxicology studies. The waiver was granted, as shown in Dr. Paul Brown's supervisory memorandum.

Local irritation studies in rabbits showed the drug produced no injection site histopathology; no specific toxicology studies were performed for impurities due to the known tolerability nature of the impurities (b) (4) and their low concentrations.

5. Clinical Pharmacology/Biopharmaceutics:

I have read the review performed by Dr. Christy John and I concur with his recommendations to approve the "same day" surgery dose of Lymphoseek (b) (4)

Dr. John described the proposed Lymphoseek dose as a "micro-dose" with low systemic exposure. He noted that immunogenicity tests were not performed but he did not regard immunogenicity as a concern (Lymphatic mapping is likely to be rarely, if ever, performed more than one time in a patient).

Dr. John further noted that in dose-ranging clinical studies, injection site clearance rates were similar across all Lymphoseek doses (4 to 200 mcg) with a mean elimination rate constant in the range of 0.222 to 0.396/hr, resulting in a drug half-life at the injection site of 1.75 to 3.05 hours. The amount of the accumulated radioactive dose in the liver, kidney, and bladder reached a maximum 1 hour post administration of Lymphoseek and was approximately 1% to 2% injected dose in each tissue.

6. Clinical Microbiology:

Dr. John Metcalfe completed the review of the applicant's microbiology-related information; he detected no deficiencies and I concur with his findings. No post-marketing studies were proposed.

7. Clinical/Statistical-Efficacy:

Dr. Brenda Ye performed the primary clinical review and Dr. Alex Gorovets performed the Cross Discipline Team Leader review. Dr. Satish Misra performed the statistical review. I have read the reviews and concur with the findings.

The applicant performed two phase 3 clinical studies that succeeded upon their study objectives and verified the ability of Lymphoseek to provide clinically useful information. In both phase 3 studies, patients with breast cancer or melanoma had injection of Lymphoseek and blue dye ("tracers"). Subsequently, surgeons performed

intraoperative lymph node resection, removing all visible, palpable or tracer-identified lymph nodes. Both phase 3 studies achieved the primary endpoints of showing “concordance” with blue dye.

Perhaps the most notable finding from Dr. Misra and Ye’s review was that the clinical data were (b) (4)

[REDACTED]

The following comments are an excerpt from the proposed labeling that succinctly summarizes the ability of Lymphoseek to tag lymph nodes and allows a comparison to the blue dye tracer.

Lymphoseek safety and efficacy were assessed in two open-label, multicenter, single arm, within-subject active comparator trials of patients with melanoma or breast cancer. Prior to the nodal mapping procedure, the patients had no nodal or metastatic disease by standard tumor staging criteria. Diagnostic efficacy was determined by the number of histology-confirmed lymph nodes detected by Lymphoseek. Lymphoseek (50 mcg; 0.5) was injected into patients at least 15 minutes prior to the scheduled surgery, and blue dye was injected shortly prior to initiation of the surgery. Intraoperative lymphatic mapping was performed using a handheld gamma detection probe followed by excision of lymph nodes identified by Lymphoseek, blue dye or the surgeon’s visual and palpation examination. The resected lymph nodes were sent for histopathology evaluation.

In Study One, of 179 patients who received Lymphoseek, 94 (53%) had known or suspected breast cancer and 85 (48%) had known or suspected melanoma. The median age was 59 years (range 20 to 90 years) and most (72%) were women.

In Study Two, of 153 patients who received Lymphoseek, 77 (50%) had known or suspected breast cancer and 76 (50%) had known or suspected melanoma. The median age was 61 years (range 26 to 88 years) and most (68%) were women.

Approximately 94% of patients from the two studies underwent preoperative lymphoscintigraphy to help identify nodal basins and to facilitate intraoperative identification of lymph nodes. (b) (4)

[REDACTED]

Efficacy analyses were based upon comparisons of the number and proportion of resected lymph nodes that contained a lymph node tracer (Lymphoseek and/or blue dye) or neither tracer. Evaluable lymph nodes were resected from 138 Study One patients and 150 Study Two patients who received Lymphoseek at the dose of 0.5 mCi in 50 mcg administered 15 minutes to 15 hours prior to surgery. Table 9 shows the distribution of resected lymph

nodes by the presence or absence of a tracer. Most of the resected lymph nodes were identified by either Lymphoseek (LS) or blue dye (BD) or both.

Table 1. Resected Lymph Nodes and Content of Lymphoseek (LS) and/or Blue Dye (BD)

Study	T	Nodes n	BD Present n (%); 95% CI	LS Present n (%); 95% CI	Only BD Present, n (%); 95% CI	Only LS Present, n (%); 95% CI	Neither BD nor LS Present, n (%); 95% CI
One	M	155	99 (64%) (56 - 71%)	145 (94%) (89 - 97%)	1 (1%) (0 - 4%)	47 (30%) (23 - 38%)	9 (6%) (3 - 11%)
	B	154	108 (70%) (62 - 77 %)	146 (95%) (90 - 98%)	7 (5%) (2 - 9%)	45 (29%) (22 - 37%)	1 (1%) (0 - 4%)
Two	M	196	115 (59%) (51 - 66%)	196 (100%) (98 - 100%)	0 (0 - 2%)	81 (41%) (34 - 49%)	0 (0 - 2%)
	B	180	112 (62%) (55 - 69%)	180 100%) (98 - 100%)	0 (0 - .2%)	68 (38%) (31- 45%)	0 (0 - 2%)

T = tumor; M = melanoma; B = breast cancer; The percents may not add to 100% due to rounding. 95% Confidence Intervals are based on Exact Binomial and represent the spread in the individual estimates.

8. Safety:

Based upon the exposure of 531 patients to Lymphoseek, the most notable safety findings pertain to the radiation risks implicit for radiopharmaceuticals as well as the *potential* for a hypersensitivity reaction (especially considering the dextran-nature of the Lymphoseek active moiety. Clinical studies identified only mild injection site pain/discomfort (in less than 1% of patients) as adverse reactions. No hypersensitivity reactions were detected.

Post-marketing Requirements (PMR): none identified in this review cycle.

Post-marketing Commitments (PMC):

As noted above, Dr. Kasliwal envisions a need for certain manufacturing post-marketing commitments. Conceivably, the sponsor may resolve these concerns following issuance of a Complete Response letter.

9. Advisory Committee Meeting:

This application was not reviewed at an Advisory Committee because the clinical data presented no unique concerns and the nature of the proposed indication is similar to

currently approved products. Advisory Consultation was not necessary due to the lack of any unsettled clinical or statistical matters. The main issues during the review pertained to manufacturing and facility information.

10. Pediatrics:

Based upon the proposed indication, Ms. Jeanine Best documented that the applicant has been granted a full waiver for pediatric studies under the PREA expectation because melanoma and breast cancer are considered “adult indications” such that clinical studies would be impossible or impracticable in the pediatric population.

11. Other Relevant Regulatory Issues:

Dr. Lee’s review documents no notable deficiencies from inspection of the clinical data obtained from clinical sites involved in the phase 3 studies. Five good clinical practice inspections were performed; four clinical sites and the sponsor site.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAFEL D RIEVES
08/25/2012

CLINICAL REVIEW

Application Type	New Drug Application 505(b)(1)
Application Number(s)	NDA 202207
Priority or Standard	Standard
Submit Date(s)	8/10/2011 (Major Amendments: 10/6/2011, 10/21/2011, 11/4/2011, 1/19/2012, 2/2/2012, 3/22/2012, 3/30/2012)
Received Date(s)	8/10/2011 (Major Amendments: 10/6/2011, 10/21/2011, 11/4/2011, 1/19/2012, 2/2/2012, 3/22/2012, 3/30/2012)
PDUFA Goal Date	6/10/2012 (Extended to 9/10/2012 due to a major amendment submitted on 3/30/2012)
Reviewer Name(s)	Brenda Ye, MD
Review Completion Date	7/16/2012
Established Name	Tilmanocept (DTPA mannosyl dextran)
(Proposed) Trade Name	Lymphoseek: Kit for the Preparation of Technetium Tc99m Tilmanocept for Injection
Therapeutic Class	Class 1 Diagnostic Radiopharmaceutical
Applicant	Neoprobe Corporation (changed to

Navidea Biopharmaceuticals, Inc.
on January 12, 2012)

Formulation(s) Powder for Injection
Dosing Regimen Administer 18.5 MBq (0.5 mCi) of Lymphoseek within 15 hours of scheduled time of the surgery and intraoperative detection.

Administer by intradermal or subareolar injection, based on cancer type.

Indication(s) Lymphoseek[®] is a radioactive diagnostic agent used in the  localization of lymph nodes in patients with breast cancer or melanoma.

Intended Population(s) Patients with breast cancer or melanoma

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

- 1) Recommend approval of the NDA from clinical perspective
- 2) Recommend granting the pediatric waiver request based on the modified proposed indications (for use in patients with breast cancer or melanoma patients)

Multiple CMC deficiencies were identified by the review team (please see CMC review for further detail). At the time of completion of this primary clinical review, CMC review is still ongoing and some CMC deficiencies remain unresolved.

1.2 Risk Benefit Assessment

The benefit-risk assessment in Section 1.2 is represented by the clinical review team's conclusions drawn within each of five key decision factors: analysis of condition, unmet medical need, clinical benefit, risk, and risk management.

1.2.1 Analysis of Condition

Intraoperative lymphatic mapping (ILM) is a standard surgical practice for staging of certain types of tumors, including breast cancer and melanoma, which were studied in this NDA. Staging is crucial for treatment decisions & prognostic assessments of these cancers. The use of ILM may reduce the need for more invasive procedures, such as axillary lymph node dissection in breast cancer patients.

1.2.2 Unmet Medical Need

It is becoming a standard practice for surgeons to use a radiopharmaceutical agent in combination with a blue dye (Lymphazurin) for ILM procedures. Although several radiopharmaceutical agents are currently used, only one is approved for this indication, and only for breast cancer [REDACTED] (b) (4). The availability of another radiopharmaceutical agent indicated for the delineation of lymph nodes through ILM would be beneficial by enhancing availability of a diagnostic agent but is not critical.

(b) (4)

1.2.3 Clinical Benefit

The FDA review team conducted an independent analysis on the data, with histopathology as the standard of truth. In both phase 3 trials, Lymphoseek is highly proficient in the identification of lymph nodes draining a primary tumor, which establishes its utility as an imaging agent in detecting lymph nodes. Based on the FDA's independent analysis, Lymphoseek was able to identify more lymph nodes than the comparator agent (Lymphazurin, aka blue dye). The efficacy findings were acceptable for both melanoma and breast cancer patients. Although Lymphoseek was not directly compared to Tc-99m sulfur colloid (TcSC) in the clinical trials, it is expected to provide comparable clinical utility. One review consideration is whether Lymphoseek and other lymphatic mapping agents may be active in patients with other types of cancers since the product's actions do not appear to be specific to a given tumor type. Based on consultation with the FDA Division of Oncology Drug Products (OHOP), although literature reports exist for the use of ILM in other cancer types, only breast cancer and melanoma commonly use ILM in standard clinical practice.

(b) (4)
The presence of Lymphoseek in most of the nodes with positive pathology for malignancy supports the concept that Lymphoseek is useful for ILM. (b) (4)

1.2.4 Risk

Lymphoseek appears to have an acceptable safety profile for its proposed indication. However, the size of the safety database is minimal for this indication and is not adequate to assess the potential for less frequent events, including hypersensitivity. Most reported AEs were associated with the surgical procedure and underlying condition. However even for events attributable to drug (e.g. injection site reaction) it is difficult to discern whether these events were caused by Lymphoseek or the comparator (blue dye), since the comparator was used in all cases.

1.2.5 Risk Management

There is no risk management required beyond product labeling. Although the safety database is small, a postmarket commitment for evaluation of the potential for hypersensitivity is likely not necessary, since postmarket risks should be adequately addressed through adverse event reporting.

1.3 Recommendations for Postmarket Risk Management Activities

None.

1.4 Recommendations for Postmarket Studies/Clinical Trials

The review recommends that Navidea completes the ongoing NEO3-06, which uses complete neck/regional dissection as the standard of truth in patients with head and neck cancer:

NEO3-06, IND 61,757, *A Phase 3, Prospective, Open-Label, Multicenter Study of Lymphoseek-Identified Sentinel Lymph Nodes (SLNs) Relative to the Pathological Status of Non-Sentinel Lymph Nodes in an Elective Neck Dissection (END) in Cutaneous Head & Neck, and Intraoral Squamous Cell Carcinoma (SCC)*

(b) (4)

Neoprobe initially anticipated completing the patient accrual for this study in the 2nd quarter of 2012, and anticipated reviewing the study efficacy results through 2012, based on Pre-NDA meeting discussion in October 2010. Neoprobe provided safety information to the NDA submission with 57 completed patients (including the 19 patients reported in the NDA's 120 safety update). Neoprobe intended to meet with the Agency following the completion of the study NEO3-06 to review the safety and efficacy results for submission to the IND and the possible submission of the safety and efficacy results to the NDA.

2 Introduction and Regulatory Background

2.1 Product Information

Lymphoseek is a relatively low molecular weight macromolecule (~20 kDa) consisting of multiple units of diethylenetriaminepentaacetic acid (DTPA) and mannose, each synthetically

attached to a 10 kDa dextran backbone. The mannose acts as a substrate for the receptor, and the DTPA serves as a chelating agent for labeling with Tc 99m.

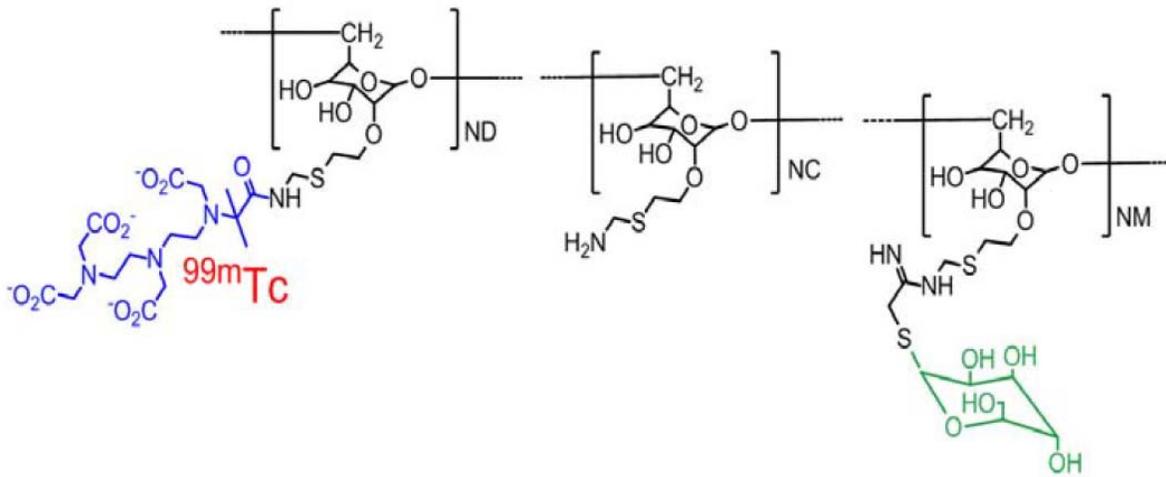


Figure 1: The Tc 99m Lymphoseek (Tilmanocept) Molecule

Lyophilized Lymphoseek is intended to be radiolabeled with Tc 99m prior to administration for lymph node mapping. The intended dose of Lymphoseek is 50 µg (intradermal, subcutaneous, subareolar, or peritumoral injection). Tc 99m Lymphoseek is to be injected in close proximity to the primary tumor and “visualized” (localized) intraoperatively utilizing a handheld gamma detection probe.

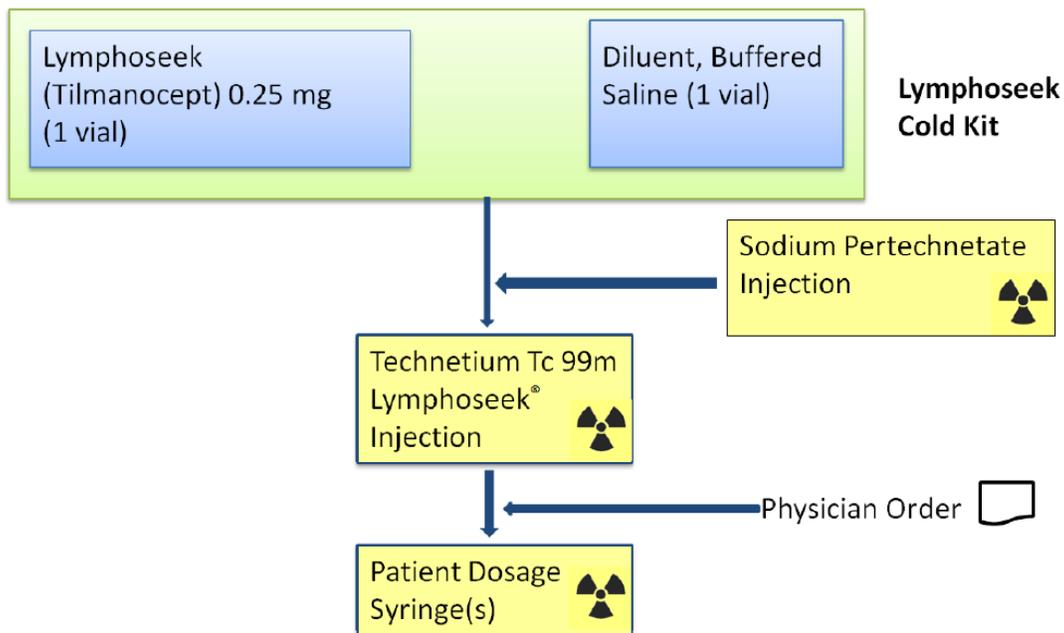


Figure 2: Upon Receipt of a Physician Order the Nuclear Pharmacist Compounds the Dosage Form

2.1.1 Product Mechanism of Action

Lymphoseek targets lymphatic tissue via mannose binding receptors on macrophages and dendritic cells. Lymphoseek is a macromolecule consisting of multiple units of diethylenetriaminepentaacetic acid (DTPA; chelation moiety for Tc 99m) and mannose (receptor interaction group), synthetically attached to a 10 kilodalton dextran core.

The diameter of Lymphoseek is ~7 nm, making it substantially smaller than Tc-99m sulfur colloid (TcSC). Lymphoseek's small diameter facilitates its rapid injection site clearance via lymphatic channels and capillaries.

2.2 Currently Available Products for Proposed Indication (Intraoperative Lymphatic Mapping)

The proposed indications for Lymphoseek based on an Amendment to the NDA on November 4, 2011 are as follows:



Currently, two products are FDA-approved for lymphatic mapping procedures:

- Lymphazurin ('blue dye'): FDA-approved as a contrast agent for the delineation of lymphatic vessels draining the region of injection
- Tc-99m Sulfur colloid: FDA-approved for localization of lymph nodes draining a primary tumor in patients with breast cancer when used with a hand-held gamma counter (approved on July 22, 2011)

Lymphazurin

Lymphazurin (1% isosulfan blue) is a sterile aqueous solution for subcutaneous (SC) administration. Lymphazurin is used for visualization of the lymphatic system draining the region of injection. Lymphazurin is approved by the U.S. Food and Drug Administration (FDA) for the following indication:

Lymphazurin™ 1% (isosulfan blue) upon subcutaneous administration, delineates lymphatic vessels draining the region of injection. It is an adjunct to lymphography in: primary and secondary lymphedema of the extremities; chyluria, chylous ascites or chylothorax; lymph node involvement by primary or secondary neoplasm; and lymph node response to therapeutic modalities.

Tc-99m Sulfur Colloid (TcSC)

Tc-99m TcSC (Pharmalucence, Bedford, MA) is currently the primary radiopharmaceutical agent employed in the U.S. for intraoperative lymphatic mapping (ILM). Although it is widely used, TcSC was only recently approved by the FDA for "localization of lymph nodes draining a primary tumor in patients with breast cancer when used with a handheld gamma counter and the

associated new route of administration, subcutaneous injection.” TcSC has not been approved for lymphatic mapping in other cancer applications.

2.3 Availability of Proposed Active Ingredient in the United States

Lymphoseek is a new molecular entity. None of its active ingredients are available in the United States or other countries.

2.4 Important Safety Issues with Consideration to Related Drugs

None.

Lymphazurin have noted histories of anaphylaxis which are documented as warnings on its product label (at ~2% incidence). However, Lymphoseek is not structurally related to Lymphazurin.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The IND 61757 for Lymphoseek was granted on January 5, 2001 for conduction of a Phase 1 clinical study. USCD was the IND holder until 2005 when the ownership of the IND was transferred to Neoprobe, and Neoprobe submitted a proposal for Phase 2 clinical studies. The IND was placed on full clinical hold due to lack of required additional nonclinical and Chemistry, Manufacturing, and Control (CMC) information in September 2005. Neoprobe later submitted the required information and the clinical hold removed and the Phase 2 clinical study was allowed to resume in May 2006.

During a Pre-Phase 3 meeting held in May 2007, Neoprobe proposed two Phase 3 clinical

(b) (4)

FDA felt that the use of a comparator diagnostic agent might be helpful in this regard, and the primary efficacy endpoint should be expressed in terms of sensitivity and specificity of Lymphoseek as compared to other diagnostic agents. FDA suggested that Neoprobe redesign the phase 3 clinical studies and compare the diagnostic performance of Lymphoseek to the standard of care in the oncologic community. FDA indicated to Neoprobe that both Vital Blue Dye (VBD, e.g., Lymphazurin) and Tc-99m sulfur colloid (TcSC) were used and considered standard agents by the oncologic community for lymph node mapping. To obtain approval of Tc 99m Lymphoseek as a diagnostic agent, Neoprobe needed to show concurrence of findings with a current standard, and that the choice of the standard should be justified based on supportive literature.

Based upon a literature search and summary statistics, Neoprobe concluded that VBD represented the standard diagnostic agent for tumor types for which lymphatic mapping is the

standard-of-care. At the End of Phase 2 meeting held in October 2007, FDA agreed that Lymphazurin, an FDA-approved lymphatic mapping agent, was a reasonable comparator for the proposed Phase 3 study of Tc 99m Lymphoseek for th (b) (4)

(b) (4) proposed primary efficacy endpoint of concordance in lymph node detection. The FDA also emphasized at the October 2007 EOP2 meeting that (b) (4)

(b) (4) Neoprobe designed a phase 3 study (NEO3-06) in which patients were to undergo intraoperative lymphatic mapping (ILM) for sentinel lymph node (SLN) resection followed by elective neck dissection (END). Neoprobe later reported that patient recruitment to the study was slow (see below), and therefore only a progress report of the study was submitted for the NDA.

Meanwhile Neoprobe completed a Phase 3 Study, NEO3-05, with the primary efficacy point being the concordance rate between Lymphoseek and the blue dye. At the End-of-Phase 3 (EOP3) meeting held in March 2010, the FDA commented that the primary endpoint of the completed phase 3 study (NEO3-05), concordance, is really Lymphoseek sensitivity with respect to Blue Dye. That is, it measures the extent to which Lymphoseek also finds lymph nodes found by Blue Dye. This places Blue Dye in the position of a Truth Standard and ignores the possibility that Lymphoseek might identify more lymph nodes than Blue Dye. Based on this premise, FDA requested Neoprobe perform the following additional secondary exploratory analyses to examine the comparative ability of blue dye and Lymphoseek to detect lymph nodes:

Collect all tissue samples found by either Lymphoseek or Blue Dye, or by other means, and determine which are actually lymph nodes, and then examine the table of frequencies of four outcomes over this sample. Entries are:

- *Found by Both*
- *Found by Neither*
- *Found by Blue Dye, not by Lymphoseek*
- *Found by Lymphoseek, not by Blue Dye*

FDA also commented at the EOP3 meeting in March 2010 that the comparator in completed Phase 3 Study (NEO3-05), the blue dye Lymphazurin (Isosulfan Blue) is indicated (b) (4)

FDA encouraged Neoprobe to submit results of both NEO3-05 (completed) and NEO3-06 (ongoing) for a proposed NDA submission for Lymphoseek.

Following the EOP3 meeting, in April 2010, Neoprobe submitted a proposed protocol for another phase 3 clinical study, NEO3-09. The proposed design of this study was almost identical to that of the completed phase 3 study, NEO3-05.

At the Pre-NDA meeting held in October 2010, Neoprobe proposed to submit efficacy and safety data from NEO3-05 and NEO3-09 to support a marketing application for Lymphoseek. The third phase 3 Study (NEO3-06) had been a long term enrolling study anticipated for completion of enrollment in the 2nd quarter of 2012. Neoprobe also agreed to include in the NDA safety data from the enrolled patients in study NEO3-06. Neoprobe anticipates reviewing the efficacy results of study NEO3-06 through 2012.

At the Pre-NDA meeting in October 2010, Neoprobe also indicated its plan to submit a pediatric waiver request in the proposed NDA. Neoprobe stated for the two proposed indications for adult patients, breast cancer and melanoma, both are considered to be rare and sufficient pediatric patients are not available for adequate and well controlled trials. FDA commented that while Neoprobe may request a waiver

(b) (4)

While breast cancer or melanoma may be rare in the pediatric population, there are other oncologic conditions in the pediatric population that lymphatic mapping procedures may be indicated.

2.6 Other Relevant Background Information

In early June 2011, before the Lymphoseek NDA was submitted to the FDA, MSMB Capital Management LLC, a hedge fund investment firm who was a short-seller of the Neoprobe stock, submitted a citizen petition to the FDA Office of Regulatory Policy. The petition requested FDA refrain from approving the then not yet submitted or filed Lymphoseek NDA:

MSMB respectfully requests that the Food and Drug Administration (FDA) refrain from approving and refrain from considering approval of investigational radioactive sentinel lymph node detection agents without accompanying data from successful controlled trials of such agents compared against the standard of care for sentinel lymph node detection, namely, the combination of radioactive colloid and blue dye. Neoprobe Corporation (Neoprobe) has announced their intention to submit a New Drug Application (NDA) for their investigational sentinel lymph node detection agent, "Lymphoseek", without proving equivalence or superiority to the best available standard of care.

Neoprobe has completed two Phase III clinical trials for Lymphoseek, "NE03-05" and "NE03-09". Both trials failed to compare the current standard of care to Lymphoseek. As the best available standard of care is the combination of radioactive colloid and blue dye, and Lymphoseek would not be synergistic and combinable with radioactive colloid, the study

schema and results are not informative for improving or modifying current best clinical practice. Neoprobe should conduct a head-to-head study against the best standard of care and the FDA should enforce this requirement to preserve and protect human healthcare in the United States.

MSMB also respectfully requests that the FDA refrain from approving and refrain from considering approval of investigational radioactive sentinel lymph node detection agents without data from controlled trials which employ a reference truth standard, in this case, complete axillary dissection. While the FDA has already communicated this requirement to Neoprobe, Neoprobe plans on filing a Lymphoseek NDA without fulfilling this request. The FDA should reiterate and enforce this requirement by refusing to approve or review for approval the Lymphoseek NDA.

The FDA Office of Regulatory Policy (ORP) consulted the review division regarding this citizen petition, and a draft of the DMIP consult report to ORP is attached as an appendix (9.3).

3 Pediatric Research Equity Act (PREA) Requirements

3.1 Pediatric Waiver Request

Neoprobe submitted a request for a Full Waiver Request in all pediatric ages regarding the intended use of Lymphoseek®: Kit for the Preparation of Technetium Tc 99m Tilmanocept for Injection. Neoprobe's rationale for the pediatric waiver request is based on the follows:

“The available pediatric populations will not provide adequate patient accrual to result in a statistically structured study for the evaluation of Lymphoseek in pediatric breast cancer or melanoma.”

3.2 Initial Denial of the Pediatric Waiver Request

A sponsor is required to adequately address the Pediatric Research Equity Act (PREA) of 2007, with the submission of a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. A full waiver of required pediatric studies can be granted if any of the following criteria are met (505B(a)(4) of the Federal Food, Drug, and Cosmetic Act):

- 1) Necessary studies are impossible or highly impracticable (e.g. the number of pediatric patients is so small or is geographically dispersed).
- 2) There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups.
- 3) The drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and is not likely to be used in a substantial number of pediatric patients.

Neoprobe's proposed indication for Lymphoseek is for the intraoperative evaluation of tumor-draining lymph nodes. No specific tumor types are mentioned in the indication, yet Neoprobe based their full waiver request of required pediatric studies on the evaluation of Lymphoseek in pediatric breast cancer or melanoma, both of which occur rarely in the pediatric populations. The Division consulted Pediatric and Maternal Health Staff (PMHS), who in turn consulted FDA pediatric oncology colleagues who reported that Lymphoseek could potentially be used in the intraoperative mapping of lymph nodes in multiple pediatric malignancies, including soft tissue sarcomas, germ cell tumors, neuroblastoma, Wilms tumor, and melanoma, etc.

The reviewer conducted independent literature search and concluded that lymphatic mapping procedure is performed in the pediatric population. In fact Neoprobe also acknowledged this in the pediatric waiver request. Neoprobe's rationale for a waiver is based on the argument that "The available pediatric populations will not provide adequate patient accrual to result in a statistically structured study for the evaluation of Lymphoseek in pediatric breast cancer or melanoma."

Although there might be insufficient number of patients to conduct an adequate and well-controlled pediatric efficacy and safety study, the clinical review team believes that there is adequate number of pediatric patients to conduct a pediatric pharmacokinetic, safety, and feasibility study.

A teleconference was held with Neoprobe on December 20, 2011 to discuss the pending denial of the (original) pediatric waiver request. A Pediatric Waiver Denied Letter issued on December 23, 2011:

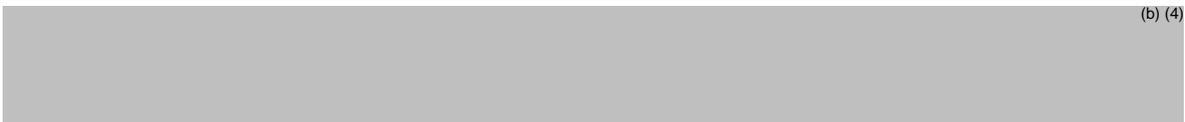
We are denying this waiver for the following reasons:

- 1) The pediatric waiver request fails to provide justifications for such a waiver based on epidemiologic data for pediatric malignancies which could be likely to spread to the lymph nodes and for which Lymphoseek could be used intra-operatively for evaluation of tumor-draining lymph nodes.*
- 2) You have indicated in your waiver request that, in fact, lymphatic mapping is performed in the pediatric population.*
- 3) Although there might be insufficient number of patients to conduct an adequate and well-controlled pediatric efficacy and safety study, we believe there is adequate number of pediatric patients to conduct a pediatric pharmacokinetic, safety, and feasibility study.*

If you believe extrapolation of efficacy would be appropriate, provide a rationale for extrapolating efficacy from adult studies to the pediatric population.

In your proposed pediatric drug development plan, address the following:

1.



(b) (4)

2.

(b) (4)

3. *Pharmacokinetics and safety of your product in children*

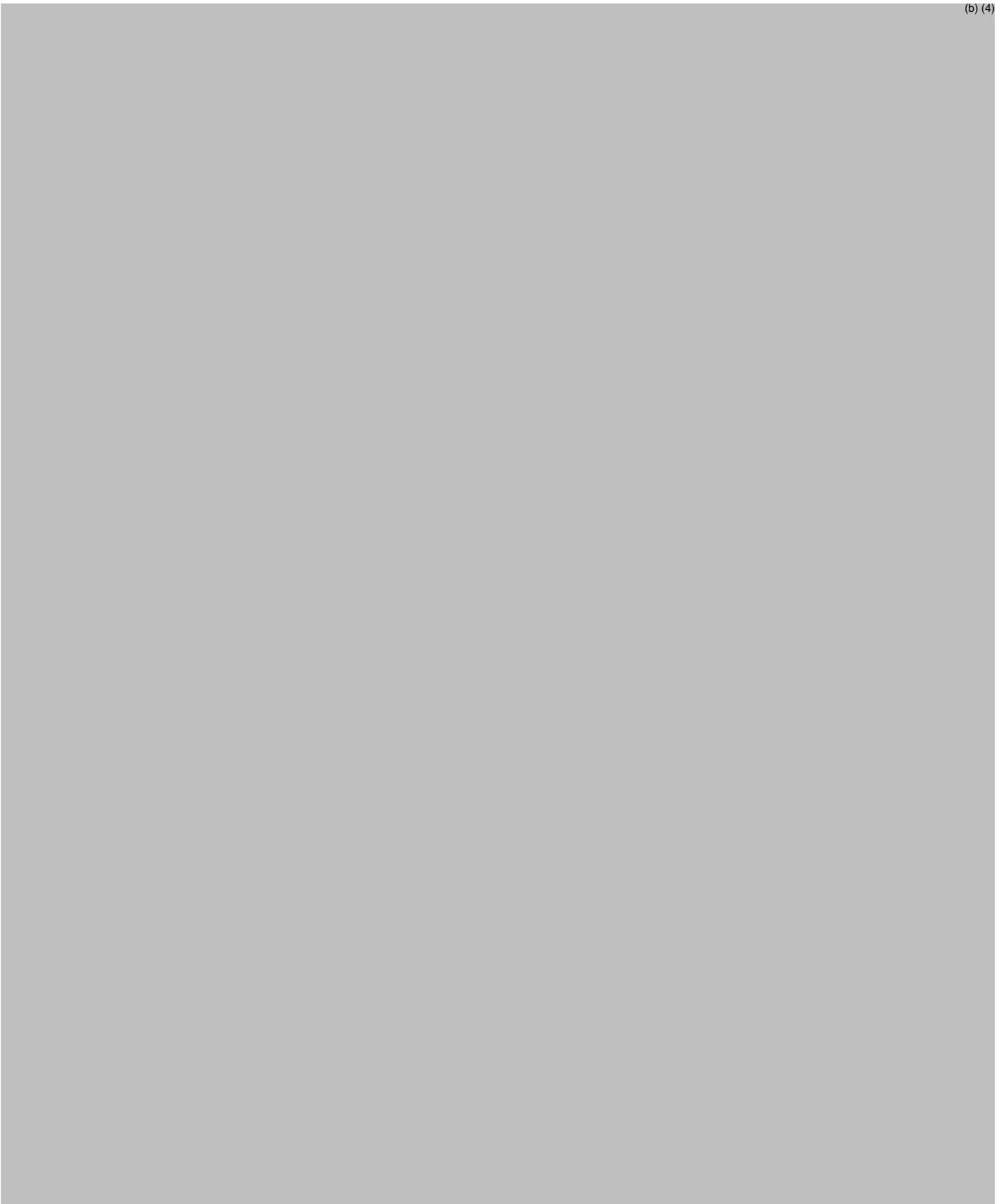
4. *Pediatric dosing (including time interval between drug administration and surgery) and pediatric dosing adjustments, if any*

We recommend that, in a planned pediatric study, you propose to enroll a representative number of patients (e.g. up to ten) from each of the age groups (0 to 2, 2 to 6, 6 to 12, and 12 to 18). If you plan to request a partial waiver applicable to a particular age group, submit a complete justification based on epidemiology, safety and other applicable considerations.

3.3 Proposed Pediatric Drug Development Plan

In response to FDA's denial of the pediatric waiver request, Navidea submitted a pediatric study plan to the NDA on 2/2/2012.

(b) (4)



3.4 Lymphoseek Labeling Indication Change and Granting of Full Pediatric Waiver Request

3.4.1 Lymphoseek Labeling Indication Change and Consultation with the Division of Oncology Drug Products (OHOP)

As the clinical review progressed further, the clinical review team felt that since both phase 3 clinical studies were conducted in patients with breast cancer or melanoma, the submitted clinical data can only support indications for use in patients with breast cancer or melanoma.

The review team further consulted the FDA Division of Oncology Drug Products (OHOP) on the prevalence of the use of intraoperative lymphatic mapping (ILM) in oncology patients and the sponsor's (b) (4) proposed approaches for the pediatric development plan. The oncology consult reviewer reported that although multiple publications can be found in the literature regarding the use of ILM, the only diseases where ILM is widely used include malignant melanoma and breast cancer. (b) (4)

Based on the submitted clinical data and recommendations from the FDA Division of Oncology Drug Products, the clinical reviewer recommends narrowing the labeling indication to “the (b) (4) localization of lymph nodes in patients with breast cancer or melanoma”. This was discussed at a teleconference with Navidea on 3/27/2012.

3.4.2 Granting of Full Pediatric Waiver Request

Given that Lymphoseek's labeling indication is to be narrowed to patients with breast cancer or melanoma, and that breast cancer and melanoma are rare in the pediatric population, the clinical reviewer recommends granting the pediatric waiver request.

On April 11, 2012, the FDA Pediatric Review Committee PREA subcommittee agreed with the Division's recommendation to grant full pediatric waiver request. The Division presented a full waiver in pediatric patients because studies are impossible or highly impracticable for the (b) (4) localization of lymph nodes in patients with breast cancer and the (b) (4) localization of lymph nodes in patients with melanoma because breast cancer does not occur in the pediatric population and melanoma is very rare in pediatric patients.

4 Labeling Recommendations

4.1 Removal of labeling Indications for [REDACTED]

(b) (4)

The Day 74 Filing Issues Identified Letter indicated the following labeling indication deficiency:

[REDACTED]

(b) (4)

In response Neoprobe proposed indication to be changed to the following statement in the November 4, 2011 amendment to the NDA:

[REDACTED]

(b) (4)

Reviewer's comments: Although the revised labeling indication [REDACTED] the new proposed indication now implies [REDACTED] without providing sufficient supporting evidence (see further comments below).

(b) (4)

(b) (4)

4.2 Narrowing the Product's Patient Population to Patients with Breast Cancer or Melanoma

Both phase 3 clinical studies, NEO3-05 and NEO3-09, were conducted in patients with breast cancer or melanoma. Therefore, reviewer felt that the submitted clinical data can only support the efficacy and safety of Lymphoseek in patients with breast cancer or melanoma. Furthermore, based on inputs from the FDA Division of Oncology Drug Products, the only diseases in which intraoperative lymphatic mapping is widely used are breast cancer and melanoma. The reviewer recommends narrowing the product's patient population in labeling indication to patients with breast cancer or melanoma.

4.3 Removal of Labeling Indication for [REDACTED] (b) (4)

On November 22, 2011, an information request was sent to Neoprobe on the revised labeling indication on [REDACTED] (b) (4)

In the new Draft Labeling Text you appear to seek [REDACTED] (b) (4)

Please identify or provide the data supporting this claim.

A teleconference was further held with Neoprobe on December 20, 2011 to discuss the required data analyses to support this labeling indication.

[REDACTED] (b) (4)

4.4 Labeling Dosing Recommendations

[REDACTED] (b) (4)

4.5 Post-Injection Time Interval to Surgery [REDACTED] (b) (4)

[REDACTED]

5 Significant Efficacy/Safety Issues Related to Other Review Disciplines

5.1 CMC Review Issues

Multiple CMC deficiencies were identified by the review team (please see CMC review for further detail). Multiple FDA Information Requests were sent and teleconferences conducted with Navidea, and the review clock was extended for 3 months due to a major CMC amendment submitted on 3/31/2012, which is during the last 3 months of the original 10-month PDUFA clock. At the time of completion of this primary clinical review, the CMC review is ongoing.

5.2 Consultation to the Division of Scientific Investigation (DSI) and Results of Site Inspection

In April 2009, Neoprobe informed the FDA that they planned to exclude efficacy data from Sites 05 and 06 of the then ongoing phase 3 Study NEO3-05 from the efficacy analysis. The review team noticed that the discordance rate (standard of truth is concordance with blue dye) at the lymph node level (node positive by blue dye but negative by the test drug) was higher (12/40) than at the other study sites (3/135). Neoprobe believed that the discordance was due to dilution of the test drug (Lymphoseek) by higher than recommended volumes of diluent at sites #5 (3.4 ml average) and #6 (8 ml average) compared to the other 12 study sites (averages ranged from 0.1 ml to 3 ml). The review team advised the company to still include these two sites in the efficacy analysis. In the August 2011 NDA submission, Neoprobe included efficacy analyses both including and excluding sites 05 and 06.

It is not clear if the drug was formulated with a larger than recommended volume of diluent, e.g. by co-administration of a correctly formulated drug with other tracers). The sponsor did not provide experimental data to show the effect of dilution on binding of the test drug to lymph nodes and does not show. A by-patient listing of the volumes administered and concordance would be useful.

After the NDA was submitted, the review team requested additional site-specific information. Neoprobe submitted additional site-specific information to the NDA as an amendment on September 16, 2011.

The FDA Office of Compliance Office of Scientific Investigation (OSI) was consulted. The consult report showed that the protocol violations in product dilution involving clinical sites 05 and 06 were most likely isolated events.

At a clinical site inspection (Kenneth Deck) linked to this sponsor inspection, this use of incorrect injection/diluent volumes was verified as reported by the sponsor. For all subjects at this clinical study site, the injection/diluent volumes were up to 10-fold larger than that specified in the study protocol (0.2 - 0.4 mL). Navidea claimed that the use of larger than recommended injection volumes decreases Lymphoseek® efficacy and proposed to exclude the affected data from the NDA. Based on the inspectional verification, the OSI inspection team concluded that the affected data were reliable for inclusion in sensitivity analyses with and without the affected data as part of the analysis data set.

6 Review of Efficacy

Efficacy Summary

Both Phase 3 studies used ‘concordance’ as the primary efficacy endpoint. During the product development, through multiple milestone industry meetings, the FDA review team repeatedly expressed concerns regarding the use of so called ‘concordance’ as the primary efficacy endpoint, as the sponsor’s definition of ‘concordance’ is essentially the sensitivity of Lymphoseek using blue dye as the standard of truth. In reviewing the NDA, the FDA review team conducted its own analysis, using histopathology (lymphoid tissue vs. non-lymphoid tissue) as the standard of truth. Based on the independent FDA analysis, the review team concluded that Lymphoseek is highly predictive of lymphoid tissue in intra-operative lymphatic mapping. The clinical team’s recommendation for the approval of the product is largely based on Lymphoseek’s high proficiency in identifying lymph nodes draining an injection site. In addition, the FDA review team examined the applicant’s proposed labeling indications and concluded that available clinical data are adequate to support (b) (4)



6.1 Tables of Studies/Clinical Trials

The following table lists clinical studies in the development program of Lymphoseek. Efficacy and safety data of the NDA are mainly derived from the two phase 3 studies: NEO-05 and NEO-09. NEO-06 is listed as a Phase 3 efficacy and safety study in the following table, but the study is ongoing at the time of the NDA submission. Safety data from 63 patients that had been studied in the NEO-06 study and the study’s progress report were included in the NDA submission. No efficacy data from NEO-06 was submitted.

Table 1: Studies in the Tc 99m Lymphoseek Clinical Development Program

Phase	Study	Study Design / Cancer Type	Primary Objectives
1	NEO3-A	Randomized, four-arm, open-label / Primary Breast Cancer	PK and Safety
	NEO3-B	Randomized, four-arm, open-label / Cutaneous Melanoma	PK and Safety
	NEO3-C	Randomized, four-arm, single-blinded / Primary Breast Cancer	PK and Safety
2	NEO3-01	Single-arm, open-label / Breast Cancer and Melanoma	PD and Safety
3	NEO3-05	Single-arm, open-label / Breast Cancer and Melanoma	Efficacy and Safety
	NEO3-09	Single-arm, open-label / Breast Cancer and Melanoma	Efficacy and Safety
	NEO3-06 ^a	Single-arm, open-label / Head and Neck Squamous Cell Carcinoma	Efficacy and Safety

Ongoing study; the database from this study was frozen for assessment of safety parameters only for inclusion in this marketing application.

Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics

6.2 Discussion of Individual Studies/Clinical Trials

The two phase 3 clinical studies submitted in the NDA, NEO-05 and NEO-09, are almost identical in study design. Both studies are titled “A Phase 3, Prospective, Open-Label, Multicenter Comparison Studies of Lymphoseek® and Vital Blue Dye as Lymphoid Tissue Targeting Agents in Patients With Known Melanoma or Breast Cancer Who Are Undergoing Lymph Node Mapping”. Both studies were prospective, multicenter, open-label, single arm, within-patient comparative studies conducted in patients 18 years of age or older with known melanoma or breast cancer who were candidates for surgical intervention and who met the study entry criteria. All patients received a single dose of 50 µg Tc 99m Lymphoseek and VBD prior to ILM. The primary objective of both studies was to determine the concordance between Tc 99m Lymphoseek and VBD in the in vivo detection of the excised lymph node(s) as confirmed by histopathology.

6.2.1 Study NEO3-05

For study NEO3-05, the planned sample size was 238 patients with an expected yield of 203 VBD-stained nodes to meet the primary endpoint analysis. The study enrolled 195 patients with a safety population of 179 patients, of which 85 patients had melanoma and 94 patients had breast cancer. Three hundred and eighty surgical specimens from intra-operative lymphatic mapping were submitted to surgical pathology, and under the microscope some of the surgical specimens contained more than one lymph nodes. Altogether, 475 lymph nodes were harvested from 176 patients during intra-operative lymphatic mapping. Thirty-eight patients underwent next day surgery, for which they received 2 mCi (50 mcg) of Lymphoseek injected 12 – 30 hours prior to surgery. The rest of the patients had same day surgery and received 0.5 mCi (50 mcg) of

Lymphoseek injected 15 minutes to 12 hours prior to surgery. In Study NEO3-05, methods of injection were intradermal for melanoma patients, and intradermal, subareolar, or peritumoral for breast cancer patients.

6.2.2 Study NEO3-09

For study NEO3-09, the planned sample size was up to 155 patients in order to yield 196 VBD-stained nodes to meet the primary endpoint analysis. The study enrolled 163 patients with a safety population of 153 patients, of which 76 patients had melanoma and 77 patients had breast cancer. The vast majority of patients had same day surgery, and received 0.5 mCi (50 mcg) of Lymphoseek injected 30 minutes to 15 hours prior to surgery. Two patients, one with breast cancer and one with melanoma, underwent next day surgery, for which they received 2 mCi (50 mcg) of Lymphoseek injected 15-30 hours prior to surgery. In Study NEO3-09, methods of injection were intradermal for melanoma, and intradermal or subareolar for breast cancer.

Reviewer's comments: Note that although the mass dose of Lymphoseek is the same 50 mcg for all patients, the radiopharmaceutical dose of Lymphoseek differs for the next day surgery patients between the two trials – 1 mCi in NEO3-05 and 2 mCi in NEO3-09. The radiopharmaceutical dose for the same day surgery patients are the same 0.5 mCi for the two trials. The majority of patients from the two trials underwent same day surgery, while a small number of patients (40 patients) from the two trials underwent next day surgery.

6.3 Methods

6.3.1 Definition of Efficacy Endpoints

The primary efficacy analysis was conducted at the node level. In the sponsor's primary efficacy analysis, concordance is based on the comparator blue dye and is essentially the sensitivity of Lymphoseek using blue dye as the standard of truth:

$$P_{C1} = \frac{\# \text{ of nodes that were VBD-stained and were also Tc 99m Lymphoseek hot}}{\# \text{ of VBD-stained nodes}}$$

Throughout the milestone meetings, the FDA review team expressed concerns on using this so called 'concordance' as the primary efficacy endpoint. One situation the FDA review team asked the sponsor to consider was that Lymphoseek could potentially identify more lymph nodes than the comparator blue dye. Therefore in secondary efficacy analyses, Navidea also conducted analysis on the 'reverse concordance', which is taking all the Lymphoseek identified lymph nodes, and look to see how many of them were also identified by the blue dye:

$$P_{C3} = \frac{\# \text{ of Tc 99m Lymphoseek hot nodes that were VBD-stained}}{\# \text{ of Tc 99m Lymphoseek hot nodes}}$$

The FDA review team conducted its own analysis during the NDA review. The FDA review was conducted on a node level, using each surgical specimen’s histopathology (lymphoid tissue vs. non-lymphoid tissue) as the standard of truth.

6.3.2 Definition of ‘Hot’ Lymph Nodes

In NEO3-05, Tc 99m Lymphoseek-designated lymph nodes were defined as lymph nodes that had:

- 1) greater than 50 mean counts per 2 seconds or 250 total counts per 10 seconds; or
- 2) greater than the quantity of three square roots of the mean background count (i.e., standard deviations) added to the mean background count (“3σ rule”); or
- 3) nodes that were greater than 10% of the mean counts of the node with the highest 2 second counts.

The 3σ rule provided for discrimination in greater than 99.7% of the nodes studied in NEO-05, criteria #1 and #3 were eliminated in the NEO-09 study.

Table 2: Threshold Definitions for ‘Hot’ Lymph Nodes

Table 2 Threshold Definitions for “Hot” Lymph Nodes			
Counting Method	Total Counts	3σ	10% Rule
2-second counts	>50 counts	Yes	Yes
10-second counts	>250 counts	Yes	Yes

6.4 Analysis of Primary Endpoint(s) – Concordance with Blue Dye

In the sponsor’s primary efficacy analysis, ‘concordance’ with blue dye at the node level was used the primary efficacy endpoint. In the two phase 3 trials, the blue dye identified 485 lymph nodes from 291 patients, with 256 nodes from NEO3-05 and 229 nodes from NEO3-09. Since the blue dye is essentially the standard of truth, these blue dye identified lymph nodes form the ITT nodal population. Of the 485 ITT nodes, Lymphoseek identified 468 nodes, with 239 nodes from NEO3-05 and 229 nodes from NEO3-09 (Table 3, reproduced from the Application). Note that the lower bound of the 95% confidence interval in study NEO3-05 was 0.8958, slightly lower than the prespecified threshold level of 0.90. Therefore study NEO3-05 only marginally won.

Table 3: Count and Proportion of Concordant Nodes

	ITT Population (N=291)		
	NEO3-05 (Total ITT Nodes ^a =256)	NEO3-09 (Total ITT Nodes ^a =229)	Meta-Analysis (Total ITT Nodes ^a =485)
Number (Proportion) of Concordant Nodes ^a	239 (0.9336)	229 (1.0000)	468 (0.9999)
95% Confidence Interval for Proportion	(0.8958, 0.9608)	(0.9840, 1.0000)	(0.9986, 1.0000)
1-Sided p-Value ^b for One-Sample Test of $H_0: P_{C1} \leq 0.90$	0.0401	<0.0001	<0.0001
Melanoma ^c (Total ITT Nodes=237)	118 (0.9752)	116 (1.0000)	234 (0.9999)
Breast Cancer ^d (Total ITT Nodes=248)	121 (0.8963)	113 (1.0000)	234 (0.9999)

^a Concordant Nodes – Nodes that were determined in vivo to be “blue” (due to presence of vital blue dye) were also “hot” (due to presence of Tc 99m Lymphoseek).

^b $\alpha=0.05$ for NEO3-05 (per protocol); $\alpha=0.025$ for NEO3-09 (per protocol); $\alpha=0.025$ for meta-analysis

^c Concordant Nodes from Melanoma Patients.

^d Concordant Nodes from Breast Cancer Patients.

Abbreviation: ITT, intent-to-treat

6.5 Analysis of Secondary Endpoint(s) – Reverse Concordance

Reverse Concordant Nodes are Nodes that were determined in vivo to be “hot” (due to presence of Tc 99m Lymphoseek) that were also “blue” (due to the presence of vital blue dye). There are total of 721 reverse ITT (RITT) nodes, lymph nodes that were identified by Lymphoseek from the two phase 3 studies. This is more than the 485 total ITT nodes, lymph nodes that were identified by blue dye from the two phase 3 studies. Therefore Lymphoseek identified many more lymph nodes than blue dye (Table 4, reproduced from the Application).

Table 4: Count and Proportion of Reverse Concordant Nodes

	RITT Population (N=319) ^a		
	NEO3-05 (Total RITT Nodes=343)	NEO3-09 (Total RITT Nodes=378)	Meta-Analysis (Total RITT Nodes=721)
Number (Proportion) of Reverse Concordant Nodes ^b	239 (0.6968)	229 (0.6058)	468 (0.6519)
95% Confidence Interval for Proportion	(0.6451, 0.7450)	(0.5546, 0.6554)	(0.6173, 0.6865)
1-Sided p-Value for Test of $H_0: P_{C1} \leq P_{C3}$ ^c	<0.0001	<0.0001	<0.0001
Melanoma ^d (Total RITT Nodes =370)	118 (0.6821)	116 (0.5888)	234 (0.6350)
Breast Cancer ^e (Total RITT Nodes =351)	121 (0.7118)	113 (0.6243)	234 (0.6696)

^a The population used for the superiority analysis ($P_{C1} \leq P_{C3}$) consists of all patients that are in the RITT and/or ITT population.

^b Reverse Concordant Nodes - Nodes that were determined in vivo to be “hot” (due to presence of Tc 99m Lymphoseek) that were also “blue” (due to the presence of vital blue dye).

^c P_{C1} refers to the concordance rate of Tc 99m Lymphoseek relative to vital blue dye and P_{C3} refers to the reverse concordance rate of vital blue dye relative to Tc 99m Lymphoseek.

^d Reverse Concordant Nodes from Melanoma Patients

^e Reverse Concordant Nodes from Breast Cancer Patients

6.6 Independent FDA Analysis – Correlation with Histopathology

Because of the performance limitations of the comparator blue dye as shown by the reverse concordance analysis, the FDA review team concludes that the sponsor’s ‘concordance’ is not a properly defined primary endpoint. The reviewer considers the histopathology (whether a piece of submitted surgical specimen is lymphoid tissue or not regardless of its cancer status) of the identified lymph nodes an appropriate primary endpoint (b) (4)

The FDA review team conducted an independent analysis at the node level using histopathology as the standard of truth. Note this is different from the sponsor’s analysis, in which histopathology status refers to whether a lymph node contains cancer. In the independent FDA analysis, histopathology refers

to whether a surgical specimen is lymphoid tissue. This analysis aims for the question of ‘how good is Lymphoseek in identifying lymph nodes draining an injection site’.

6.6.1 FDA Analysis on NEO3-05

According to the NEO3-05 study report, 380 lymph nodes were identified during surgery by the combination of palpation, blue dye, and Lymphoseek. However further histopathological analysis of these 380 ‘lymph nodes’ revealed that some of these ‘nodes’ contained multiple individual lymph nodes. Therefore the total number of lymph nodes according to histopathology was 476 nodes (identified by any combination of Lymphoseek or blue dye or other means during surgery, such as by palpation), plus two additional palpable masses (presumably identified before surgery).

Table 5 summaries the FDA analysis on study NEO3-05. There are 478 surgical specimens submitted from intra-operative lymphatic mapping for histopathology analysis. All but one were confirmed to be lymph nodes by histopathology. Therefore Lymphoseek has high positive predicative value for identifying lymph nodes draining an injection site.

Of the 478 submitted surgical specimens, 421 (88.1%) were identified by Lymphoseek (regardless of whether the blue dye identified them or not), 323 (67.6%) were identified by the blue dye (regardless of whether Lymphoseek identified them or not), 303 (63.4%) were identified by both the blue dye and Lymphoseek, 118 (24.7%) were identified by Lymphoseek only (blue dye negative), and 17 (3.6%) were identified by blue dye only (Lymphoseek negative). Twenty-three of the submitted specimens (4.8%) were identified by neither the blue dye nor Lymphoseek, presumably identified by other means such as palpation during intraoperative lymphatic mapping.

Table 5: FDA Analysis - Histopathology as the Reference Standard: NEO3-05

Mode of Identification	Number identified (% total identified and submitted for histopathology)	Confirmed to be lymph nodes by histopathology (% identified)
Identified by Lymphoseek (Lymphoseek+/BD+ or BD-)	421 (88.1%)	420 (99.8%)
Identified by Blue Dye (BD+/Lymphoseek + or -)	323 (67.6%)	322 (99.7%)
Identified by Both BD and Lymphoseek (BD+/Lymphoseek+)	303 (63.4%)	302 (99.7%)
Identified Only by Lymphoseek (Lymphoseek+/BD-)	118 (24.7%)	118 (100%)
Identified Only by BD (Lymphoseek-/BD+)	17 (3.6%)	17 (100%)
Identified by Neither Lymphoseek Nor BD	23 (4.8%)	23 (100%)

(Lymphoseek-/BD-)		
Total submitted surgical specimen	478 (100%)	477 (99.8%)

BD: blue dye. +: identified by a particular tracer.

6.6.2 FDA Analysis on NEO3-09

Similar results were seen with study NEO3-09. Table 6 summaries the FDA analysis on study NEO3-09. There are 461 surgical specimens submitted from intra-operative lymphatic mapping for histopathology analysis. All but three were confirmed to be lymph nodes by histopathology. Therefore Lymphoseek has high positive predicative value for identifying lymph nodes draining a site of injection. Lymphoseek identified far more lymph nodes than blue dye in study NEO3-09. All the identified lymph nodes were also identified by Lymphoseek. There were no lymph nodes that were identified by blue dye alone or other means (e.g. palpation) alone.

Table 6: FDA Analysis - Histopathology as the Reference Standard: NEO3-09

Mode of Identification	Number identified (% total identified and submitted for histopathology)	Confirmed to be lymph nodes by histopathology (% identified)
Identified by Lymphoseek (Lymphoseek+/BD+ or BD-)	449 (97.4%)	448 (99.8%)
Identified by Blue Dye (BD+/Lymphoseek + or -)	276 (59.9%)	276 (100%)
Identified by Both BD and Lymphoseek (BD+/Lymphoseek+)	276 (59.9%)	276 (100%)
Identified Only by Lymphoseek (Lymphoseek+/BD-)	173 (37.5%)	172 (99.4%)
Identified Only by BD (Lymphoseek-/BD+)	0	0
Identified by Neither Lymphoseek Nor BD (Lymphoseek-/BD-)	0	0
Total submitted surgical specimen	461 (100%)	458 (99.3%)

BD: blue dye. +: identified by a particular tracer.

6.7 Analysis of Efficacy for Pre-Operative Lymphoscintigraphy

(b) (4)

The submission states that lymphoscintigraphy data were collected in both of the completed pivotal Phase 3 trials, NEO3-05 and NEO3-09. However, these data were not required by either of the study protocols, hence preoperative scans were not performed for every study patient. Table 7 summarizes the use of preoperative lymphoscintigraphy in NEO3-05 and NEO3-09.

Table 7: Summary of Preoperative Lymphoscintigraphy Utilization

	Tumor Type		
	Melanoma	Breast Cancer	Overall
NEO3-05 Safety Population [n]	85	94	179
Lymphoscintigraphy was performed [n (%)]	85 (100.0%)	82 (87.2%)	167 (93.3%)
NEO3-09 Safety Population [n]	76	77	153
Lymphoscintigraphy was performed [n (%)]	76 (100.0%)	58 (75.3%)	134 (87.6%)
Combined Safety Population [n]	161	171	332
Lymphoscintigraphy was performed [n (%)]	161 (100.0%)	140 (81.9%)	301 (90.7%)

Table 8 summarizes hot spot localization rates on a patient level in NEO3-05 and NEO3-09. Overall hot spots were located for 94.4% of patients who received lymphoscintigraphy in the two Phase 3 studies.

Table 8: Summary of Hot Spot Localization Rates by Lymphoscintigraphy

	Tumor Type		
	Melanoma	Breast Cancer	Overall
NEO3-05 Lymphoscintigraphy Population [n]	85	82	167
Hot spot was identified [m (%)]	83 (97.6%)	67 (81.7%)	150 (89.8%)
NEO3-09 Lymphoscintigraphy Population [n]	76	58	134
Hot spot was identified [m (%)]	76 (100.0%)	58 (100.0%)	134 (100.0%)
Combined Lymphoscintigraphy Population [n]	161	140	301
Hot spot was identified [m (%)]	159 (98.8%)	125 (89.3%)	284 (94.4%)

Table 9 presents the per patient correlation of lymphoscintigraphy hot spots to in vivo Tc 99m Lymphoseek hot lymph node status, by study and by tumor type. In this post-hoc patient level analysis, a positive agreement was determined if:

- 1) a patient had a lymphoscintigraphy hot spot and also was hot in vivo (i.e., the patient had ≥ 1 lymph node with in vivo gamma counts that met the 3 sigma rule), or
- 2) a patient did not have a lymphoscintigraphy hot spot and was also not hot in vivo (i.e., the patient had no lymph nodes with in vivo gamma counts that met the 3 sigma rule)

Disagreement categories included:

- 1) a patient had a lymphoscintigraphy hot spot but was not hot in vivo, and
- 2) a patient did not have a lymphoscintigraphy hot spot but was hot in vivo.

Table 9: Summary of Lymphoscintigraphy and In Vivo Agreement Per Patient

	Tumor Type		
	Melanoma	Breast Cancer	Overall
Agreement Between LS and In Vivo Results – NEO3-05			
Evaluable Patients [n]	83	81	164
Agreement [n (%)]	81 (97.6%)	70 (86.4%)	151 (92.1%)
Agreement Between LS and In Vivo Results – NEO3-09			
Evaluable Patients [n]	75	58	133
Agreement [n (%)]	75 (100.0%)	58 (100.0%)	133 (100.0%)
Agreement Between LS and In Vivo Results – Combined			
Evaluable Patients [n]	158	139	297
Agreement [n (%)]	156 (98.7%)	128 (92.1%)	284 (95.6%)
Agreement Between LS and In Vivo Results – NEO3-05 without Sites 05 and 06			
Evaluable Patients [n]	78	67	145
Agreement [n (%)]	76 (97.4%)	65 (97.0%)	141 (97.2%)
Agreement Between LS and In Vivo Results – Combined without NEO3-05 Sites 05 and 06			
Evaluable Patients [n]	153	125	278
Agreement [n (%)]	151 (98.7%)	123 (98.4%)	274 (98.6%)

Reviewer's comments:

1) *In the summary analysis, if a patient has a hot spot identified on the lymphoscintigraphy, then this patient is counted as an 'agreement', regardless of whether the number and location of lymphoscintigraphy 'hot spots' correlate with 'hot' lymph nodes identified during intra-operative lymphatic mapping with hand-held gamma counter.*

2) *The analysis is post-hot analysis. Neither phase 3 studies had pre-op lymphoscintigraphy in the pre-specified protocols and endpoints.*

3) *Lymphoscintigraphy was not pre-specified in the phase 3 clinical protocols. Individual study sites performed this procedure according to its institutional practice or even individual investigator's preference. The timing of lymphoscintigraphy (time interval after Lymphoseek injection) and image acquisition parameters of this pre-op lymphoscintigraphy were not standardized.*

4) *Overall the reviewer considers the submitted summary analysis*

(b) (4)

6.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Neoprobe proposes the following labeling dosing recommendation for Lymphoseek:

Table 10: Neoprobe Proposed Labeling Dosing Recommendations

(b) (4)

The Lymphoseek route of administration differs for cancer types. Table 11 summarizes Lymphoseek route of administration used for various cancer types.

Table 11: Tc 99m Lymphoseek Administration by Injection and Cancer Type

Injection Type	Cancer Type				Overall N=531
	Melanoma N=228	Breast Cancer N=240	HNSCC Cutaneous N=6	HNSCC Intraoral N=57	
Intradermal	191 (83.8%)	151 (62.9%)	0 (0.0%)	0 (0.0%)	342 (64.4%)
Peritumoral	5 (2.2%)	31 (12.9%)	6 (100.0%)	57 (100.0%)	99 (18.6%)
Subareolar	0 (0.0%)	40 (16.7%)	0 (0.0%)	0 (0.0%)	40 (7.5%)
Subcutaneous	32 (14.0%)	18 (7.5%)	0 (0.0%)	0 (0.0%)	50 (9.4%)

6.8.1 Subgroup Analysis Based on Post-Injection Time Interval

Of the 328 patients who had in vivo detection data (patients who underwent surgery with intraoperative evaluation of lymph nodes per protocol) in the two phase 3 clinical studies, the majority of the patients (288 patients, 87.8%) had same day surgery, and a small number of patients (40 patients, 12.2%) had next day surgery. Of note, the vast majority of these 40 patients were from NEO3-05. Only 2 of the 40 next day surgery patients were from NEO3-09.

In NEO3-05, the 38 patients who underwent next day surgery received 1 mCi (50 mcg) of Lymphoseek injected 12 – 30 hours prior to surgery. The rest of the patients in NEO3-05 had same day surgery and received 0.5 mCi (50 mcg) of Lymphoseek injected 15 minutes to 12 hours prior to surgery. In NEO3-09, the vast majority of patients had same day surgery, and received 0.5 mCi (50 mcg) of Lymphoseek injected 30 minutes to 15 hours prior to surgery. Two patients from NEO3-09, one with breast cancer and one with melanoma, underwent next day surgery, for which they received 2 mCi (50 mcg) of Lymphoseek injected 15-30 hours prior to surgery. Table 12 summarizes the study drug dosing regimen in the two phase 3 trials.

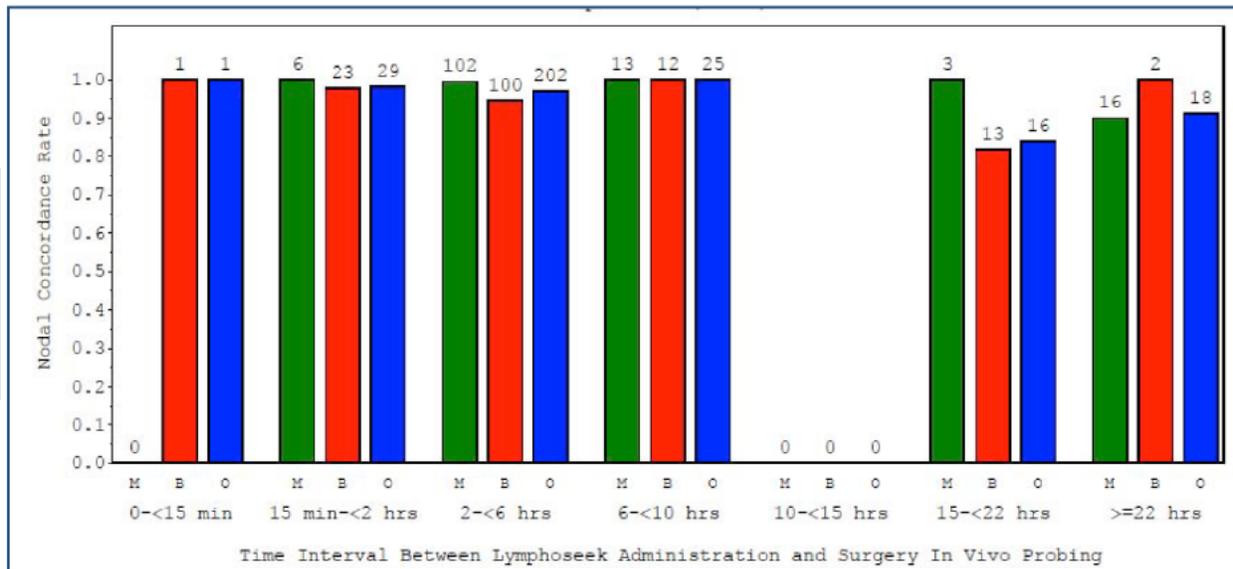
Table 12: NEO3-05 and NEO3-09 Post-Injection Surgery Schedule and Tc 99m Lymphoseek Dose

Post-injection Surgery Schedule ^a	Dose of Tc 99m Lymphoseek
NEO3-05	
15 min – 12 hr	0.5 mCi Tc 99m-labeled Lymphoseek
12 hr – 30 hr	1.0 mCi Tc 99m-labeled Lymphoseek
NEO3-09	
30 min – 15 hr	0.5 mCi Tc 99m-labeled Lymphoseek
15 hr – 30 hr	2.0 mCi Tc 99m-labeled Lymphoseek

^a The adjustment of radiolabeling based on timing of ILM surgery was required to account for isotopic decay (Tc 99m half-life is 6.02 hours)

Reviewer's comments: Navidea's proposed dosing recommendation for [REDACTED] (b) (4)

Figure 3: Integrated Analysis: Nodal Concordance Rate by Post-Injection Time Interval of Tc 99m Lymphoseek Relative to Vital Blue Dye (ITT Population, N=291)



M = melanoma. B = breast cancer. O = both. 15-<22 hrs and >= 22hrs are the next day surgery groups.

From Figure 3, we see a trend that the next day surgery groups (15-<22 hrs and >=22 hrs) have lower concordance rate than the same day surgery groups (0-<15 min, 15 min-<22 hrs, 2-<6 hrs, 6-<10 hrs). Table 13 below lists concordance rate in each of the post-injection time interval from NEO3-05 and NEO3-09, respectively.

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Table 13: Nodal Concordance Rates by Post-Injection Time Interval of Tc 99m Lymphoseek in NEO3-05 and NEO3-09

	ITT Population (N=291)						
	Time Interval Between Tc 99m Lymphoseek Administration and Surgery In Vivo Probing						
	0 - <15 min	15 min - <2 hrs	2 - <6 hrs	6- <10 hrs	10 - <15 hrs	15 - <22 hrs	≥22 hrs
Concordance Rate – Study NEO3-05							
Overall [p(m)] ^a	1.0000 (1)	0.9444 (18)	0.9387 (163)	1.0000 (28)	0.0000 (0)	0.8261 (23)	0.9130 (23)
Melanoma [p(m)]	0.0000 (0)	1.0000 (6)	0.9863 (73)	1.0000 (20)	0.0000 (0)	1.0000 (2)	0.9000 (20)
Breast Cancer [p(m)]	1.0000 (1)	0.9167 (12)	0.9000 (90)	1.0000 (8)	0.0000 (0)	0.8095 (21)	1.0000 (3)
Concordance Rate – Study NEO3-09							
Overall [p(m)]	0.0000 (0)	1.0000 (38)	1.0000 (176)	1.0000 (13)	0.0000 (0)	1.0000 (2)	0.0000 (0)
Melanoma [p(m)]	0.0000 (0)	1.0000 (5)	1.0000 (104)	1.0000 (6)	0.0000 (0)	1.0000 (1)	0.0000 (0)
Breast Cancer [p(m)]	0.0000 (0)	1.0000 (33)	1.0000 (72)	1.0000 (7)	0.0000 (0)	1.0000 (1)	0.0000 (0)
Concordance Rate – Combined							
Overall [p(m)]	1.0000 (1)	0.9821 (56)	0.9705 (339)	1.0000 (41)	0.0000 (0)	0.8400 (25)	0.9130 (23)
Melanoma [p(m)]	0.0000 (0)	1.0000 (11)	0.9944 (177)	1.0000 (26)	0.0000 (0)	1.0000 (3)	0.9000 (20)
Breast Cancer [p(m)]	1.0000 (1)	0.9778 (45)	0.9444 (162)	1.0000 (15)	0.0000 (0)	0.8182 (22)	1.0000 (3)

^a p is the concordance rate, and m is the number of vital blue dye-stained nodes from patients who belong to each post-injection time interval.

Note NEO3-09 only has two lymph nodes in the next day surgery group (15-<22 hrs), one each from breast cancer and melanoma.

Reviewer's comments: Based on data from Tables 10-13 and Figure 3, the reviewer concludes that:

- 1) Dosing experience from next day surgery is very limited, deriving from only 40 patients from the two phase 3 studies combined.
- 2) The 40 patients who underwent next day surgery were mostly from NEO3-05. Only 2 of the 40 next day surgery patients were from NEO3-09.

(b) (4)

6.9 Subgroup Analyses Based on Study Sites and Injection Volume (NEO3-08)

Neoprobe reported clinical study deviation to the FDA in April 2009 that in Study NEO3-05, Sites 05 and 06 violated study protocol and had used larger than specified injection volumes. As part of the safety and QA/QC investigations, Neoprobe sponsored an in vitro binding study (NEO3-08) that investigated the in vitro binding properties of Lymphoseek in macrophages expressing Human Mannose Binding Receptors. The study indicated a relative V_{max} at ~2.0 mL of the total volume injected. It is also the conclusion of the investigation that Tc 99m Lymphoseek usage at the 50 µg dose in volumes greater than a total of 2.0 mL (aliquoted) or a single injection greater than 0.5 mL should be strongly discouraged. Neoprobe's recommended injection volumes based on the study are summarized below in Table 14.

Table 14: Recommended Injection Volumes for 50 µg Dose of Lymphoseek

Recommended Lymphoseek Injection Concentration	2.67 – 26.7 µM
Total Injection Volume	0.1 – 1.0 mL / 50 µg 0.1 – 0.4 mL / 10 µg x 5
Injection Aliquot Ranges	0.1 – 0.5 mL / 12.5 µg x 4 0.1 – 0.5 mL / 25 µg x 2 0.1 – 0.5 mL / 50 µg x 1

7 Review of Safety

Safety Summary

The safety database for Lymphoseek is small – 531 patients from all the clinical studies including 63 patients from the ongoing NEO3-06 study (Table 15). This means that if a particular adverse reaction is observed in one patient in the clinical trials, it represents a 0.2% incidence rate. The size of the safety population would be inadequate to assess adverse reactions occurring at incidence rates below 0.2%. However within this small safety population, observed product safety profile appears acceptable. There was no death or adverse drop-outs from Lymphoseek. None of the serious adverse reactions were considered related to Lymphoseek. Approximately 3% of patients had adverse reactions that were considered related to Lymphoseek, including possibly related, probably related, and definitely related. The review team paid particular attention to hypersensitivity reactions during in the safety analysis because of Lymphoseek’s chemical structure – its backbone dextran is known to cause hypersensitivity reactions, including anaphylactic reactions. No systemic anaphylactic or anaphylactoid reactions were observed in the clinical studies. Approximately 3% of patients experienced local allergic reactions, manifested as rash (1%), erythema (1%), skin irritation (0.4%), pruritus (0.4%), or urticaria (0.2%). However these observations were confounded by the comparator blue dye (Lymphazurin), which was administered to each patient in the two completed phase 3 clinical studies, and Lymphazurin is known to cause hypersensitivity reactions (including anaphylactic reactions) in approximately 2% of patients.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 15: Safety Population: Clinical Studies Used to Evaluate the Safety of Tc 99m Lymphoseek

Study	Study Phase, Design; Cancer Type	Objectives	Safety Patients Contributing to the ISS Database
NEO3-A	Phase 1, single center, four-arm; breast cancer	PK and Safety	18
NEO3-B	Phase 1, single center, four-arm; breast cancer	PK and Safety	18
NEO3-C	Phase 1, single center, four-arm; breast cancer	PK and Safety	20
NEO3-01	Phase 2, single-arm; breast cancer and melanoma	PD and Safety	80
NEO3-05	Phase 3, single-arm; breast cancer and melanoma	Efficacy and Safety	179
NEO3-09	Phase 3, single-arm; breast cancer and melanoma	Efficacy and Safety	153
NEO3-06 ^a	Phase 3, single-arm; head and neck squamous cell carcinoma	Efficacy and Safety	63
Total Patients in ISS Database			531

^aOngoing study

PD: pharmacodynamics. PK: pharmacokinetics.

During the NDA review cycle, a phase 3 clinical study, NEO3-06, conducted in patients with head and neck cancer, is still ongoing. Neoprobe submitted the 120-day and 240-day safety update amendments (at 120 and 240 days after NDA submission) to the NDA from new patients enrolled and injected with Tc 99m Lymphoseek from the NEO3-06 trial. The 120-day update included 19 new HNSCC patients, and the 240-day update included another 6 new HNSCC patients (total 63 patients from NEO3-06) to the integrated safety database.

7.1.2 Categorization of Adverse Events

The coding dictionary used for mapping investigator verbatim terms to preferred terms was MedDRA Dictionary version 12.0. A Lymphoseek-specific “coding dictionary” for mapping all adverse event verbatim terms to preferred terms for studies included in the Integrated Summary of Safety (ISS) was submitted in the ISS SDTM dataset ae.xpt. The investigator verbatim terms (or “reported terms”) are coded AETERM, and the MedDRA preferred terms (or “dictionary-derived terms”) are coded AEDECOD in this tabulated dataset. The MedDRA lower level terms (or the “modified reported terms” used to obtain the preferred terms) are coded AEMODIFY.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The cumulative number of subjects exposed to Tc 99m Lymphoseek in integrated safety database, including patients in either the ongoing or completed clinical trials with complete safety data, at the time of the review completion is 531 patients. This population includes patients with melanoma (228), breast cancer (240), cutaneous HNSCC (6), and intraoral HNSCC (57).

7.2 Adequacy of Safety Assessments

The safety database for Lymphoseek is small. Data from a total of 531 patients contributed to a pooled safety database; the integrated safety analysis of the pooled data is presented in the Integrated Summary of Safety (ISS). Enrolled patients in these studies included patients with breast cancer, melanoma, and head and neck squamous cell cancer (HNSCC). Table 16 summarizes patient age and tumor type in the Lymphoseek safety population.

Table 16: Cumulative Subject Exposure to Investigational Drug from Ongoing and Completed Clinical Trials by Age and Tumor Type

Age Range	Number of Subjects				Total
	Melanoma	Breast Cancer	Cutaneous HNSCC	Intraoral HNSCC	
< 35 years of age	13	6	0	1	20
35 - 65 years of age	140	173	3	35	351
> 65 years of age	75	61	3	21	160
Total	228	240	6	57	531

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during any clinical study.

7.3.2 Nonfatal Serious Adverse Events

Table 17 presents the number and percent of patients with serious adverse events, by system organ class and preferred term.

The SOC most frequently associated with SAEs (≥ 3 patients) were:

- Cardiac disorders (four patients: one melanoma patient each experienced bradycardia, myocardial infarction, or tachycardia; one cutaneous HNSCC patient with atrial fibrillation)
- Gastrointestinal disorders (three patients: one melanoma patient experienced, intraabdominal hematoma, one melanoma patient experienced nausea and vomiting, and one intraoral HNSCC patient experienced tongue hemorrhage)
- Infections and infestations (six patients: three melanoma patients experienced cellulitis; two breast cancer patients, one with cellulitis and one with herpes zoster ophthalmic; and one intraoral HNSCC patient with wound infection)
- Injury, poisoning and procedural complications (three patients: one melanoma patient with seroma, one breast cancer patient with vascular injury, and one intraoral HNSCC patient with arterial injury)
- Respiratory, thoracic, and mediastinal disorders (four patients: one melanoma patient with asthma; one breast cancer patient with pneumothorax; and two intraoral HNSCC patients, one with acute respiratory failure and one with atelectasis)

Table 17: Cumulative Summary Tabulations of Serious Adverse Events (SAEs) in the Lymphoseek Integrated Safety Database

Adverse Event Category	Cancer Type				Overall (N=531)
	Melanoma (N=228)	Breast Cancer (N=240)	HNSCC Cutaneous (N=6)	HNSCC Intraoral (N=57)	
Total Number of SAEs	13	5	2	7	27
Patients with at Least One SAE	12 (5.3%)	5 (2.1%)	1 (16.7%)	7 (12.3%)	25 (4.7%)
Cardiac Disorders	3 (1.3%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	4 (0.8%)
Atrial Fibrillation	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	1 (0.2%)
Bradycardia	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Myocardial Infarction	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Tachycardia	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Gastrointestinal Disorders	2 (0.9%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	3 (0.6%)
Intra-Abdominal Haematoma	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Nausea	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Tongue Haemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (0.2%)
Vomiting	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Infections And Infestations	3 (1.3%)	2 (0.8%)	0 (0.0%)	1 (1.8%)	6 (1.1%)
Cellulitis	3 (1.3%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	4 (0.8%)
Herpes Zoster Ophthalmic	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Wound Infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (0.2%)
Injury, Poisoning And Procedural Complications	1 (0.4%)	1 (0.4%)	0 (0.0%)	1 (1.8%)	3 (0.6%)
Arterial Injury	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (0.2%)
Seroma	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Vascular Injury	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Nervous System Disorders	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	2 (0.4%)
Syncope	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	2 (0.4%)
Renal And Urinary Disorders	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Bladder Perforation	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Respiratory, Thoracic And Mediastinal Disorders	1 (0.4%)	1 (0.4%)	0 (0.0%)	2 (3.5%)	4 (0.8%)
Acute Respiratory Failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (0.2%)
Asthma	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Atelectasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (0.2%)

Pneumothorax	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Surgical And Medical Procedures	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Hospitalisation	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Vascular Disorders	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (1.8%)	2 (0.4%)
Haematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (0.2%)
Hypotension	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	1 (0.2%)

All SAEs resolved, and no patients were withdrawn due to an SAE or AE. No SAEs were considered to be related to Tc 99m Lymphoseek.

7.3.3 Dropouts and/or Discontinuations

No drug-related AEs led to drop-outs.

7.3.4 AEs of Special Interest

Because of known anaphylactic reactions over dextran, which serves as a backbone in Lymphoseek, AEs were reviewed for potential allergic or hypersensitivity reactions. These AEs were selected prospectively to include rash, hives/urticaria, pruritus/itching, anaphylaxis, hypotension, and skin irritation or reaction. A small number of patients experienced AEs of special interest, and most were patients with melanoma or breast cancer.

Table 18 Number and Percent of Patients with Adverse Events of Special Interest, by System Organ Class and Preferred Term

Adverse Event Category ^{a,b}	Cancer Type				Overall (N=525)
	Melanoma (N=228)	Breast Cancer (N=240)	HNSCC Cutaneous (N=6)	HNSCC Intraoral (N=51)	
Immune System Disorders	0 (0.0%)	4 (1.7%)	0 (0.0%)	1 (2.0%)	5 (1.0%)
Drug Hypersensitivity	0 (0.0%)	2 (0.8%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Hypersensitivity	0 (0.0%)	2 (0.8%)	0 (0.0%)	1 (2.0%)	3 (0.6%)
Skin And Subcutaneous Tissue Disorders	8 (3.5%)	7 (2.9%)	1 (16.7%)	1 (2.0%)	17 (3.2%)
Erythema	3 (1.3%)	2 (0.8%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
Pruritus	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Pruritus Allergic	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (0.2%)
Rash	1 (0.4%)	3 (1.3%)	0 (0.0%)	1 (2.0%)	5 (1.0%)
Skin Irritation	1 (0.4%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Urticaria	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)

a Adverse events coded with MedDRA Coding Dictionary Version 12.0.

b MedDRA terms searched for rash, hypersensitivity, rash, skin irritation, erythema, pruritus, urticaria.

Abbreviations: HNSCC, head and neck squamous cell carcinoma.

Reviewer's comments: Approximately 3% of patients had local allergic reactions, as manifested by rash, erythema, skin irritation, urticaria, and pruritus. No systemic anaphylactic or anaphylactoid reactions were reported in the relatively small safety population of 531 patients. In the two completed phase 3 studies (NEO3-05 and NEO3-09), each patient was administered both Lymphoseek and the blue dye (Lymphazurin). According to the Lymphazurin label, hypersensitivity reactions (including anaphylactic reactions) occur in approximately 2% of patients receiving the drug. Therefore it is difficult to attribute the observed local allergic reactions to Lymphoseek alone.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 19 summarizes adverse reactions possibly, probability, or definitely related to Lymphoseek, arranged by System Organ Class (SOC) and Preferred Term (PT). Overall approximately 3% of patients had adverse reaction(s) related to Lymphoseek. The three System Organ Classes mostly involved are: Administration Site Conditions (1%), Nervous System Disorders (1%), and Musculoskeletal and Connective Tissue Disorders (0.8%). The three most common adverse reactions in Preferred Term are injection site irritation (0.8%), headache (0.4%), and neck pain (0.4%).

Table 19 Number and Percent of Patients with Adverse Events, Relationship to Tc 99m Lymphoseek = Possibly, Probably, or Definitely, by System Organ Class and Preferred Term

Adverse Event Category ^a	Cancer Type				Overall (N=525)
	Melanoma (N=228)	Breast Cancer (N=240)	HNSCC Cutaneous (N=6)	HNSCC Intraoral (N=51)	
Number of Adverse Events	5	8	2	14	29
Patients with at Least One AE	3 (1.3%)	8 (3.3%)	1 (16.7%)	4 (7.8%)	16 (3.0%)
Cardiac Disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (0.2%)
Sinus Tachycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (0.2%)
Eye Disorders	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Vision Blurred	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Gastrointestinal Disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (0.2%)
Nausea	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (0.2%)
General Disorders And Administration Site Conditions	0 (0.0%)	4 (1.7%)	0 (0.0%)	1 (2.0%)	5 (1.0%)
Feeling Hot	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (0.2%)
Injection Site Irritation	0 (0.0%)	3 (1.3%)	0 (0.0%)	1 (2.0%)	4 (0.8%)
Injection Site Pain	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Injury, Poisoning And Procedural Complications	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	2 (0.4%)
Incision Site Pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (0.2%)
Seroma	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (0.2%)
Wound Dehiscence	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Metabolism And Nutrition Disorders	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Hypercalcaemia	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Musculoskeletal And Connective Tissue Disorders	0 (0.0%)	1 (0.4%)	0 (0.0%)	3 (5.9%)	4 (0.8%)
Musculoskeletal Pain	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Neck Pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.9%)	2 (0.4%)
Pain In Extremity	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (0.2%)
Pain In Jaw	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (0.2%)
Nervous System Disorders	1 (0.4%)	0 (0.0%)	1 (16.7%)	3 (5.9%)	5 (1.0%)
Aphasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (0.2%)
Dizziness	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	1 (0.2%)
Headache	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.9%)	2 (0.4%)
Paraesthesia	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Renal And Urinary Disorders	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Micturition Urgency	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Pollakiuria	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Reproductive System And Breast Disorders	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Breast Pain	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)

Skin And Subcutaneous Tissue Disorders	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Skin Irritation	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Vascular Disorders	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	1 (0.2%)
Flushing	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	1 (0.2%)

8 Postmarket Experience

Not applicable for this New Molecular Entity.

9 Appendices

9.1 Advisory Committee Meeting

Since there are already two other products on the market for similar indications, the Division decided not to hold an advisory committee meeting for the application.

9.2 Draft DMIP Consultation Report to ORP on the MSMB Capital Citizen Petition

The following is a draft consult report completed by the primary clinical reviewer on the MSMB Capital Citizen Petition. At the time the Lymphoseek primary clinical review is due in DARRTS based on 21st century review timeline (July 16, 2012), the draft consult report has not been reviewed by division upper management. In subsequent weeks the draft consult report will be reviewed and revised by division directors and office directors, and an official copy of the finalized DMIP consultation report to ORP on the citizen petition will be checked in DARRTS separately.

7 pages have been Withheld in Full as b5 immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRENDA Q YE
07/16/2012

ALEXANDER GOROVETS
07/16/2012

Clinical Team Leader confirms that the filed primary clinical review is complete.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202207

Applicant: Lymphoseek

Stamp Date: August 10, 2011

Drug Name: Lymphoseek

NDA/BLA Type: 505(b)(1)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			Draft labeling is in PLR format.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?		X		The Clinical Overview contains a section on Benefits and Risks Conclusions (2.5.6), which lists benefits and risks of the product. No other benefit-risk analysis included.
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: NEO3-A, NEO3-B Sample Size: 24 in each study Arms: 4 Location in submission: Module 5.3.3.2.1, 5.3.3.2.2	X			NEO3-A enrolled 24 patients with breast cancer and tested 4, 20, 100 µg dose of Lymphoseek. NEO3-B enrolled 24 patients with melanoma and tested 20, 100, 200 µg

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					dose of Lymphoseek.
EFFICACY					
14.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>Pivotal Study #1: NEO3-05 Indication: (b) (4)</p> <p>Pivotal Study #2: NEO3-09 Indication: (b) (4)</p>	X			Same indication tested for both Phase 3 studies.
15.	<p>Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?</p>	X			<p>In the proposed labeling indication, after the above tested indications, the following is added:</p> <p>(b) (4)</p> <p><i>Reviewer's comments:</i> the addition of (b) (4)</p>
16.	<p>Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.</p>	X			The endpoints of Concordance with blue dye were agreed upon by the Agency
17.	<p>Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?</p>			X	The vast majority of study centers and subjects are in the U.S.
SAFETY					
18.	<p>Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?</p>	X			
19.	<p>Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?</p>	X			Table 44 of Appendix 17 lists summary statistics of QT Interval
20.	<p>Has the applicant presented a safety assessment based on all</p>	X			

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	current worldwide knowledge regarding this product?				
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			Safety population of the application = 506 (including the 38 patients from the ongoing NEO3-06 study), which is small and represents the bare minimum safety population requirement.
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		X		Can request for this in the filing letter.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			NME and a new class chemically by itself
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	No deaths in patients given Lymphoseek. No adverse dropouts.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Progress report of the ongoing study NEO3-06 submitted with the NDA; its available safety data (safety population = 38) included in the ISS.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Requested full pediatric waiver
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	The vast majority of study centers and subjects are in the

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					U.S.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			The sponsor submitted the missing efficacy analysis datasets as an amendment to the NDA on 10/7/2011 (Sequence No. 3)
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			List of IRB and sample consent forms included

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1) Provide an integrated summary of the risk and benefit assessment. While Module 2.5 Clinical Overview includes a section on risk benefit conclusions, the technical sections of the application lack an integrated summary of the risk and benefit assessment as defined under 21CFR314.50(d)(5)(viii) - "an integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling".

2) Provide the coding dictionary used for mapping investigator verbatim terms to preferred terms. The "coding dictionary" consists of a list of all investigator verbatim terms used in safety reporting and the preferred terms to which they were mapped.

Brenda Ye, M.D. 10/13/2011

 Reviewing Medical Officer Date

Alex Gorovets, M.D. 10/13/2011

 Clinical Team Leader Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRENDA Q YE
10/13/2011