CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 202-207	Submission Dates: August 10, 2011 SDN 1 November 22, 2011 SDN 8 January 19, 2012 SDN 13
Brand Name	Lymphoseek®: Kit for the Preparation of Technetium Tc 99m Tilmanocept for Injection
Generic Name	Technetium Tc 99m Tilmanocept for Injection.
Reviewer	Christy S John, Ph.D.
Team Leader	Gene Williams, Ph.D.
OCP Division	Division of Clinical Pharmacology V
OND Division	Division of Medical Imaging Products
Applicant	Navidea Biopharmaceuticals, Inc.
Relevant IND(s)	IND 61,757
Submission Type; Code	New NDA; 1S
Formulation; Strength(s)	(b) (4) Injection
Proposed Indication	(b) (4)

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1. Executive Summary

The applicant, Navidea Biopharmaceuticals, Inc (formerly Neoprobe), submitted NDA 202-207 for Lymphoseek® Kit for the Preparation of Technetium Tc 99m Tilmanocept for Injection on August 10, 2011. The proposed indication is, (b) (4)

Lymphoseek (Tilmanocept) is a synthetic macromolecule (~19 kDa) and has a mean diameter of about 7 nm. Lymphoseek was designed with mannose moiety leashes to biotarget uptake and retention in lymph nodes via binding to the macrophage mannose binding receptor (MBR, CD206).

The 50 ug (2.7 nmol) dose selected for subsequent efficacy and safety studies was selected based on two Phase I studies that also tested higher and lower doses.

Technetium Tc 99m Lymphoseek Injection can be administered either by intradermal, subcutaneous, subareolar, or peritumoral injection. The proposed dose for same day surgery is 50 µg Lymphoseek radiolabeled with 18.5 MBq (0.5 mCi) Technetium Tc 99m. (b) (4) Total injection volume should be no greater than 1.0 mL and no less than 0.1 mL. Individual injection volumes should not exceed 0.5 mL or be less than 0.1 mL. Imaging/mapping should be initiated no sooner than (b) (4) minutes post-injection (for same day surgery) (b) (4)

The primary efficacy clinical endpoint was the concordance of "hot node detected by Tc-99m-Lymphoseek" vs. "node detected by Vital Blue Dye." Two Phase 3 studies (NEO3-05 and NEO3-09) were prospective, open-label, multicenter, within-patient, comparison studies of Tc 99m Lymphoseek and Vital Blue Dye (VBD) in patients with primary melanoma or breast cancer. For Study NEO3-05, the nodal concordance between Tc 99m Lymphoseek and VBD was 97.52% among patients with melanoma and 89.63% in patients with breast cancer. For Study NEO3-09, concordance rate was 100.0% in both melanoma and breast cancer patients.

While the studies were not designed to make comparisons, data suggest that efficacy is reduced when Lymphoseek is administered the day before surgery rather than on the day of surgery. (b) (4)

There were no drug-interaction studies or special population studies conducted. Since the drug is injected as a local microdose, there is low systemic exposure of drug and metabolites were

not characterized. The immunogenicity of tilmanocept was not studied in humans. No immunogenic events were reported in the clinical trials.

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology V has reviewed NDA 202-207. The application is acceptable from a clinical pharmacology standpoint, provided agreement is reached on package insert language.

1.2 Post-marketing Requirements/Commitments

We have no recommendations for post-marketing requirements or commitments.

1.3 Summary of Clinical Pharmacology Findings

Intraoperative Lymph node Mapping (ILM) is an intraoperative examination that can be performed with a radiopharmaceutical (such as Tc-99m-sulfur colloid or Tc-99m-Lymphoseek) or vital blue dye. When a radiopharmaceutical is used, a handheld gamma isotope detection device is employed. ILM has the goal of identifying the first lymph node(s) to receive lymphatic flow from the primary tumor site or tumor bed to allow selective excision of these nodes. Technetium Tc 99m Lymphoseek® Injection (abbreviated Tc 99m Lymphoseek) is a radiotracer that accumulates in lymphatic tissue by binding to a mannose binding receptor (MBR) protein that resides on the surface of macrophages and dendritic cells. Chemically, Tc 99m Lymphoseek (drug substance: tilmanocept) is technetium-99m labeled diethylenetriamine pentaacetic acid (DTPA) mannosyl dextran.

Technetium Tc 99m Lymphoseek Injection can be administered either by intradermal, subcutaneous, subareolar, or peritumoral injection. The proposed dose for same day surgery is 50 µg Lymphoseek radiolabeled with 18.5 MBq (0.5 mCi) Technetium Tc 99m. (b) (4) Total injection volume should be no greater than 1.0 mL and no less than 0.1 mL. Individual injection volumes should not exceed 0.5 mL nor be less than 0.1 mL. Imaging/mapping should be initiated no sooner than (b) (4) minutes post-injection (for same day surgery) (b) (4) Next day surgery will be a topic of discussion, below.

The applicant, Navidea, conducted two Phase I dose finding trials. These studies included a range of Tc 99m Lymphoseek drug doses (doses of 0.2, 1.0, and 5.0 nmol in NEO3-A and 1.0, 5.0, and 10.0 nmol in NEO3-B). The lowest dose tested (0.2 nmol; NEO3-A) failed to localize lymphatic structures in greater than 60% of patients, indicating that this dose would likely be suboptimal. The next higher doses (1.0 and 5.0 nmol) were not significantly different in intra-operative imaging performance (**Table 1.**). Thus, an overall analysis of dose performance predicted that a dose of 50 µg Tc 99m Lymphoseek (~2.7 nmol) would provide clinically relevant localization without exceeding an apparently asymptotic dose. Additionally, the Phase 1 NEO3-C study, using a single Lymphoseek dose of 1.0 nmol, evaluated two Tc 99m labeling doses (0.5 mCi and 1.0 mCi) between same day and next day surgery procedures. "No

significant" differences were indicated between Tc 99m Lymphoseek radiolabeling amounts in terms of uptake into the sentinel nodes at the 3 hour (0.5 mCi) or 16 hour (1.0 mCi) post-surgery injection times.

Table 1. Dose determination in breast and melanoma patients		
	Breast Cancer	Melanoma
	(0.25 mL X 4)	(0.1 or 0.2 mL X 4)
Cold dose (nmoles; hot dose is constant = 0.5 mCi)	Amount of radioactivity in nodes in pmoles	
0.2	0.09 + 0.20	
1	6.5 + 2.5	5.0 + 8.0
2.7	50 ug – dose selected for Phase 3	
5	10.6 + 8.4	17.5 + 13.7
10		58.2 + 41.2

The primary clinical efficacy endpoint was the concordance of "hot node detected by Tc-99m-Lymphoseek" with nodes detected by Vital Blue Dye (VBD). Two Phase 3 studies (NEO3-05 and NEO3-09) were prospective, open-label, multicenter, within-patient, comparison studies of Tc 99m Lymphoseek and VBD as lymphoid tissue targeting agents in patients with primary melanoma or breast cancer. NEO3-05 was conducted in 14 study centers in the U.S. and one center in Israel. NEO3-09 was conducted in eight study centers in the U.S.

In both studies, patients received 50 µg Tc 99m Lymphoseek by injection in close proximity to the primary tumor followed by ILM. For Study NEO3-05 the primary endpoint, the overall concordance rate of Tc 99m Lymphoseek and VBD, 93.4%, was statistically significant at the 0.05 one-sided α level ($p = 0.0401$). The nodal concordance between Tc 99m Lymphoseek and VBD was higher among patients with melanoma (97.5%) than those with breast cancer (89.6%) in the primary analysis. On a patient level, the overall concordance rate was 92.4%, with concordance remaining higher among melanoma patients (96.0%) than among breast cancer patients (89.2%).

For Study NEO3-09 the primary endpoint, the overall concordance rate of Tc 99m Lymphoseek and VBD (100.0%), was statistically significant ($p < 0.0001$). The nodal concordance between Tc 99m Lymphoseek and VBD was the same (100.0%) among patients with melanoma and those with breast cancer in the primary analysis. The concordance at a patient level in the ITT population was also 100.0%, and was the same in patients with melanoma (100.0%) and breast cancer (100.0%).

Navidea conducted an analysis for efficacy (nodal concordance) as a function of time post-injection (same day surgery and next day surgery). The analysis showed that the overall nodal concordance rates for breast cancer patients for same day surgery and next day surgery were 0.94 and 0.83, respectively (**Table 2.**) (b)(4)

(b) (4)

Table 2. Nodal Concordance Rate (# patients) as a Function of Time Post-Injection.			
	15min- 2 Hrs	2- <6 Hrs	15-22 Hrs
	Combined: NEO-3-05 & NEO3-09		
Overall	0.98(56)	0.97(339)	0.84(25)
	NEO-3-05		
Overall	0.94(18)	0.94 (163)	0.83(23)
Melanoma	1.00(6)	0.99(73)	1.00(2)
Breast	0.91(12)	0.90(90)	0.81(21)
	NEO3-09		
Overall	1.00(38)	1.00(176)	1.00(2)
Melanoma	1.00(5)	1.00(104)	1.00(1)
Breast	1.00(33)	1.00(72)	1.00(1)

There were no drug-interaction studies or special population studies conducted. Since the drug is injected as a local microdose, there is low systemic exposure of drug and metabolites were not characterized. The immunogenicity of tilmanocept was not studied in humans. No immunogenic events were reported in the clinical trials.

2. Question Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Lymphoseek is tilmanocpet labeled with Tc 99m. Tilmanocept 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. Tilmanocept (**Figure 1.**) is a synthetic, low molecular weight macromolecule (~19 kDa) with a mean diameter of about 7 nm.

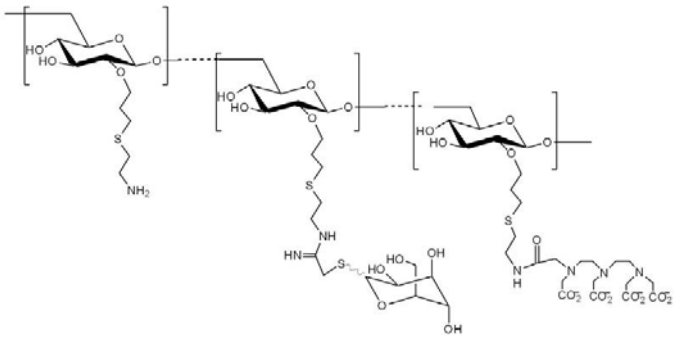

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Figure 1. Chemical construct of Tilmanocept

Lymphoseek® is supplied as a cold kit (non-radiolabeled) containing a sterile, lyophilized preparation of Tilmanocept 0.25 mg and Sterile Buffered Saline diluent.

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Tilmanocept is a (b) (4) synthetic macromolecule consisting of multiple units of diethylenetriaminepentaacetic acid (DTPA) and mannose, each attached to a 10 kDa dextran backbone. Tilmanocept accumulates in lymphatic tissue by specifically binding to mannose binding receptors (MBRs; CD206) that reside on the surface of resident dendritic cells and macrophages. The mannose moieties act as a substrate for the receptor, and the DTPA serves as a chelating moiety for radiolabeling with Tc 99m.

CD206 or macrophage mannose binding receptor (MBR) is an endocytic and phagocytic receptor that recognizes appropriately configured carbohydrate ligands in target molecules. It is a type I membrane protein whose primary structure predicts the presence of an N-terminal, extracellular cysteine-rich domain, followed by a fibronectin type II-like repeat and eight C-type lectin carbohydrate recognition domains (CRDs) repeated in tandem.

The dissociation constant (K_D) for tilmanocept binding in rabbit liver homogenate (likely stellate and Kupffer cells and other reticuloendothelial cells) was $1.2\pm0.7x10^{-10}$ M. The binding of GMP-prepared Tc 99m Lymphoseek to the human MBR (hMBR) was evaluated in human monocyte-derived macrophages (MDMs) expressing the native hMBR and in human embryonic kidney 293 (HEK 293) cells transfected with plasmid expressing full-length recombinant hMBR (rhMBR) or empty vector. Binding was evaluated by Western blot and autoradiography, and all experiments were conducted both with and without pre-incubation of unlabeled Lymphoseek. Results of this study demonstrated that Tc 99m Lymphoseek selectively binds to its intended receptor target, the hMBR.

An *in vitro* study was conducted to evaluate the effect of varying the number of mannose moieties per molecule of tilmanocept drug substance on in vitro binding to human macrophage MBRs using a competitive binding paradigm. Binding efficacy was evaluated for tilmanocept batches containing 7.4, 13.6, and 19.1 mannose moieties/dextran and in a reference standard containing 17.2 mannose moieties/dextran. This range effectively represents the GMP manufacturing specification range for mannose conjugation (12 to 20 mannose moieties) in the

tilmanocept drug substance structure. Relative to these batches, binding was reduced in the tilmanocept batch containing 7.4 mannose moieties/dextran, which is below the lower boundary of the manufacturing specification range of 12 mannose moieties. From these data, a break point value for reduced binding performance was estimated at 11.7 mannose moieties.

2.1.3 What are the proposed dosages and routes of administration?

Technetium Tc 99m Lymphoseek Injection can be administered either by intradermal, subcutaneous, subareolar, or peritumoral injection.

For same day surgery: administer 50 µg Lymphoseek radiolabeled with 18.5 MBq (0.5 mCi) Technetium Tc 99m.

(b) (4)

Total injection volume should be no greater than 1.0 mL and no less than 0.1 mL. Individual injection volumes should not exceed 0.5 mL or be less than 0.1 mL. Imaging/mapping is to begin no sooner than (b) (4) minutes post-injection (b) (4) for intraoperative lymphatic mapping.

2.1.4 What drugs (substances, products) indicated for the same indication are approved in the US?

Two agents are currently approved for mapping lymph nodes:
1) Lymphazurin (isosulfan blue, vital blue dye). The package insert indication states, "… 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."
2) Technetium Tc 99m Sulfur Colloid Injection. The package insert states, " … is indicated for the localization of lymph nodes in the lymphatic pathway draining a primary tumor in patients with breast cancer."

2.2 General Clinical Pharmacology

2.2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA.

Four Phase 1 studies and one Phase 2 study were submitted as support for the clinical pharmacology section of this NDA. The studies are listed below in **Table 3.**

Table 3. Clinical Pharmacology Studies

Study No.	Study Title	IND Holder at Study Initiation / Report Prepared By	No. of Enrolled Patients
NEO3-B	A Phase 1 Study of Tc^{99m} Labeled Lymphoseek Used in Sentinel Lymph Node Mapping in Patients with Cutaneous Melanoma	UCSD / UCSD	24
NEO3-C	NCI Phase 1 Study of Lymphoseek® in Patients with Breast Cancer	UCSD / Neoprobe	32
[redacted] (b) (4)			
Phase 2			
NEO3-01	A Phase 2, Single Arm, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of Lymphoseek as a Lymphoid Tissue Targeting Agent in Patients With Known or Suspected Melanoma or Breast Cancer Who Are Undergoing Lymph Node Mapping	Neoprobe / Neoprobe	84

Abbreviations: UCSD, University of California, San Diego

Data from two of these studies [redacted] (b) (4) were insufficient for PK analysis, thus radiopharmacokinetic properties were described for only three studies: two in breast cancer patients (NEO3-A and NEO3-C) and one in melanoma patients (NEO3-B).

The Phase 1 studies enrolled adult patients with breast cancer (N = 56; NEO3-A + NEO3-C), melanoma (N = 24; NEO3-B). [redacted] (b) (4)

2.2.2 What are the design features of the clinical pharmacology studies and the clinical studies used to support dosing or claims?

2.2.3 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

The primary clinical efficacy endpoint was the concordance of "hot node detected by Tc-99m-Lymphoseek" with nodes detected by Vital Blue Dye (VBD). Detection by Tc 99m Lymphoseek was based on handheld gamma probe counts meeting the threshold criteria (i.e., "3σ rule"). A set of three 2-second counts was recorded *in vivo* and a separate set of three 2-second counts was recorded on non-lymphoid tissue as background. A positive finding (i.e., localization) was defined as a mean lymph node count greater than 3 standard deviations above background. Any lymph node count not meeting the 3σ rule was considered a negative (non-

localized) finding. The primary measure of concordance, based on a per node calculation, was of the form:

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

Two Phase 3 studies (NEO3-05 and NEO3-09) were prospective, open-label, multicenter, within-patient, comparison studies of Tc 99m Lymphoseek and VBD as lymphoid tissue targeting agents in patients with primary melanoma or breast cancer. NEO3-05 was conducted in 14 study centers in the U.S. and one center in Israel. NEO3-09 was conducted in eight study centers in the U.S.

In both studies, patients received 50 µg Tc 99m Lymphoseek by injection in close proximity to the primary tumor followed by Intraoperative Lymph node Mapping (ILM). For Study NEO3-05 the primary endpoint, the overall concordance rate of Tc 99m Lymphoseek and VBD, 93.4%, (**Table 4.**) was statistically significant at the 0.05 one-sided α level ($p = 0.0401$). The nodal concordance between Tc 99m Lymphoseek and VBD was higher among patients with melanoma (97.5%) than those with breast cancer (89.6%) in the primary analysis. On a patient level, the overall concordance rate was 92.4%, with concordance remaining higher among melanoma patients (96.0%) than among breast cancer patients (89.2%).

For Study NEO3-09 the primary endpoint, the overall concordance rate of Tc 99m Lymphoseek and VBD (100.0%), was statistically significant ($p < 0.0001$). The nodal concordance between Tc 99m Lymphoseek and VBD was the same (100.0%) among patients with melanoma and those with breast cancer in the primary analysis (**Table 4.**).

Table 4. Primary efficacy results in pivotal trials

Study No	Treatment Group	Number enrolled /Injected/completed	Primary endpoint	Efficacy result	p-Value
NEO3-05	50 ug	195/179/169	*In vivo* nodal concordance rate of lymphoseek to VBD	93.36% 95% Exact CI = 0.896, 0.961	0.040 (one-sided)
NEO3-09	50 ug	163/153/152	*In vivo* nodal concordance rate of lymphoseek to VBD	100% 95% Exact CI = 0.984, 1.00	<0.0001

2.2.4 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Systematic metabolite profiling was not performed. The package insert dose is 50 µg (2.7 nmoles) -- a microdose. Navidea writes the following (indented) in the study summary for Study NEO3-A,

> Plasma Metabolites
> A portion of the blood sampled at 15 minutes, 2.5, and 6 hours post injection was assayed for TcDTPA-mannosyl-dextran concentration, possible metabolic products and the concentration, and free technetium-99m. After separation of plasma by centrifugation two 0.250 ml sample were applied to a Superdex Peptide HR (10 x 300mm) and a Superdex 75 (10 x 300mm) FPLC column. The eluate (0.37 ml 0.9% saline per min) of each column was collected for 79 minutes into eighteen 4-minute fractions (with an initial 7 minutes to waste) and counted in an autowell gamma counter using a 100 - 200 keV window.

Although the method indicates that 4-minute fractions were collected, Navidea does not present results as a function of elution time. Rather, a single data data point is reported for each blood sample collection time point. Across the sampled time points, 6-61% of recovered gamma radioactivity was "non-parent" (**Table 5.,** for details of the dose regimen and patient population of the patients sampled see the first three rows of **Table 6.**). Further interpretation of these data is not possible, as attempts to characterize "non-parent" are not reported.

Table 5. Percentage of gamma-emission in blood not attributable to parent across doses and time

	Column A			Column B		
Time (h)	Dose			Dose		
	0.2 nmol = 3.8 ug	1 nmol = 19 ug	5 nmol = 95 ug	0.2 nmol = 3.8 ug	1 nmol = 19 ug	5 nmol = 95 ug
0.25	40%	55%	61%	6%	49%	58%
2	25%	35%	43%	6%	37%	38%
6	16%	33%	12%	16%	22%	17%

2.2.5 Exposure-Response

2.2.5.1 What are the characteristics of the exposure-response relationship for effectiveness?

2.2.5.2 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Two of the Phase 1 studies included a range of Tc 99m Lymphoseek drug doses (doses of 0.2, 1.0, and 5.0 nmol in NEO3-A and 1.0, 5.0, and 10.0 nmol in NEO3-B). In these studies, the lowest dose tested (0.2 nmol; NEO3-A) failed to localize lymphatic structures in greater than 60% of patients, indicating that this dose would likely be suboptimal. The next higher doses (1.0 and 5.0 nmol) were not significantly different in intraoperative imaging performance. A dose of 50 µg Tc 99m Lymphoseek (~2.7 nmol) was selected to provide

clinically relevant localization (**Table 1.**) without exceeding a potentially asymptotic dose.

Table 1. Dose determination in breast and melanoma patients		
	Breast Cancer	Melanoma
	(0.25 mL X 4)	(0.1 or 0.2 mL X 4)
Cold dose (nmoles; hot dose is constant = 0.5 mCi)	Amount of radioactivity in nodes in pmoles	
0.2	0.09 + 0.20	
1	6.5 + 2.5	5.0 + 8.0
2.7	50 ug – dose selected for Phase 3	
5	10.6 + 8.4	17.5 + 13.7
10		58.2 + 41.2

The Phase 1 NEO3-C study, using a single Lymphoseek dose of 1.0 nmol, evaluated two Tc 99m labeling doses (0.5 mCi and 1.0 mCi) given at varied times relative to surgery (same day and next day surgery). The applicant, Navidea, concluded that there were not "significant differences" in uptake into sentinel nodes at the 3 hour (0.5 mCi) or 16 hour (1.0 mCi) post-surgery injection times. The results of the Phase 3 studies, stratified by time, are shown in **Table 2.** It can be seen that the data acquired for Day 2 surgery is more limited than that acquired for Day 1 surgery. The data in **Table 2**. suggests that, in spite of the larger radioactive dose (2 mCi vs. 0.5 mCi), Day 2 surgery may have resulted in lower concordance. (b) (4)

[redacted]

Table 2. Nodal Concordance Rate (# patients) as a Function of Time Post-Injection.			
	15min- 2 Hrs	2- <6 Hrs	15-22 Hrs
	Combined: NEO-3-05 & NEO3-09		
Overall	0.98(56)	0.97(339)	0.84(25)
	NEO-3-05		
Overall	0.94(18)	0.94 (163)	0.83(23)
Melanoma	1.00(6)	0.99(73)	1.00(2)
Breast	0.91(12)	0.90(90)	0.81(21)
	NEO3-09		
Overall	1.00(38)	1.00(176)	1.00(2)
Melanoma	1.00(5)	1.00(104)	1.00(1)
Breast	1.00(33)	1.00(72)	1.00(1)

2.2.5.3 What are the characteristics of the exposure-response relationships for safety?

No exposure-response relationship was determined for this single administration drug given as a microdose.

2.2.5.4 Does this drug prolong QT/QTc Interval?

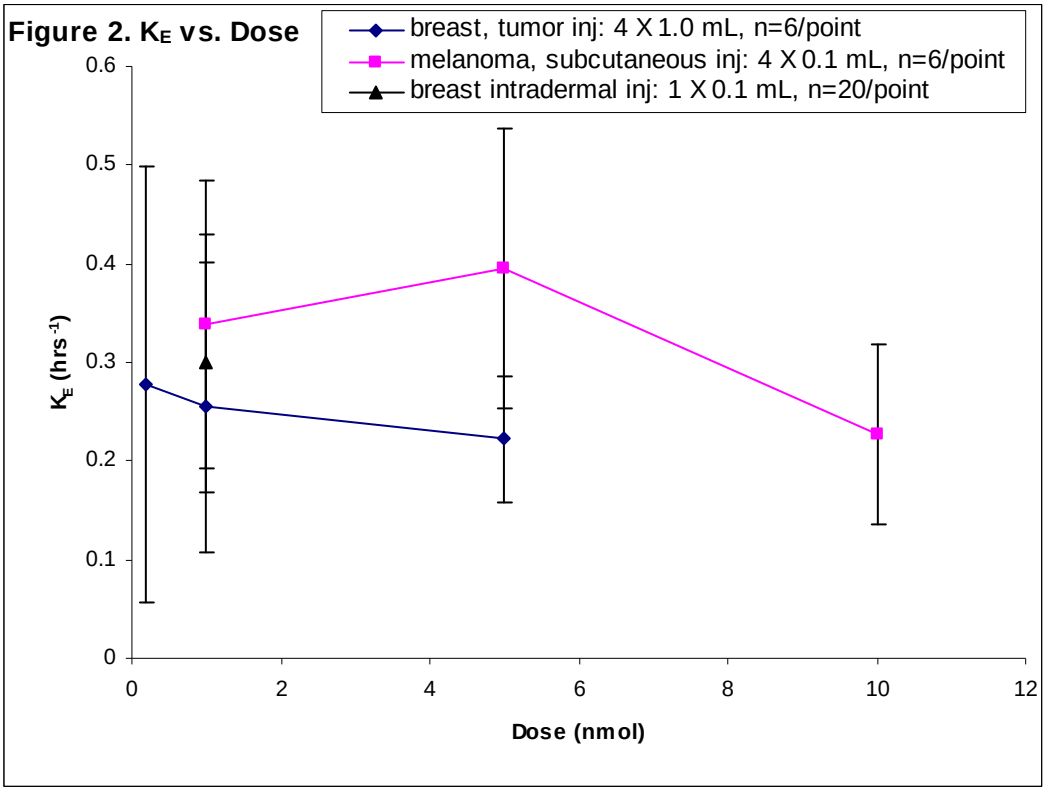
Navidea writes, "Changes in mean ECG parameters, overall, from baseline to the 6 to 30 hour safety assessment period were minimal (increases in HR of 5.0 bpm, PR of 3.4 msec, QRS of 0.4 msec, QT of 4.6 msec; decreases in QRS of 1.4 degrees) and not clinically significant." The reviewer finds this acceptable for this drug which is administered a single time, locally, as a microdose.

2.2.6 What are the PK characteristics of the drug?
2.2.7 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?
2.2.8 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?
2.2.9 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?
2.2.10 What are the characteristics of drug absorption?
2.2.11 What are the characteristics of drug distribution?
2.2.12 What are the single and multiple dose PK parameters of parent drug and metabolites?

Lymphoseek has not been studied in healthy volunteers. Three studies contributed "pharmacokinetics" data from patients. The primary end of "pharmacokinetics" determinations was to describe the elimination of Tc 99m (what was quantitated was gamma emission; it is known that metabolites are present – see section **2.2.4.**) from the site of administration. Results are summarized in **Table 6.** The elimination rate (K_E) data from these results are shown graphically in **Figure 2.**

Table 6. Elimination rate of gamma radioactivity from injection site (K_E)

				Total Tc 99m Tilmanocept dose			K_E	K_E	$t_{1/2}$ (rough estimate) = ln(2) ÷ mean K_E
Study	Disease	Injections	n	mCi	nmol	ug	mean	std dev	h
NEO3-A	breast cancer	4 X 1.0 mL tumor site	6	0.5	0.2	3.8	0.278	0.221	2.49
NEO3-A	breast cancer	4 X 1.0 mL tumor site	6	0.5	1	19	0.255	0.147	2.72
NEO3-A	breast cancer	4 X 1.0 mL tumor site	6	0.5	5	95	0.222	0.064	3.12
NEO3-C	breast cancer	1 X 0.1 mL intradermal	20	0.5 or 1.0	1	19	0.299	0.13	2.32
NEO3-B	melanoma	4 X 0.1 mL subcutaneous	6	0.5	1	19	0.338	0.146	2.05
NEO3-B	melanoma	4 X 0.1 mL subcutaneous	6	0.5	5	95	0.396	0.142	1.75
NEO3-B	melanoma	4 X 0.1 mL subcutaneous	6	0.5	10	190	0.227	0.092	3.05



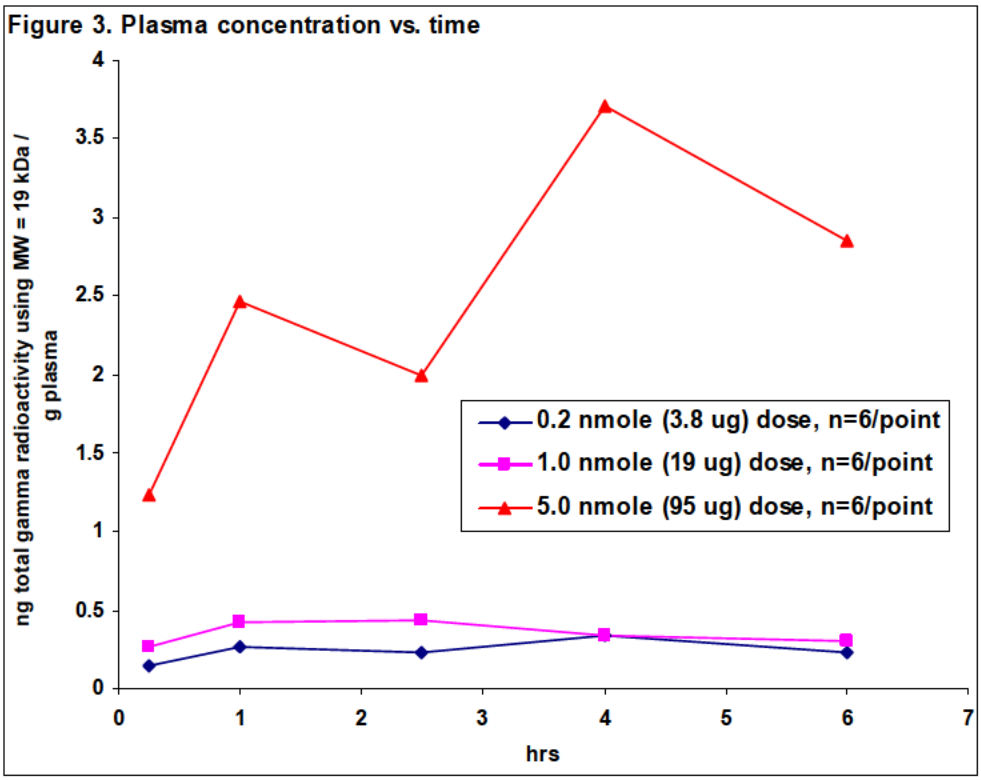
Although the number of patients studied (most often 6/group) is too small to draw nuanced conclusions, the reviewer sees no clear effects of 1) dose, 2) route, or 3) number of injections on elimination rate from the injection site.

The sampling schedules (i.e., the schedule for imaging of the injection site region) used to acquire the data in **Table 6.** and **Figure 2.** are shown in **Table 7.** The reviewer notes that sampling was for only approximately one half life (compare half-life estimates in last column of **Table 6.** to the sampling time points in **Table 7.**), and is insufficient if a late elimination phase is present. While suboptimal, the reviewer judges the lack of extended sampling to not be an approval issue for this radioimaging drug which 1) is administered only a single time, 2) exhibits fairly rapid decay of radioactivity (physical half-life of Tc 99m = 6.0 hours), and 3) is given as at a low radioactivity dose (0.5 mCi).

Table 7. Injection site sampling schedule for determination of elimination rate of gamma radioactivity (K_E)

Study	Injection site sampling (imaging) times
NEO3-A	immediately post-injection 0.25, 0.5, 0.75, 1, 2 and 3 h post-injection
NEO3-C	2.5 h post-injection
NEO3-B	immediately post-injection 0.25, 0.5, 0.75, 1 and 2 h post-injection

Figure 3. presents plasma pharmacokinetics data from breast cancer patients (Study NEO3-A, see **Table 5.** for a description of how these patients were dosed, and **Table 6.** and **Figure 2.** for injection site elimination data from these same patients).



The concentrations (y-axis) in **Figure 3.** are in units of mass, not units of moles. Tc 99m tilmanocept has a molecular weight of approximately 19 kDa. Thus, the C_{MAX} of 3.7 ng/g plasma observed at the highest dose (5.0 nmole dose) would correspond, after adjustment on a molar basis, to a C_{MAX} of 0.098 ng/g plasma for a small molecule drug with a molecular weight of 500 Da.

2.2.13 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study was conducted.

2.2.14 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

Systematic metabolite profiling was not performed (see section **2.2.4.**). The administered dose was 50 µg -- a microdose. Systemic circulation of drug is low (see **Figure 3.** and accompanying text).

2.2.15 What are the characteristics of drug metabolism

Metabolite profiling was not performed. The administered dose was 50 μg -- a microdose.

2.2.16 Is there evidence for excretion of parent drug and/or metabolites into bile?

A mass balance study was not performed and biliary excretion was not investigated.

2.2.17 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

There is very little systemic circulation of the drug (see **Figure 3.** and accompanying text). Enterohepatic recirculation for parent and /or metabolites was not investigated.

2.2.18 What are the characteristics of drug excretion in urine?

Routes of drug excretion from the body were not investigated.

2.2.19 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Figure 2. presents dose-concentration linearity data. The drug is indicated for a single administration. Changes in linearity with 1) repeat dosing and 2) time were not studied.

2.2.20 How do the PK parameters change with time following chronic dosing?

The drug is indicated for a single administration. Chronic dosing was not investigated.

2.2.21 Is there evidence for a circadian rhythm of the PK?

The drug is indicated for a single time administration. Data regarding circadian rhythm was not collected.

2.3 Intrinsic Factors

2.3.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

Limited pharmacokinetics data were accumulated; the data are too sparse to allow for an assessment of the impact of intrinsic factors on pharmacokinetics.

2.3.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

2.3.2.1 Severity of Disease State

2.3.2.2 Body Weight

2.3.2.3 Elderly
2.3.2.4 Pediatric Patients
2.3.2.5 Race/Ethnicity
2.3.2.6 Renal Impairment
2.3.2.7 Hepatic Impairment

Limited pharmacokinetics data were accumulated: no specific population studies studies were performed and pharmacokinetics data to allow for covariate screening was not performed. The ability of systemic pharmacokinetics to predict for responses for this locally administered drug is unknown. The utility of adjusting dose in specific populations is also unknown.

2.3.3 What pregnancy and lactation use information is available?

No pregnancy and lactation use information is available.

2.3.4 Does genetic variation impact exposure and/or response?

No information on the impact of genetic variation on exposure and/or response is available.

2.3.5 Does Tc-99m Lymphoseek cause immune response?
2.3.5.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?
2.3.5.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?
2.3.5.3 Do the anti-product antibodies have neutralizing activity?
2.3.5.4 What is the impact of anti-product antibodies on clinical efficacy?
2.3.5.5 What is the impact of anti-product antibodies on clinical safety?

The immunogenic effect of Tc-99m Lymphoseek was not formally studied. No anaphylactic reactions were observed in clinical trials. As the molecular weight of the drug is ~19 kDa, the theoretical possibility of immunogenic reaction does exist. However, given the heretofore negative clinical results, and that the drug will be administered largely if not exclusively a single time per patient, we find it acceptable to not have formal immunogenicity studies.

2.4 Extrinsic Factors
2.4.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?
2.4.2 Is the drug a substrate of CYP enzymes?
2.4.3 What are the drug-drug interactions?
2.4.4 Does the label specify co-administration of another drug?
2.4.5 What other co-medications are likely to be administered to the target population?
2.4.6 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

No *in vitro* metabolism or *in vivo* drug-drug interaction studies were conducted for this large molecule administered a single time as a microdose. Navidea states that literature suggests that the use of co-injected anesthetics may reduce lymphatic pulsing. This information is included in

the package insert. There is no known mechanistic basis for pharmacodynamic drug-drug interactions.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.5.2.1 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

2.5.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.5.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

2.5.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

2.5.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?

2.5.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

2.5.6 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?

2.5.7 What is evidence that MR formulation displays less variability in Cmax, AUC and Cmin than IR formulation?

2.5.8 Does the MR product show dose dumping *in vivo*?

2.5.9 Does ethanol *in vitro* have a dose-dumping effect on the MR product?

2.5.10 Are the MR and IR products marketed simultaneously?

2.5.11 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PKPD relationship?

2.5.12 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?

Lymphoseek is a non-controlled release product administered as a microdose at a single point in time via non-oral routes. Navidea writes,

> "No changes to the dosage formulation occurred during development, or are anticipated, that would affect the bioavailability of the product. Therefore, no biopharmaceutic studies (dissolution, bioavailability, or bioequivalence) were conducted for Lymphoseek,"

2.6 Analytical Section

2.6.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

2.6.2 Which metabolites have been selected for analysis and why?

2.6.3 For all moieties measured, is free, bound, or total measured?

2.6.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

2.6.5.1 What are the lower and upper limits of quantitation?

2.6.5.2 What are the accuracy, precision, and selectivity at these limits?

2.6.5.3 What is the sample stability under conditions used in the study?

2.6.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?

Navidea writes,

> "… no biopharmaceutic studies (dissolution, bioavailability, or bioequivalence) were conducted for Lymphoseek, and no validation reports for any associated analytical methods are provided."

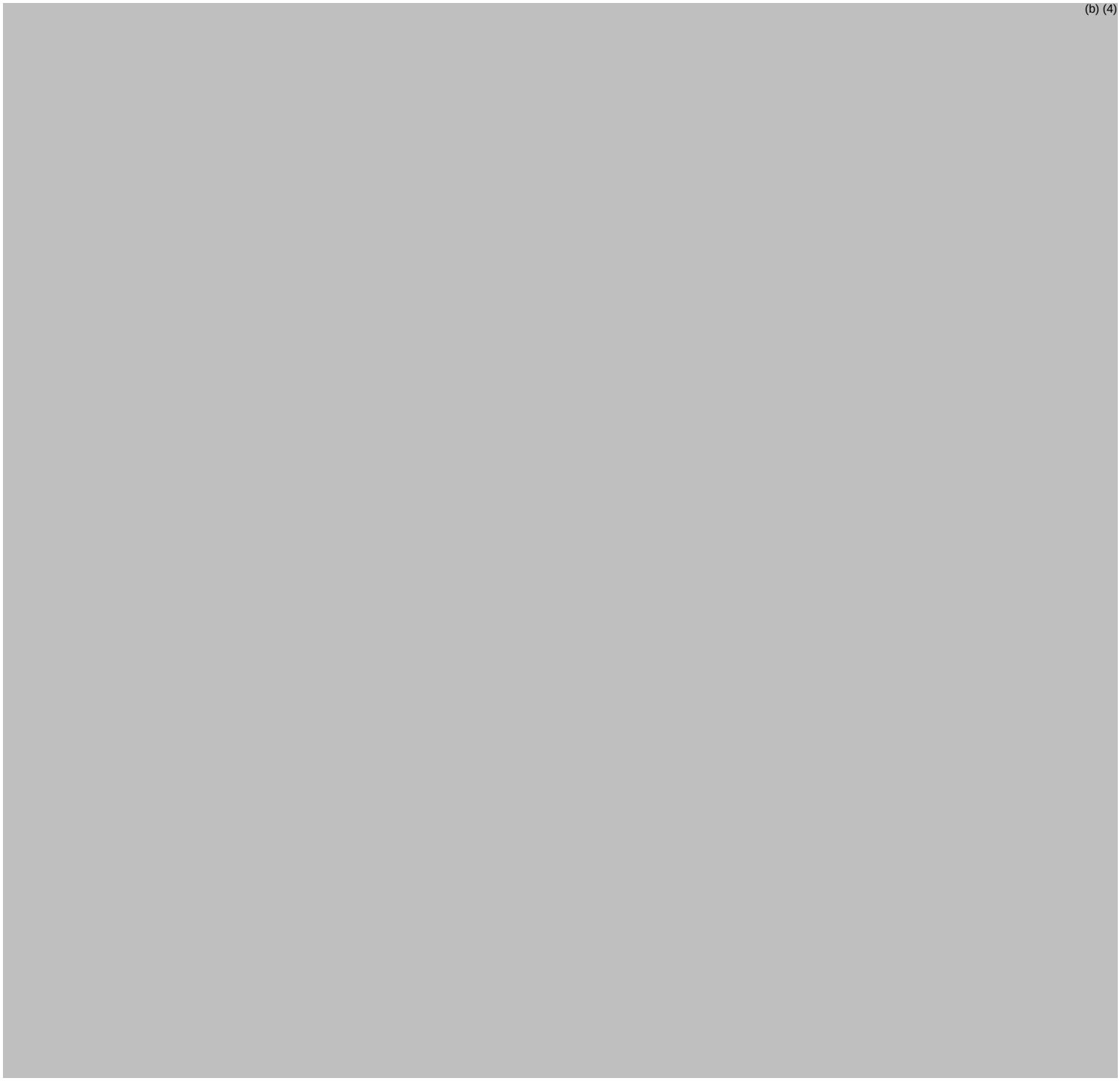
All pharmacokinetics studies employed radio-detection; non-radioactive tilmanocept and metabolites were not quantitated, except for the limited description of the existence of non-parent (see section **2.2.4.**). The reviewer finds the lack of assay validation acceptable for the current NDA, as

1) quantitation of total gamma radioactivity is unlikely to be unreliable, and
2) the pharmacokinetics data has limited impact on dosing and the package insert.

3. Detailed Labeling Recommendations

The reviewer's recommendations for changes to sections **7 DRUG INTERACTIONS** and **12 CLINICAL PHARMACOLOGY** of Navidea's proposed package insert appear on the next page as "track changes." Although the reviewer has no recommendations for changes to the section, section **5.4 Concomitant Use or Co-injection with Local Anesthetics** is included because it regards a drug interaction issue. The reviewer also recommends that (b) (4)

Appendix 4.2. Reviewer's Proposed Package Insert.


(b) (4)

4 Appendices

4.1 Applicant's Proposed Package Insert (original, annotated)

4.2 Reviewer's Proposed Package Insert

4.3 Cover sheet and OCPB Filing/Review Form

48 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.3 Cover sheet and OCPB Filing/Review Form

5 pages of the Duplicate Clinical Pharmacology and Biopharmaceutics Filing Checklist dated 10/24/2011 have been Withheld in Full immediately following this page, and can be found in this review

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

/s/

CHRISTY S JOHN
07/12/2012

GENE M WILLIAMS
07/12/2012
I concur with Dr. John's recommendations.

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	202-207	**Brand Name**	Tc-99m Lymphoseek
OCP Division (I, II, III, IV, V)	V	**Generic Name**	Tc-99mTilmanocept
Medical Division	Division of Medical Imaging Products	**Drug Class**	Imaging
OCP Reviewer	Christy S. John, Ph.D.	**Indication(s)**	(b) (4)
OCP Team Leader	Gene Williams, Ph.D.	**Dosage Form**	Clear Solution
		Dosing Regimen	50 µg of Lymphoseek 0.5 mCi for the same day surgery (b) (4)
Date of Submission	08/10/2011	**Route of Administration**	Intradermal, peritumoral, subcutaneous or subareolar

Estimated Due Date of OCP Review	2/10/2012	**Sponsor**	Neoprobe Corporation
PDUFA Due Date	06/10/2012	**Priority Classification**	S
Division Due Date	4/10/2012		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology	**X**			
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X	5		
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	5			

Filability and QBR comments		
	"X" if yes	**Comments**
Application fileable ?	**X**	
Comments sent to firm ?	None	
QBR questions (key issues to be considered)	What are the major metabolites? How are they eliminated? Do the metabolite(s) have binding affinity for mannose binding receptors (MBR)?	
Other comments or information not included above		
Primary reviewer signature	**Christy S. John, Ph.D.**	
Secondary reviewer Signature and date	**Gene Williams, Ph.D.**	

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

/s/

CHRISTY S JOHN
10/24/2011

GENE M WILLIAMS
10/24/2011