NDA/BLA Multidisciplinary Review and Evaluation

Application Type	NDA Efficacy Supplement
Application Number(s)	NDA 202207 S012
Priority or Standard	Standard
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Division/Office	Division of Imaging and Radiation Medicine/Office of Specialty Medicine
Review Completion Date	
Established/Proper Name	Technetium 99m Tilmanocept
(Proposed) Trade Name	Lymphoseek
Pharmacologic Class	Radioactive diagnostic agent
Applicant	Cardinal Health 414, LLC
Dosage form	Kit for preparation of Lymphoseek injection
Applicant Proposed Indication(s)/Population(s)	Lymphatic mapping using a handheld gamma counter to locate lymph nodes draining a primary tumor site in adult and pediatric patients with solid tumors for which this procedure is a component of intraoperative management.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	396487001 |Sentinel lymph node biopsy (procedure)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Lymphatic mapping using a handheld gamma counter to locate lymph nodes draining a primary tumor site in adult and pediatric patients age 1 month and older with solid tumors for which this procedure is a component of intraoperative management.
Recommended SNOMED CT Indication Disease Term for each Indication	178292004 |Sampling of lymph node (procedure)

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DIRM, Division of Imaging and Radiation Medicine
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DPMH, Division of Pediatric and Maternal Health
OB, Office of Biostatistics
OCP, Office of Clinical Pharmacology
OPQ, Office of Pharmaceutical Quality
OPDP, Office of Prescription Drug Promotion
OSE, Office of Surveillance and Epidemiology

Glossary

AE	adverse event
CD	cluster of differentiation
CT	computed tomography
DTPA	diethylenetriaminepentaacetic acid
FDA	Food and Drug Administration
ILM	intraoperative lymphocyte mapping
ITT	intent-to-treat
LN	lymph node
PeRC	Pediatric Review Committee
PK	pharmacokinetic
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
SAE	serious adverse event
SLNB	sentinel lymph node biopsy
sNDA	supplemental new drug application
SOC	system organ class
SPECT	single photon emission computed tomography

1. Executive Summary

1.1. Product Introduction

Lymphoseek is a diagnostic radiopharmaceutical consisting of a relatively low molecular weight macromolecule (~20 kDa) containing 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 mannose binding receptor found in lymphatic tissues (macrophages and dendritic cells), and the DTPA serves as a chelating agent for labeling with technetium-99m.

Lymphoseek was originally approved in 2013 for an anatomical delineation claim based on colocalization relative to a comparable approved imaging agent. In particular, Lymphoseek was approved for a lymphatic mapping indication in adult patients with breast cancer and melanoma because the proportion of excised lymph nodes with uptake of Lymphoseek radiolabel alone and colocalized with uptake of Lymphazurin was adequately high in two studies.

In June 2014, the approved indication was expanded to include a new indication associated with pathology detection based on study in a new patient population in which performance against a reliable truth standard could be evaluated. In particular, Lymphoseek was approved for a sentinel node biopsy indication in adult patients with squamous cell carcinoma of the oral cavity because the false-negative rate for cancer in an interpretable sample of excised lymph nodes (with and without uptake of the Lymphoseek radiolabel) was adequately low in a third study.

In October 2014, following additional analysis of results from the three studies previously relied upon, a lymphoscintigraphy claim was added, the sentinel node biopsy indication was expanded to include adults patients with melanoma and breast cancer, and the lymphatic mapping indication was expanded to include adult patient with solid tumors for which lymphatic mapping is a component of intraoperative management.

The subject of this multidisciplinary review and evaluation is the Applicant's third efficacy supplement. The Applicant seeks to expand Lymphoseek's lymphoscintigraphy and lymphatic mapping indication to pediatric patients in fulfillment of a postmarketing requirement for pediatric study in patients age 1 month and older.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Based on convergent results of new pediatric study NAV3-18 and findings previously relied upon from three adequate and well controlled studies in adults, the review team recommends fulfillment of Pediatric Research Equity Act postmarketing requirement 2789-1 and finds substantial evidence of favorable benefit-risk for expansion of Lymphoseek's lymphatic mapping indication to pediatric patients age 1 month and older.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Applicant has completed Pediatric Research Equity Act postmarketing requirement study 2789-1 (NAV3-18) in 23 pediatric patients with melanoma, rhabdomyosarcoma, or other solid tumor. Efficacy results from this pediatric study support those from three larger adequate and well controlled studies previously relied upon for finding Lymphoseek effective for lymphoscintigraphy and lymphatic mapping in adults with solid tumors. In the pediatric study, efficacy results notably included numerically high rates for identifying at least one Lymphoseek-positive lesion per patient on preoperative lymphoscintigraphy (22 of 23 patients); resecting at least one Lymphoseek-positive node during lymphatic mapping (22 of 23 patients); colocalization of Lymphoseek-positive and Lymphazurin-positive nodes (47 of 47); and colocalization of Lymphoseek-positive and Lymphazurin-negative nodes in both subjects with cancer-positive nodes on pathology. No new safety signals were identified. Together, these results support the review team's assessment that Lymphoseek is safe and effective for lymphoscintigraphy and lymphatic mapping in pediatric patients with solid tumors age 1 month and older.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Intraoperative identification of lymph nodes draining primary sites of solid tumor growth is a prerequisite for accurate cancer staging. • Substantial evidence has been found to support use of Lymphoseek with or without preoperative imaging for intraoperative lymphatic mapping in adults with solid tumors. • Lack of evidence from pediatric patients leaves uncertainty regarding the safety and effectiveness of Lymphoseek for lymphoscintigraphy and lymphatic mapping in pediatric patients.	Pediatric study of Lymphoseek was required to address evidentiary gaps.
Current Treatment Options	• Lymphazurin, Lymphoseek, and technetium-99m sulfur colloid have been approved for lymphatic mapping in adults. • No imaging agent has been approved for lymphatic mapping in pediatric patients.	Approval of Lymphoseek for lymphatic mapping in pediatric subjects would address an unmet medical need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Of 23 pediatric patients with melanoma, rhabdomyosarcoma, or other solid tumor studied under Pediatric Research Equity Act postmarketing requirement study 2789-1, the Applicant reported: • In 22, at least one Lymphoseek-positive location per patient was identified on preoperative lymphoscintigraphy • In 22, at least one Lymphoseek-positive node was resected during lymphatic mapping surgery • In 47 of 47 nodes positive for Lymphazurin, Lymphoseek-positive nodes were colocalized • In both patients with cancer-positive nodes on pathology, all nodes were Lymphoseek-positive and Lymphazurin-negative	Combined with convergent findings from previously relied upon adult studies, Lymphoseek is effective for lymphoscintigraphy and lymphatic mapping in pediatric patients with solid tumors age 1 month and older.
Risk and Risk Management	• Lymphoseek is a microdose imaging radiopharmaceutical with a generally benign safety based on use under approved labeling for adults. • No new safety signals were identified from the Applicant's analysis of adverse events observed under study 2789-1 or based on the Applicant's analysis of postmarketing data.	Combined with convergent findings from previously relied adult studies, Lymphoseek is safe for lymphoscintigraphy and lymphatic mapping in pediatric patients with solid tumors age 1 month and older.

1.4. Patient Experience Data

Patient Experience Data Relevant to This Application (check all that apply)

□	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		
		□	Patient-reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
x	**Patient experience data were not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

A summary of pediatric solid tumors with a propensity for regional lymphatic spread was provided via consultation with the Center for Drug Evaluation and Research Office of Oncologic Disease. Relevant portions of this consultative review are excerpted in the indented text below.

> "Pediatric solid tumors encompass a heterogeneous group of nonhematologic cancers. As with adult cancers, the role of lymph node biopsy depends upon the tumors' propensity for regional lymphatic spread. Lymph node sampling is an integral component of the pre-treatment staging process for selected pediatric solid tumors such as paratesticular rhabdomyosarcoma, epithelioid sarcoma, clear cell sarcoma, and Wilms tumor. Selection of lymph nodes for sampling is based upon a variety of factors, including proximity to the primary tumor, radiographic changes suggestive of lymph node involvement, gross appearance at the time of surgery, and in some cases, lymphatic mapping and sentinel lymph node detection… Among pediatric solid tumors, lymphatic mapping and SLN biopsy appear to be most promising for staging in melanoma, subtypes of rhabdomyosarcoma (particularly rhabdomyosarcoma of the extremities and paratesticular rhabdomyosarcoma), epithelioid sarcoma, and clear cell sarcoma. Lymphatic mapping and SLN biopsy may also be beneficial for pre-treatment staging of germ cell tumors, neuroblastoma, and anaplastic Wilms tumor."

2.2. Analysis of Current Treatment Options

The U.S. Food and Drug Administration (FDA) has yet to approve any imaging agent for lymphatic mapping in pediatric patients. Approved options for lymphatic mapping in adults have been previously summarized and remain unchanged. Relevant prior review excerpts are provided in the indented text below.

> "Two radiopharmaceuticals (sulfur colloid and Lymphoseek, radiolabeled with technetium 99m) and an optical imaging agent (Lymphazurin, a blue dye) are approved for use for the visualization/localization of lymphatics draining the region of injection in specific clinical settings that include primary cancers.
>
> The excerpts below describe the indications for adjunctive use of these three products in patients with cancer and the evidence that supported the indication. As explained further below, the localization of lymph vessels and nodes draining a tumor is an indication related only to structure delineation. The term lymphatic mapping is applied to this use. A tracer that helps to identify any lymph nodes to which cancer cells have spread may be useful to surgeons during cancer surgery.
>
> *Lymphoseek*. Lymphoseek was approved in 2013. Efficacy for lymphatic mapping was determined by the number of histology-confirmed lymph nodes identified with

Lymphoseek and a comparator lymphatic tracer. Efficacy analyses were based upon comparisons of the number and proportion of resected lymph nodes that contained a lymph node tracer or neither tracer.

Lymphazurin. Lymphazurin was approved in 1981 and is indicated for use in structural delineation of lymphatics in a number of clinical conditions including cancer. The diagnostic performance data for these uses are not cited in the labeling. The following is excerpted from the prescribing information's indication statement: Lymphazurin 1% (isosulfan blue) upon subcutaneous administration delineates lymphatic vessels draining the region of injection. It is an adjunct to lymphography in lymph node involvement by primary or secondary neoplasm.

Sulfur colloid. The currently marketed sulfur colloid drug was initially approved in 1978. An indication for lymphatic delineation in breast cancer and melanoma was added in 2012 based on a review of the literature showing the tracer localization rate defined as the percentage of procedures in which at least one lymph node containing the tracer was identified. The following is excerpted from the prescribing information's indication statement: Technetium Tc 99m Sulfur Colloid Injection is indicated in adults, to assist in the localization of lymph nodes draining a primary tumor in patients with breast cancer or malignant melanoma when used with a hand-held gamma counter."

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Lymphoseek was approved on 3/13/2013.

The Original Pediatric Research Equity Act (PREA) postmarketing requirement (PMR): evaluating the use of the drug in pediatric patients ages 1 month to 16 years and scheduled plan as:

- Draft protocol submission: 1/31/2015
- Final protocol submission: 4/30/2015
- Study completion: 9/30/2017
- Final report submission: 3/31/2018

3.2. Summary of Presubmission/Submission Regulatory Activity

- 2/23/2018: First PREA/Pediatric Deferral Extension Request due subject enrollment difficulty (granted 4/9/2018)
- 3/12/2019: Second PREA/Pediatric Deferral Extension Request due the subject enrollment difficulty (granted 5/6/2019)

(b) (4)

(b) (4)

- 2/19/2020: The Division of Information Resources Management sent out the PMR/Postmarketing Commitment Supplement Request letter
- 7/22/2020: PMR/Postmarketing Commitment/Clinical—current, Final Report, PREA sNDA S-12, submitted.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

In this efficacy supplement, the Applicant submitted no data requiring Office of Scientific Investigations review, and none was needed.

4.2. Product Quality

In this efficacy supplement, the Applicant submitted no new product quality data, and none was needed.

4.3. Clinical Microbiology

In this efficacy supplement, the Applicant submitted no new microbiology data, and none was needed.

4.4. Devices and Companion Diagnostic Issues

In this efficacy supplement, the Applicant submitted no new device and companion diagnostic data, and none was needed.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The purpose of this review is to provide a nonclinical assessment of Lymphoseek® (technetium Tc 99m tilmanocept) Injection to support a completed PREA postmarketing requirement phase 2 study 2789-1 (NAV3-18) in pediatric patients with melanoma, rhabdomyosarcoma, or

other solid tumor. NAV3-18 is a phase 2, prospective, open-label, nonrandomized, multicenter, blinded pathology assessment study to evaluate the tolerability and the diagnostic utility of Lymphoseek in pediatric subjects from neonatal to less than 18 years of age. The Applicant has filed this sNDA for indication and labeling changes. No nonclinical studies were provided, and none were needed, to support an indication of lymphatic mapping in pediatric solid tumor patients (see also Section 5.5.1 General Toxicology).

This sNDA is being submitted for the following new proposed indication. Lymphoseek® (technetium Tc 99m tilmanocept) injection is a radioactive diagnostic agent indicated with or without scintigraphic imaging for the underlisted:

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

It is recommended that this sNDA s-012 for the proposed use of Lymphoseek (Technetium Tc 99m tilmanocept) injection in pediatric patients aged 1 month to 16 years be approved from a nonclinical perspective.

5.2. Referenced New Drug Applications, Biologics License Applications, Drug Master Files

NDA 202207; investigational new drug 61757

5.3. Pharmacology

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Mechanism of Action: Lymphoseek (tilmanocept) is a macromolecule consisting of multiple units of diethylenetriaminepentaacetic acid (DTPA) and mannose, each covalently attached to a 10 kDa linear dextran backbone. The mannose acts as a ligand for cluster of differentiation (CD) 206, and the DTPA serves as a chelating agent for labeling with technetium Tc 99m. Lymphoseek accumulates in lymphatic tissue and selectively binds to mannose-binding receptor (CD206) located on the surface of macrophages and dendritic cells residing in the lymph nodes.

5.4. Absorption, Distribution, Metabolism, Excretion/ Pharmacokinetics

The Applicant did not submit any dedicated pharmacokinetic (PK) or toxicokinetic studies to support the efficacy supplement and no such data are needed.

5.5. Toxicology

5.5.1. General Toxicology

Dedicated juvenile toxicology studies were not submitted.

Juvenile animal studies may be required to support approval of an indication including a pediatric population based on a nonclinical safety assessment of the mechanism of action, toxicity findings from pivotal animal studies, and other safety signals. However, the Pharmacology/Toxicology reviewer does not consider dedicated juvenile animal studies necessary to support the use of Lymphoseek for this supplement.

A key reason for this consideration is that tilmanocept (DTPA-mannosyl-dextran) binds to the mannose-binding receptor (CD206) expressed on the surface of dendritic cells and macrophages in lymph nodes and is unlikely to cause untoward effects in adult and pediatric populations. As noted in the labeling for the radioactive diagnostic SPECT imaging agent, Lymphoseek (technetium Tc 99m tilmanocept) enables intraoperative lymphatic mapping (ILM) and sentinel lymph node biopsy (SLNB) through CD206 binding.

In the 10/13/2016 Type C meeting background materials (Seq. 134, Supporting Document 218, §10.1.4, p. 14 of 16), the Applicant justified the inclusion of a pediatric population at the same 50-microgram dose level for Lymphoseek used in adult studies via subcutaneous, intradermal, or peritumoral injection. This recommendation was based upon published studies that support the finding that the lymphatic system is functional in human infants, such that the migration of Lymphoseek from the site of injection to the draining lymph nodes should be essentially that as observed in adults (Emery and Dinsdale 1973; Luscieti et al. 1980; Butter et al. 2005; Roaten et al. 2005; De Corti et al. 2009; Alcorn et al. 2013).

Lastly, the Applicant noted that there was no evidence to suggest that injection site clearance or lymph node uptake should differ in the pediatric population based on the mechanism of action of Lymphoseek or characteristics of the lymphatic system in juveniles.

5.5.2. Genetic Toxicology

Genetic toxicology studies were not submitted and are not needed.

5.5.3. Carcinogenicity

Carcinogenicity studies were not submitted and are not needed.

5.5.4. Reproductive and Developmental Toxicology

Reproductive and Developmental toxicology studies were not submitted and are not needed.

6. Clinical Pharmacology

6.1. Executive Summary

The subject of this efficacy supplement is the following indication, which is supported by the included clinical study, extrapolation from previously submitted adult data, and the mechanism of action of the drug product [changes noted in **bold**]:

Lymphoseek® (technetium Tc 99m tilmanocept) injection is a radioactive diagnostic agent indicated with or without scintigraphic imaging for:

- Lymphatic mapping using a handheld gamma counter to locate lymph nodes draining a primary tumor site in **adult and pediatric** patients **age 1 month and older** with solid tumors for which this procedure is a component of intraoperative management.

There is no new clinical pharmacology study performed for pediatric indication for this efficacy supplement.

6.2. Summary of Clinical Pharmacology Assessment

NAV3-18 is a phase 2, prospective, open-label, nonrandomized, multicenter, blinded pathology assessment study to evaluate the tolerability and the diagnostic utility of Lymphoseek in pediatric patients from neonatal to less than 18 years of age with melanoma, rhabdomyosarcoma, or other solid tumors where ILM and SLNB were appropriate and tumor resection or biopsy were planned. For the proposed ILM indication, this study provided similar diagnostic endpoints compared with data obtained in the previously submitted phase 3 studies conducted in adult patients with melanoma and breast cancer (NEO3-05 and NEO3-09) and head and neck cancer (NEO3-06) that support the use of Lymphoseek during preoperative scintigraphic mapping and ILM procedures, allowing for extrapolation to the pediatric population.

There is no new pharmacokinetic data in support of pediatric indication for this sNDA submission.

6.2.1. General Dosing and Therapeutic Individualization

General Dosing

The general dosing for the pediatric population is the same as for the adult population. There are no changes in the dosing and administration section of the prescribing information. The recommended dose of Lymphoseek is 18.5 MBq (0.5 mCi) as a radioactivity dose and 50 mcg as a mass dose. Administer Lymphoseek at least 15 minutes prior to initiating intraoperative lymphatic mapping and sentinel node biopsy; complete these procedures within 15 hours after Lymphoseek injection.

Route of Administration and Injection Method

The route of administration depends on the tumor location and the planned injection technique and includes: subcutaneous, intradermal, subareolar, or peritumoral injection.

Lymphoseek may be administered to a patient as a single injection or as multiple injections. The recommended total injection volume for each patient is 0.1 mL administered in a single syringe; 0.5 mL administered in a single syringe or in multiple syringes (0.1 mL to 0.25 mL each); or 1 mL administered in multiple syringes (0.2 mL to 0.5 mL each).

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

There is no new PK study conducted by the Applicant for this efficacy supplement.

6.3.2. Clinical Pharmacology Questions

Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

The imaging which is the result of the drug concentration in vivo provides the supportive evidence of efficacy.

Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

The proposed dosing is appropriate for the general population for which the indication is being sought.

Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

There is no alternative dosing or management strategy required for subpopulations based on intrinsic patient factors.

Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

There are no clinically relevant food-drug or drug-drug interactions or any management strategy needed as drug is administered as a microdose (50 mcg), only once.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The 2789-1 trial (Protocol NAV3-18) is a phase 2 study in pediatric patients with melanoma, rhabdomyosarcoma, or other solid tumor (Table 1). There were six clinical study sites for NAV3-18, 24 patients enrolled, 23 received the drug injection, 23 with efficacy data and 2 protocol violations, but no protocol violations led to a withdrawal from the study.

Table 1. Listing of Clinical Trials Relevant to this NDA

Trial Identity	NCT No.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
NAV318		A prospective, open label, nonrandomized, multicenter, blinded pathology assessment study to evaluate the tolerability and the diagnostic utility of Lymphoseek in pediatric subjects from neonatal to less than 18 years of age with melanoma, rhabdomyosarcoma, or other solid tumors where ILM and SLNB is appropriate and tumor resection or biopsy is planned. 3 visits: A screening for initial determination of eligibility and evaluation of clinical status, a baseline visit on the day of surgery, and a 4- to 14-day (in person) safety follow-up visit to assess subject disease management.	Lymphoseek with 18.5 MBq (0.5 mCi). For those subjects diagnosed with melanoma, Lymphoseek was to be administered as 1, 2, or 4 intradermal, peritumoral injections at or around the excision biopsy site. For those subjects with rhabdomyosarcoma or other solid tumors, Lymphoseek was to be administered as intradermal peritumoral injection(s) if anatomically appropriate or, if not possible, injection was to be performed as determined clinically appropriate by the surgeon.	• Subject localization rate (defined as the proportion of subjects with Lymphoseek-identified LNs) • Number of LNs identified intraoperatively by Lymphoseek per subject • Proportion of subjects who underwent preoperative SPECT or SPECT/CT imaging • Proportion of subjects with LNs identified preoperatively using SPECT or SPECT/CT imaging • Number of LNs identified preoperatively using SPECT or SPECT/CT imaging • Agreement of the number of nodes identified by preoperative SPECT or SPECT/CT imaging to intraoperative localization • Subject and nodal agreement of central pathology assessment with local pathology assessment of the excised LN(s) to confirm the presence/absence of tumor metastases	A baseline visit on the day of surgery, and a 4- to 14-day (in person) safety follow-up visit to assess AEs and subject disease management.	24	23	6 centers and 1 country (USA)
		Studies to Support Safety						
-								
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
-								

Source: "Table 5.2-1. Tabular Listing of Newly Submitted Clinical Studies" from submission 5.2 Tabular Listing of All Clinical Studies, p. 3/44.
Abbreviations: AE, adverse event; ILM, intraoperative lymphocyte mapping; LN, lymph node; NCT, National Clinical Trials Register; NDA, new drug application; SPECT/CT, single photon emission computed tomography/computed tomography

7.2. Review Strategy

The clinical and statistical review teams reviewed the single NAV3-18 study protocol, efficacy and safety data, and made conclusions.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. NAV3-18

Trial Design

NAV3-18 was a prospective, open-label, nonrandomized, multicenter, blinded pathology assessment study to evaluate the tolerability and the diagnostic utility of Lymphoseek in pediatric subjects from neonatal to less than 18 years of age with melanoma, rhabdomyosarcoma, or other solid tumors where ILM and SLNB is appropriate and tumor resection or biopsy is planned. In accordance with local institutional practice, subjects may also have received Lymphazurin (a vital blue dye) for a within-subject comparison of lymph node (LN) mapping.

The study included three visits: a screening visit for initial determination of eligibility and evaluation of clinical status, a baseline visit on the day of surgery, and a 4- to 14-day safety (in person) follow-up visit to assess subject disease management. Subjects were enrolled in the study for approximately 1.5 months depending on the duration of the screening window (up to 30 days) (Table 2).

Table 2. Schedule of Events

Assessment	Screen (Day -29 to Day 0)	Pre and Postinjection Day 1 (hour: minute relative to Lymphoseek injection)							Safety Follow-up (4 to 14 days; in person)
		Before Injection	0:00	00:10	0:30	1:00	Surgery	After Surgery	
Informed consent	X								
Entry criteria	X								
Medical history and demography	X								
Performance status	X								
Cancer staging	X								X
Vital signs[a]	X	X		X	X	X			X
ECG	X					X			
Physical examination	X								X
Review of medications	X							X	X
Collect blood and urine for central lab[b]	X							X	
Urine or serum pregnancy test[c]	X								
Lymphoseek administration			X						
Lymphoscintigraphy SPECT/CT[d]					X				
Lymphazurin administration[e]							X		
Surgery and SLNB[f]							X		
Treatment plan									X
Adverse event monitoring		X	X	X	X	X	X	X	X

Source: NAV3-18 Protocol Amendment 4 (date 9/1/2017)
[a] Body weight and height will only be collected at screening.
[b] Blood and urine may be collected on day 1 if performed before Lymphoseek injection.
[c] Pregnancy testing should be performed within 48 hours before Lymphoseek injection.
[d] Imaging may begin at the time of injection when performing dynamic imaging. STATIC planar imaging should begin approximately 15 minutes postinjection.
[e] When used, vital blue dye will be administered at the start of or during surgery in accordance with the standard of care at the clinical site.
[f] Surgery, node probing, and harvesting should occur between 15 minutes and 8 hours after Lymphoseek injection.
Abbreviations: ECG, electrocardiogram; SLNB, sentinel lymph node biopsy; SPECT/CT, single photon emission computed tomography/computed tomography

According to the protocol, a total of 0.5 mCi±20% of Lymphoseek was administrated intradermally or subcutaneously as a single injection or as multiple injections. Surgery, node probing, and harvesting were to occur between 30 minutes and 8 hours after Lymphoseek injection.

Study Endpoints

- Subject localization rate (defined as the proportion of subjects with Lymphoseek identified LNs)
- Number of LNs identified intraoperatively by Lymphoseek per subject
- Proportion of subjects who underwent preoperative single photon emission computed tomography (SPECT) or SPECT/computed tomography (CT) imaging
- Proportion of subjects with LNs identified preoperatively using SPECT or SPECT/CT imaging
- Number of LNs identified preoperatively using SPECT or SPECT/CT imaging
- Agreement of the number of nodes identified by preoperative SPECT or SPECT/CT imaging to intraoperative localization
- Subject and nodal agreement of central pathology assessment with local pathology assessment of the excised LN(s) to confirm the presence/absence of tumor metastases

- Nodal false negative rate for Lymphoseek-identified nodes (using blinded central pathology assessment and local pathology assessment)
- Nodal sensitivity for Lymphoseek-identified nodes (using blinded central pathology assessment and local pathology assessment)
- Upstaging (defined as the proportion of patients with pathology-positive LNs who had at least one pathology-positive LN that was identified by Lymphoseek and had no other pathology-positive LNs [i.e., identified by any other method])
- Change in subject nodal staging before and after surgery based upon Lymphoseek-identified nodes
- Changes in treatment plan and relation to LNs identified by Lymphoseek

Statistical Analysis Plan

The safety population is defined as all enrolled subjects with administration of Lymphoseek.

The intent-to-treat (ITT) population is defined as all protocol-eligible subjects with administration of Lymphoseek (with or without Lymphazurin) and complete intraoperative lymphatic mapping.

The blue dye intent-to-treat population is defined as all ITT subjects who were also administered blue dye prior to ILM.

No formal statistical tests were prespecified for the primary diagnostic variables. Planning of the sample size of the study was driven by practical considerations rather than power calculation.

Protocol Amendments

The original study protocol was approved in April 2015. A total of four protocol amendments was made (Amendment 1, August 2015; Amendment 2, January 2016; Amendment 3, January 2017; and Amendment 4, September 2017). These protocol amendments were agreed by the FDA.

8.1.2. Study Results

Compliance with Good Clinical Practices

This investigation was carried out in accordance with the basic ethical principles put forth in the Declaration of Helsinki of the World Medical Assembly and its revisions, as well as the rules of Good Clinical Practices of the U.S. FDA (Protection of Human Subjects, 21 CFR 50; IRB, 21 CFR 56; and IND, 21 CFR 312).

Financial Disclosure

Please see Section 15.2 Financial Disclosure in the Appendices.

Patient Disposition

The disposition of subjects by age group and tumor type is listed in Table 3 and Table 4, respectively, and a flow chart is provided in Figure 1.

Table 3. Subject Disposition by Age Group, Study NAV3-18

	Number (%) of Patients				
	Age 12 to 18 Years	Age 6 to < 12 Years	Age 2 to < 6 Years	Age 1 Month to < 2 Years	Overall
Screen failures	0	0	0	0	0
Enrolled	17	1	4	2	24
Completed	17 (100.0%)	1 (100.0%)	3 (75.0%)	2 (100.0%)	23 (95.8%)
Withdrawn	0 (0.0%)	0 (0.0%)	1[a] (25.0%)	0 (0.0%)	1[a] (4.2%)
Reason for withdrawal:					
Adverse event	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Physician decision	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol deviation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study terminated by sponsor	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrawal by subject	0 (0.0%)	0 (0.0%)	1[a] (25.0%)	0 (0.0%)	1[a] (4.2.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

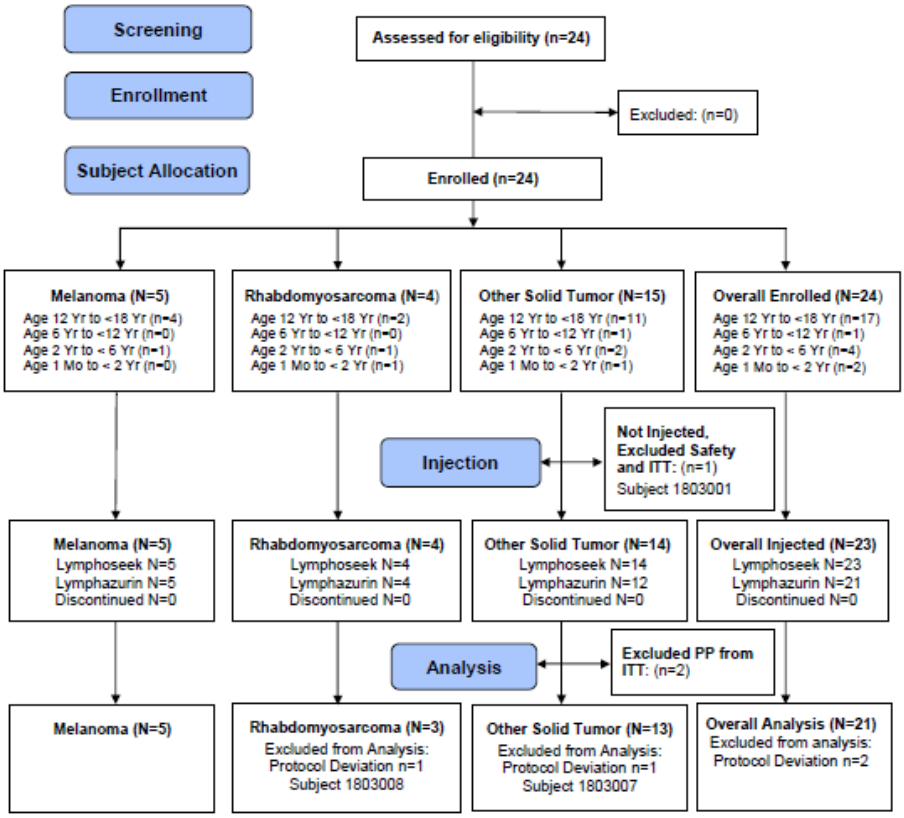
Source: "Table 4. Subject Disposition by Age Group. Study NAV3-18" from NAV3-18 Clinical Study Report, p. 61/316.

Table 4. Subject Disposition by Tumor Type, Study NAV3-18

	Number (%) of Patients			
	Melanoma	Rhabdomyo-sarcoma	Other Solid Tumors	Overall
Screen failures	0	0	0	0
Enrolled	5	4	15	24
Completed	5 (100.0%)	4 (100.0%)	14 (93.3%)	23 (95.8%)
Withdrawn	0 (0.0%)	0 (0.0%)	1[a] (6.7%)	1[a] (4.2%)
Reason for withdrawal:				
Adverse event	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Physician decision	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol deviation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study terminated by sponsor	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrawal by subject	0 (0.0%)	0 (0.0%)	1[a] (6.7%)	1[a] (4.2%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: "Table 5. Subject Disposition by Tumor Type. Study NAV3-18" from NAV3-18 Clinical Study Report, p. 62/316.

Figure 1. Subject Disposition in Study NAV3-18 (N=24)



Source: "Figure 1. Subject Disposition in Study NAV3-18 (N=24)" from NAV3-18 Clinical Study Report, p. 63/316.
Abbreviations: ITT, intent-to-treat; PP, per protocol

Protocol Violations/Deviations

One enrolled subject (b) (6) did not receive Lymphoseek and was therefore excluded from the Safety, ITT, and per protocol populations.

Major protocol violations occurred for two enrolled subjects (b) (6) LN mapping and surgery was not able to be completed for Subject (b) (6) Due to the subject's condition (epidermolysis bullosa dystrophica), upon injecting Lymphoseek, the drug was distributed systemically throughout the body without associated adverse events (AEs).

Subject (b) (6) did not meet inclusion criterion 3; the subject was enrolled then identified as clinically node positive when imaging results became available after screening.

Instances of protocol noncompliance are provided in Table 5.

Table 5. Categories and Frequencies of Protocol Noncompliance, Study NAV3-18

Subject Number	Tumor Type	Age/ Range	Number of Deviations	Comments
(b) (6)	Other	3	1	Subject not in the ITT population
	Other	15	4	At least 1 major protocol deviation
	Rhabdomyosarcoma	14	3	At least 1 major protocol deviation
TOTALS	2	3-15	8	

Source: "Table 6 Categories and Frequencies of Protocol Noncompliance. Study NAV3-18" from NAV3-18 Clinical Study Report, p. 64/316.
[a] Subject (b) (6) (withdrawn) was excluded from the ITT population because Lymphoseek was not administered.
Abbreviation: ITT, intent-to-treat

Table of Demographic Characteristics

Demographic characteristics and baseline data are listed in Table 6.

Table 6. Demographics and Baseline Data Summary by Tumor Type, Age, Height, Weight, and Overall, Continuous Variables, Study NAV3-18, Safety Population (N=23)

Variable	Tumor Type	Mean	Std Dev	n
Age (years)	Melanoma	13.0	5.34	5
	Rhabdomyosarcoma	8.9	7.14	4
	Other solid tumors	11.8	4.09	14
	Age 12 to < 18 years	14.2	1.55	17
	Age 6 to < 12 years	10.0		1
	Age 2 to < 6 years	4.0	0.00	3
	Age 1 month to < 2 years	1.7	0.04	2
	Overall	11.6	4.88	23
Height (in)	Melanoma	61.02	10.615	5
	Rhabdomyosarcoma	52.70	17.672	4
	Other solid tumors	60.21	10.571	14
	Age 12 to < 18 years	64.78	4.430	17
	Age 6 to < 12 years	60.90		1
	Age 2 to < 6 years	44.47	3.800	3
	Age 1 month to < 2 years	31.70	1.414	2
	Overall	59.08	11.755	23
Weight (lb)	Melanoma	51.04	23.695	5
	Rhabdomyosarcoma	39.83	30.537	4
	Other solid tumors	57.64	38.861	14
	Age 12 to < 18 years	64.02	32.434	17
	Age 6 to < 12 years	49.80		1
	Age 2 to < 6 years	20.77	5.713	3
	Age 1 month to < 2 years	10.55	0.212	2
	Overall	53.11	34.173	23

Source: "Table 6 Categories and Frequencies of Protocol Noncompliance. Study NAV3-18" from NAV3-18 Clinical Study Report, p. 64/316.
Abbreviation: Std Dev, standard deviation

The age of the 23 subjects ranged from 1.65 to 17 years. There were two subjects in the youngest group of age 1 month to <2 years in the trial, and both were around 1.7 years old (Table 7). The demographics and baseline data of the subjects are summarized in Table 8.

Table 7. Subjects in the Age Group of 1 Month to <2 Years

Subject #	Tumor	Age	Gender	Race	Pre- Surgical TNM Staging
(b) (6)	RHABDOMYO-SARCOMA	1.65	M	White	T1B, N0, M1, S TAGE 4
	Other solid tumor	1.7	F	White	1, 0, 0, 1

Source: "Table 4. Subject Disposition by Age Group. Study NAV3-18" from NAV3-18 Clinical Study Report, p. 61/316.

Table 8. Demographics and Baseline Data Summary by Tumor Type, Age Group, and Overall—Categorical Variables, Study NAV3-18, Safety Population (N=23)

Demographics Variable	Category	Melanoma (N = 5)	Rhabdomyo-sarcoma (N = 4)	Other Solid Tumors (N = 14)	Overall (N = 23)
Gender	Male	0 (0.0%)	3 (75.0%)	5 (35.7%)	8 (34.8%)
	Female	5 (100.0%)	1 (25.0%)	9 (64.3%)	15 (65.2%)
Race	American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Black or African American	0 (0.0%)	2 (50.0%)	0 (0.0%)	2 (8.7%)
	Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	White	5 (100.0%)	2 (50.0%)	14 (100.0%)	21 (91.3%)
	Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity	Hispanic or Latino	1 (20.0%)	0 (0.0%)	1 (7.1%)	2 (8.7%)
	Not Hispanic or Latino	4 (80.0%)	4 (100.0%)	13 (92.9%)	21 (91.3%)

Source: "Table 10. Demographics and Baseline Data Summary by Tumor Type, Age Group, and Overall - Categorical Variables. Study NAV3-18. Safety Population (N = 23)" from NAV3-18 Clinical Study Report, p. 68/316.

Disease Characteristics (N=23)

Disease characteristics by tumor type are listed in Table 9.

Table 9. Disease Characteristics by Tumor Type

Tumor type	N	%
Melanoma	5	21.7
Rhabdomyosarcoma	4	17.4
Other Solid Tumor	14	60.9
atypical spitz	2	
squamous cell	2	
synovial sarcoma	2	
high-grade undifferentiated sarcoma	1	
Ewing's sarcoma	2	
low-grade sarcoma	1	
epitheliod sarcoma	1	
low-grade fibromyxoid sarcoma	1	
Dabska tumor angiosarcoma	1	
fibrohistiocytoma	1	

Source: Generated by clinical reviewer based on the description "Tumor types being treated in this study were divided between melanoma (21.7%), rhabdomyosarcoma (17.4%), and other solid tumor types (60.9%). The other solid tumors breakdown as follows: atypical spitz (2), squamous cell (2), synovial sarcoma (2), high-grade undifferentiated sarcoma (1), Ewing's sarcoma (2), low-grade sarcoma (1), epitheliod sarcoma (1), low-grade f bromyxoid sarcoma (1), Dabska tumor angiosarcoma (1), and fibrohistiocytoma (1)." From 10.4.2 Disease Characteristics, NAV3-18 Clinical Study Report, p. 68/316.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The radiation dose administered ranged from 0.19 mCi (b) (6) to 0.83 mCi (b) (6) and the duration between the Lymphoseek administration and LN mapping surgery ranged from 25 minutes (Subject (b) (6) to 5.31 hours (Subject (b) (6). The treatments are listed in Table 10.

Table 10. Patient Treatment Information

Line No.	Patient Code	Tumor Type	Dose (mCi)	Route	Injection at Time (date, hr:min)	Planar/SPECT Time (date, hr:min)	LN Mapping Surgery Time* (date, hr:min	Time From A to B (hr:min)	Time From A to C (hr:min)
1	(b) (6)	Melanoma	0.19	ID	(b) (6)		(b) (6)	0:00	2:01
2		Other-Low grade fibromyxoid sarcoma	0.71	ID			NA, Lymphazurin not administered	0:06	NA
3		Melanoma	0.42	ID			(b) (6)	NA	1:19
4		Melanoma	0.48	ID				0:35	2:34
5		Rhabdomyosarcoma	0.40	SubC				0:13	2:11
6		Other-Synovial sarcoma	0.33	SubC				0:12	1:36
7		Melanoma	0.25	SubC				0:05	1:57
8		Other-Squamous Cell	0.76	SubC				1:42	2:26
9		Other-High grade undifferentiated sarcoma	0.83	ID				1:17	2:27
10		Other-Ewing sarcoma	0.57	ID				0:22	2:00
11		Other-Fibrohistiocytoma	0.50	SubC				0:13	2:58
12		Other-Epithelioid sarcoma	0.72	SubC				0:10	2:24
13		Other-Squamous cell carcinoma	0.51	SubC			NA, Lymphazurin not administered	NA	NA
14		Rhabdomyosarcoma	0.71	SubC			(b) (6)	0:02	3:00
15		Rhabdomyosarcoma	0.49	SubC				0:14	2:21
16		Other-Dabska tumor	0.56	SubC				0:13	5:31

Line No.	Patient Code	Tumor Type	Dose (mCi)	Route	Injection at Time (date, hr:min)	Planar/SPECT Time (date, hr:min)	LN Mapping Surgery Time* (date, hr:min	Time From A to B (hr:min)	Time From A to C (hr:min)
17	(b) (6)	Other-Low grade sarcoma	0.39	SubC		(b) (6)	(b) (6)	0:06	1:44
18		Rhabdomyosarcoma	0.59	SubC				0:07	1:38
19		Other-Ewing sarcoma	0.76	SubC				0:05	4:26
20		Other-Atypical spitz nevus	0.45	ID				0:15	0:25
21		Other-Atypical spitz nevus	0.49	ID				0:13	3:06
22		Other-Synovial cell sarcoma	0.53	ID				0:00	3:21
23		Melanoma	0.43	ID				0:04	0:36

Source: Based on the sponsor's 2/17/2021 response to the clinical information request sent out on 2/11/2021.
* Lymphazurin (blue dye) time of injection used as a surrogate to estimate the time of initiation of LN mapping surgery.
Abbreviations: ID, intradermal, LN, lymph node; NA, not available, SPECT, single photon emission computed tomography; SubC, subcutaneous

Overall treatment compliance was evaluated by subject as expressed in the per protocol population. The per protocol population (21/23 subjects, 91.3%) included all ITT subjects reported without major protocol violations. The data sets analyzed are listed in Table 11.

Table 11. Data Sets Analyzed by Age Group, Study NAV3-18 (N=24)

Data Sets	Age 12 to < 18 Years	Age 6 to < 12 Years	Age 2 to < 6 Years	Age 1 Month to < 2 Years	Overall
Enrolled subjects	17	1	4	2	24
Safety population[a]	17 (100.0%)	1 (100.0%)	3 (75.0%)	2 (100.0%)	23 (95.8%)
ITT population[b]	17 (100.0%)	1 (100.0%)	3 (75.0%)	2 (100.0%)	23 (95.8%)
BITT population[c]	15 (88.2%)	1 (100.0%)	3 (75.0%)	2 (100.0%)	21 (87.5%)
PP population[d]	15 (88.2%)	1 (100.0%)	3 (75.0%)	2 (100.0%)	21 (87.5%)

Source: "Table 7. Data Sets Analyzed by Age Group (N = 24). Study NAV3-18" from NAV3-18 Clinical Study Report, p. 65/316
[a] Safety population consists of all enrolled subjects with administration of Lymphoseek. One subject (b) (6) was not injected with Lymphoseek and was excluded from the Safety, ITT, and PP populations.
[b] ITT population consists of all protocol-eligible patients who received Lymphoseek (with or without Lymphazurin) and completed ILM.
[c] BITT population includes all ITT subjects who were also administered Lymphazurin prior to ILM. Three subjects were excluded from the BITT population: (b) (6) (subject not injected with Lymphazurin); (b) (6) (subject not in the safety population); and (b) (6) (subject not injected with Lymphazurin)
[d] PP population includes all ITT subjects without major protocol violations. Three subjects were excluded from the PP population: (b) (6) (subject not in the ITT population) (b) (6) (subject had at least 1 major protocol deviation); and (b) (6) (subject had at least 1 major protocol deviation).
Abbreviations: BITT, blue intent-to-treat; FAS, full analysis set; ILM, intraoperative lymphatic mapping; ITT, intent-to-treat; PP, per protocol

Efficacy Results—Primary Endpoint

1. Degree of Lymphoseek localization

The range of LN number was from 0 to 14 per subject (Table 12). Of the 23 subjects studied, 22 had LNs localized using Lymphoseek. The localization rate by subject in the ITT population was 0.96. One subject (b) (6) did not localize LNs by Lymphoseek because LN mapping and surgery was not able to be completed. According to the site investigators, the reason was due to the subject's condition (epidermolysis bullosa dystrophica).

Table 12. LN Number Localized by Lymphoseek and Lymphazurin by Individual Subject

	Subject	Tumor Type	Age	Number of Nodes Localized by Lymphoseek	Number of Nodes Localized by Lymphazurin
1	(b) (6)	MELANOMA	14	4	3
2		OTHER	13	2	0
3		MELANOMA	17	3	2
4		MELANOMA	17	7	0
5		RHABDOMYO SARCOMA	1.65	8	7
6		OTHER	15	14	14
7		MELANOMA	13	2	1
8		OTHER	12	1	1
9		OTHER	13	2	2
10		OTHER	13	2	1
11		OTHER	12	4	4
12		OTHER	15	2	2
13		OTHER	15	0	0
14		RHABDOMYO SARCOMA	14	2	2
15		RHABDOMYO SARCOMA	16	1	0
16		OTHER	10	2	2
17		OTHER	1.7	1	1
18		RHABDOMYO SARCOMA	4	1	1
19		OTHER	13	1	1
20		OTHER	4	4	1
21		OTHER	14	2	2
22		OTHER	15	6	0
23		MELANOMA	4	5	0

Source: Based on "Subject-Level Results Data (Data Listing 24)" of the NAV3-18 Clinical Study Report.

Of the 23 subjects in the ITT population, a total of 76 LNs were identified intraoperatively by Lymphoseek. The overall degree of Lymphoseek localization was approximately three LNs per subject (Table 13).

Table 13. Degree of Lymphoseek Localization, Study NAV3-18, ITT Population (N=23)

	Lymphoseek Results
Number of LNs identified intraoperatively by Lymphoseek	76
Av. number of LNs identified intraoperatively per subject (ie, degree of localization)	3.30
Two-sided 95% CI	(1.9592, 4.6495)
Degree of localization for melanoma subjects (N = 5)	4.20
Degree of localization for rhabdomyosarcoma subjects (N = 4)	3.00
Degree of localization for other solid tumor subjects (N = 14)	3.07
Degree of localization for 12- to < 18-year-old subjects (N = 17)	3.24
Degree of localization for 6- to < 12-year-old subjects (N = 1)	2.00
Degree of localization for 2- to < 6-year-old subjects (N = 3)	3.33
Degree of localization for 1-month to < 2-year-old subjects (N = 2)	4.50

Source: "Table 12. Degree of Lymphoseek Localization. Study NAV3-18. ITT Population (N = 23)" from NAV3-18 Clinical Study Report, p 73/316.
Abbreviations: Av., average; CI, confidence interval; ITT, intent-to-treat; LN, lymph node(s)

For reference, (refer to the studies summarized in the Lymphoseek labeling), the average number of lymph nodes identified in adults ranged from two to four per subject.

2. Per-subject Lymphoseek localization rate

Of the 23 subjects in the ITT population, 22 had LNs localized using Lymphoseek (Table 14). The localization rate by subject in the ITT population was 0.96 (0.781, 0.999; exact two-sided 95% confidence interval). No clinically meaningful differences in the by subject Lymphoseek localization rate were noted between tumor types (range from 0.93 to 1.00) or by subject age (range from 0.94 to 1.00).

Table 14. Per-Subject Lymphoseek Localization Rate, Study NAV3-18, ITT Population (N=23)

	Lymphoseek Results
Number of subjects localized by Lymphoseek	22
Localization rate	0.96
Exact two-sided 95% CI for localization rate	(0.7805, 0.9989)
Localization rate for melanoma subjects (N = 5)	1.00
Localization rate for rhabdomyosarcoma subjects (N = 4)	1.00
Localization rate for other solid tumor subjects (N = 14)	0.93
Localization rate for 12- to < 18-year-old subjects (N = 17)	0.94
Localization rate for 6- to < 12-year-old subjects (N = 1)	1.00
Localization rate for 2- to < 6-year-old subjects (N = 3)	1.00
Localization rate for 1-month to < 2-year-old subjects (N = 2)	1.00

Source: "Table 13. Per Subject Lymphoseek Localization Rate. Study NAV3-18. ITT Population (N = 23)" from NAV3-18 Clinical Study Report, p 74/316.
Abbreviations: CI, confidence interval; ITT, intent-to-treat

For reference, (referto the studies summarized in the Lymphoseek labeling), the overall rate of LN detection by Lymphoseek at the adult patient level ranged from 97% to 98%.

3. Proportion of subjects who underwent SPECT or SPECT/CT imaging, agreement with intraoperative findings

In the ITT population, the overall proportion of subjects who underwent preoperative SPECT/CT was 21/23 (0.91); the findings are listed in Table 15.

Table 15. Preoperative With SPECT/CT Findings, Study NAV3-18, ITT Population (N=23)

Tumor Type	Melanoma (N = 5)	Rhabdomyo-sarcoma (N = 4)	Other Solid Tumors (N = 14)	Overall (N = 23)
Proportion of subjects who underwent preoperative SPECT/CT	0.80	1.00	0.93	0.91
Proportion of subjects with a LN preoperatively identified on SPECT/CT[a]	1.00	0.75	1.00	0.95
Number of LNs identified preoperatively with SPECT/CT	11	3	41	55
Av. number of LNs identified preoperatively with SPECT/CT per subject[b]	2.75	1.00	3.15	2.75
Two-sided 95% CI	(-0.7783, 6.2783)	NA	(1.9241, 4.3836)	(1.8155, 3.6845)
Av. difference in number of LNs identified preoperatively with SPECT/CT and number of LNs identified intraoperatively per subject	-1.75	-2.25	-0.15	-0.86
Two-sided 95% CI for the difference	(-6.5015, 3.0015)	(-7.3444, 2.8444)	(-2.7395, 2.4318)	(-2.6041, 0.8898)

Source: "Table 14. Preoperative with SPECT/CT Findings. Study NAV3-18. ITT Population (N = 23)" from NAV3-18 Clinical Study Report, p 76/316.
[a] Denominator is all subjects who underwent preoperative SPECT/CT.
[b] Average computed relative to all subjects who underwent preoperative SPECT/CT
Abbreviations: Av., average; CI, confidence interval; ITT, intent-to-treat; LN, lymph node(s); NA, not applicable; SPECT/CT, single photon emission computed tomography/computed tomography

4. Upstaging rate

The upstaging rate reported for the overall ITT population was 0.09 . The two subjects with pathology-positive LNs identified after ILM, were upstaged by Lymphoseek (Table 16). One subject (b) (6) converted from cN0 to pN1, and another subject (b) (6) converted from cN0 to pN3.The two pathology-positive subjects had additional treatment plans.

Table 16. Subjects With Pathology-Positive Nodes and Upstaged Post Surgery

Subject	Tumor type	Age	Total LN Detected	Identified by Lymphoseek?	Identified by Lymphazurin?	Pos by Local Pathology	Pos by Central Pathology	Pre-Surgery Nodal Staging	Post-Surgery Nodal Staging	Pre-Surgery TNM Staging	Post-Surgery TNM Staging
(b) (6)	RHABDOMYO-SARCOMA	16	1	Y	N	Y	Y	N0	N1	T1A, N0, M0, STAGE 2	T2A, N1, M1, STAGE 2
	Melanoma	4	5	Y	N	4Y, 1N	3Y, 2N	NX	N3	T3A, NX, M0, STAGE IIA	T4A, N3, M0,STAGE IIIC

Source: More detailed search on the "Table 15. Lymphoseek Upstaging Rate. Study NAV3-18. ITT Population (N = 23)" from NAV3-18 Clinical Study Report, p 77/316.
* Lymph nodal staging: NX: no info about the nearby lymph nodes; N0: nearby lymph nodes do not contain cancer. A number after the N (such as N1, N2, or N3) might describe the size, location, and/or the number of nearby lymph nodes affected by cancer.
Abbreviations: LN, lymph node(s); Pos, positive

5. Lymphoseek nodal sensitivity and false-negative rates for Lymphoseek identified nodes
6. In the ITT population, four of four pathology-positive nodes identified by central pathology were detected compared with five of five pathology-positive nodes identified by local pathology evaluationSubject and nodal agreement of central and local pathology assessment with local pathology assessment of Lymphoseek-identified excised lymph nodes

Nodal agreement between local and central pathology in 23 subjects was 57/58 nodes with overall agreement proportions of 98% in the ITT population. The nodal agreement ranged from 0.88 to 1.0 across tumor types and age categories.

Data Quality and Integrity

Acceptable.

Dose/Dose Response

Lymphoseek

All study subjects were to receive Lymphoseek as an injection of 50 µg tilmanocept radiolabeled with 0.5 mCi 99mTc administered as either a single injection or as multiple injections.

Vital Blue Dye

Any investigational site with appropriate current experience and standard institutional practice with vital blue dye was to use Lymphazurin (1% isosulfan blue injection). This was a change in protocol Amendment 4; Lymphazurin/vital blue dye use was required in earlier protocol amendments.

8.1.3. Assessment of Efficacy Across Trials

In this efficacy supplement, the Applicant submitted results from one pediatric clinical study, NAV3-18; no additional studies were needed..

8.1.4. Integrated Assessment of Effectiveness

The primary efficacy result of the NAV3-18 study is that at least one Lymphoseek-positive lymph node was detected in 22 of 23 (96%) pediatric subjects. Numerically, this 96% rate confirms the 97% rate for Lymphoseek relied on for approval of the lymphatic mapping indication in adults with solid tumors (400 of 411 adult subjects with at least one Lymphoseek-positive LN detected, integrating across the three study/tumor types described in the prescribing information). Together, these results provide substantial evidence that Lymphoseek is effective for lymphatic mapping to locate lymph nodes draining a primary tumor site in adult and pediatric patents age 1 month and older with solid tumors for which this procedure is a component of intraoperative management.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety data from NAV3-18 with 23 sample size were reviewed for qualitative signals.

8.2.2. Review of the Safety Database

Adequacy of the Safety Database

Acceptable for this partient poipulation.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No issues were identified.

Categorization of Adverse Events

By definition for this study, all untoward medical occurrences beginning on the day of injection through the follow-up assessment (4 to 14 days or 62±7 days, depending on protocol at time of enrollment) were to be reported as AEs. Additionally, untoward medical events occurring prior to the day of injection were only be captured as AEs if they were related to a study procedure. All serious adverse events (SAEs) were to be reported from the time of consent through the end of participation. All AEs were to be followed until resolution or stabilization as determined by the investigator.

Routine Clinical Tests

1. Laboratory data related to screening and safety

Clinical laboratory tests to be evaluated in this study include hematology, serum chemistry, and urinalysis (Table 17). Blood and urine samples for safety were obtained according to the schedule of events.

Table 17. Minimum Clinical Laboratory Parameters

Hematology	Hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelets, neutrophils, eosinophils, basophils, lymphocytes, monocytes, red blood cells (RBC), RBC morphology, white blood cells
Serum chemistry	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase, alkaline phosphatase, total bilirubin, creatinine, chloride, potassium, sodium, total protein, albumin, globulin, Bicarbonate, blood urea nitrogen
Urinalysis	Color, clarity, specific gravity, pH, bilirubin, glucose, ketones, leukocyte esterase, nitrites, protein, urobilinogen

Source: More detailed search on the "Table 15. Lymphoseek Upstaging Rate. Study NAV3-18. ITT Population (N = 23)" from NAV3-18 Clinical Study Report, p 77/316.

Physical examination data, including vital signs and electrocardiograms were also obtained.

8.2.4. Safety Results

Deaths

No deaths were reported during the conduct of this study.

Serious Adverse Events

A total of eight SAEs was reported during the conduct of the study in three subjects (Table 18).

Of these SAEs, two SAEs under the system organ class (SOC) for Blood and Lymphatic System Disorders (b) (6) one SAE under the SOC for Metabolism and Tissue Disorders (b) (6) one SAE under the SOC Renal and Urinary Disorders (b) (6); and one SAE under the SOC of General Disorders and Administration Site Conditions (b) (6) No obvious pattern for either SAE incidence or SOC reported was apparent from review of the data.

All of the SAEs were evaluated as not related to either Lymphoseek administration or the study procedure(s). All subjects recovered and the issue(s) were reported as resolved.

Table 18. Summary of Serious Adverse Events Reported in Study NAV3-18 and Relationship to Lymphoseek Procedure and Outcome by Subject, Study NAV3-18, Safety Population (N=23)

Subject No.	Tumor Type	Age	Start Date and Time/ End Date and Time	MedDRA System Organ Class[a]/ MedDRA Preferred Term/ CRF Verbatim Term	Severity	Relation to Lymphoseek/ Procedure	Serious	Outcome
(b) (6)	Other	13	(b) (6)	Blood and lymphatic system disorders/ febrile neutropenia/ febrile neutropenia	Moderate	Definitely not related/ Definitely not related	Y	Recovered/resolved
	Other	13		Blood and lymphatic system disorders/ febrile neutropenia/ neutropenic fever	Moderate	Definitely not related/ Definitely not related	Y	Recovered/resolved
	Other	13		Blood and lymphatic system disorders/ febrile neutropenia/ neutropenic fever	Moderate	Definitely not related/ Definitely not related	Y	Recovered/resolved
	Other	13		Blood and lymphatic system disorders/ febrile neutropenia/ neutropenic fever	Moderate	Definitely not related/ Definitely not related	Y	Recovered/resolved
	Other	13		Blood and lymphatic system disorders/ anaemia/ critical anemia	Severe	Definitely not related/ Definitely not related	Y	Recovered/resolved
	Other	13		Metabolism and nutrition disorders/ hypokalaemia/ hypokalemia	Severe	Definitely not related/ Definitely not related	Y	Recovered/resolved

Source: More detailed search on the "Table 15. Lymphoseek Upstaging Rate. Study NAV3-18. ITT Population (N = 23)" from NAV3-18 Clinical Study Report, p 77/316.
Abbreviations: CRF, case report form; MedDRA, Medical Dictionary for Regulatory Activities; Y, yes

Dropouts and/or Discontinuations Due to Adverse Effects

A total of 24 subjects were screened. All screened subjects were enrolled in the study. A total of 23 subjects completed the study and 1 subject withdrew prior to the drug injection.

Significant Adverse Events

No other significant AEs were determined to be related to Lymphoseek.

Treatment-Emergent Adverse Events and Adverse Reactions

A total of 29 AEs was reported in 9 subjects during the study. Adverse events are summarized by SOC, preferred term, tumor type and age group in Table 19.

Table 19. Summary of All Adverse Events[a] by Tumor Type and Age, Study NAV3-18, Safety Population (N=23)

	Tumor Type			Age				
Adverse Event	**Melanoma (N=5) n (%)**	**Rhabdomyo-Sarcoma (N=4) n (%)**	**Other Solid Tumors (N=14) n (%)**	**12 to <18 Years (N=17) n (%)**	**6 to <12 Years (N=1) n (%)**	**2 to <6 Years (N=3) n (%)**	**1 Month to <2 Years (N=2) n (%)**	**Overall (N=23) n (%)**
Patients with at least 1 AE	1 (20.0)	3 (75.0)	5 (35.7)	8 (47.1)	0 (0)	1 (33.3)	0 (0)	9 (39.1)
Blood and lymphatic system disorders	0 (0)	0 (0)	2 (14.3)	2 (11.8)	0 (0)	0 (0)	0 (0)	2 (8.7)
Anemia	0 (0)	0 (0)	1 (7.1)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Febrile neutropenia	0 (0)	0 (0)	2 (14.3)	2 (11.8)	0 (0)	0 (0)	0 (0)	2 (8.7)
Gastrointestinal disorders	1 (20)	3 (75.0)	3 (21.4)	6 (35.3)	0 (0)	1 (33.3)	0 (0)	7 (30.4)
Abdominal discomfort	0 (0)	0 (0)	1 (7.1)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Gastroesophagael reflux disease	1 (20.0)	0 (0)	0 (0)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Glossodynia	0 (0)	0 (0)	1 (7.1)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Nausea	0 (0)	2 (50.0)	2 (14.3)	3 (17.6)	0 (0)	1 (33.3)	0 (0)	4 (17.4)
Vomiting	0 (0)	2 (50.0)	1 (7.1)	3 (17.6)	0 (0)	0 (0)	0 (0)	3 (13.0)
General disorders and administration site conditions	1 (20.0)	1 (25.0)	2 (14.3)	4 (23.5)	0 (0)	0 (0)	0 (0)	4 (17.4)
Gait disturbance	1 (20.0)	0 (0)	0 (0)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Pain	0 (0)	0 (0)	1 (7.1)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Pyrexia	0 (0)	1 (25.0)	1 (7.1)	2 (11.8)	0 (0)	0 (0)	0 (0)	2 (8.7)
Infections and infestations	0 (0)	1 (25.0)	1 (7.1)	2 (11.8)	0 (0)	0 (0)	0 (0)	2 (8.7)
Candida infection	0 (0)	1 (25.0)	0 (0)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Urinary tract infection	0 (0)	0 (0)	1 (7.1)	1 (.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Metabolism and nutrition disorders	0 (0)	0 (0)	1(7.1)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Hypokalemia	0 (0)	0 (0)	1 (7.1)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Nervous system disorders	0 (0)	0 (0)	2 (14.3)	2 (11.8)	0 (0)	0 (0)	0 (0)	2 (8.7)
Dizziness	0 (0)	0 (0)	1 (7.1)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Headache	0 (0)	0 (0)	1 (7.1)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Renal and urinary disorders	0 (0)	1 (25.0)	0 (0)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Acute kidney injury	0 (0)	1 (25.0)	0 (0)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Respiratory, thoracic, and mediastinal disorders	0 (0)	0 (0)	1 (7.1)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Atelectasis	0 (0)	0 (0)	1 (7.1)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Pneumothorax	0 (0)	0 (0)	1 (7.1)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)

	Tumor Type			Age				
Adverse Event	**Melanoma (N=5) n (%)**	**Rhabdomyo-Sarcoma (N=4) n (%)**	**Other Solid Tumors (N=14) n (%)**	**12 to <18 Years (N=17) n (%)**	**6 to <12 Years (N=1) n (%)**	**2 to <6 Years (N=3) n (%)**	**1 Month to <2 Years (N=2) n (%)**	**Overall (N=23) n (%)**
Skin, subcutaneous tissue disorders	0 (0)	1 (25.0)	0 (0)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)
Rash	0 (0)	1 (25.0)	0 (0)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (4.3)

Source: "Table 29. Summary of All Adverse Eventsa by Tumor Type and Age. Study NAV3-18. Safety Population (N = 23)" from NAV3-18 Clinical Study Report, p 93/316.
[a] Adverse events coded with MedDRA Coding Dictionary, Version 18.0.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities

The most frequently reported AEs (greater than a 5% incidence) were in the SOCs of Gastrointestinal Disorders (nausea and vomiting), General Disorders and Administration Site Conditions (pyrexia), and Blood and Lymphatic Disorders (febrile neutropenia).

There were no AEs related to Lymphoseek administration. One AE (gait disturbance) of mild severity in Subject 1801001 was judged to be related to study porocedures.

Laboratory Findings

Values for 11 clinical laboratory parameters within hematology (for subject (b) (6) and serum chemistry (for subject (b) (6) were classified as clinically significant (Table 20). No causal linkage to Lymphoseek administration or clinically significant change from baseline was identified.

Table 20. Clinically Significant Laboratory Abnormalities, Study NAV3-18, Safety Population (N=23)

	Normal Range[a]		Number of Subjects with Clinically Significant[b] Results	
Lab Test (unit)	Lab Low	Lab High	Time Point	Result
Hematology				
Erythrocytes (TI/L)	4.1	5.3	1, Day 1 postinjection	2.9
Hemoglobin (g/L)	110	145	1, Screening	83
			1, Day 1 postinjection	75
Hematocrit	0.33	0.43	1, Screening	0.25
			1, Day 1 postinjection	0.21
Leukocytes (GI/L)	5.5	12.3	1, Screening	1.48
			1, Day 1 postinjection	0.88
Lymphocytes (GI/L)	1.5	8	1, Day 1 postinjection	0.19
Mean corpuscular volume (fL)	74	89	1, Day 1 postinjection	73
Monocytes (GI/L)	0.3	1.2	1, Day 1 postinjection	0.29
Serum chemistry				
Alkaline phosphatase (U/L)	31	110	1, Screening	278

Source: "Table 37. Clinically Significant Laboratory Abnormalities. Study NAV3-18. Safety Population (N = 23)" from NAV3-18 Clinical Study Report, p 108/316.
[a] Lab normal ranges are specific to sex and/or age of subjects.
[b] Clinically significant changes from baseline refer to any laboratory value that was deemed clinically significant from baseline by the investigator.

Vital Signs

Vital signs group mean values and changes from baseline at 1 and 24 hour postinjection are shown in Table 28. No clinically important changes were identified (Table 21).

Table 21. Summary of Vital Signs at 1 h, 24 h Postinjection, Study NAV3-18, Safety Population (N=23)

	Melanoma			Rhabdomyosarcoma			Other Tumor Type			Overall		
	Mean	Std Dev	n	Mean	Std Dev	n	Mean	Std Dev	n	Mean	Std Dev	n
Temperature (°C)												
Preinjection (baseline)	36.20	1.442	5	36.75	0.212	2	36.75	0.468	13	36.61	0.799	20
Δ 1 h Postinjection	-0.16	0.706	5	-0.05	0.212	2	-0.11	0.441	10	-0.12	0.488	17
24 h Postinjection	-0.60	—	1	—	—	0	-0.40	0.458	5	-0.43	0.418	6
Systolic BP (mm Hg)												
Preinjection (baseline)	103.60	25.086	5	95.67	7.234	3	109.38	17.476	13	106.05	18.419	21
Δ 1 h Postinjection	-9.40	14.775	5	-6.33	4.041	3	-6.08	12.169	12	-6.95	11.641	20
24 h Postinjection	-38.00	—	1	—	—	0	-7.40	20.231	5	-12.50	21.989	6
Diastolic BP (mm Hg)												
Preinjection (baseline)	55.40	19.982	5	51.67	5.686	3	60.46	11.465	13	58.00	13.176	21
Δ 1 h Postinjection	-5.00	15.379	5	-9.67	3.512	3	-4.42	7.255	12	-5.35	9.224	20
24 h Postinjection	-35.00	—	1	—	—	0	-5.40	16.727	5	-10.33	19.232	6
Heart rate (beats/min)												
Preinjection (baseline)	87.00	15.297	5	113.25	23.372	4	92.15	23.748	13	94.82	22.990	22
Δ 1 h Postinjection	-11.20	8.228	5	-10.25	15.305	4	-7.92	12.019	12	-9.14	11.416	21
24 h Postinjection	-18.00	—	1	—	—	0	-14.40	13.957	5	-14.40	13.957	5
Respiration rate (breaths/min)												
Preinjection (baseline)	16.20	4.919	5	21.50	11.240	4	17.69	4.309	13	18.05	6.035	22
Δ 1 h Postinjection	13.60	3.912	5	-2.00	2.309	4	0.00	4.328	12	-1.00	3.808	21
24 h Postinjection	-2.00	—	1	—	—	0	-0.60	5.727	5	-0.83	5.154	6

Source: "Table 40. Summary of Vital Signs at 1 h, 24 h Postinjection. Study NAV3-18. Safety Population (N=23)" from from NAV3-18 Clinical Study Report, p 115/316.
Abbreviations: BP, blood pressure; mm HG, millimeter(s) of mercury; Δ, difference compared with baseline; Std Dev, standard deviation

Electrocardiograms

The electrocardiogram-observed group mean values and changes from baseline are shown in Table 28,. Mean changes from baseline to postinjection were small; the mean change from baseline for heart rate was -3.7 bpm, for PR interval was -3.0 milliseconds, for QRS duration was +1.2 milliseconds, and for QT interval was +6.5 milliseconds. No findings were considered to be clinically importnat.

QT

The QT interval was +6.5 milliseconds compared to the baseline. No findings were considered to be clinically important.

8.2.5. Analysis of Submission-Specific Safety Issues

No new safety issues were identified in this efficacy supplement.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

The Applicant did not submit any safety or tolerability data based on clinical outcome assessment, and none was needed.

8.2.7. Safety Analyses by Demographic Subgroups

These analyses were not possible due to the small number of study subjects.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant did not submit any safety studies/clinical trials data based on clinical outcome assessment, and none were needed.

8.2.9. Additional Safety Explorations

No additional safety explorations were conducted or needed.

8.2.10. Safety in the Postmarket Setting

The Applicant reports no new safety signals based on review of its postmarket safety database through 5/11/2020.

8.3. Statistical Issues

There are no statistical issues for study NAV 3-18 that affect the approvability of Lymphoseek from a statistical standpoint.

In version 2.1 of the statistical analysis plan, the subject localization rate is defined as “the proportion of subjects with Lymphoseek-identified lymph nodes.” This definition is unclear on whether it is (i) the proportion of subjects with at least one Lymphoseek-identified LN, or (ii) the proportion of subjects weighted by the number of LNs identified by Lymphoseek (another way of reporting).

The overall rate of LN detection by Lymphoseek at the patient level was 96% (22/23) when the detection rate is defined as at least one LN in a patient can be detected. This percentage is approximately 90% if the detection rate is weighted by number of LNs identified equally in a patient. The average number of LNs detected by Lymphoseek was approximately three per patient.

Table 22 compares the LN detection rates of Lymphoseek with those of blue dye in the 21 subjects administrated both. Numerically, Lymphoseek detected more LNs than blue dye overall and in subgroups with different types of tumors.

Table 22. Lymph Node Detection Rates of Lymphoseek (LS) and Blue Dye (BD) in 21 Subjects Administrated Both

Tumor Type	Node N	BD Present n (%) (95% CI* for %)	LS Present n (%) (95% CI* for %)	Only BD Present n (%) (95% CI* for %)	Only LS Present n (%) (95% CI* for %)	Neither Present n (%) (95% CI* for %)
All	79	47 (59%) (48%. 70%)	74 (94%) (86%, 98%)	0 (0%) (0%, 5%)	27 (34%) (24%, 46%)	5 (6%) (2%, 14%)
Melanoma	24	6 (25%) (10%, 47%)	21 (88%) (68%, 97%)	0 (0%) (0%, 14%)	15 (63%) (41%, 81%)	3 (13%) (3%, 32%)
Rhabdomyosarcoma	14	10 (71%) (42%. 92%)	12 (86%) (57%, 98%)	0 (0%) (0%, 23%)	2 (14%) (2%, 43%)	2 (14%) (2%, 43%)
Other solid tumors	41	31 (76%) (60%, 88%)	41 (100%) (91%, 100%)	0 (0%) (0%, 9%)	10 (24%) (12%, 40%)	0 (0%) (0%, 9%)

Source: FDA statistical reviewer analysis.
* 95% Confidence intervals (CI) are based on exact binomial and represent the variability in the individual estimates.

The total number of nodes found and the number of nodes detected by Lymphoseek by age group in the ITT population are summarized in Table 23.

Table 23. Number of Nodes and Those Detected by Lymphoseek by Age Group

Age (in years)	Number of Subjects in the ITT Population	Total Number of Nodes	Number of Nodes Detected by Lymphoseek
1.65	1	8	8
1.7	1	1	1
4	3	10	10
10	1	2	2
12	2	5	5
13	5	10	9
14	3	9	8
15	4	25	22
16	1	2	1
17	2	12	10
Overall	23	84	76

Source: FDA statistical reviewer analysis.
Abbreviation: ITT, intent-to-treat

8.4. Conclusions and Recommendations

Based on convergent results of pediatric study NAV3-18 and previously relied upon findings from three studies in sdults , the review team recommends fulfillment of PREA PMR 2789-1 and finds substantial evidence of favorable benefit-risk for expansion of Lymphoseek's lymphatic mapping indication to pediatric patients age 1 month and older.

9. Advisory Committee Meeting and Other External Consultations

The product was not referred for review to an advisory committee because of the consensus by the NDA reviewers that this supplemental application did not raise new regulatory issues and the study'sdesign was consistent with FDA guidance.

10. Pediatrics

The review team presented to the Pediatric Review Committee on 3/23/2021. Relevant portions of the final meeting minutes are excerpted below.

- Proposed indication and usage: a radioactive diagnostic agent indicated with or without scintigraphic imaging for lymphatic mapping using a handheld gamma counter to locate LNs draining a primary tumor site in adult and pediatric patients with solid tumors for which this procedure is a component of intraoperative management.

- The purpose of this clinical efficacy supplement is to provide study results to fulfill PMR 2789-1 for the deferred pediatric study under PREA evaluating the use of Lymphoseek guided lymphatic mapping and SLNB in the treatment of solid tumors in pediatric patients 1 month to 16 years of age.
- The Pediatric Review Committee (PeRC) discussed the pediatric assessment which consisted of data from an open-label single-arm trial designed to evaluate intraoperative mapping in pediatric patients with certain types of cancers (melanoma, rhabdomyosarcoma, and other solid tumors). Top-level efficacy data showed that 22/23 pediatric patients had LN detection with Lymphoseek. The number of LNs identified per patients was similar to other methodologies. The Division has concluded that these data support efficacy in pediatric patients down to 1 month of age. The PeRC noted that adult efficacy of this product was also established in adults with different cancers based on open-label, single-arm studies comparing lymph node detection of Lymphoseek to other methodologies.
- *PeRC Recommendations*: The PeRC agrees that the assessment in pediatric patients 1 month to 16 years of age is complete, and the PMR is fulfilled for this age group based on safety and efficacy data. The package insert was already appropriately labeled for intended use in pediatric patients 1 month to 16 years of age.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

In this efficacy supplement, the Applicant proposed changes to the approved prescribing information most notably under 1 INDICATIONS AND USAGE, 8 USE IN SPECIFIC POPULATIONS, and 14 CLINICAL STUDIES. For detailed documentation of all final or near-final tracked changes, see the labeling review filed in the Document Archiving, Reporting and Regulatory Tracking System on 4/21/2021.

12. Risk Evaluation and Mitigation Strategies

In this efficacy supplement, the Applicant did not propose any Risk Evaluation and Mitigation Strategy, and no Risk Evaluation and Mitigation Strategy is needed.

13. Postmarketing Requirements and Commitment

Based on this review of the conduct and results of NAV3-18, the PREA PMR **2789-1** titled: "Deferred pediatric study under PREA evaluating the use of Lymphoseek guided lymphatic

mapping and sentinel lymph node biopsy in the treatment of solid tumors in pediatric patients ages 1 month to 16 years of age" is fulfilled

14. Division Director (Clinical) Comments

I concur with the NDA reviewers' assessments and their recommendations for approval of the supplmental application. I concur that the PREA PREA PMR 2789-1 has been fulfilled.

15. Appendices

15.1. References

Alcorn, KM, KJ Deans, A Congeni, JP Sulkowski, R Bagatell, P Mattei, and PC Minneci, 2013, Sentinel lymph node biopsy in pediatric soft tissue sarcoma patients: utility and concordance with imaging, J Pediatr Surg, 48(9):1903-1906.

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De Corti, F, P Dall'Igna, G Bisogno, D Casara, CR Rossi, M Foletto, R Alaggio, M Carli, and G Cecchetto, 2009, Sentinel node biopsy in pediatric soft tissue sarcomas of extremities, Pediatr Blood Cancer, 52(1):51-54.

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Roaten, JB, DA Partrick, N Pearlman, RJ Gonzalez, R Gonzalez, and MD McCarter, 2005, Sentinel lymph node biopsy for melanoma and other melanocytic tumors in adolescents, J Pediatr Surg, 40(1):232-235.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): NAV3-18 Study (A Prospective, Open-Label, Multicenter Study of Lymphoseek® as a Lymphoid Tissue Targeting Agent in Pediatric Patients with Melanoma, Rhabdomyosarcoma, or Other Solid Tumors Who Are Undergoing Lymph Node Mapping).

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 44		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The study's Sponsor certifies that:

- They that I have not entered into any financial arrangement with the clinical investigators as defined in 21 CFR 54.2(a)
- The clinical investigators have not had a proprietary interest in Lymphoseek or a significant equity in
- The Sponsor as defined in 21 CFR 54.2(b)
- No clinical investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Olayinka Dina, DVM, PhD	ORDPURM/DPTRDPURM	Section: 5	Select one: x Authored ___ Approved
	Signature: Olayinka Dina -S Digitally signed by Olayinka Dina -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olayinka Dina -S, 0.9.2342.19200300.100.1.1=2000594003 Date: 2021.05.13 13:36:25 -04'00'			
Nonclinical Team Leader	Ronald Honchel PhD	ORDPURM/DPTRDPURM	Sections: 5	Select one: ___ Authored x Approved
	Signature: Ronald Honchel -S Digitally signed by Ronald Honchel -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ronald Honchel -S, 0.9.2342.19200300.100.1.1=1300124657 Date: 2021.05.13 14:16:21 -04'00'			
Clinical Pharmacology Reviewer	Edwin C. Y. Chow, PhD	OCP/DCPII	Section: 6	Select one: x Authored ___ Approved
	Signature: Edwin C. Chow -S Digitally signed by Edwin C. Chow -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Edwin C. Chow -S, 0.9.2342.19200300.100.1.1=2001621378 Date: 2021.05.13 09:09:05 -04'00'			
Clinical Pharmacology Team Leader	Christy John, PhD	OCP/DCPII	Section: 6	Select one: ___ Authored x Approved
	Signature: Christy S. John -S Digitally signed by Christy S. John -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300150005, cn=Christy S. John -S Date: 2021.05.13 17:40:21 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Reviewer	Qi Feng, MD, PhD	OSM/DIRM	Sections: 1, 2,3,7,8,11,15	Select one: x Authored ___ Approved
	Signature: Qi Feng -S Digitally signed by Qi Feng -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=QI Feng -S, 0.9.2342.19200300.100.1.1=2000218762 Date: 2021.05.13 11:27:20 -04'00'			
CDTL/Clinical Team Leader	Anthony Fotenos, MD, PhD	OSM/DIRM	Sections: all sections	Select one: x Authored x Approved
	Signature: Anthony F. Fotenos -S Digitally signed by Anthony F. Fotenos -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001526313, cn=Anthony F. Fotenos -S Date: 2021.05.14 12:38:12 -04'00'			
Statistical Primary Reviewer	Xiangmin Zhang,PhD	OB/DBI	Section: 8	Select one: x Authored ___ Approved
	Signature: Xiangmin Zhang -S Digitally signed by Xiangmin Zhang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiangmin Zhang -S, 0.9.2342.19200300.100.1.1=2001050700 Date: 2021.05.13 13:11:26 -04'00'			
Statistical Secondary Reviewer	Jyoti Zalkikar, PhD	OB/DBI	Section: 8	Select one: x Authored ___ Approved
	Signature: Jyoti Zalkikar -S Digitally signed by Jyoti Zalkikar -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jyoti Zalkikar -S, 0.9.2342.19200300.100.1.1=1300162261 Date: 2021.05.13 15:51:59 -04'00'			
Statistical Deputy Division Director (OB))	Sue-Jane Wang, PhD	OB/DBI	Section: 8	Select one: ___ Authored x Approved
	Signature: Suejane Wang -S Digitally signed by Suejane Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suejane Wang -S, 0.9.2342.19200300.100.1.1=1300088741 Date: 2021.05.13 18:26:56 -04'00'			
Division Director (Clinical) (DIRM)	Libero Marzella, MD, PhD	OSM/DIRM	Sections: all sections	Select one: ___ Authored x Approved
	Signature: Libero L. Marzella -S Digitally signed by Libero L. Marzella -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300088188, cn=Libero L. Marzella -S Date: 2021.05.13 09:43:04 -04'00'			

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/s/

ALBERTA E DAVIS WARREN
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