# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

Device Generic Name: Magnetic Sentinel Node Detection System

Device Trade Name: Magtrace™ and Sentimag® Magnetic Localization System

Device Procode: PUV

Applicant's Name and Address: Endomagnetics Ltd.
The Jeffreys Building
Cowley Road, Cambridge, CB4 0WS, UK

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160053

Date of FDA Notice of Approval: July 24, 2018

## II. INDICATIONS FOR USE

The Magtrace™ and Sentimag® Magnetic Localization System is indicated to assist in localizing lymph nodes draining a tumor site, as part of a sentinel lymph node biopsy procedure, in patients with breast cancer undergoing a mastectomy.

Magtrace™ is intended and calibrated for use ONLY with the Sentimag® system.

## III. CONTRAINDICATIONS

- Known hypersensitivity to iron oxide or dextran compounds.
- Iron overload disease
- A metal implant in the axilla or in the chest.

## IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Magtrace™ and Sentimag® Magnetic Localization System labeling.

## V. DEVICE DESCRIPTION

The Magtrace™ and Sentimag® Magnetic Localization System is indicated to assist in localizing lymph nodes draining a tumor site, as part of a sentinel lymph node biopsy procedure, in patients with breast cancer undergoing a mastectomy and consists of:

- The Magtrace™
- The Sentimag®

Magtrace™

Magtrace™ is a combination device/drug product consisting of a blackish-brown sterile aqueous suspension of carboxydextran-coated superparamagnetic iron oxide particles in Water for Injection (WFI) containing 0.3% w/v sodium chloride. Magtrace™ is supplied as sterile (aseptically filled) in single-use glass vials containing a minimum of 2.2 ml to allow for a consistent 2.0 ml injection volume.

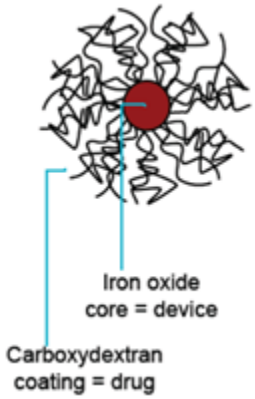
Each milliliter of Magtrace™ contains approximately 28 milligrams of iron in the form of iron oxide. The recommended quantity of Magtrace™ administered for use in patients is 2 ml with the equivalent iron content of 55 mg +/- 4 mg per injection.

Magtrace™ key characteristics include:

- Magnetic iron oxide core of 3.5-10 nm in diameter provides detectability by the Sentimag®
- Carboxydextran coating which brings the overall particle diameter to 45-65 nm, keeps the particles in solution, and prevents iron oxide aggregation
- 0.3% saline provides tonicity and allows uptake of the particles into the lymphatic system.

An schematic of the Magtrace™ particles is shown below in Figure 1.

**Figure 1:** Magtrace™ Particle Schematic



Sentimag®

Sentimag® is a susceptometer designed to deliver a small alternating magnetic field via a hand-held probe, and to electronically detect the presence of magnetic material in the vicinity of the probe head.

Detection is performed via pick-up coils in the probe head, which generate electrical current from the magnetic materials response. This response current is passed through the probe cables and connectors to the Sentimag® base unit, where it is transformed into both audible and visual feedback for the surgeon. The base unit also contains the controls for operating the Sentimag® system that are located on the front of the unit, with a power switch on the back.

The main features of the Sentimag® are:

- Portable base unit that can sit on a flat surface
- Audible and visual indications of magnetic material proximity:
    - Magnetic signals indicated by variable pitch (audible), that increases as the probe is brought near Magtrace magnetic tracer material, and yellow LCD digits (visual);
    - Extraneous or background signals indicated by low and constant pitch (audible) and red LCD digits (visual);
    - Liquid crystal display (LCD) for numerical indication of signal strength and general unit information (e.g., volume, sensitivity setting).
- Choice of three (3) sensitivity settings, controlled by a knob mounted on the base unit
- Volume control knob on the base unit
- Push button mounted on the base unit that activates instrument balancing function that readies the system for measurement
- Detachable air-operated footswitch allowing remote operation of the balance function
- The detachable applied part is the probe assembly comprising a hand-held probe, a flexible cable of just under three (3) meters length, and colour-coded (black and white) connectors to plug the probe into the base unit.
- Applied Probe assembly is to be used in conjunction with a standard single-use sterile sheath (sold separately by OEM suppliers). Sheaths should be latex-free and at least 1 inch wide and 72 inches long.

The Base Unit, Probe, and Footswitch are shown in Figure 2 below.

**Figure 2:** Sentimag® Probe and Base Unit


## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives to assist in localizing lymph nodes draining a tumor site, as part of a sentinel lymph node biopsy procedure. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle. The only alternative is Technetium radioisotope-labelled tracers, such as sulfur colloid and blue dye tracers.

## VII. MARKETING HISTORY

Sentimag®/Sienna+ (an earlier variant of the Magtrace™) has been commercially available in the European Union (EU) since 2013 and is currently available in the following countries: United Kingdom, Germany, France, Italy, Spain, Portugal, Netherlands, Austria, Czech Republic, Denmark, Croatia, Sweden, Slovakia, Turkey, Poland, Switzerland, Hong Kong, Singapore, New Zealand, and Australia. The

Sentimag®/Sienna+ product has not been withdrawn from any foreign market for any reason relating to the safety and effectiveness of the device.

Regarding the differences between Magtrace™ and Sienna+, the Sienna+ was designed to be pre-mixed with saline immediately prior to administration, whereas Magtrace™ has been formulated to contain 0.3% w/v sodium chloride and does not require premixing with saline. Apart from this addition of sodium chloride, Magtrace™ is identical to Sienna+ and is considered acceptable a market history comparison.

## VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the probable adverse effects (e.g., complications) associated with Magtrace™ and Sentimag® Magnetic Localization System include:

Magtrace™ is intended for injection into the breast ONLY (interstitial injection).

When similar material to that used in Magtrace™ has been injected directly into the bloodstream (intravenously), the following undesirable effects have been reported:

- Common (<2%) – pain at the injection site, vasodilation, paresthesia
- Uncommon (≥0.1% to <1%) – asthenia, back pain, injection site reactions, chest pain, nausea, vomiting, headache, taste changes, itching, rash, inflammatory response (localized redness and swelling) with intradermal injection.
- Rare (≥0.01% to <0.1%) – Hypersensitivity and anaphylaxis, hypertension, phlebitis, hyperesthesia, anxiety, dizziness, convulsion, parosmia, dyspnea, increased cough, rhinitis, eczema, urticaria.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

## IX. SUMMARY OF NONCLINICAL STUDIES

### A. Laboratory Studies

**Table 1-** Summary of Laboratory Studies

| Test | Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| **Biocompatability- Sienna+/Magtrace™** | | | |
| Cytotoxicity<br>EN ISO 10993-5 | In Vitro Cytotoxicity test on Sienna+ | No toxicological or biologically critical cell damage.<br>Note: Based on the close formulation similarity of Magtrace™ to Sienna+, further cytotoxicity testing was considered unnecessary and was not repeated for the new formulation. | PASS |

| Test | Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| Sensitization<br>EN ISO 10993-10 | In Vitro maximization – Allergenicity test on Magtrace™ equivalent | To show no allergenic potential in guinea pig. | PASS |
| Irritation & Intracutaneous Reactivity<br>DIN ISO 10993-10 | In Vitro Irritation & Intracutaneous Reactivity Test on Sienna+ | Polar and apolar extracts not to cause any intracutaneous reactivity in rabbits within an observation period of 72 hours.<br>Based on the close formulation similarity of Magtrace™ to Sienna+, further cytotoxicity testing was considered unnecessary | PASS |
| Systemic Toxicity<br>EN ISO 10993-11 | Acute Toxicity: on Magtrace™ equivalent | Single dose toxicity studies in rats, mice and dogs to show No toxicity or a Low acute toxicity with doses in the 12.5-20 mmol iron per kilogram of body weight range. | PASS |
| Systemic Toxicity<br>EN ISO 10993-11 | Subacute & Sub-chronic Toxicity on Magtrace™ equivalent | In dogs an increase in serum iron and decrease in iron binding capacity was dose-dependent. In 4-week studies in rats, an increase in serum iron and increase in liver and spleen weights was observed as dose-dependent at the end of the dosing period. A transient decrease in platelet counts was also observed this was shown to be due to the iron moiety and only observed in animal models only and not observed in human tests.<br>Chronic toxicity (6-12 month repeated dose) is not deemed necessary as Sienna+/Magtrace™ is given in single dose only.<br>In conclusion, Sienna+ with a single dose of 1mmol per patient can be considered safe with regards to subacute toxicity. | PASS |
| Genotoxicity EN ISO 10993-3 | In-vitro (Ames test) and in-vivo tests (mice, micronucleus) tests on Magtrace™ equivalent to detect mutagenic potential | To show no mutagenic potential. | PASS |
| **Cleaning – Sentimag®** | | | |
| Cleaning Validation Study | Validate the cleaning instructions for the Sentimag® system | Acceptance criteria in accordance with Guidance for Industry and FDA Staff – Processing/Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labelling and AAMI TIR30 (2011). | PASS |

| Test | Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| **Lifetime Evaluation – Sentimag®** | | | |
| Lifetime Evaluation of the Sentimag® System | Estimate the maximum lifetime of the Sentimag® system | Lifetime of the device is estimated to last 5 years. | Pass |
| **Performance Testing – Pre-Clinical Bench Top Testing:** | | | |
| Investigation of performance for Sienna+ with Sentimag® system | Measure the detection distance of Sienna+ with the Sentimag® probe at the three sensitivity settings available on the device. | Maximum sensing distance of the 28µg Fe magnetic tracer sample was 8mm, 11mm and 14mm for Sensitivity setting 1, 2, and 3 respectively.<br>For the 140µg sample, maximum sensing was achieved at 13mm, 18mm and 19mm for sensitivity setting 1, 2, and 3 current settings respectively. | PASS |
| Comparison of Generation 1 Sentimag® system and Generation 2 Sentimag® system | The second generation probe was developed for:<br>•Reduction in probe diameter to be similar to a Gamma probe<br>•Increase in sensitivity for transcutaneous and small node detection<br>•Greater resistance to thermal drift. | **Diameter** reduced from 24mm (Gen 1) to 18.5mm (Gen 2).<br>**Sensitivity** of Gen 2 system increased approximately 3.5x over that of the Gen 1 System. | Pass |

**B. <u>Electrical Safety Testing – Sentimag®</u>**

The purpose of these tests is to demonstrate the electrical safety of the Sentimag® System in accordance with the FDA Recognized Consensus Standard: AAMI/ANSI ES60601-1:2005 / IEC 60601-1:2005 + Corrigenda 2006 and 2007 Medical electrical equipment — Part 1: General requirements for basic safety and essential performance, and CAN/CSA-C22.2 No. 60601-1:08 - Medical electrical equipment - Part 1: General requirements for safety and essential performance.

**Table 2:** Electrical Safety Testing

| Test Name | Acceptance Criteria | Results |
|---|---|---|
| **Electrical Safety Testing – Sentimag®** | | |
| Marking Durability and Legibility Test | As defined in the standard | PASS |
| Power Input Test | As defined in the standard | PASS |
| Limitation of Voltage and/or Energy (Capacitance Discharge Test) | As defined in the standard | PASS |
| Enclosures and Protective covers (Access to live parts) | As defined in the standard | PASS |

| Test Name | Acceptance Criteria | Results |
|---|---|---|
| Grounding Impedance Test | As defined in the standard | PASS |
| Leakage Current Test | As defined in the standard | PASS |
| Dielectric Voltage Withstand Test | As defined in the standard | PASS |
| Mechanical Tests and Stability | As defined in the standard | PASS |
| Temperature Test | As defined in the standard | PASS |
| Spillage, Cleaning/Disinfection and Humidity Preconditioning | As defined in the standard | PASS |
| Abnormal Operation Tests | As defined in the standard | PASS |
| Creepage Distance and Air Clearance measurements | As defined in the standard | PASS |
| Insulation – Ball pressure test | As defined in the standard | PASS |
| Acoustic Energy Test | As defined in the standard | PASS |
| Actuating Parts Test | As defined in the standard | PASS |

The Sentimag® system has been tested, examined, and found to comply with the applicable requirements of UL 60601-1 Medical Electrical Equipment, Part 1 Requirements for Safety April 25, 2003, US National standard ANSI/AAMI ES60601-1: 2005 / A2:2010 – Medical Electrical Equipment, Part 1: General Requirements for Safety and Essential Performance, and CAN/CSA-C22.2 No. 60601-1:08 - Medical electrical equipment - Part 1: General requirements for safety and essential performance.

**C. Electromagnetic Compatibility Testing**

The purpose of these tests is to demonstrate the electromagnetic compatibility of the Sentimag® system in accordance with these standards:

- FDA Recognized Consensus Standard: AAMI/ANSI IEC 60601-1-2:2007 Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests (Edition 3).

- FCC Rules

**Table 3:** Electromagnetic compatibility testing

| Test Name | Acceptance Criteria | Results |
|---|---|---|
| **EMC Testing – Sentimag®** | | |
| EMC Testing | As defined in the standard | PASS |
| Verification EMC Testing | As defined in the standard | PASS |
| FCC EMC Testing | As defined in the FCC Rules - FCC Rules CFR47: 2008 Part 15.107 and 15.109 Class B | PASS |
| Conducted RF Immunity | As defined in the standard RF Immunity (EN61000-4-6) | PASS |
| Radiated Immunity Test | As defined in the standard Radiated Immunity (EN61000-4-3) | PASS |

### D. Animal Studies

**Table 4:** Animal Studies

| Test Name | Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| **Systemic Transport – Sienna+** | | | |
| Sienna+ Transport Mechanism (Murine) | To determine Transport time and mechanism of transport of Sienna+ into Sentinel Lymph Node (SLN).<br>Transport of Sienna+ into SLN was monitored in contrast to transport of immunologically marked Tetramethylrhodamine (TRITC)-positive Leukocytes.<br>Time points: 10min, 30min, 1hr, 2hr, 24hr | Sienna+ appeared in SLN after 10 minutes, whereas TRITC-positive leukocytes were only detected at 24 hours.<br>Rapid transport (minutes) - non interactive transport into lymphatic system.<br>Slow transport (hours) - phagocytosis.<br><br>Results demonstrate that the transport of the Sienna+ particles was mechanical and did not depend on cells or chemical means to transport the particles in to the lymphatic system. | PASS |
| **Formulation – Sienna+** | | | |
| Sienna+ Formulation in Porcine model | Optimization of formulation for uptake into the lymphatic system in presence of different formulation components.<br>Time points: 5min, 10min, 15 min, 30min, 1hr, 2hr, 24hr, 72hr | Presence of ion pair is essential for uptake into the lymphatic system. Presence of 0.3% w/w NaCl is the optimal concentration of excipient to enhance the uptake of Sienna+ into the lymphatic system | PASS |

## X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of Magtrace™ and Sentimag® Magnetic Localization System for localizing lymph nodes draining a tumor site in patients with breast cancer, as part of a sentinel lymph node biopsy procedure in the U.S. (IDE #G140208, NCT02336737).

An additional supporting study was conducted in France (NCT01790399, See section XI), which was an open-label, multicenter, paired comparison of Sentimag® and Sienna+ and radioisotope with or without blue dye for sentinel lymph node detection in patients with breast cancer scheduled for sentinel node biopsy. Sienna+ is an earlier formulation of Magnecarbodex requiring dilution with saline prior to injection. Note: The French Sentimag Feasibliity Trial is discussed in the Summary of Supplemental Clinical Information section (Section XI) because it was only supporting clinical data.

**Table 6:** Clinical Studies

| Study | Products used | Study design | Location | Number of subjects (sites) |
|---|---|---|---|---|
| U.S. SentimagIC trial G140208, NCT02336737 | Magtrace™, Sentimag® | Multi-center paired comparison with Radioisotope + Blue dye | US | 160 (6) |
| French Sentimag® Feasibility Trial, NCT01790399 | Sienna+, Sentimag® | Multi-center paired comparison with Radioisotope ± Blue dye | France | 115 (4) |

## A. Study Design

Patients were treated between January 9, 2015 and December 16, 2015. The database for this PMA reflected data collected through December 16, 2015 and included 160 patients. There were six (6) investigational sites in the United States.

The study was a pivotal, prospective, open label, multicenter, paired comparison study of the Magtrace™/Sentimag® system with the standard of care (Tc-99m radioisotope with blue dye) for the detection of lymph nodes in patients with breast cancer undergoing a sentinel lymph node biopsy (G140208). The trial was designed to provide powered evidence that the lymph node detection rate of the Magtrace™/Sentimag® system is non-inferior to the standard of care in patients with breast cancer and to summarize measures of product safety and performance.

The active control was Technetium 99 labeled sulfur colloid radioisotope in combination with isosulfan blue dye. The control was administered according to the standard of care at each site. All subjects underwent simultaneous lymph node mapping using Magtrace™, and with radioisotope with blue dye.

The trial sought to reject a null hypothesis that the true per lymph node detection rate for Magtrace™ was worse than or equal to the true lymph node detection rate for standard of care by more than the non-inferiority margin $\delta$, and support the alternative hypothesis that the true lymph node detection rate of Magtrace™ was no worse than the true lymph node detection rate for standard of care less the non-inferiority margin $\delta$. That is:

$H_0$: $P_T - P_C \leq -\delta$ (inferior)
$H_a$: $P_T - P_C > -\delta$ (non-inferior),

where $P_T$ and $P_C$ are the lymph node detection rates for Magtrace™ and standard of care Control, respectively, and $\delta$ is the non-inferiority margin.

The sample size calculation for the primary endpoint was performed using PASS 2008 and was based on a non-inferiority (one-sided) test of correlated proportions and the method of Nam with the following assumptions:

- Expected Sentimag®/Magtrace™ (test) rate = 95%
- Expected standard of care (Control) rate = 95%
- Non-inferiority margin ($\delta$) = 5%
- Assumed discordance rate = 8%
- Test significance level ($\alpha$) = 0.05 (1-sided)
- Power (1-$\beta$) ≈ 0.85

A minimum of 265 nodes were required for each method. Given that ~ two (2) lymph nodes were expected per subject, it was anticipated that a total of 140 subjects would be required.

The expected per node detection rate for the standard of care combined technique was 94.6% based on the NSABP B-32 trial (Krag et al.[1]).

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the Sentimag® study (G140208) was limited to patients who met the following inclusion criteria:

- Subjects with a diagnosis of primary breast cancer or subjects with pure ductal carcinoma in situ (DCIS)
- Subjects scheduled for surgical intervention, with a sentinel lymph node biopsy procedure being a part of the surgical plan
- Subjects aged 18 years or more at the time of consent
- Subjects with an Eastern Cooperative Oncology Group (ECOG) performance status of Grade 0-2
- Subject has a clinical negative node status (i.e., T0-3, N0, M0)

Patients were not permitted to enroll in the Sentimag® study if they met any of the following exclusion criteria:

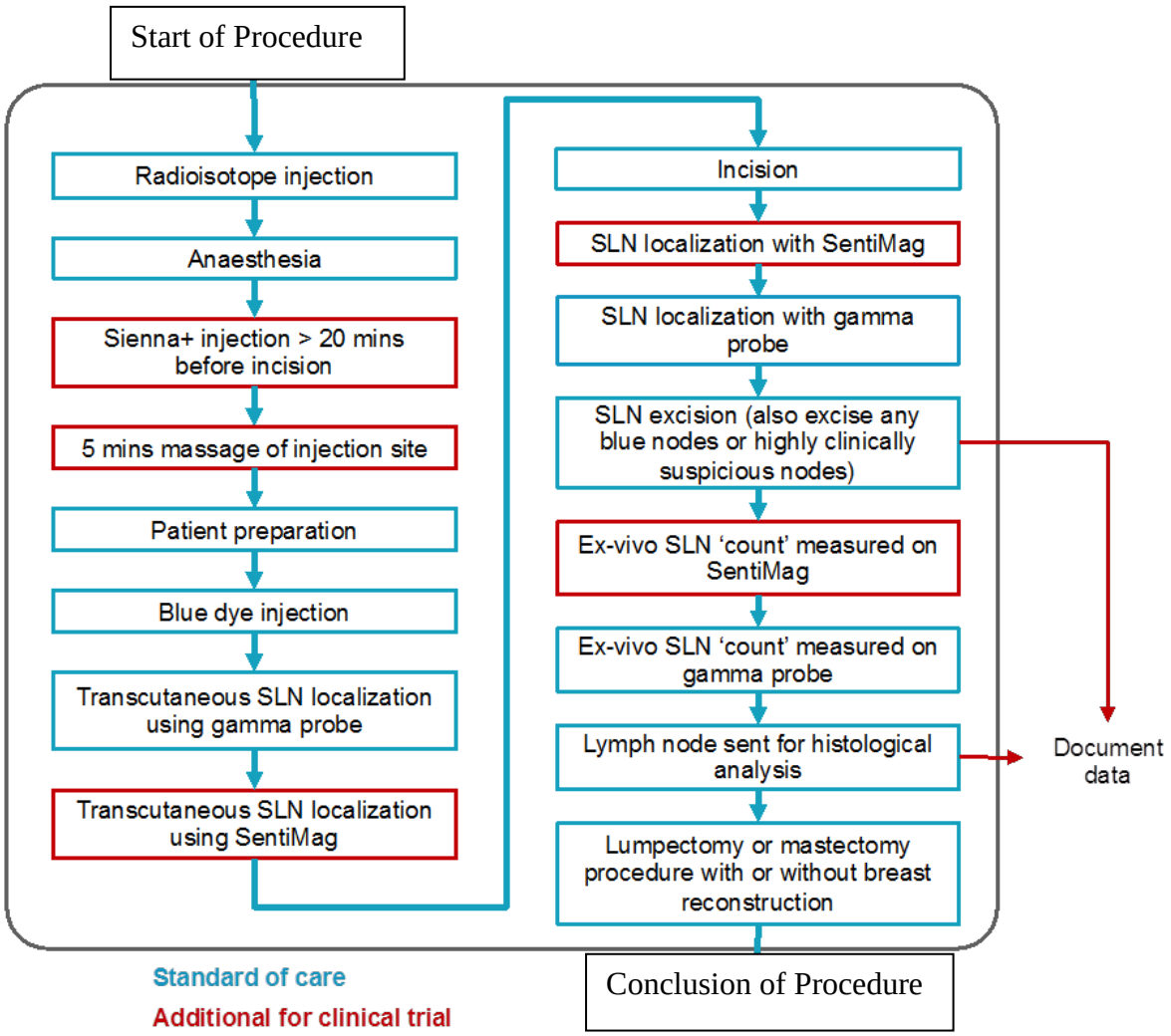
- The subject is pregnant or lactating
- The subject has clinical or radiological evidence of metastatic cancer including palpably abnormal or enlarged lymph nodes
- The subject has a known hypersensitivity to Isosulfan blue dye

- The subject has participated in another investigational drug study within 30 days of scheduled surgery
- Subject has had either a) previous axilla surgery, b) reduction mammoplasty, or c) lymphatic function that is impaired in the surgeon's judgment
- Subject has had preoperative radiation therapy to the affected breast or axilla
- Subject has received a Feraheme® (ferumoxytol) Injection within the past 6 months
- Subject has intolerance or hypersensitivity to iron or dextran compounds or to Magtrace™
- Subject has an iron overload disease
- Subject has pacemaker or other implantable device in the chest wall

2. Study Procedure and Follow-up Schedule

The study procedure flow is depicted in Figure 3 below.

**Figure 3:** Sentinel Node Biopsy Procedure Flow



Each SLN identified by Sentimag® and/or gamma probe or stained blue or black was excised and additional counts, with the excised node on the end of the probe, were taken with each detection system (Sentimag® and gamma probe) and recorded. In addition, nodes that were deemed highly clinically suspicious nodes (e.g., very hard and firm, or white colored consistant with gross tumor in the lymph node) were excised as sentinel nodes. Sentinel lymph node biopsy (SLNB) was stopped when the residual count/signal in the axilla was less than 10% of the largest ex-vivo reading from an already excised node using that detection method.

All patients were scheduled to return for follow-up examinations at between 6 and 22 days post-procedure for a safety assessment postoperatively.

The study visits and assessments are summarized in Table 7.

**Table 7:** Study Visits and Data Collection Overview

| Procedure/ Assessment | Screening/ Enrollment | Visit 1 Baseline / Medical History | Visit 2 Sentinel Node Biopsy Procedure | Visit 3 Post-procedure Evaluation (14 days +/- 8 days) | Unscheduled Visit |
|---|---|---|---|---|---|
| Inclusion / Exclusion Criteria | X | | | | |
| Informed Consent | X | | | | |
| Demographics, Medical / Surgical History | | X | | | |
| Pregnancy test | | | X | | |
| Lymph node mapping and sentinel node biopsy procedure | | | X | | |
| Excised nodes sent for histological analysis & pathology evaluation | | | X | | |
| SLN Biopsy results | | | | X | |
| Adverse Event Assessment | | X | X | X | X |
| Medications | | X | X | X | X |
| Device Deficiency Assessment | | | X | | |
| Study Completion | | | | X | |

3. Clinical Endpoints

**Primary Safety Endpoint:**
To provide evidence of the safety of Magtrace™/Sentimag® as indicated by adverse events and serious adverse events and their relatedness to the detection method or procedure.

**Primary Effectivness Endpoint:**
The primary effectivness endpoint was the lymph node detection rate, which is defined as the number of lymph nodes identified by a specific method (Magtrace™/Sentimag® or Control) divided by the total number of lymph nodes detected.

**Success/Failure Criteria:**
The study was considered a success if Magtrace™/Sentimag® demonstrated a statistically significantly non-inferior lymph node detection rate compared to the Control, with a 5% non-inferiority margin. If the lower bound of the one-sided 95% confidence interval for the difference between detection rates at the nodal level was greater than -5%, then the study was considered a success.

## B. Accountability of PMA Cohort

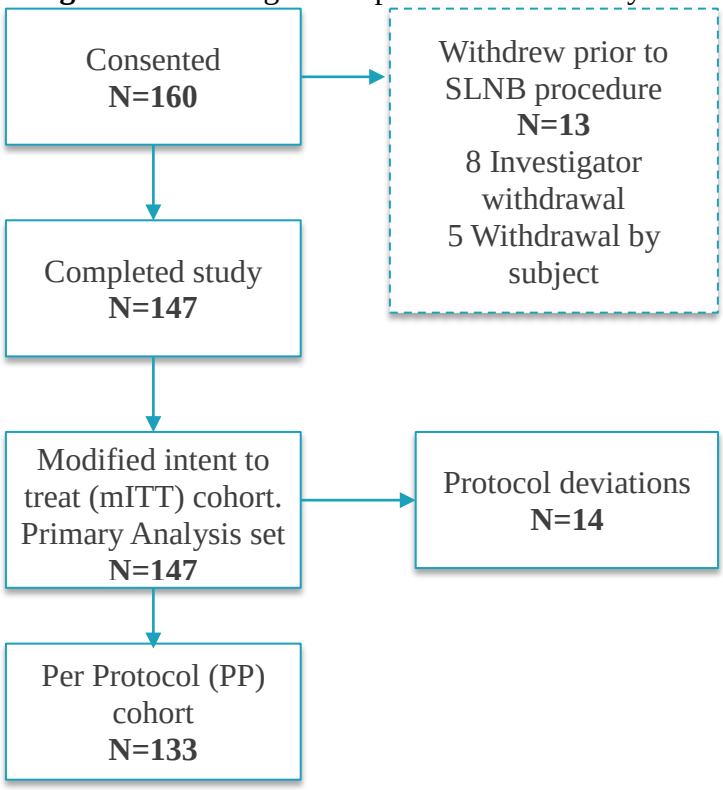
At the time of database lock, of 160 patients enrolled in the PMA study, 147 patients (91.9%) completed the study and are available for analysis. Patient accountability is shown in Figure 4.

Thirteen (13) patients withdrew from the study prior to sentinel lymph node biopsy procedure as follows: five (5) patients withdrew themselves, and eight (8) patients were withdrawn by investigators for the following reasons:

- Two (2) received the incorrect isotope injection (Lymphoseek (technetium Tc 99m tilmanocept) instead of Tc-99m sulfur colloid)
- Two (2) were found not to meet the inclusion/exclusion criteria
- One (1) was withdrawn due to concerns regarding her history of thalassemia
- One (1) was found to have axillary metastasis on a PET scan
- One (1) was withdrawn as there was no study coordinator on site to record the study data
- One (1) patient opted for chemotherapy prior to surgery

The primary analysis set was the modified intent to treat (mITT) cohort comprising all subjects who completed the study procedures (n=147).

**Figure 4:** SentimagIC trial patient accountability tree




C. **Study Population Demographics and Baseline Clinicopathological Characteristics**

Patient demographic characteristics are shown in Table 8 with the patient baseline clinicopathological characteristics given in Table 9.

**Table 8:** Study Population Demographics

| | **Overall (N=147)** |
|---|---|
| Race (not mutually exclusive, %) | |
| American Indian or Alaska Native | 0.0% |
| Asian | 4.8 % |
| Black or African American | 7.5% |
| Pacific Islander | 0.0% |
| White | 82.3% |
| Other | 6.1% |
| Ethnicity (n/N (%)) | |
| Hispanic or Latino | 11.6% |
| Not Hispanic or Latino | 88.4% |
| Mean Age (SD) | 61.1 (12.3) |
| Mean Weight in lbs (SD) | 167.1 (38.5) |

| | Overall (N=147) |
|---|---|
| Mean Height in inches (SD) | 63.7 (2.6) |
| Mean Body Mass Index (BMI Kg/$m^2$ (SD)) | 29.0 (6.9) |
| Menopausal status | |
| Premenopausal | 19.0% |
| Perimenopausal | 3.4% |
| Postmenopausal | 77.6% |

**Table 9:** Baseline Patient Clinicopathological Characteristics

| | |
|---|---|
| Type of surgery* | |
| Wide local excision/Lumpectomy | 103/147 (70.1) |
| Mastectomy | 43/147 (29.3) |
| Tumor location | |
| Upper Outer Quadrant (UOQ) | 74/147 (50.3) |
| Upper Inner Quadrant (UIQ) | 28/147 (19) |
| Lower Inner Quadrant (LIQ) | 10/147 (6.8) |
| Lower Outer Quadrant (LOQ) | 26/147 (17.7) |
| Central/Areolar | 9/147 (6.1) |
| Pathological tumor size | |
| pTis | 13/135 (9.6) |
| pT1a | 19/135 (14.1) |
| pT1b | 30/135 (22.2) |
| pT1c | 33/135 (24.4) |
| pT2 | 33/135 (24.4) |
| pT3 | 7/135 (5.2) |
| Tumor grade | |
| I | 45/135 (33.3) |
| II | 51/135 (37.8) |
| III | 37/135 (27.4) |
| IV | 0/135 (0.0) |
| Not assessable | 2/135 (1.5) |
| Estrogen Receptor (ER) Status (n/N (%)) | |
| Positive | 113/135 (83.7) |
| Negative | 13/135 (9.6) |
| Not performed | 9/135 (6.7) |
| Progestrone Receptor (PR) Status (n/N (%)) | |
| Positive | 87/135 (64.4) |
| Negative | 39/135 (28.9) |
| Not performed | 9/135 (6.7) |

| | |
|---|---|
| Human Epidermal Growth Factor Receptor (HER2) Status (n/N (%)) | |
| Positive | 13/135 (9.6) |
| Negative | 105/135 (77.8) |
| Not performed | 17/135 (12.6) |

* One patient had SLNB only

## D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of 147 evaluable patients. The key safety outcomes for this study are presented below. Adverse effects are reported in Tables 10 and 11.

**Adverse events that occurred in the PMA clinical study:**

A total of 69 adverse events were reported in 56/147 (38.1%) subjects, and of these adverse events, 9 (13.0%) were considered serious adverse events (SAE).

The most common adverse events were breast discoloration/hyperpigmentation, which occurred in 16.3% (24/147) of subjects and ecchymosis/bruising, which occurred in 6.8% (10/147) of subjects. Breast dicoloration was not observed in patients that underwent mastectomy (43/147 or 29.3%) at follow up visit between 6-22 days post surgery.

**Table 10:** Adverse events by type

| **Adverse Event Type** | **Events (N)** | **Subjects n (%)** |
|---|---|---|
| **Total Adverse Events** | **69** | **56 (38.1)** |
| Breast Discoloration/Hyperpigmentation | 24 | 24 (16.3) |
| Ecchymosis / Bruising | 10 | 10 (6.8) |
| Pain | 5 | 5 (3.4) |
| Other | 5 | 5 (3.4) |
| Gastrointestinal Disorder | 3 | 3 (2.0) |
| Cellulitis | 3 | 3 (2.0) |
| Skin Ischemia | 3 | 3 (2.0) |
| Cardiac Disorder | 3 | 3 (2.0) |
| Rash | 2 | 2 (1.4) |
| Erythema | 2 | 2 (1.4) |
| Respiratory Disorder | 1 | 1 (0.7) |
| Hypertension | 1 | 1 (0.7) |
| Hypotension | 1 | 1 (0.7) |
| Pulmonary Embolism | 1 | 1 (0.7) |
| Musculoskeletal Disorder | 1 | 1 (0.7) |
| Psychological Disorder | 1 | 1 (0.7) |
| Allergic Reaction | 1 | 1 (0.7) |
| Pleural Effusion | 1 | 1 (0.7) |
| Inflammation | 1 | 1 (0.7) |

Table 11 shows Magtrace™-related adverse events. If an adverse event was assessed as having an "undetermined" relationship, it was conservatively considered "related."

Twenty (20) events occurring in 20 subjects (13.6%) were related to Magtrace™, and six (6) events occurring in six (6) subjects (4.1%) were assessed as having an undetermined relatedness in relation to Magtrace™. There were nine (9) serirous adverse events in the study. After data analysis, seven (7) out of the nine (9) SAEs were unrelated to the Magtrace™$^{M}$, and two (2) of the nine (9) SAEs were found to be undetermined (Bradycardia and Anaphylaxis).

**Table 11:** Magtrace™-Related Adverse Events

| | **Magtrace™-Related Adverse Events** | |
|---|---|---|
| **Adverse Event Type** | **Events N** | **Subjects n (%)** |
| **Total Adverse Events** | **26** | **25 (16.3)** |
| Breast Discoloration/Hyperpigmentation[1] | 23 | 23 (15.6) |
| Erythema | 1 | 1 (0.7) |
| Anaphlaxis[2] | 1 | 1 (0.7) |
| Cardiac Disorder[3] | 1 | 1 (0.7) |

[1]Breast Discoloration: The degree and duration of skin staining is unknown. Skin staining was not observed in patients that underwent mastectomy (43/147) at follow-up visit between 6-22 days post surgery.

[2]Anaphlaxis: During the procedure the patient developed tongue swelling, hypotension, and tachycardia and was treated with epinephrine and steroids and the event resolved that day.

[3]Cardiac Disorder: Thirty (30) minutes after injection bradycardia followed by pulselessness treated with atropine, CPR with intubation and the event resolved.

2. Effectiveness Results

The analysis of effectiveness was based on the 147 evaluable patients who completed the study. Key effectiveness outcomes are presented in Tables 12 to Table 17.

**Primary Endpoint Analysis**

The primary endpoint was the lymph node detection rate, which is defined as the number of lymph nodes identified by a specific method (Magtrace™ or Control) divided by the total number of lymph nodes detected (n=369). The Magtrace™/Sentimag® had a detection rate 94.3% and the control detected 93.5% of the total nodes detected. The difference in detection rates between the methods (Magtrace™ - Control) was 0.8% with a 95% one-sided lower confidence bound of -2.1%.

**Table 12:** Summary of Overall mITT Study Results

| | G140208 Pivotal Study Breast Cancer | |
|---|---|---|
| | Magtrace™ n = 147 | Radioisotope with blue dye n = 147 |
| Nodes detected (n) | 348 | 345 |
| Per node lymph node detection rate % (95% CI) | 94.3% (91.9%, 96.7%) | 93.5% (91.0%, 96.0%) |
| Per patient lymph node detection rate % (95% CI) | 98.6% (95.2%, 99.8%) | 98.0% (94.2%, 99.6%) |
| Overall per patient concordance % (95% CI) | 98.0% (94.2%, 99.6%) | |
| Patients with at least one positive (metastatic) node (n) | 22 | |
| Detection rate for patients with at least one metastatic node % (95% CI) | 95.5% (86.8%, 100.0%) | 95.5% (86.8%, 100.0%) |

**Table 13:** The nodal detection rates

| | **Magtrace™** | | |
|---|---|---|---|
| **Control (Radioisotope and Blue Dye)** | **Detected** | **Not Detected** | **Total** |
| **Dectected** | 326 (88.3%) | 19 (5.2%) | **345 (93.5%)** |
| **Not Detected** | 22 (6.0%) | 2 (0.5%) | -- |
| **Total** | **348 (94.3%)** | -- | **369[1] (100.0%)** |

[1]Four sentinel lymph nodes are excluded due to missing data for Magnetic (Magtrace™) count, Radioisotope count and/or Blue Dye.

There were 41 discordant nodes in 29 subjects; 19 were found by control only and 22 were found by Sentimag® only.

**Table 14:** Findings of Discordant Lymph Nodes

| **Overall discordant Nodes** | **Rate** | **Number of Nodes Detected by Test but not Control** | **Number of Nodes Detected by Control but not Test** |
|---|---|---|---|
| 41/369 | 11.1% | 22 (in 16/29 patients) | 19 (in 13/29 patients) |

All of the discordant nodes had no clinical impact as:

- All malignant SLNs were concordant
- All discordant SLNs were benign. (See Table 20 malignant nodes table)

**Table 15:** Sentinel Node per-Node Detection Rates by Radioisotope Alone

| | **Magtrace™** | | |
|---|---|---|---|
| **Radioisotope** | **Detected** | **Not Detected** | **Total** |
| **Detected** | 319 (86.4%) | 19 (5.1%) | **338 (91.6%)** |
| **Not Detected** | 29 (7.9%) | 2 (0.5%) | -- |
| **Total** | **348 (94.3%)** | -- | **369[1] (100.0%)** |

[1]Four sentinel lymph nodes are excluded due to missing data for Magnetic (Magtrace™) count, Radioisotope count and/or Blue Dye.

**Table 16:** Sentinel Node per-Node Detection Rates by Blue Dye Alone

| | **Magtrace™** | | |
|---|---|---|---|
| **Blue Dye** | **Detected** | **Not Detected** | **Total** |
| **Detected** | 175 (47.4%) | 5 (1.4%) | **180 (48.8%)** |
| **Not Detected** | 173 (46.9%) | 16 (4.3%) | -- |
| **Total** | **348 (94.3%)** | -- | **369[1] (100.0%)** |

[1]Four sentinel lymph nodes are excluded due to missing data for Magnetic (Magtrace™) count, Radioisotope count and/or Blue Dye.

**Table 17:** Sentinel Node per-Subject Detection Rates by Method

| | **Magtrace™** | | |
|---|---|---|---|
| **Control (Radioisotope and Blue Dye)** | **At Least 1 Node Detected** | **No Nodes Detected** | **Total** |
| **At Least 1 Node Detected** | 144/147 (98.0%) | 0 (0.0%) | **144 (98.0%)** |
| **No Nodes Detected** | 1/147 (0.7%) | 1/147 (0.7%) | -- |
| **Total** | **145/147 (98.6%)** | -- | **147 (100.0%)** |

**Other Endpoint Analysis**

**Table 18:** Results of Other Per Node Endpoints

| **Per Node Endpoints** | |
|---|---|
| | **n/N Rate (95% CI)** |
| **Overall Nodal Concordance**<br>Number of nodes identified by both test and Control out of all nodes identified | 326/369 (88.3%)<br>CI (85.1%, 91.6%) |
| **Overall Nodal Discordance**<br>Number of nodes identified by either test or Control (but not by both) out of all nodes identified | 41/369 (11.1%)<br>CI (7.9%, 14.3%) |
| **Nodal concordance**<br>Number of nodes identified by both test and Control out of nodes identified by Control | 326/345 (94.5%)<br>CI (92.1%, 96.9%) |
| **Reverse nodal concordance**<br>Number of nodes identified by both test and Control out of nodes identified by test | 326/348 (93.7%)<br>CI (91.1%, 96.2%) |

**Table 19:** Number of Lymph Nodes Detected per Subject Assessed for Each Method.

| | Mean (S.D) | Median | Range |
|---|---|---|---|
| Magtrace™ | 2.4 (1.19) | 2 | 0-6 |
| Control | 2.4 (1.34) | 2 | 0-6 |
| Radioisotope | 2.3 (1.38) | 2 | 0-6 |
| Blue Dye | 1.2 (0.93) | 1 | 0-4 |

3. Subgroup Analysis

**Per node endpoints for cancer positive (malignant) nodes**
The nodal status was reported as the percentage of histologically malignant nodes detected by a specific detection method (magnetic; combined radioisotope and blue dye; radioisotope alone; blue dye alone) on a per node and a per subject basis.

Of the 25 confirmed analyzable positive (malignant) nodes in the mITT analysis set, 96.0% (24/25) with a 95% CI of (88.3%, 100.0%) were identified by both the Control radioisotope or blue dye, and Magtrace™. One (1) node was not identified by either Control or Magtrace™, but was considered 'highly clinically suspicious' in the judgment of the investigator. All the nodes identified by either Magtrace™ or Control were identified by both Magtrace™ and Control. Blue dye detected 60.0% (15/25).

Of the 24 malignant nodes identified by both Magtrace™ and Control, 19 contained macrometastasis, and five (5) contained micrometastasis. The one node that was not identified by either Control or Magtrace™ but was considered clinically suspicious contained a macrometastasis.

**Table 20:** Sentinel lymph node detection of malignant nodes - per node

| | **Magtrace™** | | |
|---|---|---|---|
| **Control (Radioisotope or Blue Dye)** | **Cancer Positive Detected** | **Cancer Postive Not Detected** | **Total** |
| **Cancer Positive Detected** | 24 (96.0%) | 0 (0.0%) | **24 (96.0%)** |
| **Cancer Positive Not Detected** | 0 (0.0%) | 1 (4.0%) | **--** |
| **Total** | **24 (96.0%)** | **--** | **25[1] (100.0%)** |

One additional positive node (and the one subject with this node) is excluded from analyses discussed above since it did not meet any of the criteria for a sentinel lymph node. This node, subject 06-018, Node 4, was one of two (2) nodes excised in a single piece of tissue: subject 06-018, Nodes 3 and 4. Node 3 had a Magtrace™ and radioisotope signal and was recorded as a sentinel lymph node. Node 4 did not meet any of the pre-determined criteria for a sentinel lymph node and was therefore recorded as a non-sentinel lymph node. Upon histopathological analysis Node 4 was found to be malignant.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

## E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 13 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

## XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The supplemental clinical information includes:

1. French Clinical Study NCT01790399
2. Subgroup Analyses of Mastectomy Cohort
3. Protocol Deviations in the Pivotal (Sentimag®) study
4. Device Failures in the Pivotal (Sentimag®) Study
5. Magnetic Resonace Imaging (MRI) Artifact
6. Published literature studies

1. French Feasability Study Summary:

A feasability study was conducted in France (NCT No: NCT01790399). This was an investigator-led multi-center paired comparison of Sienna+ and Sentimag® with radioisotope ± Blue dye. Sienna+ is a previous formulation of the same iron oxide particles, which required dilution with saline prior to injection.

A. French Study Title: Detection of Sentinel Node using Sentimag®/Sienna+ for breast cancer: A feasibility study.

B. Overview of Feasibility Trial

Patients were treated between January 30, 2013, and January 22, 2014.

C. Patient Disposition

Number enrolled: n=115
Number of evaluable patients: n=108
Withdrew: n=7, 1 withdrew consent, 1 did not receive study drug, the remainder had missing data due to data entry fault at the time of surgery
Number of participating Centers: n=4

D. Study Objectives

- Primary: To evaluate the feasibility of the sentinel lymph node identification technique using the Sentimag® device (manual magnetometer)/Sienna+ (superparamagnetic iron-oxide tracer).
- Secondary: To evaluate the reliability of the technique compared with benchmark methods (isotopic and/or colorimetric).

E. Clinical Endpoints

Safety Endpoint:
- Rates of adverse events and serious adverse events were recorded.

Primary Endpoint:

- The primary endpoint of this trial was the proportion of successful procedures for SLN identification (identification rate per patient) by the magnetic method compared with the standard method (isotopes with or without patent blue).

Other Endpoints:

- The secondary endpoint evaluated the concordance of sentinel nodes detected with magnetic and standard method. The concordance is reported by patient and by node.
- Concordance per subject is defined as the number of subjects in whom the magnetic technique agrees with the standard technique (i.e., subjects in whom either both identified a node, or neither identified a node) divided by the total number of evaluable subjects.
- Concordance per node is defined as the number of nodes in whom the magnetic technique agrees with the standard technique (i.e., nodes detected by either both techniques or neither technique) divided by the total number of evaluable nodes.

Success/Failure Criteria:

- A successful procedure was defined as the detection of at least one magnetic sentinel node for the magnetic method; and at least one node radioactive and/or blue (if blue dye was used) for the standard method.

F. Study Design

**Methodology:**

- The investigated devices were the Sentimag® probe system and Sienna+ magnetic tracer. Sienna+ was diluted with 3ml of 0.9% saline prior to injection.

The control products used were: Nanocis® or Nanocoll albumin colloids radiolabelled with Technetium 99m isotope; with or without patent blue dye.

- Patients received the radioisotope injection first; either the day before or day of surgery, per the usual custom of the center. After induction of anesthesia, the Sienna+ was administered followed by blue dye.
- Sentinel Node Detection was first performed with Sentimag® followed by gamma probe and blue dye. All nodes identified by any method were removed.

Radioisotope (Technetium albumin colloid) was injected according to the standard of care protocol at each site. Forty-five (45) of 108 patients (45/108, 42%) also received a blue dye injection shortly prior to surgery at sites where blue dye was standard protocol. Sienna+ was injected at least 20 minutes prior to initiating sentinel lymph node mapping.

Lymph node detection was performed intraoperatively using the Sentimag® probe to identify magnetic nodes, followed by the use of a handheld gamma probe to identify radioactive ('hot') nodes. Any blue or black/brown stained nodes, and any nodes

judged to be highly clinically suspicious by the surgeon were also excised. The excised nodes were evaluated using histopathology.

The percentage of lymph nodes identified by each technique was presented with a 95% confidence interval. The comparison of discordant pairs (identified or non identified SLN) was conducted using the McNemar test per patient and per lymph node. To detect a 5% discrepancy percentage between the two (2) techniques with a 95% confidence interval of 0.04, 115 evaluable patients needed to be enrolled.

G. Clinical Inclusion and Exclusion Criteria

Enrollment in the French Study was limited to patients who met the following inclusion criteria:

- Female patients with invasive or micro-invasive breast cancer proven by histology or cytology regardless of the histology type
- cT0/cT1/cT2 (up to 5 cm) cN0 clinic and/or echographic previously untreated (chemotherapy or neo-adjuvant hormonotherapy)
- Aged 18 years or over
- Scheduled for breast surgery and axillary staging by sentinel lymph node
- Female patient using effective contraception (BHCG negative)
- Patient affiliated to a health insurance system
- Informed consent signed by the patient

Patients were not permitted to enroll in the French Study if they met any of the following exclusion criteria:

- T3 or T4 tumor (> 5 cm, cutaneous or muscular infiltration, or inflammatory cancer)
- Existence of an axillary adenopathy suspected clinically or in imaging
- Bifocal or multi-focal tumors known before surgery
- History of mammary of axillary surgery
- Metastatic patient
- Patient with a contra-indication to anaesthesia and/or surgery
- Intolerance or hypersensitivity:
    - to iron or dextran or superparamagnetic iron oxide particles
    - to the patent blue dye in centers where it is currently used
- Patient unable to receive a radioactive isotope for excision of the sentinel lymph node
- Allergy to radioactive product
- Iron excess disease
- Cardiac stimulator or any other device implantable in the thoracic wall
- Unable to be medically monitored in the study for geographic, social or mental reasons
- Patient deprived of their freedom or under guardianship

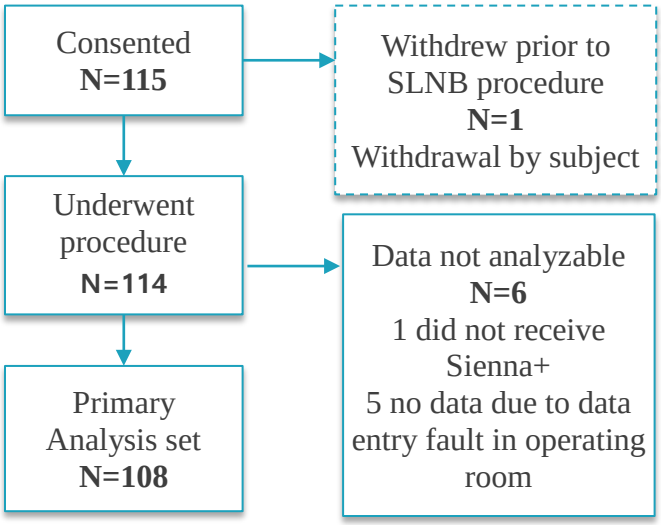
- Pregnant or breast-feeding

H. Patient accountability

One hundred fifteen (115) subjects were enrolled at four (4) investigational sites in France and 108 subjects completed the Sentinel Lymph Node Biopsy (SLNB) procedure. Seven (7) subjects were not evaluable: one (1) did not receive the Sienna+ injection; one (1) subject withdrew consent prior to the SLNB procedure; and five (5) had missing data for the Sentimag® technique due to a data entry fault in the operating room.

The patient accountability tree is shown in Figure 5.

**Figure 5:** Study 2 patient accountability tree




I. Study population demographics

The median age was 58 years (range 29-79). Histopathological analysis showed that 89% of tumors were invasive carcinoma. Baseline clinicopathologic characteristics for the French Study population are shown in Table 21.

**Table 21.** Demographic and Baseline Clinicopathologic Characteristics for the French Study Population

| | N = 108 | % |
|---|---|---|
| **Age** | | |
| ≤ 50 | 29 | 27 |
| 51-69 | 62 | 57 |
| ≥ 70 | 17 | 16 |
| **BMI** | | |
| Thin | 3 | 3 |
| Normal | 44 | 41 |
| Overweight | 40 | 37 |

| | N = 108 | % |
|---|---|---|
| Obese | 18 | 17 |
| Morbidly obese | 2 | 2 |
| Missing | 1 | |
| **Hormonal status** | | |
| Active | 26 | 24 |
| Pre-menopausal | 5 | 5 |
| Menopausal | 77 | 71 |
| **Location of the lesion** | | |
| Upper inner quadrant | 26 | 24 |
| Upper outer quadrant | 62 | 57 |
| Lower-inner quadrant | 5 | 5 |
| Lower-outer quadrant | 9 | 8 |
| Retro-areolar | 5 | 1 |
| **Histology type** | | |
| Invasive root carcinoma | 96 | 89 |
| Invasive lobular | 9 | 8 |
| Other | 3 | 3 |
| **SBR Grade** | 37 | 34 |
| II | 58 | 54 |
| III | 13 | 12 |
| **Hormonal receptors** | | |
| Estrogen receptors | | |
| Negative | 9 | 8 |
| Positive | 99 | 92 |
| Progesterone receptors | | |
| Negative | 28 | 26 |
| Positive | 80 | 74 |
| **HER status (in IHC)** | | |
| 0 | 60 | 57 |
| + | 29 | 27 |
| ++ | 8 | 8 |
| +++ | 9 | 8 |
| Missing (#5, #6) | 2 | |
| **KI67** | | |
| ≤ 15 | 70 | 67 |
| >15 | 35 | 33 |
| Median (range) | 10 | (0- |
| Missing (#6, #8, #99) | 3 | 90) |

J. Safety & Effectiveness Results

**Safety results:**

Seventy (70) subjects had post-operative complications. The most common adverse events were breast discoloration/hyperpigmentation, which occurred in 22 subjects and seroma (noted as "punctured lymphocele") which occurred in 14 subjects.

Three (3) serious adverse events were recorded in two (2) subjects: one subject was hospitalized for a bacterial infection and one subject had two (2) separate haematoma events not related to the study. No serious adverse events related to the device were reported.

**Effectiveness results:**

**Table 22:** Primary Endpoint Analysis

| | **Sienna + (Magnecarbodex) n=108** | **Radioisotope with/without Blue Dye n= 108** |
|---|---|---|
| **Nodes Detected (n)** | 208 | 193 |
| **Per Patient Lymph Node Detection Rate % (95% CI)** | 97.2% (92.1%, 99.4%) | 95.4% (89.5%, 98.5%) |
| **Overall per Patient Concordance % (95% CI)** | 96.3% (90.8%, 99.0%) | |

**Table 23:** Detection Concordance for Cancer Positive Nodes

| **Per Patient** | **Sienna cancer +** | **Sienna Cancer -** |
|---|---|---|
| Control cancer + | 43 | 1 |
| Control cancer - | 2 | 0 |

**Primary endpoint analysis**
The primary endpoint of this trial was the proportion of successful procedures for Sentinel Lymph Node (SLN) identification (identification rate per patient) by the magnetic method compared with the standard method (isotopes with or without patent blue).

In total, 220 SLNs were collected from 106 patients. The identification of at least one SLN with standard method was achieved in 95.4% of patients (103/108, 95%CI: 89.5–98.5) and with Sienna+ in 97.2% of patients (105/108, 95%CI: 92.1–99.4).

The concordance rate per subject of the two (2) mapping methods (magnetic and isotopic ± patent blue) was 96.3%, 95%CI: 90.8–99.0). The discordance rate of both methods per subject was 3.7% (4/108, CI: 1.0–9.2%). The p-value for the Exact McNemar test was $p = 0.6250$, which means that there is insufficient statistical evidence that the two methods are discordant.

**Per node endpoints**
Among the 220 SLNs removed, 214 were subjected to statistical analysis (six (6) nodes had intraoperative tracer values missing). A mean [SD] of 2.08 [0.943] SLNs per subject were identified. The mean number of magnetic nodes identified was 2.01 [0.976] per subject and the mean of standard nodes identified was 1.94 [0.968]. The nodal concordance rate was 88.3% (95%CI: 83.2–92.3).

**Endpoints for subjects with positive nodes**
Forty-six patients (46, 43.4%) had nodal involvement with 21 (45.7%) presenting micrometastasis and 25 (54.3%) presenting macrometastasis. The per subject malignancy detection rate was 95.7% (44/46, 95%CI: 85.2–99.5) for the standard method and 97.8% (45/46, 95%CI: 88.4–99.9) for the magnetic technique.

Among these node-positive patients, the concordance rate was 93.5% (43/46, 95% CI: 82.1%; 98.6%). For the 61 involved SLNs included in the calculation, the concordance rate was 86.9% (53/61, 95% CI: 75.8%; 94.2%).

Table 24 summarizes the per-patient and per-node endpoints.

**Table 24:** Per node and per patient lymph node detection rates for Sienna+ and Radioisotope in NCT01790399

| | **French NCT01790399Study** | |
|---|---|---|
| | **Sienna+**<br><br>**n = 108** | **Radioisotope with or without blue dye**<br>**n = 108** |
| **Nodes detected (n)** | 208 | 193 |
| **Per node lymph node detection rate % (95% CI)** | 97.2% | 90.2% |
| **Per patient lymph node detection rate % (95% CI)** | 97.2%<br>(92.1%, 99.4%) | 95.4%<br>(89.5%,98.5%) |
| **Overall per patient concordance % (95% CI)** | 96.3%<br>(90.8%, 99.0%) | |
| **Patients with at least one positive node n** | 46 | |
| **Detection rate for patients with at least one metastatic node % (95% CI)** | 97.8%<br>(88.4, 99.9) | 95.7%<br>(85.2, 99.5) |

K. Protocol Deviations

A total of 36 protocol deviations was reported in 29.6% (34) of subjects. The most common protocol deviation was incorrect βHCG pregnancy testing or testing out of the specified timeframe. This deviation occurred 13 times and at all four (4) sites. The deviations that occurred did not negatively impact the scientific soundness or the data integrity of the clinical study.

L. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The supplemental clinical study included 14 investigators. None of the clinical investigators had disclosable financial

interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

M. NCT01790399 Feasability Safety & Effectiveness Conclusions

The study success criterion was met showing no significant discrepancy between the per subject detection rates for the two (2) techniques. The investigational device produced a similar risk profile to Control with no unanticipated adverse device effects. The analysis of this study provides valid scientific evidence to support the safety and effectiveness of Sentimag®/Sienna+ to assist in detecting and localizing lymph nodes draining a tumor site in breast cancer, as part of a SLNB procedure.

1. Subgroup Analyses of Mastectomy Cohort

Fourty-three (43) of the 160 patients in the pivotal trial underwent mastectomy with SLNB. The demographics of this cohort are shown in Table 25 below.

**Table 25:** Demographics of the Mastectomy Patient Cohort (Pivotal Study)

| **Characteristic** | **n/N (%) or Mean (SD)** |
|---|---|
| Race (not mutually exclusive, n/N (%)) | |
| American Indian or Alaska Native | 0/43 (0%) |
| Asian | 2/43 (4.7%) |
| Black or African American | 2/43 (4.7%) |
| Native Hawaiian or Other Pacific Islander | 0/43 (0%) |
| White | 36/43 (83.7%) |
| Other | 3/43 (7.0%) |
| Ethnicity (n/N (%)) | |
| Hispanic or Latino | 5/43 (11.6%) |
| Not Hispanic or Latino | 38/43 (88.4%) |
| Age | 54.7 (11.7) |
| BMI | 26.8 (5.4) |
| **Endpoint** | |
| Magtrace™ per node detection rate | 116/123 (94.3%) |
| Control per node detection rate | 115/123 (93.5%) |
| Magtrace™ per subject detection rate | 43/43 (100%) |
| Control per subject detection rate | 43/43 (100%) |
| Node positive subjects: | 6/43 (14.0%) |

The baseline clinical pathological characteristics of the mastectomy cohort are shown in Table 26 below:

**Table 26:** Baseline Clinicopathologic Characteristics of the Mastectomy Patient Cohort

| | |
|---|---|
| Tumor location | |
| Upper Outer Quadrant (UOQ) | 23/43 (53.5%) |
| Upper Inner Quadrant (UIQ) | 10/43 (23.3%) |
| Lower Inner Quadrant (LIQ) | 1/43 (2.3%) |
| Lower Outer Quadrant (LOQ) | 5/43 (11.6%) |
| Central/Areolar | 4/43 (9.3%) |
| Pathological tumor size | |
| pTis | 6/38 (15.8%) |
| pT1a | 2/38 (5.3%) |
| pT1b | 4/38 (10.5%) |
| pT1c | 9/38 (23.7%) |
| pT2 | 13/38 (34.2%) |
| pT3 | 4/38 (10.5%) |
| Tumor grade | |
| I | 6/38 (15.8%) |
| II | 19/38 (50%) |
| III | 11/38 (28.9%) |
| IV | 0/38 (0%) |
| Not assessable | 2/38 (5.3%) |
| Estrogen Receptor (ER) Status (n/N (%)) | |
| Positive | 34/43 (79.1%) |
| Negative | 4/43 (9.3%) |
| Not performed | 5/43 (11.6%) |
| Progesterone Receptor (PR) Status (n/N (%)) | |
| Positive | 25/43 (58.1%) |
| Negative | 13/43 (30.2%) |
| Not performed | 5/43 (11.6%) |
| Human Epidermal Growth Factor Receptor (HER2) Status (n/N (%)) | |
| Positive | 2/43 (4.7%) |
| Negative | 33/43 (76.7%) |
| Not performed | 8/43 (18.6%) |

**Table 27:** Per node detection rates for mastectomy patients from the mITT group

| | **Magtrace™ (mITT nodal analysis)** | | |
|---|---|---|---|
| **Control (Radioisotope and Blue Dye)** | **Detected** | **Not Detected** | **Total** |
| **Detected**<br>**Not Detected** | 108/123 (87.8%)<br>8/123 (6.5%) | 7/123 (5.7%)<br>0/123 (0%) | 115/123 (93.5%) |
| **Total** | 116/123 (94.3%) | | 123/123 (100%) |

**Table 28:** Malignant node per node detection rates for mastectomy patients from the mITT group

| | **Magtrace™ (mITT nodal analysis of malignant nodes)** | | |
|---|---|---|---|
| **Control (Radioisotope and Blue Dye)** | **Malignant Detected** | **Malignant Not Detected** | **Total** |
| **Detected**<br>**Not Detected** | 8/8 (100%)<br>0/8 (0%) | 0/8 (0%)<br>0/8 (0%) | 8/8 (100%) |
| **Total** | 8/8 (100%) | | 8/8 (100%) |

2. Protocol Deviations in the Pivotal (Sentimag®) study

   In total, 29 protocol deviations were reported in 17.5% (28) of subjects. The most common protocol deviation was the use of Lymphoseek (technetium Tc 99m tilmanocept) as the radioisotope Control versus the protocol-required radiolabelled sulfur colloid radioisotope. This deviation occurred 13 times at three (3) different sites. The deviations that occurred did not negatively impact the scientific soundness or the data integrity of the clinical study. However, subjects in whom Lymphoseek was used were excluded from the PP analysis as this met one of the pre-specified criteria for exclusion from the PP analysis set.

3. Device Failures in the Pivotal (Sentimag®) Study

   Four (4) Sentimag® device failures were reported in four (4) subjects. No adverse effects occurred as a result of the device failures.

4. Magnetic Resonace Imaging (MRI) Artifact

   Magtrace™ can cause image artifacts during magnetic resonance imaging (MRI) near injection and drainage site. These artifacts may be present long-term.

   - Information from European sample cases and reports indicate that the artifact persists, often unchanged, for at least 25 months.

- The artifact from the device may make large parts of the images completely uninterpretable and nondiagnostic.

Magtrace™ may also travel to regions away from the injection site such as liver, spleen, etc. if injected directly into the blood stream. In such cases the presence of Magtrace™ may cause image artifacts during Magnetic Resonance Imaging (MRI) of those regions. Some manipulation of scan parameters may be required to compensate for the artifact. Magtrace™ residues have not been reported to produce artifacts affecting imaging in X-ray, PET, PET/CT, CT, or ultrasound studies.

Table 29 summarises per patient or per breast occurrence of imaging artifacts in mastectomy patients.

In the study conducted by Krischer et al.[2], 24 subjects participated of which two (2) had bilateral mastectomy treatment making in total 26 breast cancer cases. Of these, 18 underwent Breast Conserving Surgery (BCS), and eight (8) underwent mastectomy. Of the BCS cases, the data from one subject (PID 15) was not interpretable due to breathing artifacts, leaving 17 interpretable BCS cases. There were two (2) bilateral surgeries, but no bilateral mastectomies. Subject PID 3 had a Right mastectomy and a left lumpectomy and subject PID 17 had bilaterallumpectomy. Therefore, in total, eight (8) patients underwent mastectomy, of whom one also had a lumpectomy in the contralateral breast. None of the cases show the occurrence of artifact.

In the SentimagIC pivotal study, 43/147 subjects had mastectomy. Of these, imaging was available for 2/43 plus a further subject 05-012 who received lumpectomy in the study and mastectomy after the study completed. None of the cases show the occurrence of artifact.

**Table 29:** Per patient and per breast occurrence of artifact in post-mastectomy MRI

| **Source** | **Number of post mastectomy images** | **Per patient (per breast) occrence of artifact** |
|---|---|---|
| Krischer et al.[2] (see reference: Krischer et al., Feasibility of breast MRI after sentinel procedure for breast cancer with superparamagnetic tracers, Eur J Surg Oncol. 2018 Jan;44(1):74-79.) | 24 subjects participated, of which two (2) had bilateral mastectomy, making 26 total breast cancer cases.<br>• eight (8) mastectomies<br>• 18 BCS (including one after chemotherapy)<br>One subject (PID 15) not interpretable due to breathing artifacts and movement.<br>Therefore 25 breast cancers eligible for analysis:<br>• eight (8) mastectomies<br>• 17 BCS<br>Bilateral cases were: PID 3 right mastectomy, left lumpectomy; and PID 17 bilaterallumpectomy | 0/8 (0/8) |

| Source | Number of post mastectomy images | Per patient (per breast) occrence of artifact |
|---|---|---|
| SentimagIC pivotal study | 43/147 subjects had mastectomy. Of these, imaging was available for 2/43 plus a further subject 05-012 who received lumpectomy in the study and mastectomy after the study completed. | 0/3 (0/5)<br>(Only 3/5 breasts received Magtrace™) |
| Total | | 0/11 (0/15) |

Table 30 summarises the type of mastectomy conducted after which the subject underwent MRI treatment. As noted above, there is no incidence of MRI artifacts observed in any of the cases outlined below.

**Table 30:** Type of mastectomy before MRI

| Study | Type of mastectomy | Sienna injection technique | Incidence of MRI artifact |
|---|---|---|---|
| **Krischer, 2018 paper** | 8 subjects received mastectomy (non-skin or nipplesparing)** | Sub-areolar interstitial | 0/8 (None visible) |
| **SentimagIC pivotal study Subject 05-012b,c*** | Bilateral. Non-skin or nipple sparing | Sub-cutaneous, sub-areolar | None visible |
| **SentimagIC pivotal study Subject 05-018** | Bilateral. Non-skin or nipple sparing | Sub-cutaneous, sub-areolar | None visible |
| **SentimagIC pivotal study Subject 06-030** | Skin-sparing | Sub-cutaneous, sub-areolar | None visible |

*Subject 05-012 received lumpectomy surgery in the study, but subsequently bilateral mastectomy, after which these MRI scans were obtained.

**Data on the type of mastectomy obtained from the author via a personal communication.

5. Published literature studies

Further studies: Seven (7) European studies have been carried out for which the data are published. These are summarized in the Table 31 along with the supporting publications (Note: The French NCT01790399 Study is the Houpeau study in Table 31).

**Table 31:** Summary of Published European Studies

| Author | Douek[7] | Thill[8] | Rubio[10] | Ghilli[11] | Houpeau[12] | Pinero[13] | Karakatsanis[14] |
|---|---|---|---|---|---|---|---|
| **Centers** | 7 | 4 | 1 | 3 | 4 | 9 | 7 |
| **Locations** | UK, Netherlands | Germany, Poland, Switzerland | Spain | Italy | France | Spain | Sweden, Denmark |
| **Patients enrolled** | 160 | 150 | 100 | 185 | 108 | 181 | 206 |
| **Control technique** | Isotope + Blue dye | Isotope | Isotope | Isotope | Isotope + Blue dye | Isotope | Isotope + Blue dye |
| **Per patient detection rate** (proportion of patients in whom at least one node is found) | | | | | | | |
| **Test:** | 94.4% | 98.0% | 96.0% | 98.4% | 97.2% | 97.8% | 97.6% |
| | 151/160 | 147/150 | 96/100 | 182/185 | 105/108 | 177/181 | 201/206 |
| **Control:** | 95.0% | 97.3% | 93.0% | 97.8% | 95.4% | 98.3% | 97.1% |
| | 152/160 | 146/150 | 93/100 | 181/185 | 103/108 | 178/181 | 200/206 |
| **Per node detection rate:** (Proportion of total nodes found) | | | | | | | |
| **Test:** | 80.0% | 97.3% | N/A | 95.0% | 97.2% | 91.0% | 93.3% |
| | 323/404 | 283/291 | | 342/360 | 208/214 | 292/321 | 376/403 |
| **Control:** | 73.5% | 91.8% | N/A | 94.2% | 90.2% | 86.3% | 91.3% |
| | 297/404 | 267/291 | | 339/360 | 193/214 | 277/321 | 368/403 |
| **Mean nodes detected per patient:** | | | | | | | |
| **Test:** | 2.0 | 1.9 | 2.2 | 1.8 | 1.9 | 1.6 | 1.8 |
| **Control:** | 1.9 | 1.8 | 1.77 | 1.8 | 1.8 | 1.5 | 1.8 |

Skin staining was observed only in the MONOS study (Karakatsanis study in Table 31, above**)** in which two (2) of a total of 57 mastectomy patients who had received Sienna+ (Magtrace™) showed signs of skin staining. Skin staining was resolved in both patients in 3 months post-surgery. The first subject had received sub-cutaneous, peri-areolar injection subsequent to which she had undergone skin sparing mastectomy. The position of the stain was towards upper outer quadrant and the size of the stain 1 x 2 cm. The stain had disappeared after 3 months. The second subject also received sub-cutaneous, peri-areolar injection subsequent to which she underwent classic mastectomy. The position of the stain was also towards upper outer quadrant and the size of the stain 1 x 2 cm. In this case the stain also disappeared after 3 months.

In the SentimagIC pivotal study (G140208, NCT02336737) where 43 of 147 patients underwent mastectomy, no skin staining was observed at follow-up visit between 6-22 days post-surgery and the surgeons did not record the type of mastectomy. No subsequent follow up was recorded. Table 32 summarizes skin staining in patients that underwent mastectomy in the MONOS study and SentimagIC study.

**Table 32:** Summary of skin staining in patients that underwent mastectomy

| **Study** | **Type of mastectomy** | **Sienna+/Magtrace™ injection technique** | **Position of skin staining** | **Duration of skin staining** |
|---|---|---|---|---|
| MONOS study - First mastectomy subject with skin staining | Skin sparing | Sub-cutaneous, peri-areolar injection | 1 x 2 cm staining towards upper outer quadrant | Disappeared after 3 months |
| MONOS study - Second mastectomy subject with skin staining | 'Classic' mastectomy | Sub-cutaneous, peri-areolar injection | 1 x 2 cm staining towards upper outer quadrant | Disappeared after 3 months |
| SentimagIC pivotal study report (G140208, NCT02336737) | Not recorded | Sub-cutaneous, sub-areolar | Not recorded | At follow-up visit between 6 - 22days post surgery, 0/43 patients recorded an AE for skin staining. No subsequent follow-up |

## XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Panel, an FDA advisory committee, for review and recommendation because there were no outstanding issues regarding the safety and effectiveness of the device.

## XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

### A. Effectiveness Conclusions

The pivotal multi-center clinical study in 160 US patients with breast cancer met the pre-specified success criterion as the null hypothesis was rejected for the primary endpoint. This was clinically meaningful because of the strong concordance. The analysis of this study provides valid scientific evidence to support the effectiveness of Magtrace™/Sentimag® which can be considered clinically and statistically non-inferior to the combined technique

of radioisotope and blue dye to assist in detecting and localizing lymph nodes draining a tumor site in breast cancer, as part of a SLNB procedure.

Supporting evidence from the French study together with the meta-analyses (see Table 32: Summary of Published European Studies) provide further support for the safety and effectiveness of Magtrace™/Sentimag® in the detection of lymph nodes in breast cancer patients undergoing mastectomy.

## B. Safety Conclusions

In the pivotal clinical study, Magtrace™ produced a similar risk profile to the standard technique with no unanticipated adverse device effects with the exception of MRI artifact and breast skin staining. Further, the risk of MRI artifacts and breast skin staining appeared minimal in patients that underwent mastectomy. There were no adverse events related to the Sentimag® device.

The risk profile of Sienna+ in the supporting French clinical study is also similar to the standard technique, providing further support for the safety of the product.

## C. Benefit-Risk Determination

Benefits:

The Magtrace™ and Sentimag® magnetic localization system offers the following benefits over the combined radioisotope and isosulfan blue dye standard technique for SLNB:

- The use of Magtrace™/Sentimag® spares the patient and healthcare team exposure to the ionizing radiation associated with the alternative.
- Magtrace™/Sentimag® allows these procedures to be conducted in locations without the need for special handling of radioistopes, therefore, it can be provided outside of a hospital setting.
- As opposed to radioistopes which must be injected while the patient is awake, Magtrace™ can be injected while the patient is under anesthesia, sparing the patient a painful procedure.
- Magtrace™/Sentimag® saves time as it provides greater flexibility in deciding when to inject the patient with the Magtrace™ particles from 20 minutes before the procedure as opposed to using the radioisotopes which requires a more restrictive schedule window of 4-24 hours.
- Magtrace™ has a long shelf life (and no half-life), allowing it to be shipped to hospitals that do not have access to nuclear medicine.

Risks:

The risks include:

- Bradycardia
- Anaphylaxis
- MRI artifact
- Skin Staining

Bradycardia (1 event) and anaphalaxis (1 event) in two (2) separate patients, were reported as undertermined in relatedness to the device.

MRI Artifact:

The device creates artifact on Magnetic Resonace Images which:

- persists, often unchanged, for at least 25 months.
- makes large parts of the images completely uninterpretable and nondiagnostic.

The MRI artifact risks can be mitigated by the following means:

1. As Magtrace™ may alter post-operative magnetic resonance imaging (MRI) scans and such alteration may be long-term, the product should be limited to use in mastectomy patients as they will have an extremely low need for future MRI of the ipsilateral region.
2. Patient labelling and user manual will inform patients and users of the risk of MRI artifact after Magtrace™ injection.

Skin Staining:

Magtrace™ can create skin staining (16.3 % in the US trial, 0% in mastectomy patients after 6-22 days follow-up). This can be mitigated by the following means:

1. Patient labelling and user manual will inform patients and users that some long-term skin dis-coloration may occur.

2. Limiting the use of the device in breast cancer patients undergoing mastectomy. Skin staining was not observed in patients that underwent mastectomy after 3 months post-surgery.

There is a risk of a learning curve to new users of this product. This risk could be mitigated in the labeling recommendation for concurrent use with standard of care sentinel lymph node identification techniques for the first number of cases.

Patient Perspectives:

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for breast cancer patients who undergo mastectomy with sentinel lymph node biopsy the benefits outweigh the probable risks.

### D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The analysis of the pivotal clinical study provides valid scientific evidence to support the safety and effectiveness of Magtrace™/Sentimag®, which can be considered clinically and statistically non-inferior to the combined technique of radioisotope and blue dye, to assist in detecting and localizing lymph nodes draining a tumor site in breast cancer, as part of a SLNB procedure.

Taken together with the analysis of the supporting studies, the overall clinical data package provides support for the safety and efficacy of Magtrace™/Sentimag® when used in accordance with the indications for use.

## XIV. CDRH DECISION

CDRH issued an approval order on July 24, 2018.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

## XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

## XVI. REFERENCES

1. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, Ashikaga T, Weaver DL, Mamounas EP, Jalovec LM, Frazier TG, Noyes RD, Robidoux A, Scarth HM, Wolmark N., Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast

cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial., Lancet Oncol. 2010 Oct;11(10):927-33.

2. Krischer et al., Feasibility of breast MRI after sentinel procedure for breast cancer with superparamagnetic tracers, Eur J Surg Oncol. 2018 Jan;44(1):74-79.

3. The American Society of Breast Surgeons guidelines. https://www.breastsurgeons.org/new_layout/about/statements/

4. Nam J, Kwon D (2009) Non-inferiority tests for clustered matched-pair data Statistics in Medicine 28: 1668-1679.

5. McMasters KM, Tuttle TM, Carlson DJ, et al. Sentinel lymph node biopsy for breast cancer: a suitable alternative to routine axillary dissection in multi-institutional practice when optimal technique is used. J Clin Oncol 2000;18:2560–2566.

6. Liu, L-C, et al., Is It Necessary to Harvest Additional Lymph Nodes after Resection of the Most Radioactive Sentinel Lymph Node in Breast Cancer?, J Am Coll Surg, Vol. 207, No. 6, December 2008.

7. Douek M, et al. The Sentimag multicenter trial: Sentinel node biopsy using a magnetic technique versus the standard technique. Eur J Surg Oncol EJSO. 2013 Nov;39(11):S85–S86.

8. Thill M, Kurylcio A, Welter R, van Haasteren V, Grosse B, Berclaz G, et al. The Central-European Sentimag study: Sentinel lymph node biopsy with superparamagnetic iron oxide (SPIO) vs. radioisotope. The Breast. 2014 Apr;23(2):175–9.

9. Krag, DN., et al, Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomized phase III trial, Lancet Oncol. 2007 Oct;8(10):881-8.

10. Rubio et al. (2015): The superparamagnetic iron oxide is equivalent to the Tc99 radiotracer method for identifying the sentinel lymph node in breast cancer. Eur J Surg Oncol; 41(1):46-51.

11. Ghilli M, et al. The superparamagnetic iron oxide tracer: a valid alternative in sentinel node biopsy for breast cancer treatment. Eur J Cancer Care (Engl). 2015.

12. Houpeau et al. (2016): Sentinel Lymph Node Identification Using Superparamagnetic Iron Oxide Particles Versus Radioisotope: The French Sentimag Feasibility Trial. J Surg Oncol; 113(5):501 – 7.

13. Piñero-Madrona et al. (2015): Superparamagnetic iron oxide as a tracer for sentinel node biopsy in breast cancer: a comparative non-inferiority study. Eur J Surg Oncol; 41(8):991-7.

14. Karakatsanis A, et al., The Nordic Sentimag trial: a comparison of super paramagnetic iron oxide (SPIO) nanoparticles versus Tc99 and patent blue in the detection of sentinel node (SN) in patients with breast cancer and a meta-analysis of earlier studies. Breast Cancer Res Treat. 2016 Jun;157(2): 281-94