# 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.
330 Cambridge Science Park
Milton Road, Cambridge, CB4 0WN, UK

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160053/S002

Date of FDA Notice of Approval: December/06, 2022

The original PMA P160053 was approved on July 24, 2018 and 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. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the device to assist in localizing lymph nodes draining a tumor site, as part of a sentinel lymph node biopsy procedure, in patients with breast cancer.

## 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 or lumpectomy. For patients undergoing lumpectomy, nipple sparing, nipple areolar sparing or skin sparing procedures, Magtrace is indicated to be injected only peritumorally.

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.
- SLNB before neoadjuvant chemotherapy (NAC) where magnetic resonance imaging (MRI) will be the primary imaging used for monitoring the progress of NAC.
- Patients identified in advance to require post-lumpectomy imaging with breast MRI.

## 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.

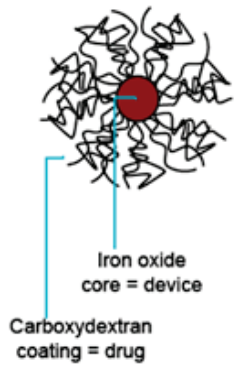
Each milliliter of Magtrace® contains approximately 28 milligrams of iron in the form of iron oxide. The recommended quantity of Magtrace® administered for use in patients is 2 ml with the equivalent iron content of 55 mg +/- 4 mg per injection.

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.

Two generations of this device are now available the original Sentimag (Sentimag Gen 2) and the new generation of the device Sentimag Gen 3.

In both cases, 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 original 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 features of Sentimag Gen 3 are:

- Portable base unit that can sit on any flat surface

- Audible and visual indications of marker proximity
- Audible signal with a variable pitch (frequency) that increases as the probe is brought near the magnetic marker
- Volume control knob on the base unit
- Liquid crystal display (LCD) for numerical indication of signal strength in Counts mode.
- Audible and visual discrimination between magnetic signals and extraneous or background signals
- Magnetic signals indicated by variable pitch (audible) and yellow LCD digits (visual); extraneous or background signals indicated by low and constant pitch (audible) and red LCD digits (visual)
- Instrument-balancing function that readies the system for measurement
- Push button mounted on the base unit activates the balance function
- Two probes are compatible with the Sentimag base unit: a Standard Sentimag probe (18.5mm in diameter) and a Thinner (13.5mm diameter) Sentimag Probe
- Detachable electronic footswitch allows remote operation of the balance function
- The detachable applied part is the probe assembly comprising a hand-held probe, a flexible cable of 9 feet in length, and colour-coded (black and white) connector 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)

Sentimag Gen 3 operates in two distinct modes, Count mode and the Measure mode. In Count mode, the Sentimag Gen 3 detector works in exactly the same way as Sentimag Gen in that it can detect and locate Magtrace® for the tissue marker to be surgically removed with the sentinel node following detection. Measure mode is not available to be used with Magtrace and should not be used to detect Magtrace.

In Sentimag Gen 3 the display of the count has been expanded to 5 digits instead of 4 in the Gen 2 and the scale multiplier has been fixed to the equivalent of sensitivity/scale setting 2 in the Gen 2. The combination of these two features means that the Sensitivity/scale control knob is no longer required in Sentimag Gen 3.

The Base Unit, Probe, and Footswitch for both Sentimag Gen 2 and Gen 3 are shown in Figure 2 below.

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

Sentimag (Gen 2) Sentimag (Gen 3)


## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are 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 alternatives are Technetium radioisotope-labelled tracers 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 was 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 . In 2017 Sienna+ was replaced with Magtrace which is currently available in the following countries: USA, Canada, United Kingdom, Germany, France, Italy, Spain, Portugal, Netherlands, Austria, Czech Republic, Denmark, Croatia, Sweden, Slovakia, Cyprus, Turkey, Israel, Poland, Switzerland, Hong Kong, South Africa, Serbia, Bosnia, Saudi Arabia, Bahrain, Morocco, New Zealand, and Australia. The Sentimag®/Sienna+ product was not withdrawn from any foreign market for any reason relating to the safety and effectiveness of the device. It was superseded by Magtrace which is a more user friendly version of the same 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 |
|---|---|---|---|
| **Biocompatibility- 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 |
| 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 |

| Test | Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| **Biocompatibility- Sienna+/Magtrace®** | | | |
| Systemic Toxicity 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 |
|---|---|---|---|
| **Biocompatibility- Sienna+/Magtrace®** | | | |
| **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, Generation 2 Sentimag® system and<br>Generation 3 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). Additionally, Gen 3 has a 13.5mm probe<br>**Sensitivity** of Gen 2 system increased approximately 3.5x over that of the Gen 1 System. The sensitivity of Gen 3 for both standard diameter probe (18.5mm) and thinner probe (13.5mm) is exactly the same as Gen 2. | 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 |
| 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 into 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 Feasibility 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, multi-center, 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 δ, 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 δ. 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 δ 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-β) ≈ 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)

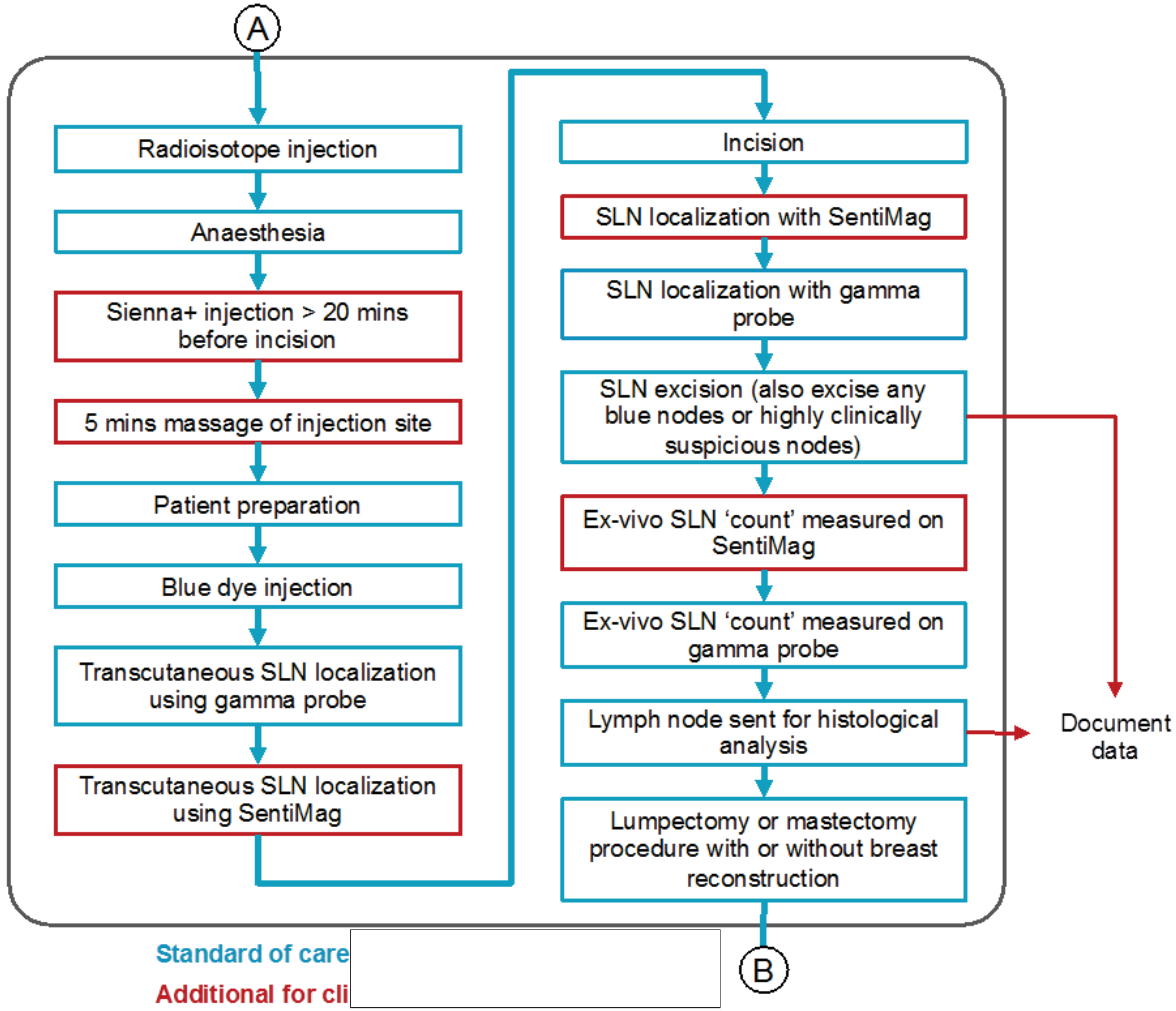
Patients were not permitted to enroll in the Sentimag® study if they met any of the following exclusion criteria:

- 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 another 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 consistent 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 | | | | | |
| Pregnancy test | | | X | | |
| Lymph node mapping and sentinel node biopsy procedure | | | X | | |
| Excised nodes sent for histological analysis & pathology evaluation | X | | 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 Effectiveness Endpoint:**
The primary effectiveness 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

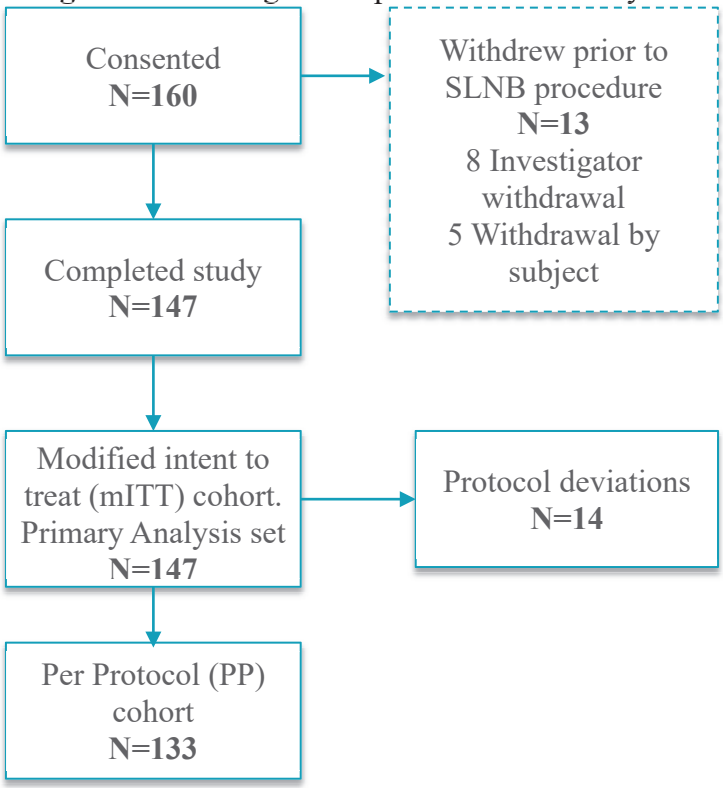
At the time of database lock, of 160 patients enrolled in the PMA study, 147 patients (91.9%) completed the study and are available for analysis. Patient accountability is shown in Figure 4.

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% |

| | Overall (N=147) |
|---|---|
| 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) |
| 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) |
| Progesterone 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 discoloration 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) serious adverse events in the study. After data analysis, seven (7) out of the nine (9) SAEs were unrelated to the Magtrace®, 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** |
| **Detected** | 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 Positive 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 Resonance Imaging (MRI) Artifact
6. Published literature studies

1. French Feasibility Study Summary:

A feasibility 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 radiolabeled 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

Enrolment 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 anesthesia 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

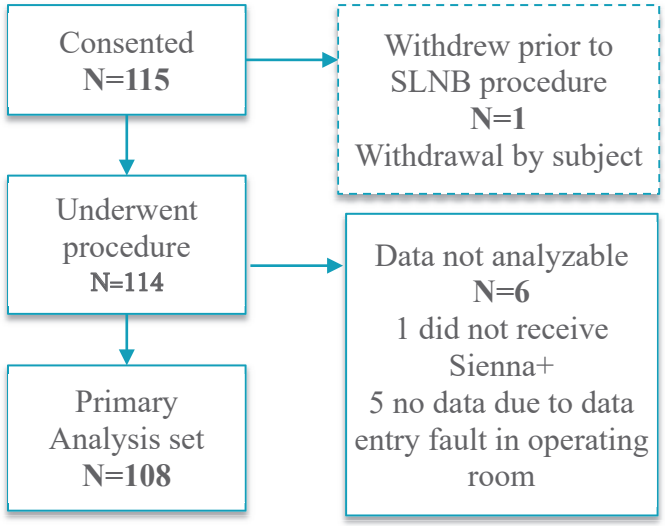
- Unable to be medically monitored in the study for geographic, social or mental reasons
- Patient deprived of their freedom or under guardianship
- Pregnant or breast-feeding

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 Clinicopathologic Baseline 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 |
| 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 |

| | N = 108 | % |
|---|---|---|
| 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 hematoma 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%,<br>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 Feasibility 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

   Forty-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** | 108/123 (87.8%) | 7/123 (5.7%) | 115/123 (93.5%) |
| **Not Detected** | 8/123 (6.5%) | 0/123 (0%) | |
| **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** | 8/8 (100%) | 0/8 (0%) | 8/8 (100%) |
| **Not Detected** | 0/8 (0%) | 0/8 (0%) | |
| **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 radiolabeled 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 Resonance 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 Contrast Enhanced Digital Mammography (CEDM), X-ray, PET, PET/CT, CT, or ultrasound studies.

Table 29 summarizes 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 bilateral lumpectomy. 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) occurrence 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 bilateral lumpectomy | 0/8 (0/8) |
| 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 summarizes 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 nipple sparing)** | 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.

The summary of studies on MRI Artifact is presented in Table 31 to Table 33.

**Table 31** (All Injection Methods)

| Study [Reference] | Amount of Magtrace Injected and Location (e.g., subareolar, periareolar, retroareolar, peritumoral, etc.) | Net Number of Subjects Participated/ Studied | Number (and %) of Subjects with Image Artifacts | Size of the Artifacts (mean, range) | Did Artifacts Resolve Completely (Yes (%), No (%)) | Time taken to resolve artifacts (mean, and range) | Radiology reported outcome (no artifacts, minimal artifacts, suitable for diagnosis/ non-diagnostic, significantly impaired) |
|---|---|---|---|---|---|---|---|
| Krischer 2018 | 2 ml Sienna+ 3ml Saline.<br>5 ml Retroareolar | n=17 evaluable | 13/17 (76.5%) | Not specified | Not specified | Not specified | 4/17 (23.5%) Grade 2 - without restriction,<br>10/17 (58.8%) Grade 1-with restriction,<br>3/17 (17.6%) Grade 0 – impossible |
| Aribal 2021 | 2 ml Sienna+ 3ml Saline.<br>5 ml Periareolar | n=25 | 21/25 (84%) | Not specified | Not specified | Not specified | No artifact 4/25(16%)<br>Focal area of signal void artifact (less than 5mm) 10/25 (40%)<br>Segmental area of signal void artifact 3/25(12%)<br>Non diagnostic 8/25(32%) |
| PostMag<br>Registry (Reference No. ISRCTN85167182)<br>This study is not yet published. | 2ml Peritumoral | n=11 | 10 (91%) | Mean artifact Volume 10 $cm^3$<br>Range: 0 $cm^3$ - 28 $cm^3$ | Yes (18%)<br>No (82%) | Mean 3 months<br>Range: 1 month to 5 months | No Artifacts 1/11 (9%)<br>Minimal Artifacts suitable for diagnosis 6/11 (55%)<br>Significantly impaired, but could be diagnostic 3/11 (25%)<br>Non diagnostic, 1/11 (9%) |
| Unpublished study | 2ml Peritumoral | n=2 | 1(50%) | Mean artifact Volume 5 $cm^3$<br>Range: 0 $cm^3$ - 10 $cm^3$ | Yes (50%)<br>No (50%) | Not applicable, Magtrace intraoperative followed by MRI | No Artifacts 0/2 (0%)<br>Minimal Artifacts suitable for diagnosis 2/2 (100%)<br>Non diagnostic, significantly impaired 0/2 (0%) |
| Sentimag IC<br>Study Reference:<br>NCT02336737 IDE No. G140208 | 2ml Subareolar | 147/13 | 12 (92%) | Mean 68 $cm^3$<br>Range 0 $cm^3$- 204 $cm^3$ | Yes (8%)<br>No (92%) | Mean: 10 months,<br>Range: 1 month to 15 months | No Artifacts 1/13 (8%)<br>Minimal Artifacts suitable for diagnosis 4/13 (31%)<br>Significantly impaired but could be diagnostic 5/13 (39%)<br>Non diagnostic, 3/13 (23%) |
| Shrotria, Stuart European Journal of Surgical Oncology 46 (2020) P136 Abstract 121. | 2ml Periareolar | 160/14 | Not confirmed, assumed 100% | Not known | Not confirmed, assumed No (100%) | Not known | No Artifacts 0/14 (0%)<br>Minimal Artifacts suitable for diagnosis 11/14 (78%)<br>Significantly impaired 0/14 (0%)<br>Non diagnostic, 3/14 (21%) |

**Table 32** (Peritumoral Injections)

| Study [Reference] | Amount of Magtrace Injected | Net Number of Subjects Participated/ Studied | Number (and %) of Subjects with Image Artifacts | Size of the Artifacts (mean, range) | Did Artifacts Resolve Completely (Yes (%), No (%)) | Time taken to resolve artifacts (mean, and range) | Radiology reported outcome (no artifacts, minimal artifacts, suitable for diagnosis/ non-diagnostic, significantly impaired) |
|---|---|---|---|---|---|---|---|
| PostMag<br>Registry (Reference No. ISRCTN85167182)<br>This study is not yet published. | 2ml Peritumoral | n=11 | 10 (91%) | Mean artifact Volume 10 $cm^3$<br>Range: 0 $cm^3$ -28 $cm^3$ | Yes (18%)<br>No (82%) | Mean 3 months<br>Range: 1 month to 5 months | No Artifacts 1/11 (9%)<br>Minimal Artifacts suitable for diagnosis 6/11 (55%)<br>Significantly impaired, but could be diagnostic 3/11 (25%)<br>Non diagnostic, 1/11 (9%) |
| Unpublished study | 2ml Peritumoral | n=2 | 1(50%) | Mean artifact Volume 5 cm3<br>Range: 0 cm3 -10 cm3 | Yes (50%)<br>No (50%) | Not applicable, Magtrace intraoperative followed by MRI | No Artifacts 0/2 (0%)<br>Minimal Artifacts suitable for diagnosis 2/2 (100%)<br>Non diagnostic, significantly impaired 0/2 (0%) |

**Table 33** (Not Peritumoral Injections, All other methods of Injection)

| Study [Reference] | Amount of Magtrace Injected | Net Number of Subjects Participated/ Studied | Number (and %) of Subjects with Image Artifacts | Size of the Artifacts (mean, range) | Did Artifacts Resolve Completely (Yes (%), No (%)) | Time taken to resolve artifacts (mean, and range) | Radiology reported outcome (no artifacts, minimal artifacts, suitable for diagnosis/ non-diagnostic, significantly impaired) |
|---|---|---|---|---|---|---|---|
| Krischer 2018 | 2 ml Sienna+ 3ml Saline.<br>5 ml Retroareolar | n=17 evaluable | 13/17 (76.5%) | Not specified | Not specified | Not specified | 3/17 (17.6%) grade 0 – impossible,<br>10/17 (58.8%) Grade 1-with restriction,<br>4/17 (23.5%) Grade 2 - without restriction |
| Aribal 2021 | 2 ml Sienna+ 3ml Saline.<br>5 ml Periareolar | n=25 | 21/25 (84%) | Not specified | Not specified | Not specified | No Artefacts 26/34 (81%)<br>Minimal Artefacts suitable for diagnosis 6/34 (18%)<br>Significantly impaired, but could be diagnostic 1/34 (3%)<br>Non diagnostic, 1/34 (6%) |
| Sentimag IC<br>Study Reference:<br>NCT02336737<br>IDE No. G140208 | 2ml Subareolar | 147/13 | 12 (92%) | Mean 68 $cm^3$<br>Range 0 $cm^3$-204 $cm^3$ | Yes (8%)<br>No (92%) | Mean: 10 months,<br>Range: 1 month to 15 months | No Artifacts 1/13 (8%)<br>Minimal Artifacts suitable for diagnosis 4/13 (31%) |

| Study [Reference] | Amount of Magtrace Injected | Net Number of Subjects Participated/ Studied | Number (and %) of Subjects with Image Artifacts | Size of the Artifacts (mean, range) | Did Artifacts Resolve Completely (Yes (%), No (%)) | Time taken to resolve artifacts (mean, and range) | Radiology reported outcome (no artifacts, minimal artifacts, suitable for diagnosis/ non-diagnostic, significantly impaired) |
|---|---|---|---|---|---|---|---|
| | | | | | | | Significantly impaired but could be diagnostic 5/13 (39%)<br>Non diagnostic, 3/13 (23%) |
| Shrotria, Stuart European Journal of Surgical Oncology 46 (2020) P136 Abstract 121. | 2ml Periareolar | 160/14 | Not confirmed, assumed 100% | Not known | Not confirmed, assumed No (100%) | Not known | No Artifacts 0/14 (0%)<br>Minimal Artifacts suitable for diagnosis 11/14 (78%)<br>Significantly impaired 0/14 (0%)<br>Non diagnostic, 3/14 (21%) |

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 34 along with the supporting publications (Note: The French NCT01790399 Study is the Houpeau study in Table 34).

**Table 34:** 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 34, 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 subcutaneous, periareolar 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 subcutaneous, periareolar 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.

Tables 35 to 38 summarize skin staining in patients for a number of studies.

## Table 35 Skin Staining with All Injection Methods

| Study [Reference] | Amount of Magtrace Injected and Location (e.g., sub-areolar (SA), peri-areolar (PA), retro-areolar (RA), peri-tumoral (PT), etc.) 5ml = 2ml Sienna+ diluted with 3ml saline | Net Number of Subjects Participated/ Studied | Numbers of lumpectomy vs mastectomy procedures | Number of Subjects with Skin Staining | Did Skin Staining Resolve Completely (Yes (%), No (%)) As % of patients with staining | Time taken to resolve skin staining (mean, and range) | Patient reported outcome (no-problem/problem-not important/problem-important/unavailable) |
|---|---|---|---|---|---|---|---|
| Rubio 2015 | 5ml SA | 120 | n=103 lumpectomy<br><br>n=17 mastectomy | 20% no timepoint specified | Not stated specifically "*The tattoo usually vanishes over time.*" | Not stated specifically "*In our study patients still have some discoloration after 6 months of the injection. This tattoo is similar to the one produced by the blue dye in terms of numbers and time of stain*" | Unavailable |
| Karakatsanis 2016 | 5ml SA | 206<br><br>Follow up for 186 | n=154 Lumpectomy<br><br>n=52 mastectomy | 35% post-op 0-3 months *"95.6% of patients with discoloration had been treated with breast conserving surgery" (lumpectomy)* | Yes:75.8%<br>No: 24.2%<br>At 15 months | "*Discoloration was present in 35.5 % of patients post-operatively (0–3 months) and faded progressively in size and color over time to 21 % of patients after a year. Staining remained present in 8.6 % 15 months after the operation, but much smaller and paler.*" | Unavailable |
| Houpeau 2016 | 5ml SA | 108 | n=100 lumpectomy<br><br>n=5 mastectomy<br><br>n=3 oncoplasty | 22 (20.4%)<br><br><30days post-operative | Not stated | Not Stated, max follow up 30 days | Unavailable |
| Ghilli 2015 | 5ml SA | 193 | n=184 lumpectomy | *"…more than 40% of cases…"* | Yes:91%<br>No: 9%<br>At 6 months<br>*"transient in more than 91% in the first 6 months after the procedure."* | *"transient in more than 91% in the first 6 months after the procedure."* | *"The pigmentation was usually very light in colour and did not represent a real problem for the patient. As soon as surgeons became more familiar* |

| Study [Reference] | Amount of Magtrace Injected and Location (e.g., sub-areolar (SA), peri-areolar (PA), retro-areolar (RA), peri-tumoral (PT), etc.) 5ml = 2ml Sienna+ diluted with 3ml saline | Net Number of Subjects Participated/ Studied | Numbers of lumpectomy vs mastectomy procedures | Number of Subjects with Skin Staining | Did Skin Staining Resolve Completely (Yes (%), No (%)) As % of patients with staining | Time taken to resolve skin staining (mean, and range) | Patient reported outcome (no-problem/problem-not important/problem-important/unavailable) |
|---|---|---|---|---|---|---|---|
| | | | n=6 bilateral reduction mammoplasty<br><br>n=2 mastectomy | | | | *with the technique, this side effect was controlled by performing the injection slightly deeper. "* |
| Karakatsanis 2017 | 5ml PA or PT | 184<br><br>PA 131,<br><br>PT 53 | n=126 lumpectomy<br><br>n=57 mastectomy | Overall: 73/184 (39.9%)<br><br>PA: 58/131 (44.3%)<br>PT: 15/53 (28.3%)<br><br>at 3 months<br><br>no staining in mastectomy patients | Yes: 9.5%<br>No: 90.5%<br>At 15 months | *"Albeit much smaller and paler, staining was still present in 36·1 per cent of patients (66 of 183) after 15months"*<br><br>*"Of patients with skin staining, 97% had been treated with BCS."* | (Likert scale was used for assessment.)<br><br>"*Patients who received a deeper peritumoral injection of SPIO had less staining immediately after surgery, as well as less staining over time. In total, 58 of 73 patients who developed staining had received a peri areolar injection, whereas only 15 had had a peritumoral injection (P = 0·046)"*<br><br>"*All 66 patients with discoloration remaining after more than 10months responded to the questionnaire at both time points. Only two patients in this subgroup (3 per cent) complained that they were affected by the stain. Views regarding skin staining and cosmesis were mixed. The majority of patients considered staining a minor problem, if an issue at all (60 per cent at the first assessment and 61 per cent at the second). No substantial change in views was noted between the two time points (P = 0·280)"* |
| Karakatsanis 2019 | Not specified | n=189 | n=129 lumpectomy | Lumpectomy: 42/129 (32.6 | Not reported | Not reported | unavailable |

| Study [Reference] | Amount of Magtrace Injected and Location (e.g., sub-areolar (SA), peri-areolar (PA), retro-areolar (RA), peri-tumoral (PT), etc.) 5ml = 2ml Sienna+ diluted with 3ml saline | Net Number of Subjects Participated/ Studied | Numbers of lumpectomy vs mastectomy procedures | Number of Subjects with Skin Staining | Did Skin Staining Resolve Completely (Yes (%), No (%)) As % of patients with staining | Time taken to resolve skin staining (mean, and range) | Patient reported outcome (no-problem/problem-not important/problem-important/unavailable) |
|---|---|---|---|---|---|---|---|
| | | | n=60 mastectomy | %) timepoint not specified No staining in mastectomy group | | | |
| Lorek 2019 | 5ml SA | n=303 | n=191 lumpectomy<br><br>n=107 mastectomy | 47 (15.5%) initial follow-up at 3 months | Yes: 76.6%<br>No: 23.4%<br>At 30 months | "*The average time needed for the discoloration to reduce by approximately 50% was 9 months and to disappear completely at approximately. 18 months. The longest persisting discoloration observed took 22 and 24 months"* | unavailable |
| Wärnberg 2019 | 5ml RA or PT | n=337<br>n=177 RA<br><br><br><br><br>n=163 PT | RA cohort: n=110 lumpectomy n=67 mastectomies.<br><br>In the PT cohort: n=148 lumpectomy n=15 mastectomies | Lumpectomy + RA injn: 74/110 (67.3%)<br><br>Lumpectomy + PT injn: 56/148 (37.8%) (p <0.001) | Lumpectomy + RA:<br>Yes: 31.3%<br>No: 68.7%<br><br>Lumpectomy + PT:<br>Yes: 75.1%<br>No: 24.9% | Analysis based upon N = 130 (74+56) patients with skin staining.<br><br>46.2% had a remaining staining after retro-areolar injections peritumoral (p \ 0.001 at 36 months)." | Analysis based upon 46 women of 75 with a remaining stain (since Likert scale was employed later).<br><br>Self-assessed cosmetic outcome (0-5 points) was worse after retro-areolar compared with peritumoral injections at 12 and 24 months: mean (median) 1.3 (0) vs. 0.5 (0) points (p \ 0.001) and 0.6 (0) vs. 0.2 (0) points (p = 0.02). However, the difference was gone after 36 months: 0.2 (0) vs. 0.1 (0) for retro-areolar and peritumoral injections, respectively (p = 0.49). Analyzing women with an actual stain at each time point showed no statistically |

| Study [Reference] | Amount of Magtrace Injected and Location (e.g., sub-areolar (SA), peri-areolar (PA), retro-areolar (RA), peri-tumoral (PT), etc.) 5ml = 2ml Sienna+ diluted with 3ml saline | Net Number of Subjects Participated/ Studied | Numbers of lumpectomy vs mastectomy procedures | Number of Subjects with Skin Staining | Did Skin Staining Resolve Completely (Yes (%), No (%)) As % of patients with staining | Time taken to resolve skin staining (mean, and range) | Patient reported outcome (no-problem/problem-not important/problem-important/unavailable) |
|---|---|---|---|---|---|---|---|
| | | | | | | | significant differences between the two injection types (data not shown). Women with a higher BMI scored lower at all time points, regardless of injection type, but the differences were not statistically significant (data not shown). |
| Alvarado 2019 | 2ml SA | n=146 | n=103 lumpectomy, n=43 mastectomy | Lumpectomy: 23/103 (22.3%) 1-3 week follow-up | Not reported | Not reported | *unavailable* |
| Vural 2019 | 5ml RA | n=104 underwent analysis | n=89 lumpectomy/oncoplastic<br><br>n=18 mastectomy | 22 (20.4%) at post-operative consultation | Not reported | Not reported | unavailable |
| Rubio 2020 | 3 groups of n=45:<br>Group 1: 1ml SA<br>Group 2: 1.5ml SA<br>Group 3: 2ml SA | n=135<br>n=118 answered questions on skin staining | n = 135 lumpectomy | 83 (70.3%) one month post-operative | Not reported | Not reported | (Likert scale was used for assessment.)<br><br>*"As answer to the question whether the skin staining was a problem for the patient, patients reported not being a problem, being 23/33 (69.7%) in group 1, 28/40 (70%) in group 2, and 30 (73.2%) in group 3"*<br><br>*"At 6 months follow up, 78.9% of the patients still felt that the skin staining was not a problem."* |
| PostMag (2020)<br><br>Registry (Reference | 2ml PT | 32/32 | n=32 Lumpectomy<br>n=0 Mastectomy | 12 (37.5%) (immediately post op) | Yes (100%)<br>No (0%) | Mean= 6 months<br>Range=3 months to 9 months | *Unavailable.* |

| Study [Reference] | Amount of Magtrace Injected and Location (e.g., sub-areolar (SA), peri-areolar (PA), retro-areolar (RA), peri-tumoral (PT), etc.)<br>5ml = 2ml Sienna+ diluted with 3ml saline | Net Number of Subjects Participated/ Studied | Numbers of lumpectomy vs mastectomy procedures | Number of Subjects with Skin Staining | Did Skin Staining Resolve Completely<br>(Yes (%), No (%))<br>As % of patients with staining | Time taken to resolve skin staining (mean, and range) | Patient reported outcome (no-problem/problem-not important/problem-important/unavailable) |
|---|---|---|---|---|---|---|---|
| No. ISRCTN8516 7182) | | | | | | | *No skin discoloration was observed in any of the subjects at 12 months* |

## Table 36 Skin Staining with Peritumoral Injections

| Study [Reference] | Amount of Magtrace Injected and Location (e.g., sub-areolar (SA), peri-areolar (PA), retro-areolar (RA), peri-tumoral (PT), etc.)<br><br>5ml = 2ml Sienna+ diluted with 3ml saline | Net Number of Subjects Participated/Studied | Numbers of lumpectomy vs mastectomy procedures | Number of Subjects with Skin Staining | Did Skin Staining Resolve Completely<br><br>(Yes (%), No (%)) | Time taken to resolve skin staining (mean, and range) | Patient reported outcome<br><br>(no-problem/problem-not important/problem-important/unavailable) |
|---|---|---|---|---|---|---|---|
| PostMag (2020)<br><br>Registry (Reference No. ISRCTN85167182) | 2ml PT | 32/32 | n=32 Lumpectomy<br>n=0 Mastectomy | 12 (37.5%) (immediately post op) | Yes (100%)<br>No (0%) | Mean= 6 months<br>Range=3 months to 9 months | *Unavailable.*<br><br>*No skin discoloration was observed in any of the subjects at 12 months* |
| Wärnberg 2019 | 5ml PT | n=163 PT | In the PT cohort: n=148 lumpectomy n=15 mastectomies | Lumpectomy + PT injn: 56/148 (37.8%)<br>(p <0.001) | Lumpectomy + PT:<br>Yes: 75.1%<br>No: 24.9% | Analysis based upon N = 130 (74+56) patients with skin staining.<br><br>"After 6, 12, 24, and 36 months, 65.4%, 63.6%, 58.1%, and 46.2% had a remaining staining after retro-areolar injections and 34.0%, 31.3%, 14.0%, and 9.4% after peritumoral (p \ 0.001 at 36 months)." | Analysis based upon 46 women of 75 with a remaining stain (since Likert scale was employed later).<br><br>Self-assessed cosmetic outcome (0-5 points) was worse after retro-areolar compared with peritumoral injections at 12 and 24 months: mean (median) 1.3 (0) vs. 0.5 (0) points (p \ 0.001) and 0.6 (0) vs. 0.2 (0) points (p = 0.02). However, the difference was gone after 36 months: 0.2 (0) vs. 0.1 (0) for retro-areolar and peritumoral injections, respectively (p = 0.49). Analyzing women with an actual stain at each time point showed no statistically significant differences between the two injection types (data not shown). Women with a higher BMI scored lower at all time points, regardless of injection type, but the differences were not statistically significant (data not shown). |
| Karakatsanis 2017 | 5ml PT | n=53 PT | Type of surgery not stratified by injection site. | PT: 15/53 (28.3%)<br>at 3 months | Not stratified by injection site.<br>Overall | *"Albeit much smaller and paler, staining was still* | (Likert scale was used for assessment.) |

| Study [Reference] | Amount of Magtrace Injected and Location (e.g., sub-areolar (SA), peri-areolar (PA), retro-areolar (RA), peri-tumoral (PT), etc.)<br><br>5ml = 2ml Sienna+ diluted with 3ml saline | Net Number of Subjects Participated/Studied | Numbers of lumpectomy vs mastectomy procedures | Number of Subjects with Skin Staining | Did Skin Staining Resolve Completely<br><br>(Yes (%), No (%)) | Time taken to resolve skin staining (mean, and range) | Patient reported outcome<br><br>(no-problem/problem-not important/problem-important/unavailable) |
|---|---|---|---|---|---|---|---|
| | | | n=126 lumpectomy n=57 mastectomy. no staining in mastectomy patients | | Yes: 9.5%<br>No: 90.5%<br>At 15 months | *present in 36·1 per cent of patients (66 of 183) after 15months"*<br><br>*"Of patients with skin staining, 97% had been treated with BCS."* | "*Patients who received a deeper peritumoral injection of SPIO had less staining immediately after surgery, as well as less staining over time. In total, 58 of 73 patients who developed staining had received a peri areolar injection, whereas only 15 had had a peritumoral injection (P = 0·046)"*<br><br>"*All 66 patients with discoloration remaining after more than 10months responded to the questionnaire at both time points. Only two patients in this subgroup (3 per cent) complained that they were affected by the stain. Views regarding skin staining and cosmesis were mixed. The majority of patients considered staining a minor problem, if an issue at all (60 per cent at the first assessment and 61 per cent at the second). No substantial change in views was noted between the two time points (P = 0·280)"* |

## Table 37 Skin Staining with Injection Methods other than Peritumoral Injection

| Study [Reference] | Amount of Magtrace Injected and Location (e.g., sub-areolar (SA), peri-areolar (PA), retro-areolar (RA), peri-tumoral (PT), etc.) 5ml = 2ml Sienna+ diluted with 3ml saline | Net Number of Subjects Participated/Studied | Numbers of lumpectomy vs mastectomy procedures | Number of Subjects with Skin Staining | Did Skin Staining Resolve Completely (Yes (%), No (%)) As % of patients with staining | Time taken to resolve skin staining (mean, and range) | Patient reported outcome (no-problem/problem-not important/problem-important/unavailable) |
|---|---|---|---|---|---|---|---|
| Rubio 2015 | 5ml SA | 120 | n=103 lumpectomy<br><br>n=17 mastectomy | 20% no timepoint specified | Not stated specifically "*The tattoo usually vanishes over time.*" | Not stated specifically "*In our study patients still have some discoloration after 6 months of the injection. This tattoo is similar to the one produced by the blue dye in terms of numbers and time of stain*" | Unavailable |
| Karakatsanis 2016 | 5ml SA | 206<br><br>Follow up for 186 | n=154 Lumpectomy<br><br>n=52 mastectomy | 35% post-op 0-3 months *"95.6% of patients with discoloration had been treated with breast conserving surgery" (lumpectomy)* | Yes:75.8%<br>No: 24.2%<br>At 15 months | "*Discoloration was present in 35.5 % of patients post- operatively (0–3 months) and faded progressively in size and color over time to 21 % of patients after a year. Staining remained present in 8.6 % 15 months after the operation, but much smaller and paler.*" | Unavailable |
| Houpeau 2016 | 5ml SA | 108 | n=100 lumpectomy<br><br>n=5 mastectomy<br><br>n=3 oncoplasty | 22 (20.4%)<br><br><30days post-operative | Not stated | Not Stated, max follow up 30 days | Unavailable |
| Ghilli 2015 | 5ml SA | 193 | n=184 lumpectomy<br><br>n=6 bilateral reduction mammoplasty<br><br>n=2 mastectomy | *"…more than 40% of cases…"* | Yes:91%<br>No: 9%<br>At 6 months *"transient in more than 91% in the first 6 months after the procedure."* | *"transient in more than 91% in the first 6 months after the procedure."* | *"The pigmentation was usually very light in colour and did not represent a real problem for the patient. As soon as surgeons became more familiar with the technique, this side effect was controlled by performing the injection slightly deeper. "* |
| Karakatsanis 2017 | 5ml PA | n=184 Total | n=126 lumpectomy | Overall: 73/184 (39.9%) | Not stratified by injection site. Overall | *"Albeit much smaller and paler, staining was still present in 36·1 per* | (Likert scale was used for assessment.) |

| Study [Reference] | Amount of Magtrace Injected and Location (e.g., sub-areolar (SA), peri-areolar (PA), retro-areolar (RA), peri-tumoral (PT), etc.) 5ml = 2ml Sienna+ diluted with 3ml saline | Net Number of Subjects Participated/Studied | Numbers of lumpectomy vs mastectomy procedures | Number of Subjects with Skin Staining | Did Skin Staining Resolve Completely (Yes (%), No (%)) As % of patients with staining | Time taken to resolve skin staining (mean, and range) | Patient reported outcome (no-problem/problem-not important/problem-important/unavailable) |
|---|---|---|---|---|---|---|---|
| | | n=131 PA | n=57 mastectomy<br><br>no staining in mastectomy patients | PA: 58/131 (44.3%)<br><br>at 3 months | Yes: 9.5%<br>No: 90.5%<br>At 15 months | *cent of patients (66 of 183) after 15months"*<br><br>*"Of patients with skin staining, 97% had been treated with BCS."* | "*Patients who received a deeper peritumoral injection of SPIO had less staining immediately after surgery, as well as less staining over time. In total, 58 of 73 patients who developed staining had received a peri areolar injection, whereas only 15 had had a peritumoral injection (P = 0·046)"*<br><br>"*All 66 patients with discoloration remaining after more than 10months responded to the questionnaire at both time points. Only two patients in this subgroup (3 per cent) complained that they were affected by the stain. Views regarding skin staining and cosmesis were mixed. The majority of patients considered staining a minor problem, if an issue at all (60 per cent at the first assessment and 61 per cent at the second). No substantial change in views was noted between the two time points (P = 0·280)"* |
| Karakatsanis 2019 | Not specified | n=189 | n=129 lumpectomy<br><br>n=60 mastectomy | Lumpectomy: 42/129 (32.6%) timepoint not specified No staining in mastectomy group | Not reported | Not reported | unavailable |
| Lorek 2019 | 5ml SA | n=303 | n=191 lumpectomy<br><br>n=107 mastectomy | 47 (15.5%) initial follow-up at 3 months | Yes: 76.6%<br>No: 23.4%<br>At 30 months | "*The average time needed for the discoloration to reduce by approximately 50% was 9 months and to disappear completely at approximately. 18 months. The longest persisting discoloration observed took 22 and 24 months"* | unavailable |

| Study [Reference] | Amount of Magtrace Injected and Location (e.g., sub-areolar (SA), peri-areolar (PA), retro-areolar (RA), peri-tumoral (PT), etc.) 5ml = 2ml Sienna+ diluted with 3ml saline | Net Number of Subjects Participated/Studied | Numbers of lumpectomy vs mastectomy procedures | Number of Subjects with Skin Staining | Did Skin Staining Resolve Completely (Yes (%), No (%)) As % of patients with staining | Time taken to resolve skin staining (mean, and range) | Patient reported outcome (no-problem/problem-not important/problem-important/unavailable) |
|---|---|---|---|---|---|---|---|
| Wärnberg 2019 | 5ml RA | n=337<br>n=177 RA | RA cohort: n=110 lumpectomy<br>n=67 mastectomies. | Lumpectomy + RA<br>injn: 74/110 (67.3%) | Lumpectomy + RA:<br>Yes: 31.3%<br>No: 68.7% | Analysis based upon N = 130 (74+56) patients with skin staining.<br><br>"After 6, 12, 24, and 36 months, 65.4%, 63.6%, 58.1%, and 46.2% had a remaining staining after retro-areolar injections and 34.0%, 31.3%, 14.0%, and 9.4% after peritumoral (p \ 0.001 at 36 months)." | Analysis based upon 46 women of 75 with a remaining stain (since Likert scale was employed later).<br><br>Self-assessed cosmetic outcome (0-5 points) was worse after retro-areolar compared with peritumoral injections at 12 and 24 months: mean (median) 1.3 (0) vs. 0.5 (0) points (p \ 0.001) and 0.6 (0) vs. 0.2 (0) points (p = 0.02). However, the difference was gone after 36 months: 0.2 (0) vs. 0.1 (0) for retro-areolar and peritumoral injections, respectively (p = 0.49). Analyzing women with an actual stain at each time point showed no statistically significant differences between the two injection types (data not shown). Women with a higher BMI scored lower at all time points, regardless of injection type, but the differences were not statistically significant (data not shown). |
| Alvarado 2019 | 2ml SA | n=146 | n=103 lumpectomy,<br>n=43 mastectomy | Lumpectomy: 23/103 (22.3%)<br>1-3 week follow-up | Not reported | Not reported | unavailable |
| Vural 2019 | 5ml RA | n=104 underwent analysis | n=89 lumpectomy/oncoplastic<br><br>n=18 mastectomy | 22 (20.4%) at post-operative consultation | Not reported | Not reported | unavailable |
| Rubio 2020 | 3 groups of n=45:<br>Group 1: 1ml SA<br>Group 2: 1.5ml SA<br>Group 3: 2ml SA | n=135<br>n=118 answered questions on skin staining | n = 135 lumpectomy | 83 (70.3%) one month post-operative | Not reported | Not reported | (Likert scale was used for assessment.)<br><br>*"As answer to the question whether the skin staining was a problem for the patient, patients reported not being a problem, being 23/33 (69.7%) in group 1, 28/40 (70%) in group 2, and 30 (73.2%) in group 3"*<br><br>*"At 6 months follow up, 78.9% of the patients still felt that the skin staining was not a problem.".* |

## Table 38 Skin Staining in Lumpectomy Patients

| Study [Reference] | Amount of Magtrace Injected and Location (e.g., sub-areolar (SA), peri-areolar (PA), retro-areolar (RA), peri-tumoral (PT), etc.) 5ml = 2ml Sienna+ diluted with 3ml saline | Net Number of Subjects Participated/Studied | Numbers of lumpectomy vs mastectomy procedures | Number of Subjects with Skin Staining | Did Skin Staining Resolve Completely (Yes (%), No (%)) | Time taken to resolve skin staining (mean, and range) | Patient reported outcome (no-problem/problem-not important/problem-important/unavailable) |
|---|---|---|---|---|---|---|---|
| PostMag (2020)<br><br>Registry (Reference No. ISRCTN85167182) | 2ml PT | 32/32 | n=32 Lumpectomy | 12 (37.5%) (immediately post op) | Yes (100%)<br>No (0%) | Mean= 6 months<br>Range=3 months to 9 months | *Unavailable.*<br><br>*No skin discoloration was observed in any of the subjects at 12 months* |
| Karakatsanis 2019 | 'Interstitial' Site not specified | n=189 | n=129 lumpectomy | Lumpectomy: 42/129 (32.6 %) timepoint not specified<br>No staining in mastectomy group | Not reported | Not reported | unavailable |
| Wärnberg 2019 | 5ml RA or PT | n=337<br>n=177 RA<br><br><br><br><br>n=163 PT | RA cohort: n=110 lumpectomy<br><br>In the PT cohort: n=148 lumpectomy | Lumpectomy + RA injn: 74/110 (67.3%)<br><br><br><br>Lumpectomy + PT injn: 56/148 (37.8%) (p <0.001) | Lumpectomy + RA:<br>Yes: 31.3%<br>No: 68.7%<br><br><br><br>Lumpectomy + PT:<br>Yes: 75.1%<br>No: 24.9% | Analysis based upon N = 130 (74+56) patients with skin staining.<br><br>"After 6, 12, 24, and 36 months, 65.4%, 63.6%, 58.1%, and 46.2% had a remaining staining after retro-areolar injections and 34.0%, 31.3%, 14.0%, and 9.4% after peritumoral (p \ 0.001 at 36 months)." | Analysis based upon 46 women of 75 with a remaining stain (since Likert scale was employed later).<br><br>Self-assessed cosmetic outcome (0-5 points) was worse after retro-areolar compared with peritumoral injections at 12 and 24 months: mean (median) 1.3 (0) vs. 0.5 (0) points (p \ 0.001) and 0.6 (0) vs. 0.2 (0) points (p = 0.02). However, the difference was gone after 36 months: 0.2 (0) vs. 0.1 (0) for retro-areolar and peritumoral injections, respectively (p = 0.49). Analyzing women with an actual stain at each time point showed no statistically significant differences between the two injection types (data not shown). Women with a higher BMI scored lower at all time points, regardless of injection type, but the differences were not statistically significant (data not shown). |
| Alvarado 2019 | 2ml SA | n=146 | n=103 lumpectomy | Lumpectomy: 23/103 (22.3%) 1-3 week follow-up | Not reported | Not reported | *unavailable* |

| Study [Reference] | Amount of Magtrace Injected and Location (e.g., sub-areolar (SA), peri-areolar (PA), retro-areolar (RA), peri-tumoral (PT), etc.) 5ml = 2ml Sienna+ diluted with 3ml saline | Net Number of Subjects Participated/Studied | Numbers of lumpectomy vs mastectomy procedures | Number of Subjects with Skin Staining | Did Skin Staining Resolve Completely (Yes (%), No (%)) | Time taken to resolve skin staining (mean, and range) | Patient reported outcome (no-problem/problem-not important/problem-important/unavailable) |
|---|---|---|---|---|---|---|---|
| Rubio 2020 | 3 groups of n=45:<br><br>Group 1: 1ml SA<br>Group 2: 1.5ml SA<br>Group 3: 2ml SA | n= 135<br><br>n=118 answered questions on skin staining | n = 135 lumpectomy | 83 (70.3%) one month post-operative | Not reported | Not reported | (Likert scale was used for assessment.)<br><br>*"As answer to the question whether the skin staining was a problem for the patient, patients reported not being a problem, being 23/33 (69.7%) in group 1, 28/40 (70%) in group 2, and 30 (73.2%) in group 3"*<br><br>*"At 6 months follow up, 78.9% of the patients still felt that the skin staining was not a problem."* |

## Table 39 Skin Staining with Blue Dye

| Study [Reference] | Injection type and Blue Dye | Net Number of Subjects Participated /Studied | Numbers of lumpectomy vs mastectomy procedures | Number of Subjects with Skin Staining | Did Skin Staining Resolve Completely (Yes (%), No (%)) | Time taken to resolve skin staining (mean, and range) | Patient reported outcome (no-problem/problem-not important/problem-important/unavailable) |
|---|---|---|---|---|---|---|---|
| Govaert 2005 | Periareolar (Patent Blue: Isomer of Isosulfan blue) | 33 | Lumpectomy (BCS) | 32 (97%) | Yes (59.4%)<br>No (40.6%) | Staining:<br>32/33 (97% @ 0 month)<br>23/33 (70% @ 3 month)<br>21/33 (64% @ 6 month)<br>14/32* (44% @ 9 month)<br>13/32* (41% @ 12 month) | -<br><br>*One patient died after 7 months.<br><br>Patients did not think it was a problem. |
| Gumus 2013 | Periareolar<br><br>(Patent Blue) | 236 | Lumpectomy (BCS) | 86 (36.5%) @ 12 mon. | Unknown | 36.5% @ 12 month<br>23.6% @ 24 month<br>8.6% @ 36 month | |
| Fattahi 2014 | Periareolar<br><br>(Patent Blue PB, Methylene Blue MB) | PB: 156<br><br>MB: 156 | Lumpectomy (BCS) | PB: 37/156 (23.7%)<br>MB: 22/156 (14.1%) | Unknown | PB: 37 (23.7% @ 0 month)<br><br>MB: 22 (14.1% @ 0 month) | 1/156 local inflammation, PB<br><br>5/156 local inflammation , MB |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Peek 2016 | Periareolar<br><br>(Patent Blue) | 160 | Lumpectomy (BCS) | 6/160 (3.8%) | - | - | - |

**Table 40 A Comparison of Skin Staining due to Magtrace and Blue dye in Lumpectomy Patients**

| Device/Product | Injection Technique | Number of Subjects | Skin Staining Incidence (Mean, Range) |
|---|---|---|---|
| Magtrace/Sienna | All<br>(Refer to Table 38) | 640 | 45.3%<br>Immediate: (22.3%-70.3%)<br>Long term: 0%-46.2% after 36 months |
| | Peritumoral<br>(Refer to Table 38) | 180 | 37.8%<br>Immediate: 37.5% - 37.8%<br>Long term: 0% - 9.4% after 36 months |
| | All but peritumoral<br>(Subareolar, retroareolar, periareolar)<br>(Refer to Table 38) | 331 | 54.4%<br>Immediate: 22.3% - 70.3%<br>Long term: 46.2% (N = 110) |
| Blue dye (excluding Methylene blue) | All<br>(Refer to Table 39) | 585 | 27.5%<br>Immediate: 3.8%-97%<br>Long term: up to 41%*<br>*Up to 41 % after 12 months and 8.6% (N = 236) after 36 months. |
| | Peritumoral<br>(Refer to Table 39) | Unknown | Unknown<br>Immediate: Unknown<br>Long Term: Unknown |
| | All but peritumoral<br>(Subareolar, retroareolar, periareolar)<br>(Refer to Table 39) | 585 | 27.5%<br>Immediate: 3.8%-97%<br>Long term: up to 41% |

**Skin Staining Overview**

The only study to date that has set out to prospectively gather data on staining including stratification by injection site and type of surgery, and recording patient reported outcomes related to staining is the Wärnberg 2019 study. The size of the staining, intensity, and cosmetic outcome was self-assessed. At first, only change of intensity was described, but later women classified the intensity of the staining according to a Likert item scale from 0 to 5, based on photos of selected cases mailed to the women . In the absence of a relevant, validated questionnaire, women were asked to evaluate the cosmetic outcome of the staining on a Likert item scale from 0 to 5 (0 = not a problem, 1 = slight problem, 2 = minor problem, 3 = clearly a problem, 4 = considerable problem, 5 = important problem). The self-assessment gave us the subjective views of the women. Follow-up was ended when the staining was gone. The study reported that the

self-assessed cosmetic outcome (0-5 points) was worse after retro-areolar compared with peritumoral injections at 12 and 24 months: mean (median) 1.3 (0) vs. 0.5 (0) points (p \ 0.001) and 0.6 (0) vs. 0.2 (0) points (p = 0.02). However, the difference was gone after 36 months: 0.2 (0) vs. 0.1 (0) for retro-areolar and peritumoral injections, respectively (p = 0.49). Analyzing women with an actual stain at each time point showed no statistically significant differences between the two injection types.

In total 337 women were included undergoing 340 operations. Lumpectomy procedures were performed in 257 women (1 bilateral case) and 80 women had a primary mastectomy. In the subareolar cohort there were 110 lumpectomy procedures and 67 mastectomies and, in the peri-tumoral cohort there were 147 lumpectomies and 15 mastectomies.

After lumpectomy 74 of 110 (67.3%) had a skin staining after a retroareolar and 56 of 148 (37.8%) after a peritumoral injection (p < 0.001) immediately after their procedures. Including all women, the mean size of staining was 16.3 (range 2-100) cm2 and 6.8 (range 1–100) cm2 after retroareolar and peritumoral injections (p < 0.001), at the first visit. Including only those 130 with an actual staining, the mean size was 24.2 and 17.9 $cm^2$ (p = 0.02), respectively. After 6, 12, 24, and 36 months, 65.4%, 63.6%, 58.1%, and 46.2% had a remaining staining after retroareolar injections and 34.0%, 31.3%, 14.0%, and 9.4% after peritumoral (p < 0.001 at 36 months). Size diminished successively over time.

Intensity was reported by the women to be paler at 554 of 738 interviews (75.1%). After introducing the intensity-scale, 46 women of 75 with a remaining stain answered, and 15 of those answered twice, with a 3-month interval. The mean score of intensity, regardless of injection type, was 2.8, 1.7, and 0.9 points at 6–12, 13–24, and 25–36 months, respectively. In those with two successive scorings, the reported intensity score was 1.2 points less at the second scoring. No difference in intensity of the staining was found at 36 months after retroareolar or peritumoral injections (p = 0.60).

Comparing the incidence of skin staining in lumpectomy patients for Magtrace and blue dye, the mean skin staining incidence for Magtrace and blue dye was ~45.3% and ~16.4%, respectively. The long term range of skin staining for Magtrace and blue dye was 0-46.2% and 0-41%, respectively.

## 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 34: 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.

### 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. 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 radioisotope tracer.

- Magtrace®/Sentimag® allows these procedures to be conducted in locations without the need for special handling of radioisotopes, therefore, it can be provided outside of a hospital setting.
- Magtrace® can be injected while the patient is under anesthesia, sparing the patient a painful injection procedure associated with radioisotopes which must be injected while the patient is awake.
- 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.
- Magtrace® is not associated with risks of life-threatening anaphylaxis and tissue necrosis seen with Blue Dye injections.

Risks:

The risks include:

- Bradycardia
- Anaphylaxis
- MRI artifact
- Skin Staining

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

Magnetic Resonance Images (MRI) Artifact:

Magtrace can produce image artifacts in patients on MRI near the injection site. These artifacts may persist, often unchanged, long term and in some cases make large parts of the images completely uninterpretable and nondiagnostic.

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

1. Patient labeling and user manual will inform patients and users of the risk of MRI artifact after Magtrace injection.
2. The use of a peritumoral injection may lead to reduction in artifacts.

Skin Staining:

- Magtrace can create skin discoloration (tattooing) which may persist long term. Published studies have reported skin discoloration in up to 37.8% patients immediately and 9.4% long term (i.e., 36 months) after peritumoral injection in lumpectomy patients.

- This can be mitigated by the following means:

    1. Restricting injection technique to peritumoral for patients undergoing lumpectomy, nipple sparing or skin sparing procedures.

    2. Recommending not using Magtrace in patients that may be adversely affected by (tattooing) skin discoloration.

    3. Magtrace package insert will include precaution of skin staining (skin discoloration).

    4. User manuals (both Magtrace and Sentimag) will inform users of the immediate and long term (tattooing) risk of skin discoloration with percentages due to peritumoral injection technique (up to 37.8% patients immediately and 9.4% long term).

    5. The patient brochure will inform patients that Magtrace may produce long term (tattooing) skin discoloration, that choice of injection technique by your provider may reduce this risk, and to talk to your provider regarding the risk of long term skin staining.

    6. User manual and patient brochure will state not to use Magtrace in patients who may be adversely affected by (tattooing) skin discoloration.

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.

Risk Mitigation

- Most high-risk patients can be excluded in advance of surgery based upon their individual risk.

- Routine pre-treatment investigation of patients enables identification of high risk patients who can be excluded from exposure through warnings.

- The risks of MRI artifact can be sufficiently mitigated through a series of warnings and contraindications so that Magtrace is not used in patients where the post-surgical need for MRI can be anticipated and reduce the potential for non-diagnostic post-surgical MRI images significantly.

  These warnings and contraindications include:
  Warnings:
- Magtrace can produce image artifacts in patients on MRI near the injection site. These artifacts may persist, often unchanged, long term and in some cases make large parts of the images completely uninterpretable and nondiagnostic. If artifact occurs on MRI, other imaging modalities may be needed which may or may not adequately compensate for the artifact present. Magtrace residues have not been reported to produce artifacts affecting imaging in Contrast Enhanced Digital Mammography (CEDM), X-ray, PET, PET/CT, CT, or ultrasound studies.

- Because of potential MRI artifacts, surgeons should consider whether Magtrace is appropriate for a patient on a case-by-case basis. Magtrace may not be appropriate for patients undergoing breast conserving surgery in whom MRI is likely to be required for subsequent screening or, in the event of recurrence, for diagnostic work-up. These groups include:
    - Patients in whom only MRI was able to visualize a primary cancer.
    - Patients with multifocal/multicentric breast cancer undergoing breast conserving surgery where clinical or conventional imaging findings are indeterminate.
    - Patients who have a high estimated lifetime risk of breast cancer (20% or greater) based on their family history or tumor gene expression testing.
    - Patients in whom the likelihood of local or regional recurrence is elevated.

- Magtrace may travel to regions away from the injection site, such as liver, spleen, etc., if inadvertently injected directly into the blood stream. In such cases, the presence of Magtrace may cause image artifacts during MRI. Some manipulation of scan parameters may be required to compensate for the artifact.

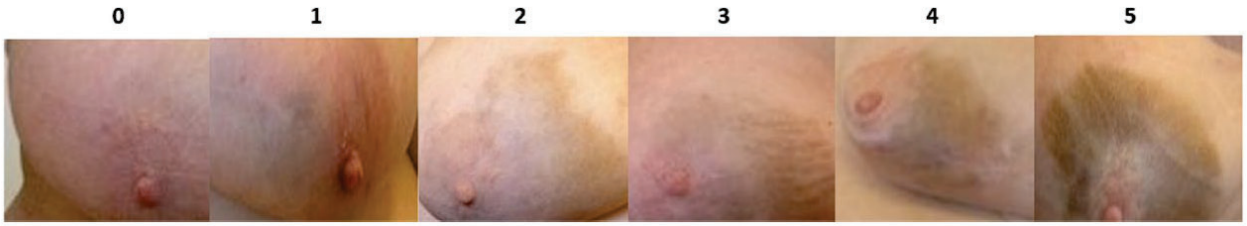
  Contraindications:
- SLNB before neoadjuvant chemotherapy (NAC) where magnetic resonance imaging (MRI) will be the primary imaging used for monitoring the progress of NAC.

- Patients identified in advance to require post-lumpectomy imaging with breast MRI

The risks of (tattooing) skin discoloration can be sufficiently mitigated through labeling so that patients and providers are informed of the risks and Magtrace is not used in patients that may be adversely affected by (tattooing) skin discoloration.

These warnings include:

- Magtrace may produce temporary or long-term (tattooing) skin discoloration. Peritumoral injection may reduce the incidence of long term (tattooing) skin discoloration. Published studies have reported skin discoloration in up to 37.8% patients immediately and 9.4% long term after peritumoral injection.
- Subareolar injection of Magtrace should not be used in the following:
    - Breast conserving Surgery (Lumpectomy)
    - Nipple, Nipple Areolar or Skin Sparing Procedures
    - Patients who may be adversely affected by (tattooing) skin discoloration.
- Intensity and Severity of skin staining in US population are unknown. Magtrace should not be used in patients who may be adversely affected by (tattooing) skin discoloration. Example images of Magtrace induced (tattooing) skin discoloration are presented below.




**Additional Precautions Include:**
Magtrace has not been evaluated for repeated use or in patients with breast implants.

**Informed Consent**

- As part of their informed consent, patients be notified in advance that the device may compromise future MRI imaging of the affected breast.

**IFU Labeling and User Training**

- Information on peritumoral injection of Magtrace may result in less skin staining.

This submission included the following specific information on patient perspectives for this product.

## Patient Perspectives

When skin discoloration is present:

- Majority $\geq 60\%$) of the patients did not consider staining a problem or "not important".
- Majority $\geq 60\%$) of the patients reported not being affected by it.
- Patient Perception (n = 193)

| **Study [Reference ]** | **Amount of Magtrace Injected and Location (e.g., sub-areolar (SA), peri-areolar (PA), retro-areolar (RA), peri-tumoral (PT), etc.)**<br><br>**5ml = 2ml Sienna+ diluted with 3ml saline** | **Net Number of Subjects Participated/Studied** | **Numbers of lumpectomy vs mastectomy procedures** | **Number of Subjects with Skin Staining** | **Did Skin Staining Resolve Completely (Yes (%), No (%))** | **Time taken to resolve skin staining (mean, and range)** | **Patient reported outcome**<br><br>**(no-problem/problem-not important/problem-important/unavailable)** |
|---|---|---|---|---|---|---|---|
| Karakatsanis 2017 | 5ml PA | n=184 Total n=131 PA | n=126 lumpectomy n=57 mastectomy no staining in mastectomy patients | Overall: 73/184 (39.9%)<br><br>PA: 58/131 (44.3%)<br><br>at 3 months | Not stratified by injection site. Overall Yes: 9.5% No: 90.5% At 15 months | *"Albeit much smaller and paler, staining was still present in 36·1 per cent of patients (66 of 183) after 15months"*<br><br>*"Of patients with skin staining, 97% had been treated with BCS."* | (Likert scale was used for assessment.)<br><br>"*Patients who received a deeper peritumoral injection of SPIO had less staining immediately after surgery, as well as less staining over time. In total, 58 of 73 patients who developed staining had received a peri areolar injection, whereas only 15 had had a peritumoral injection (P = 0·046)"* |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | "*All 66 patients with discoloration remaining after more than 10months responded to the questionnaire at both time points. Only two patients in this subgroup (3 per cent) complained that they were affected by the stain. Views regarding skin staining and cosmesis were mixed. The majority of patients considered staining a minor problem, if an issue at all (60 per cent at the first assessment and 61 per cent at the second). No substantial change in views was noted between the two time points (P = 0·280)"* |
| Wärnberg 2019 | 5ml RA or PT | n=337<br>n=177 RA<br><br><br><br><br>n=163 PT | RA cohort: n=110 lumpectomy n=67 mastectomies.<br><br>In the PT cohort: n=148 lumpectomy n=15 mastectomies | Lumpectomy + RA injn: 74/110 (67.3%)<br><br><br><br>Lumpectomy + PT injn: 56/148 (37.8%) (p <0.001) | Lumpectomy + RA: Yes: 31.3% No: 68.7%<br><br><br><br>Lumpectomy + PT: Yes: 75.1% No: 24.9% | Analysis based upon N = 130 (74+56) patients with skin staining.<br><br>"After 6, 12, 24, and 36 months, 65.4%, 63.6%, 58.1%, and 46.2% had a remaining staining after retro-areolar injections and 34.0%, 31.3%, 14.0%, and 9.4% after peritumoral (p \ 0.001 at 36 months)." | Analysis based upon 46 women of 75 with a remaining stain (since Likert scale was employed later).<br><br>Self-assessed cosmetic outcome (0-5 points) was worse after retro-areolar compared with peritumoral injections at 12 and 24 months: mean (median) 1.3 (0) vs. 0.5 (0) points (p \ 0.001) and 0.6 (0) vs. 0.2 (0) points (p = 0.02). However, the difference was gone after 36 months: 0.2 (0) vs. 0.1 (0) for retro-areolar and peritumoral injections, respectively (p = 0.49). Analyzing women with an actual stain at each time point showed no statistically significant differences between the two injection types (data not shown). Women with a higher BMI scored lower at all time points, regardless of injection type, but the differences were not statistically significant (data not shown). |
| Rubio 2020 | 3 groups of n=45:<br><br>Group 1: 1ml SA<br><br>Group 2: 1.5ml SA<br><br>Group 3: 2ml SA | n=135<br>n=118 answered questions on skin staining | n = 135 lumpectomy | 83 (70.3%) one month post-operative | Not reported | Not reported | (Likert scale was used for assessment.)<br><br>*"As answer to the question whether the skin staining was a problem for the patient, patients reported not being a problem, being 23/33 (69.7%) in group 1, 28/40 (70%) in group 2, and 30 (73.2%) in group* |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | *3" (in a survey 1month post-operative)*<br><br>*"At 6 months follow up, 78.9% of the patients still felt that the skin staining was not a problem.".* |

In conclusion, given the available information above, the data support that for breast cancer patients who undergo sentinel lymph node biopsy with Magtrace 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 December 06, 2022. The final clinical conditions of approval cited in the approval order are described below.

Post Approval Study to Evaluate the Impact of Device Induced Skin Staining on Breast Cancer Patients – Women who choose partial mastectomy (lumpectomy) as part of their treatment for breast cancer do so, in part, to preserve the appearance of their breast. The impact of device induced skin staining on breast cancer patients should be evaluated in representative US women population by providing patient perception regarding benefit of device use versus the risk of skin staining (as a function of patient age group, BMI, race, Fitzpatrick skin color, etc.) that specifically includes as part of this assessment i) the frequency, duration, intensity, and severity of the skin staining for peritumoral injection technique in lumpectomy patients; and ii) the patient perspective regarding the impact of the skin staining for the expanded indication. Patient reported outcome data may come from validated patient surveys (e.g., Breast-Q), survey methods using a Likert 5-point scale, or other patient reported

outcome methods and patient perception of the skin staining should address: satisfaction, intensity, severity, appearance, body image, emotional distress, sexual impact, other cosmetic factors (skin color, symmetry, etc.) in statistically significant number of patients.

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

References on skin staining:


1. Rubio I, Rodriguez-Revuelto R, Espinosa-Bravo M, Siso C, Rivero J, Esgueva A. A randomized study comparing different doses of superparamagnetic iron oxide tracer for sentinel lymph node biopsy in breast cancer: The SUNRISE study. European Journal of Surgical Oncology 46 (2020) 2195e2201.
2. Vural V, Yılmaz O. The Turkish SentiMAG feasibility trial: preliminary results. Breast Cancer Oct 2019
3. Michael D. Alvarado, Elizabeth A. Mittendorf, Mediget Teshome, Alastair M. Thompson, Richard J. Bold, Mark A. Gittleman, Peter D. Beitsch, Sarah L. Blair, Kaisa Kivilaid, Quentin J. Harmer, Kelly K. Hunt. SentimagIC: A Non-inferiority Trial Comparing Superparamagnetic Iron Oxide Versus Technetium-99m and Blue Dye in the Detection of Axillary Sentinel Nodes in Patients with Early-Stage Breast Cancer. Ann Surg Onco 26 (2019).
4. Wärnberg, Stigberg, Obondo, Olofsson, Abdsaleh, Wa¨rnberg, Karakatsanis. Long-Term Outcome After Retro-Areolar Versus Peri-Tumoral Injection of Superparamagnetic Iron Oxide Nanoparticles (SPIO) for Sentinel Lymph Node Detection in Breast Cancer Surgery. Ann Surg Oncol. 2019 May;26(5):1247-1253
5. Lorek, Stojčev, Zar bski, Kowalczyk, Szyluk. Analysis of Postoperative Complications After 303 Sentinel Lymph Node Identification Procedures Using the SentiMag® Method in Breast Cancer Patients. Med Sci Monit, 2019; 25: 3154-3160.
6. Karakatsanis, Hersi, Pistiolis, Olofsson Bagge, Lykoudis, Eriksson and Wärnberg, on behalf of the SentiNot Trialists Group. Effect of preoperative injection of superparamagnetic iron oxide particles on rates of sentinel lymph node dissection in women undergoing surgery for ductal carcinoma in situ (SentiNot study). Br J Surg. 2019 May;106(6):720-728
7. Karakatsanis, Daskalakis, Stålberg, Olofsson, Andersson, Eriksson, Bergkvist, Wärnberg. Superparamagnetic iron oxide nanoparticles as the sole method for sentinel node biopsy detection in patients with breast cancer. Br J Surg. 2017 Nov;104(12):1675-1685. ALSO referred to as the MONOS study
8. Ghillii, Carretta, Di Filippo, Battaglia, Fustaino, Galanou, Di Filippo, Rucci, Fantini, Roncella. The superparamagnetic iron oxide tracer: a valid alternative in sentinel node biopsy for breast cancer treatment. Eur J Cancer Care (Engl). 2015 Jul;26(4)
9. Houpeau, Chauvet, Guillemin, Bendavid-Athias, Charitansky, Kramar & Giard. Sentinel Lymph Node Identification Using Superparamagnetic Iron Oxide Particles Versus Radioisotope: The French Sentimag Feasibility Trial. J Surg Oncol. 2016 Apr;113(5):501-7

References on MRI Artefact:


1. Aribal E, Çelik L, Yilmaz C, Demirkiran Cem, Guner D. Effects of iron oxide particles on MRI and mammography in breast cancer patients after a sentinel lymph node biopsy with paramagnetic tracers. Clinical Imaging 2021
2. Krischer, Forte, Niemann, Kubik-Huch, Leo. Feasibility of breast MRI after sentinel procedure for breastcancer with superparamagnetic tracers. Eur J Surg Oncol. 2018 Jan;44(1):74-79
3. Alvarado M. SentiMag® Intraoperative Comparison in Breast Cancer (SentiMagIC) NCT02336737
4. Karakatsanis A. Postoperative breast MRI in patients undergoing sentinel node biopsy using super paramagnetic iron oxide nanoparticles ISRCTN85167182
5. Sunita Shrotria , Jack Stuart Abstracts / European Journal of Surgical Oncology 46 (2020) P136 Abstract 121