HIGHLIGHTS OF INSTRUCTIONS FOR USE

These highlights do not include all the information needed to use the Magtrace and Sentimag® Magnetic Localization System safely and effectively. See full instruction for use for Magtrace.

Magtrace® (carboxydextran-coated superparamagnetic iron oxide) injection, for subcutaneous use.
Initial U.S. Approval: 2018

Caution: Federal Law restricts this device for sale by or on the order of a physician.

----------INDICATIONS AND USAGE----------

***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 (SLNB), 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.

----------DOSAGE AND ADMINISTRATION----------

2ml of undiluted Magtrace is administered by subcutaneous injection at least 20 minutes before sentinel lymph node biopsy procedure.

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 56 mg iron & 64 mg carboxydextran/ 2ml in single use vials.

----------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.

----------WARNINGS AND PRECAUTIONS----------

- General Risks: Magtrace is intended ONLY for use with the Sentimag device, and is therefore subject to the Warnings and Precautions of the Sentimag device including the precaution that the system should not be used in patients with pacemakers. The Sentimag and Magtrace system should only be used by physicians experienced in sentinel lymph node biopsy, and who have been trained in its use. Magtrace has not been evaluated for repeated use or in patients with breast implants. Please refer to the Sentimag Instructions for Use.
- Risk of Interference with MRI: Magtrace can produce image artifacts on MRI near the injection site. These artifacts may be long-term. As such, 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 where MRI is likely to be required for subsequent screening or, in the event of recurrence, for diagnostic work-up. Magtrace may also 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.
- Risk of Anaphylaxis and Cardiovascular Reactions: If inadvertently administered intravenously, anaphylaxis or cardiovascular reactions may occur.
- Risk of Skin Staining: Magtrace may produce temporary or long-term (tattooing) skin discoloration. Magtrace should not be used in patients who may be adversely affected by (tattooing) skin discoloration. Subareolar administration is associated with higher incidence of long term skin staining compared to peritumoral administration in patients undergoing lumpectomy, nipple sparing, nipple areolar sparing or skin sparing procedures.

----------ADVERSE REACTIONS----------

To report SUSPECTED ADVERSE REACTIONS, contact Endomagnetics, Inc. at 1-512 872 2400 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

No interactions with other medications have been observed. Formal drug interaction studies have not been carried out.

----------USE IN SPECIFIC POPULATIONS----------

There have been no studies of Magtrace in pregnant women, nursing mothers or pediatric patients.

See 18 for PATIENT COUNSELING INFORMATION.

MTR-006US Iss 1.0 **Revised: 10/2022**

INSTRUCTIONS FOR USE: CONTENTS

FULL INSTRUCTIONS FOR USE

1 INDICATIONS AND USAGE

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.

2 DOSAGE AND ADMINISTRATION

Recommended dose is 2 ml with the equivalent iron content of circa 56 mg per dose. Inspect the seal of the vial before use to ensure it is unbroken. Do not use if the vial cap is broken, the vial is leaking, or if the expiration date has passed. Do not reuse, sterility cannot be guaranteed if the rubber seal on the vial has already been punctured.

Draw 2 ml of Magtrace via a sterile needle and check the quantity. Administer Magtrace by subcutaneous injection into interstitial breast tissue and follow with 5 minutes vigorous massage at the injection site. Surgeons should wait at least **20 minutes** before attempting transcutaneous measurement of the axilla. In patients where a transcutaneous signal cannot be obtained, continue the surgery as planned and continue to assess the location of the nodes in the tissue using the device. A signal may be found subcutaneously. Migration may be slower in older or larger patients (BMI >30) and may make it more difficult to obtain a transcutaneous signal.

3 DOSAGE FORMS AND STRENGTHS

Magtrace is available in single use vials. A 2ml vial volume contains ~56 mg of iron and ~64mg carboxydextran combined in the form of carboxydextran-coated superparamagnetic iron oxide.

4 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.

5 WARNINGS

5.1 General Risks

Magtrace is intended ONLY for use with the Sentimag device and is therefore subject to the Warnings and Precautions of the Sentimag device including the precaution that the system should not be used in patients with pacemakers. The Magtrace and Sentimag Magnetic Localization System should only be used by physicians experienced in sentinel lymph node biopsy, and who have been trained in its use.

Magtrace is not intended for treatment of iron deficiency anemia in patients or any other medicinal applications.

The safety and effectiveness of the system have not been established in pregnant or lactating women, or in patients less than 18 years of age.

Magtrace has not been evaluated for repeated use or in patients with breast implants.

For injection into interstitial tissue ONLY.

5.2 Risk of Interference with Magnetic Resonance Imaging

- 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 artifacts occur on MRI, other imaging modalities may be needed which may or may not adequately compensate for the artifacts 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.

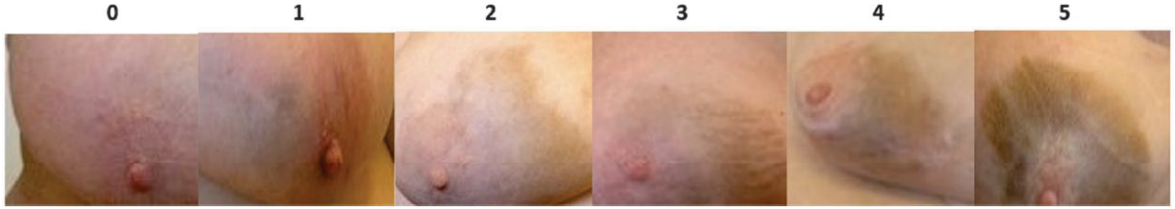
- Magtrace may travel to regions away from the injection site, such as liver, spleen, etc., if inadvertently injected directly into the blood stream. In such cases, the presence of Magtrace may cause image artifacts during MRI. Some manipulation of scan parameters may be required to compensate for the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

5.3 Risk of Anaphylaxis and Cardiovascular Reactions

If Magtrace is inadvertently administered intravenously, anaphylaxis or cardiovascular reactions may occur.

5.4 Risk of Skin Staining

- 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
- Intensity and Severity of (tattooing) skin discoloration 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.



6 POSSIBLE ADVERSE EVENTS

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.

7 DRUG INTERACTIONS

No interactions with other medications have been observed. Formal drug interaction studies have not been carried out.

8 USE IN SPECIFIC POPULATIONS

Intravenously delivered carboxydextran-coated superparamagnetic iron oxide showed no effects on fertility and general reproductive performance of male and female rats and was non-teratogenic in rats and rabbits. Some reproductive toxicity was seen at doses far beyond the recommended dose. The potential risk for humans is unknown.

8.1 Pregnancy

Risk Summary

There are no available clinical data to establish whether or not Magtrace poses a risk to pregnancy outcomes.

In animal reproductive studies in rats and rabbits no evidence of prenatal toxicity was found at daily intravenous doses of 0.01 and 0.03 mmol Fe/kg/day (rats) or 0.01, 0.03, 0.1 and 0.4 mmol Fe/kg/day (rabbits). At the maximum dose of 0.5 mmol Fe/kg/day in the rat study and at 0.8 mmol Fe/kg/day in the rabbit study, evidence of toxicity in pregnant females was accompanied by a slightly increased post-implantational/prenatal loss (rats) or increased values of death/resorption rates with a lower number of living foetuses (rabbits).

8.2 Lactation

Risk Summary

There are no available clinical data to establish whether or not Magtrace poses a risk during lactation.

When delivered intravenously, no transfer of carboxydextran-coated superparamagnetic iron oxide or metabolized iron into breast milk was observed in lactating rats, within 24 h. It is not known if Magtrace is excreted into breast milk in humans. Magtrace should only be given during lactation after special consideration.

8.3 Females and Males of Reproductive Potential

Infertility

Females

In animal studies when a similar material to that used in Magtrace has been injected intravenously n*o* effect on fertility at normal levels was seen.

Males

In animal studies when a similar material to that used in Magtrace has been injected intravenously no effect on fertility at normal levels was seen.

8.4 Pediatric Use

Safety and effectiveness of Magtrace have not been established in patients less than 18 years in age.

8.5 Geriatric Use

There is no upper age limit for the use of Magtrace.

10 OVERDOSAGE

Overdose is unlikely if used as specified with a single 2 ml volume of Magtrace administered as an interstitial injection.

11 DESCRIPTION

Magtrace, a magnetic tracer, contains carboxydextran-coated superparamagnetic iron oxide. The iron oxide is in the form of maghaemite γ -Fe_2O_3, and the chemical formula of the carboxydextran is $C_6H_{11}O_6$-$(C_6H_{10}O_5)_n$-$C_6H_{11}O_5$.

Magtrace is an aqueous suspension of carboxydextran-coated superparamagnetic iron oxide formulated with 0.3% (w/v) sodium chloride. It is a black to reddish-brown liquid, supplied in single-use vials, for a 2ml injection, with each milliliter of Magtrace contains ~28 milligrams of iron and ~32 mg of carboxydextran.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Magtrace consists of superparamagnetic iron oxide coated with a carboxydextran shell. The particles are sized for uptake into the lymphatics along with normal lymph flow draining from the injection site tissue. The particles are physically filtered in the draining lymph nodes where they accumulate, allowing them to be magnetically detected by the Sentimag system. When the Magtrace material is exposed to the excitation field of the Sentimag the Magtrace material responds with a temporarily induced magnetic field.

12.2 Pharmacodynamics

Magtrace is a combination product with a device primary mode of action. Pharmacodynamic studies of Magtrace were not conducted.

12.3 Pharmacokinetics

Magtrace is a combination product with a device primary mode of action. Human pharmacokinetic studies of Magtrace were not conducted.

In clinical studies, Magtrace has been detectable in lymph nodes within 20 minutes after injection.

Studies in mice and pigs show that Magtrace transits from the site of injection to the draining lymph nodes within 10 minutes of administration.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No animal studies for Carcinogenesis were conducted for Magtrace.

Mutagenesis

No animal studies for mutagenesis were conducted for Magtrace.

Impairment of Fertility

No animal studies for impairment of fertility were conducted for Magtrace.

In silico studies for the carboxydextran indicate no carcinogenicity.

13.2 Animal Toxicology and/or Pharmacology

Magtrace has been tested for intracutaneous sensitization according to the requirements of ISO 10993-1:2009 based on the specified site of injection and duration. These studies revealed no sensitization.

In animal studies when carboxydextran-coated superparamagnetic iron oxide has been injected intravenously the data suggested no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Intravenously administered carboxydextran-coated superparamagnetic iron oxide showed no effects on fertility and general reproductive performance of male and female rats and was non-teratogenic in rats and rabbits. Only at high multiples of the diagnostic dose given daily over the period of organogenesis, carboxydextran-coated superparamagnetic iron oxide caused post-implantation and prenatal losses and delays in development of pups in rats (at 0.5mmol Fe/kg/day representing about 50 times the diagnostic dose) and increased resorption rate and reduced the number of live fetuses in rabbits (at 0.8mmol Fe/kg/day representing about 80 times the diagnostic dose.)

No evidence of a sensitizing (contact-allergenic) potential was seen using the maximization test in guinea-pigs.

It has been observed that intravenously delivered carboxydextran-coated superparamagnetic iron oxide induces anaphylactic (hypersensitivity) reactions in dextran-sensitized dogs.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

The safety and effectiveness of Magtrace was assessed in two paired comparison clinical trials.

Study 1 was a pivotal, open-label, multicenter paired comparison of the Magtrace (carboxydextran-coated superparamagnetic iron oxide) and Sentimag Magnetic Localization System and the combined radioisotope and blue dye for sentinel lymph node detection in patients with breast cancer or ductal carcinoma *in-situ* (DCIS) scheduled for sentinel node biopsy. Radioisotope (Technetium sulfur colloid) was injected according to the standard of care protocol at each site, and blue dye was injected shortly prior to surgery according to the site protocol. Magtrace 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 detection rate in confirmed lymph nodes for the magnetic technique and the standard of care technique was determined.

In Study 1, 147 female patients underwent sentinel lymph node biopsy (SLNB). The median age was 61 years.

Study 2 was an open-label, multicenter, paired comparison of Sentimag and Sienna+ (carboxydextran-coated superparamagnetic iron oxide) 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 carboxydextran-coated superparamagnetic iron oxide requiring dilution with saline prior to injection. Radioisotope (Technetium albumin colloid) was injected according to the standard of care protocol at each site. 45/108 (42%) of patients 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.

In Study 2, 108 female patients underwent SLNB. The median age was 58 years.

14.2 Sentinel lymph node detection

In Studies 1 and 2 efficacy analyses were based on the nodal detection rate per patient and per node. Table 1 shows the per patient detection rates for the magnetic technique and the standard of care control techniques, and Table 2 shows the per node detection rates. Additional analyses were conducted to evaluate the presence or absence of Magtrace in nodes excised from patients determined by pathologic staging to have cancer spread to at least one lymph node. In Study 1 Magtrace identified 21/22 node positive breast cancer patients and in Study 2, Sienna+ identified 45/46 node positive breast cancer patients.

Table 1. Per patient lymph node detection rates for Magtrace (or Sienna+) and Radioisotope with or without blue dye in patients with breast cancer or DCIS.

Study	Number of Patients (N)	Active Comparator present (95% CI)			Magtrace Present (95% CI)	Only Active Comparator present (95% CI)			Only Magtrace present (95% CI)	Neither Active Comparator nor Magtrace present (95% CI)
		Blue Dye	Radio-pharmaceutical	Either Blue Dye and/or Radio-pharmaceutical		Only Blue Dye	Only Radio-pharmaceutical	Both Comparators		
Study 1	147	79.6% (117/147) (72.2%, 85.8%)	95.2% (140/147) (90.4%, 98.1%)	98.0% (144/147) (94.2%, 99.6%)	98.6% (145/147) (95.2%, 99.8%)	0.0% (0/147) (0.0%, 2.5%)	0.0% (0/147) (0.0%, 2.5%)	0.0% (0/147) (0.0%, 2.5%)	0.7% (1/147) (0.0%, 3.7%)	0.7% (1/147) (0.0%, 3.7%)
Study 2	108	81.0% (34/42) (65.9%, 91.4%)	95.4% (103/108) (89.5%, 98.5%)	95.4% (103/108) (89.5%, 98.5%)	97.2% (105/108) (92.1%, 99.4%)	0.0% (0/108) (0.0%, 3.4%)	0.9% (1/108) (0.0%, 5.1%)		2.8% (3/108) (0.6%, 7.9%)	1.9% (2/108) (0.2%, 6.5%)

Table 2. Per node lymph node detection rates for Magtrace (or Sienna+) and Radioisotope with or without blue dye in patients with breast cancer or DCIS.

Study	Number of Nodes (N)	Active Comparator present (95% CI)			Magtrace Present (95% CI)	Only Active Comparator present (95% CI)			Only Magtrace present (95% CI)	Neither Active Comparator nor Magtrace present (95% CI)
		Blue Dye	Radio-pharmaceutical	Either Blue Dye and/or Radio-pharmaceutical		Only Blue Dye	Only Radio-pharmaceutical	Both Comparators		
Study 1	369	48.8% (180/369) (43.6%,54.0%)	91.6% (338/369) (88.3%, 94.2%)	93.5%* (345/369) (90.5%, 95.8%)	94.3%* (348/369) (91.4%, 96.4%)	0.0% (0/369) (0.0%,1.0%)	3.8% (14/369) (2.1%, 6.3%)	1.4% (5/369) (0.4%, 3.1%)	6.0% (22/369) (3.8%, 8.9%)	0.5% (2/369) (0.1%, 1.9%)
Study 2	214	68.4% (54/79) (57.0%, 78.4%)	90.2% (193/214) (85.4%, 93.8%)	N/R	97.2% (208/214) (94.0%, 99.0%)	0.0% (0/214) (0.0%, 1.7%)	2.3% (5/214) (0.8%, 5.4%)		9.3% (20/214) (5.8%, 14.1%)	0.5% (1/214) (0.0%, 2.6%)

*$p \leq 0.01$ for main efficacy endpoint, Magtrace non-inferiority to Control.

16 HOW SUPPLIED/STORAGE AND HANDLING

Magtrace is supplied in single-use vials.
Each vial contains 2ml Magtrace.

Storage

Store between +2ºC and +30ºC (36˚F and 86˚F)
DO NOT FREEZE.

17 MRI SAFETY INFORMATION

MRI Safety Information

A person injected with Magtrace may be safely scanned under the following conditions. Failure to follow these conditions may result in injury.

Device Name	Magtrace
Static Magnetic Field Strength (B_0)	1.5T or 3.0T
Maximum Spatial Field Gradient	40 T/m (4,000 gauss/cm)
RF Excitation	Circularly Polarized (CP)
RF Transmit Coil Type	There are no Transmit Coil restrictions
Operating Mode	Normal Operating Mode
Maximum Whole-Body SAR	4 W/kg (First Level Operating Mode)
Maximum Head SAR	3.2 W/kg (Normal/First Level Operating Mode)
Scan Duration	4 W/kg whole-body average SAR for 60 minutes of continuous RF (a sequence or back to back series/scan without breaks)
MR Image Artifact	The presence of Magtrace may produce an image artifact.

The Sentimag is MR Unsafe.

Caution: The RF heating behavior does not scale with static field strength. Devices that do not exhibit detectable heating at one field strength may exhibit high values of localized heating at another field strength.

18 PATIENT COUNSELING INFORMATION

- Question patient regarding any prior history of iron overload disease, reactions to iron oxide or dextran products.
- Inform patient to report any signs and symptoms of hypersensitivity that may develop during and/or following administration, such as rash, itching, dizziness, lightheadedness.
- Advise patient that Magtrace may cause long-term (tattooing) skin coloration.
- Advise patient that Magtrace may induce image artifacts in post-operative MRI scans. These artifacts may persist, often unchanged, for a long time 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.

Symbols

Single Use

Expiration Date specified on vial

Lot or batch number specified on vial

Aseptically Filled

Read Instructions

Warnings and Cautions specified in instructions

MR Conditional

Do not use if vial is open or damaged

Store between temperatures indicated

Manufacturer

CE mark for Medical Device as specified by the Medical Device Directive 93/42/EEC

For Use by, or on the Order of, a Physician

Manufactured by:
Endomagnetics Limited
The Jeffreys Building
Cowley Road, Cambridge
CB4 0WS, United Kingdom

Endomagnetics, Inc.,
1701 Trinity Street, Mail Code Z1400
Austin, TX, 78712-1885, USA

19. SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

See Draft document submitted 19 Oct 2022

Sentimag® - Instructions For Use

Caution: Federal Law restricts this device for sale by or on the order of a physician.

The information contained in this manual is subject to change without notice. Endomagnetics Ltd assumes no responsibility for any errors that may appear in this document. Please visit www.endomag.com for the latest version.

Document number: **775L12US**
Document revision: **Issue 5.0, 13th October 2022**

Patents

Patents US8174259; US9234877; US9239314.

Manufacturer Details

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CE 0086

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Endomagnetics, Inc.,
1701 Trinity Street, Mail Code Z1400
Austin, TX, 78712-1885

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.

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.

WARNINGS

General Risks

Magtrace is intended ONLY for use with the Sentimag device and is therefore subject to the Warnings and Precautions of the Sentimag device including the precaution that the system should not be used in patients with pacemakers. The Magtrace and Sentimag Magnetic Localization System should only be used by physicians experienced in sentinel lymph node biopsy, and who have been trained in its use.

Magtrace is not intended for treatment of iron deficiency anemia in patients or any other medicinal applications.

The safety and effectiveness of the system have not been established in pregnant or lactating women, or in patients less than 18 years of age.

Magtrace has not been evaluated for repeated use or in patients with breast implants.

For injection into interstitial tissue ONLY.

5.2 Risk of Interference with Magnetic Resonance Imaging

- 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 artifacts occur on MRI, other imaging modalities may be needed which may or may not adequately compensate for the artifacts 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.

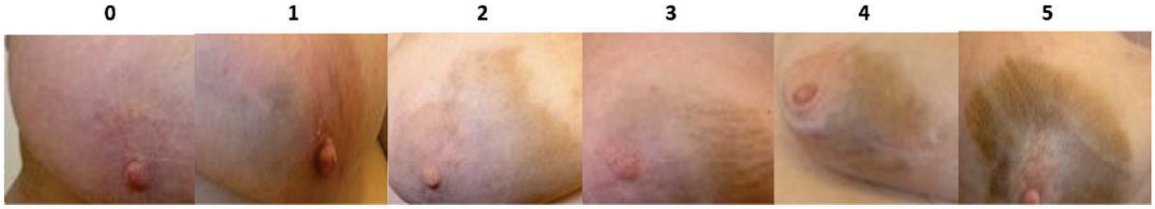
- Magtrace may travel to regions away from the injection site, such as liver, spleen, etc., if inadvertently injected directly into the blood stream. In such cases, the presence of Magtrace may cause image artifacts during MRI. Some manipulation of scan parameters may be required to compensate for the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

5.3 Risk of Anaphylaxis and Cardiovascular Reactions

If Magtrace is inadvertently administered intravenously, anaphylaxis or cardiovascular reactions may occur.

5.4 Risk of Skin Staining

- 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
- Intensity and Severity of (tattooing) skin discoloration 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.



Adverse events:

Magtrace may produce temporary or 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. Erythema may also occur near the injection site (1 out of 147 subjects in the U.S. clinical trial). One event of anaphylaxis and one event of bradycardia occurred during the U.S. clinical trial but were not clearly related to Magtrace™ use.

Potential adverse events:
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.

Operating Precautions and Limitations of Use

IMPORTANT

IT IS ESSENTIAL THAT THE USER OF THIS MANUAL IS AWARE OF THE POTENTIAL HAZARDS ASSOCIATED WITH THE INSTRUMENT AND ITS ACCESSORIES.

ALL OPERATORS SHOULD BE FAMILIAR WITH THE SAFETY PRECAUTIONS AND WARNINGS GIVEN IN THIS SECTION BEFORE ATTEMPTING TO OPERATE THE INSTRUMENT.

IF THE SYSTEM IS USED IN A MANNER THAT IS NOT SPECIFIED BY THE MANUFACTURER, THE PROTECTION PROVIDED BY THE EQUIPMENT MAY BE IMPAIRED.

THE SENTIMAG SYSTEM IS FOR USE WITH MAGTRACE™ PLEASE CONSULT MAGTRACE™ INSTRUCTIONS FOR USE.

WARNING: NO MODIFICATION OF THIS EQUIPMENT IS ALLOWED.

The following symbols are used in this manual or on the instrument labels:

WARNING

CAUTION

BIOLOGICAL RISKS

CONSULT INSTRUCTIONS FOR USE

TYPE B APPLIED PART

ALTERNATING CURRENT

MANUFACTURER

CATALOGUE NUMBER

SERIAL NUMBER

Includes year of manufacture and sequential build number

CE MARK

CE mark for Medical Device as specified by the Medical Device Directive 93/42/EEC

FRAGILE. HANDLE WITH CARE

KEEP DRY

HUMIDITY LIMITATION

ATMOSPHERIC PRESSURE LIMITATION

TEMPERATURE RANGE

Rx ONLY PRESCRIPTION ONLY

WARNING: The instrument is not suitable for use in the presence of a flammable anaesthetic mixture with air or with oxygen or nitrous oxide: equipment not suitable for use in the presence of flammable mixtures.

WARNING: The Sentimag® probe should be removed from patient contact if there is requirement to use a defibrillator.

WARNING: The Sentimag® system consisting of Sentimag® magnetic sensing probe and base unit is MR Unsafe.

CAUTION: For best results, care should be taken when using the instrument in the proximity of extraneous metallic and/or magnetic objects, as they may generate confounding signals. This includes some, but not all, implantable manufactured materials such as artificial joints, limbs, prostheses, clips or stents; as well as some, but not all, ancillary objects and tools that may be encountered in the operating room environment, such as retractors, clamps, scalpels, reinforced tracheal tubes and operating room tables. If in doubt, the user should undertake an *in situ* assessment of the operating environment before using the instrument.

CAUTION: Ensure cables and foot switch are positioned to prevent trip hazards.

CAUTION: Avoid operating the instrument in direct sunlight, as this may affect its performance. Never leave the instrument or probe in direct sunlight, even when turned off.

CAUTION: Do not expose or operate the instrument in extremes of temperature (see Section 11) and minimize any exposure to electrostatic charges.

CAUTION: For best results, operate the instrument in a stable (vibration-free) environment, with the base unit placed on a level working surface.

Instrument Power and Connector

WARNING: To avoid risk of electric shock, this equipment must only be connected to a mains supply with protective earth.

WARNING: Never use any power adapter or cable other than the one specifically supplied with the instrument. See Section 11 for details.

WARNING: Always replace any external fuse with the type and rating specified in Section 11.

CAUTION: The Sentimag® system is disconnected through use of the Mains Switch on the back of the unit followed by the mains plug. Do not position the device such that it is difficult to carry out disconnection.

CAUTION: Always switch the instrument off at the mains power outlet, before inserting or removing the power connector from the rear of the instrument. Failure to do so may damage the internal instrument electronics.

Base Unit Handling and Use

CAUTION: Care should be taken not to drop the instrument base unit, or subject it to any form of rough physical handling, either during normal use or during storage and transportation.

Detachable Probe Handling and Use

CAUTION: Care should be taken not to drop the detachable probe, or subject it to any form of rough physical handling, either during normal use or during storage and transportation. Dropping the probe will cause irrevocable damage and potentially result in service and repair.

CAUTION: The detachable probe is not suitable for autoclaving or disinfection using formaldehyde, either of which action would result in serious damage to the probe. Autoclaving or formaldehyde-treating the detachable probe will void its warranty.

CAUTION: In the unlikely occurrence of the probe becoming hot, all use of the Sentimag® system should cease and the unit sent for Service.

Detachable Probe Connection and Use

CAUTION: Refer to Section 3.7 for details on how to connect the detachable probe to the base unit and ensure that the connectors are clean and dry before plugging them into the base unit.

CAUTION: Care should be taken not to drop the detachable probe, or subject it to any form of rough physical handling, either during normal use or during storage and transportation. This includes not unduly bending or crushing the flexible cable that runs from the probe head to the connectors that plug into the base unit. Dropping the probe will cause irrevocable damage and potentially result in service and repair.

Detachable Footswitch Connection and Use

CAUTION: Refer to Section 3.9 for details on how to connect the air-operated footswitch to the base unit and ensure that the connector is clean and dry before inserting it into the base unit.

CAUTION: Care should be taken not to subject the detachable footswitch to any form of rough physical handling, both during normal use and during storage and transportation. This includes not unduly bending or crushing the air hose that runs from the foot-operated pad to the connector that plugs into the base unit.

Instrument Casework and Serviceability

WARNING: Check the instrument before use for signs of damage, particularly to cables. If the instrument is damaged or gives unexpected performance or operation, then cease using the device and ensure that it is serviced before recommencing use of the device.

WARNING: There are no user-serviceable parts inside the instrument. Removal or opening of the instrument's case will void the warranty. Only Endomagnetics or their authorized and approved service agents/personnel to repair Sentimag® and its accessories.

WARNING: Never clean the instrument or probe using an excessively wet cloth, or by washing it under running water. Do not use pure solvents or other strong cleaning solutions as these may attack and deform the system's plastic components and degrade its performance. Avoid ingress of moisture into connectors and apertures. Never immerse the central collar or the probe handle into a cleaning or disinfection solution.

CAUTION: It is recommended that an annual electrical safety test be performed in compliance with EN 62353:2008.

Instrument Transport and Storage

CAUTION: When not in use, the Sentimag® should always be securely stored. Similarly, when being transported, the Sentimag® should always be securely packed.

CAUTION: Do not dispose of this product into unsorted municipal waste or a public landfill. Please contact your local distributor for details of how to correctly dispose of this product.

Regulatory Limitations of Use

The Sentimag® has been designed to meet the following general and safety requirements:

General	• Medical Device Directive 93/42/EEC and amendments up to and including 2007/47/EC
Safety	• IEC 60601-1: 1988 including Amendments 1 and 2 • IEC 60601-1:2005 + Corrigenda 2006 and 2007 • UL 60601-1 • CAN/CSA C22.2 60601-1-08 • EN60601-1-2:2007 • FCC Rules CF 47:2008 Part 15.107 and 15.109 Class B

The Sentimag® is manufactured under ISO 13485:2012 controls.

TABLE OF CONTENTS

1. Introduction

The Sentimag® is a magnetic material sensor that is designed to detect small amounts of clinically introduced magnetic tracer. It comprises a mains-powered base unit, a detachable hand-held probe that is connected to the base unit with a flexible cable of over two meters in length, and a detachable air-operated footswitch that is connected to the base unit with a flexible hose that is also over two meters in length.

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® device.

The sensing of the magnetic signal is indicated by a change in pitch (frequency) of an audio output from the base unit, enabling the surgeon to move the hand-held probe around the area of the breast and locate the magnetic marker. A visible numerical representation of the detected signal level is simultaneously displayed on the base unit's liquid crystal display and can be noted for the surgeon's records. The hand-held probe is used in two modes: initial transcutaneous signal detection, and post incision use.

The patient population for which the device is suited is not restricted by: Age, Weight, Health, Ethnic origin, Gender. The probe contacts the skin and also tissue within the surgical site.

The system is intended for use in operating rooms. The Sentimag® probe is to be used with a single-use sterile sheath, however the instrument is designed to provide a general ability to clean all external surfaces.

Please Note: The Sentimag® is intended for use by suitably qualified, trained and authorized surgeons and/or operating room staff. Endomagnetics Ltd takes no responsibility for the possible misuse of the Sentimag® – including attempted use with non-calibrated or non-approved magnetic tracers - or for its use by inadequately qualified staff.

This Operator's Manual provides a detailed description of how to use the Sentimag®, and how to handle maintenance and troubleshooting.

For any additional technical assistance, please contact your local distributor.

1.1 Sentimag® Features

The main features of the Sentimag® are:

- Portable base unit that can sit on any flat surface
- Audible and visual indications of magnetic marker proximity
- Audible signal with a variable pitch (frequency) that increases as the probe is brought near a lymph node containing Magtrace™ magnetic signal
- Volume control knob on the base unit
- Liquid crystal display (LCD) for numerical indication of signal strength
- 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)
- Choice of three sensitivity settings, controlled by a knob mounted on the base unit
- Instrument-balancing function that readies the system for measurement
- Push button mounted on the base unit activates the balance function
- Detachable air-operated 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 over two meters length, and color-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)

1.2 Spare, Replacement or Additional Parts

The Sentimag® is supplied complete and ready for use with a base unit, a probe assembly and a footswitch.

Spare, replacement or additional probe assemblies, footswitches and mains cables may be purchased if desired: please contact your local distributor for details.

From time to time Endomagnetics Ltd intends to make available for purchase new or specially tailored probe assemblies for use with the supplied base unit. Please contact your local distributor for details of such new releases.

1.3 Principle of Operation

PLEASE NOTE

The Sentimag® is a highly sensitive and delicate measurement device. To avoid damage and degradation in performance, the instrument should be treated with the utmost care and respect at all times.

The Sentimag® is a very sensitive magnetic materials sensor.

Technically speaking, the Sentimag® is a type of susceptometer. It is designed to deliver a small amplitude, time-varying magnetic field via a hand-held probe, and to electronically detect the presence of any magnetic materials in the vicinity of the probe head. This is done via pick-up coils in the probe head, which register a very small electrical current that is passed through the probe cables and connectors to the Sentimag® base unit.

The base unit contains electronic circuits and a logical processor that interrogates the incoming signal from the probe and converts this into both (1) an analogue signal that is passed to a loudspeaker mounted underneath the handle of the base unit, and (2) a digital signal that is displayed on the liquid crystal display on the front of the base unit.

NOTE: The Sentimag® is best described as a proximity sensor – it is designed specifically for the purpose of detecting and locating small amounts of magnetic material by producing an audible and numerical signal that changes as the probe is brought closer to, or move further away from, the magnetic material. The numerical results on the Sentimag® liquid crystal display are not an absolute measure of the amount of magnetic material that is being sensed. Instead, they are a qualitative measure of the presence of magnetic material in the vicinity of the probe head.

1.4 Overview of Use

IMPORTANT

Please ensure that you have read and understood all of the "Operating Precautions and Limitations of Use" at the beginning of this manual before continuing any further.

A brief overview of how to use the Sentimag® is given below. Further details are provided in Section 2.

Ideally, the probe should be connected to the unit before it is switched on. On switching on the base unit, the display will show an image of an unbalanced set of scales,  , meaning that the unit is ready to be balanced. If the unit is switched on before the probe has been connected, a  symbol indicating that the probe assembly needs to be plugged in will be displayed. Once the probe is plugged in, the display will revert to the  symbol.

IMPORTANT

Before application of anaesthetic to patient, ensure Sentimag® device is switched on and is detecting metallic objects.

At this point the operator should press the balance button on the base unit, marked with the  symbol, which will cause the electronics within the base unit to set a baseline level for the magnetic measurements to follow.

For best results the probe head should at this time be placed or held at least half a meter away from any metallic or magnetic objects, as otherwise an incorrect balance point will be recorded, and subsequent measurements will be unreliable.

NOTE: During use, the balance point for the magnetic measurement may change or drift, e.g. as the electronics in the base unit warm up, or as the environmental conditions at the probe head change. This is normal. **For best results, it is recommended that the base unit should be switched on at least 15 minutes before the first measurements are taken.** Furthermore, it is advised that

the operator should frequently reset the measurement baseline by holding the probe head at least half a meter away from any metallic or magnetic objects, and re-pressing the balance button,  . Alternatively, as the body is weakly dielectric, the user may find it beneficial to balance the unit whilst the probe is in contact with the body. This will result in a positive signal being generated when the probe is withdrawn from the body but will have the advantage of returning to close to zero as it comes back in contact with the body.

The Sentimag® is then ready for use.

The operator may adjust the volume of the audible signal by turning the volume knob, marked  .

The operator may also adjust the sensitivity level of the probe between three pre-set levels, by turning the sensitivity knob, marked  . This applies a scaling factor to the measured signal such that the signal displayed on Setting 2 is twice that displayed on Setting 1. The signal displayed on Setting 3 is twice that displayed on Setting 2, and four times that displayed on Setting 1. It is largely a matter of operator preference as to which sensitivity setting is used, however, if the signal is small Setting 3 may give better results, and if the signal is large, Setting 1 may be preferred to avoid overloading the display limit.

2. Clinical Trials

2.1 Overview of Clinical Studies

The safety and effectiveness of the Magtrace® and Sentimag® Magnetic Localization System was assessed in two paired comparison clinical trials.

Study 1 was a pivotal, open-label, multicenter paired comparison of Sentimag® and Magtrace® (carboxydextran-coated superparamagnetic iron oxide) and the combined radioisotope and blue dye in a sentinel lymph node biopsy procedure in patients with breast cancer or ductal carcinoma *in-situ* (DCIS) scheduled for sentinel node biopsy. Radioisotope (Technetium sulfur colloid) was injected according to the standard of care protocol at each site, and blue dye was injected shortly prior to surgery according to the site protocol. Magtrace® 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 detection rate in confirmed lymph nodes for the magnetic technique and the standard of care technique was determined.

In Study 1, 147 female patients underwent sentinel lymph node biopsy (SLNB). The median age was 61 years.

Study 2 was an open-label, multicenter, paired comparison of Sentimag® and Sienna+ (carboxydextran-coated superparamagnetic iron oxide) 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 carboxydextran-coated superparamagnetic iron oxide requiring dilution with saline prior to injection. Radioisotope (Technetium albumin colloid) was injected according to the standard of care protocol at each site. 45/108 (42%) of patients 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.

In Study 2, 108 female patients underwent SLNB. The median age was 58 years.

2.2 Sentinel lymph node detection

In Studies 1 and 2 efficacy analyses were based on the nodal detection rate per patient and per node. Table A shows the per patient detection rates for the magnetic technique and the standard of care control techniques, and Table B shows the per node detection rates. Additional analyses were conducted to evaluate the presence or absence of Magtrace™ in nodes excised from patients in determined by pathologic staging to have cancer spread to at least one lymph node. In Study 1 Magtrace™ identified 21/22 node positive breast cancer patients and in Study 2, Sienna+ identified 45/46 node positive breast cancer patients.

Table A. Per patient lymph node detection rates for Magtrace™ (or Sienna+) and Radioisotope with or without blue dye in patients with breast cancer or DCIS.

Study	Number of Patients (N)	Active Comparator present (95% CI)			Magtrace™ Present (95% CI)	Only Active Comparator present (95% CI)			Only Magtrace™ present (95% CI)	Neither Active Comparator nor Magtrace™ present (95% CI)
		Blue Dye	Radio-pharmaceutical	Either Blue Dye and/or Radio-pharmaceutical		Only Blue Dye	Only Radio-pharmaceutical	Both Comparators		
Study 1	147	79.6% (117/147) (72.2%, 85.8%)	95.2% (140/147) (90.4%, 98.1%)	98.0% (144/147) (94.2%, 99.6%)	98.6% (145/147) (95.2%, 99.8%)	0.0% (0/147) (0.0%, 2.5%)	0.0% (0/147) (0.0%, 2.5%)	0.0% (0/147) (0.0%, 2.5%)	0.7% (1/147) (0.0%, 3.7%)	0.7% (1/147) (0.0%, 3.7%)
Study 2	108	81.0% (34/42) (65.9%, 91.4%)	95.4% (103/108) (89.5%, 98.5%)	95.4% (103/108) (89.5%, 98.5%)	97.2% (105/108) (92.1%, 99.4%)	0.0% (0/108) (0.0%, 3.4%)	0.9% (1/108) (0.0%, 5.1%)		2.8% (3/108) (0.6%, 7.9%)	1.9% (2/108) (0.2%, 6.5%)

Table B. Per node lymph node detection rates for Magtrace™ (or Sienna+) and Radioisotope with or without blue dye in patients with breast cancer or DCIS.

Study	Number of Nodes (N)	Active Comparator present (95% CI)			Magtrace™ Present (95% CI)	Only Active Comparator present (95% CI)			Only Magtrace™ present (95% CI)	Neither Active Comparator nor Magtrace™ present (95% CI)
		Blue Dye	Radio-pharmaceutical	Either Blue Dye and/or Radio-pharmaceutical		Only Blue Dye	Only Radio-pharmaceutical	Both Comparators		
Study 1	369	48.8% (180/369) (43.6%,54.0%)	91.6% (338/369) (88.3%, 94.2%)	93.5%* (345/369) (90.5%, 95.8%)	94.3%* (348/369) (91.4%, 96.4%)	0.0% (0/369) (0.0%,1.0%)	3.8% (14/369) (2.1%, 6.3%)	1.4% (5/369) (0.4%, 3.1%)	6.0% (22/369) (3.8%, 8.9%)	0.5% (2/369) (0.1%, 1.9%)
Study 2	214	68.4% (54/79) (57.0%, 78.4%)	90.2% (193/214) (85.4%, 93.8%)	N/R	97.2% (208/214) (94.0%, 99.0%)	0.0% (0/214) (0.0%, 1.7%)	2.3% (5/214) (0.8%, 5.4%)		9.3% (20/214) (5.8%, 14.1%)	0.5% (1/214) (0.0%, 2.6%)

*$p \leq 0.01$ for main efficacy endpoint, Magtrace™ non-inferiority to Control.

3. Installation and Basic Operation

3.1 Instrument Description

The **Base Unit (front view)** has the following external features:

Figure 1: Sentimag® Base Unit – Front View

1	Liquid crystal display	5	Sensitivity setting knob
2	Volume knob	6	Six-pin, color coded (white), probe assembly port
3	Balance button	7	Eight-pin, color-coded (black), probe assembly port
4	Footswitch port		

The **Base Unit (rear view)** has the following external features:

Figure 2: Sentimag® Base Unit – Rear View

1	Built-in handle for carrying	4	Speaker grill
2	Unique model identification label	5	Mains power on/off switch
3	Mains power inlet socket		

For details on how to connect the base unit with the mains power cable, the probe assembly, and the footswitch, please refer to Sections 3.4, 3.7 and 3.9 respectively.

The **Probe Assembly** has the following features:

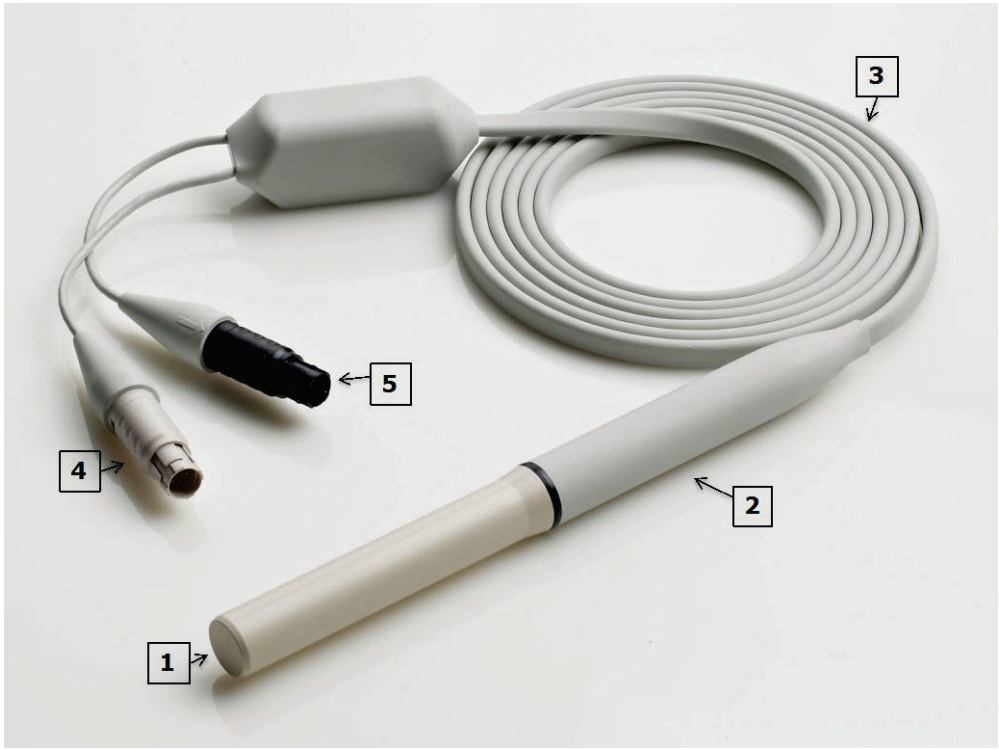


Figure 3: Sentimag® Probe Assembly

1	Probe head	4	Six-pin base unit connector – color coded with a white plastic ring
2	Probe Handle	5	Eight-pin base unit connector – color coded with a black plastic ring
3	Flexible cable		

The **Footswitch Assembly** has the following features:

Figure 4: Sentimag® Footswitch Assembly

1	Foot-operated switch	3	Base unit connector/valve
2	Flexible air hose		

3.2 Transportation and Storage

Whenever the instrument is moved from one location to another, ensure first that it has been correctly shut down to protect the internal mechanisms. Please refer to Section 3.6 for details.

To prevent any possible damage during transportation, the instrument should be securely packed, with all accessories stored in the supplied accessories box.

☣ **WARNING**: Always ensure that the instrument, power adapter and any peripherals or cables are clean and free of any potentially hazardous or infectious substances before moving or transporting them. Refer to Section 5 for the recommended cleaning and decontamination procedure.

3.3 Installation

During use the Sentimag® base unit should be placed on a stable (vibration-free) and level working surface, ideally out of direct sunlight. Refer to Section 11 for environmental limitations of use.

3.4 Powering the Instrument

The instrument is powered via a standard mains outlet supply.

With the power switched off at the wall mains outlet, insert the power cable plug into the power inlet socket at the rear of the base unit (see figure 2).

⚠ **CAUTION**: Always switch the power off at the mains socket before inserting or removing the power connector from the instrument.

⚠ **CAUTION**: Do not use if mains cable, probe/probe cable or base unit show signs of damage.

Insert the plug into the mains outlet supply and turn the power on at the wall outlet.

3.5 Turning the Instrument On

To turn the instrument on, push the rocker switch at the rear of the base unit from the '0' position to the '1' position (figure 2, feature 5).

3.6 Turning the Instrument Off

To turn the instrument off, push the rocker switch at the rear of the base unit from the '1' position to the '0' position.

Unplug from power supply and the instrument can now be safely transported.

⚠ **CAUTION**: Always turn off the instrument before physically moving it or unplugging the power.

3.7 Connecting the Probe Holder

The Sentimag® system is supplied with an optional probe holder (figure 5) that is designed to be attached to the base unit so that the probe can be securely held at the side of the unit.

Figure 5: Optional Probe Holder

The probe holder is screwed into the base of the Sentimag® unit as shown in Figure 6a. The holder can be adjusted to be held on either the left or the right of the system as required by the user. Once securely fixed, the probe will be held in an upright position (Figure 6b).

Figure 6: (a) connection of the probe holder, and (b) use of the probe holder.

3.8 Connecting the Probe Assembly

To make measurements with the Sentimag® the probe assembly must be connected to the base unit as shown in figure 7. This is achieved by inserting the two connectors on the probe assembly (Figure 3, 3 and 4) into the corresponding probe assembly ports on the base unit (Figure 1, 6 and 7 respectively). The probe should be connected before the base unit is switched on.

a. Six-pin connector with white ring is plugged into port with white surround	b. Eight-pin connector with black ring is plugged into port with black surround	c. Correct connection – white to white and black to black

Figure 7: Connecting the Probe Assembly to the Base Unit

IMPORTANT: For correct operation of the instrument, the six-pin connector with the white plastic ring (Figure 3, 3) must be inserted into the six-pin port with the white surround (Figure 1, 6), and the eight-pin connector with the black plastic ring (Figure 3, 4) must be inserted into the eight-pin port with the black surround (Figure 1, 7). In each case the small orientation arrows are uppermost on the probe and must line up with marks on the port.

⚠ CAUTION: The connectors are designed so that they cannot be plugged in to the wrong sockets, or at the wrong orientation into the correct sockets. However, damage may occur if excessive force is applied.

⚠ **WARNING: The probe assembly must be placed in a new single-use sterile sheath before use. Take special care to not drop the probe during the application and removal of the sterile sheath.**

IMPORTANT

The probe is fragile. Take extra care not to drop or damage the probe.

3.9 Optional: Connecting the Footswitch

It is not necessary to install the footswitch assembly to use the Sentimag®, however the operator may find it convenient to activate the balance function using the footswitch supplied.

IMPORTANT: The footswitch operates via an air-pressure switch in the base unit, and it must be correctly installed to function properly. This requires that there should be no air leaks between the footswitch connector/valve (Figure 4, 3) and the footswitch port on the base unit (Figure 1, 4).

a. Close-up of the footswitch port on the base unit

b. Press down on the metal clip and insert the connector/valve

c. Correct connection – it should ‘click’ into place

Figure 8: Connecting the Footswitch Assembly to the Base Unit

To insert the connector/valve into the port, first depress the metal clip on the port (see Figure 8b), then push the connector/valve into place. An audible ‘click’ may be heard as the connector/valve is pushed into place.

4. Using the Sentimag®

IMPORTANT

The Sentimag® is intended for use by suitably qualified, trained and authorized surgeons and/or operating room staff. Endomagnetics Ltd takes no responsibility for the possible misuse of the Sentimag® or for its use by inadequately qualified staff.

Please consult the Instructions For Use and prescribing information for Magtrace™.

4.1 Connecting the Probe

Before using the Sentimag® the probe assembly must be correctly connected. If at any time the following symbol is displayed on the base unit LCD:

the probe assembly will need to be plugged in. Please refer to Section 3.7 for instructions on how to do this.

The probe should be connected before the base unit is switched on.

4.1.1 Use of a Sterile Sheath

The Sentimag® probe is reusable but cannot be sterilized. It therefore needs to be used in conjunction with a single use sterile sheath. Sheaths should be latex-free and at least 1 inch wide and 72 inches long. This length will allow for the probe and a considerable length of the probe cable to be covered within the surgical field.

Such sheaths are typically common with hospitals for use with other equipment such as ultrasound probes but, if help is required in identifying a suitable sterile sheath, then please contact your local sales representative.

4.2 The Balance Function

Before using the Sentimag®, the control electronics must be balanced to account for the particular conditions of both the instrument itself and of the environment in which it is placed.

To perform a balance of the base unit, the operator should either press the button marked:

on the base unit (see Figure 1, 3), or, if the footswitch assembly is being used (see Section 4.7), depress the footswitch.

The base unit will then perform a **Balance Function**. The LCD display will then change to show a sequence in which the scales symbol rocks back and forth:

After approximately five seconds the scales symbol will stop rocking and will stay still for approximately two seconds. The display will then change to one similar to the following:

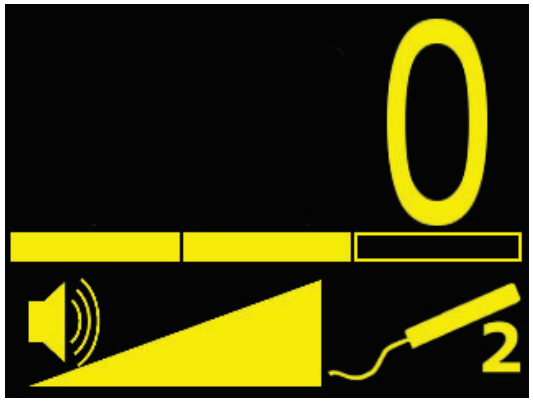


Figure 9: The 'Ready-to-Use' Screen

indicating that the Sentimag® is ready to use. A good balance results in a displayed value that is reasonably close to zero.

IMPORTANT

For best results, the probe head should be placed or held at least **half a meter away** from any metallic or magnetic objects during the balancing process. This is to avoid finding an incorrect balance point, which may render subsequent measurements unreliable.
Alternatively, as the body is weakly dielectric, the user may find it beneficial to balance the unit whilst the probe is in contact with the body. This will result in a positive signal being generated when the probe is withdrawn from the body but will have the advantage of returning to close to zero as it comes back in contact with the body.

Pre-clinical and clinical studies have demonstrated that the probe can typically detect Magtrace™ particles (and therefore sentinel nodes) at 20mm.

4.3 Using the Footswitch

The operator may choose to install and use the optional footswitch assembly (Figure 4) instead of, or as well as, the balance button on the base unit (Figure 1, 3), to operate the balance function.

When deploying the footswitch assembly, care should be taken to ensure that the foot-operated switch (Figure 4, 1) is resting flat on the floor, and that the passage of air through the flexible air hose (Figure 4, 2) is not blocked in any way.

4.4 When to Use the Balance Function

There are two times that the user will know that a balance function is either needed or desirable.

The first is when the following (stationary) symbol is displayed on the base unit LCD:

In such a case a balance function is needed, and the Sentimag® cannot be used until the balance function has been performed.

The second is when the user notices that the number displayed on the ready-to-use display (as in Figure 9) has moved significantly away from an earlier level. Such change or drift in the displayed number, and in the associated audible tone emitted by the base unit (see Section 4.5), is normal, and is the result of changes in conditions such as the thermal environment of the probe head. In this case it is not compulsory to use the balance function, and it is a matter of personal preference whether to do so or not.

4.5 Using the Speaker

The base unit contains electronic circuits and a logical processor that interrogates the incoming signal from the probe and converts this into both a digital signal that is displayed on the LCD (as described above), and an analogue signal that is passed to a loudspeaker mounted underneath the handle of the base unit (see Figure 2, 4).

The pitch (frequency) of the audible signal becomes higher or lower as the Sentimag® probe head is moved towards or away from a lymph node containing Magtrace™ magnetic tracer. This change in pitch mirrors the changes in the digital signal displayed on the LCD and can be used by the operator either in conjunction with, or in place of, the digital display, for the purpose of detecting and locating magnetic materials.

The operator may adjust the volume of the audible signal by turning the speaker volume knob on the base unit (Figure 1, 2). Turning the knob fully anti-clockwise will mute the speaker, and the following will be displayed on the base unit LCD:

Turning the knob fully clockwise will maximize the volume output of the speaker. The LCD will then display the following:

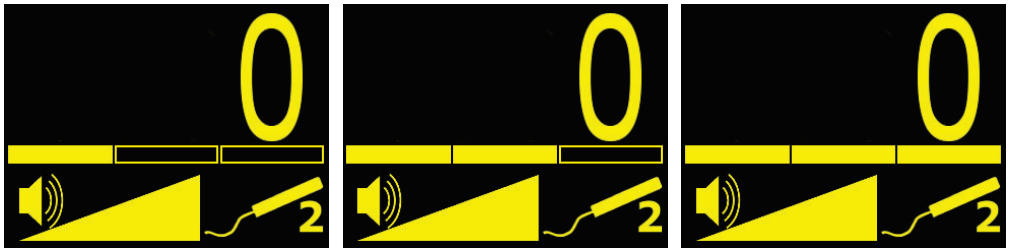
NOTE: Changing the speaker volume does not change the pitch (frequency) of the output or the sensitivity of the probe.

4.6 Changing the Instrument Sensitivity Setting

The operator may adjust the sensitivity level of the Sentimag® instrument between three pre-set levels, by turning the sensitivity setting knob on the base unit (Figure 1, 5).

This applies a scaling factor to the measured signal such that the signal displayed on Setting 2 is twice that displayed on Setting 1. The signal displayed on Setting 3 is twice that displayed on Setting 2, and four times that displayed on Setting 1. It is largely a matter of operator preference as to which sensitivity setting is used, however, if the signal is small Setting 3 may give better results, and if the signal is large, Setting 1 may be preferred to avoid overloading the display limit.

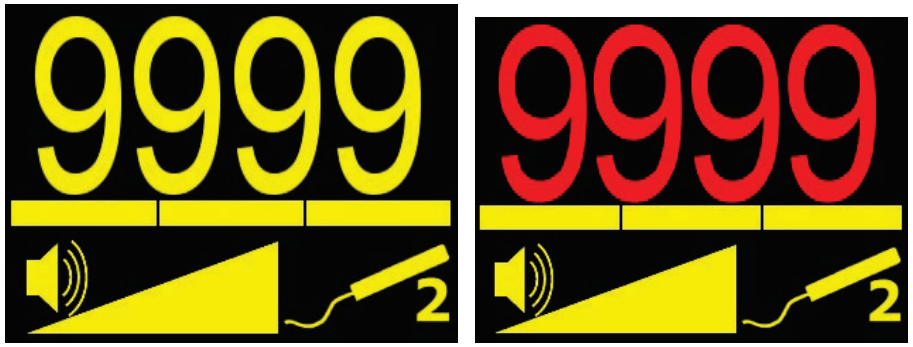
The different setting levels are displayed as bars on the ready-to-use screen as follows:



Setting 1 Setting 2 Setting 3

4.7 Over-Range Signals

On occasion, if the Sentimag® is brought close to a particularly large source of signal, such as a large mass of magnetic metal, the digital signal displayed on the base unit will register 9999:



and will start flashing. This indicates that the signal is too large for the base unit to cope with. The operator should either (1) move the probe away from the source of the large signal, or (2) change to a lower sensitivity level (see Section 4.6). Note that the signal will be YELLOW 9999 for a large ferrous signal source and will be RED 9999 for a large non-ferrous signal.

Note that when the unit is displaying an over-range signal, the sound will automatically mute after one second.

4.8 Signal Discrimination

The Sentimag® is intended to be used for the detection of approved Magtrace™ magnetic tracer materials.

However, the Sentimag® is a very sensitive instrument that can also detect other materials, including metallic and diamagnetic ones, which may produce signals that could potentially make the detection of a marker more difficult.

In some cases, such as with permanent magnets or large metallic structures, an over-range Sentimag® signal will be observed when the tip of the probe is brought close (e.g. within a few millimetres). In other cases, such as with more distant metallic objects, or when the probe tip is in close contact with diamagnetic objects, such as the human hand or body, a signal will be presented by the Sentimag® base unit:

RED DISPLAY – CONSTANT TONE

When the numbers on the liquid crystal display of the Sentimag® base unit are RED rather than YELLOW, and the audible signal is a low, constant tone rather than a varying-pitch tone, it signifies the presence of an extraneous or background signal source.

NOTE: This may be encountered as a normal part of the magnetic tracer detection process: such as when the operator checks the location of a tracer by first placing the probe tip over the suspected site, looking for a YELLOW variable-pitch signal, then places it over tissue where no marker is present, expecting to find a RED constant-pitch signal.

However, in some cases this might be a confounding issue, for example if the probe was being used in close proximity to metallic retractors, clamps or scalpels.

Therefore, for best results, it is recommended that so far as is possible, any extraneous metallic and/or magnetic objects should be removed from the vicinity of the Sentimag® probe during use.

IMPORTANT

For best results, care should be taken when using the instrument in the proximity of any extraneous metallic and/or magnetic objects, as they may generate confounding signals.

This includes some, but not all, implantable manufactured materials such as artificial joints, limbs, prostheses, clips or stents; as well as some, but not all, ancillary objects and tools that may be encountered in the operating room environment, such as retractors, clamps, scalpels, reinforced tracheal tubes and operating room tables.

If in doubt, the user should undertake an *in situ* assessment of the operating environment before using the Sentimag®, and note any particular positions or instances where potentially confounding signals are present, before making a clinical judgement as to whether the Sentimag® should be used.

NOTE: In the case of surgical instruments, in almost all cases a non-magnetic or alternative instrument or method may be found. For the case of patient-specific implanted materials, no such alternative may be available, and the individual may need to be excluded.

4.9 Indications for use and Usage

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.

5. Operator Maintenance

The Sentimag® does not require any specific routine operator or service engineer maintenance but must be checked before use for signs of damage. If the device is damaged, gives unexpected performance or operation, then cease using the device and ensure it is serviced before recommencing use.

The Sentimag® is additionally supplied with a sensitivity test "phantom" (figure 10a) that can be used to periodically check that there has been no deterioration in the system performance. The phantom is designed to fit on top of the supplied probe type.

There are two techniques to check performance. Firstly, connect and allow the unit to warm up as described in section 3 and then adjust the sensitivity setting to 3.
Method 1: Balance the unit whilst the probe is being held away from any magnetic sources, and then quickly place the phantom on top of the probe (figure 10b).
Method 2: Place the phantom on top of the probe, balance the unit and then quickly remove the phantom.

The phantom has a pre-recorded value of approximately 300 counts that is printed on the label. The Sentimag® system should display a similar value to ±10% using either method. Method 1 will give a reading where the display count is yellow, whereas method 2 will give a reading where the display count is red. Record the value that the Sentimag® achieves and compare this with future readings. If any significant difference is observed during periodic testing, then contact your local distributor for assistance.

It is recommended that the system be checked with the phantom every 12 months, or whenever it is suspected that damage may have occurred to the probe.

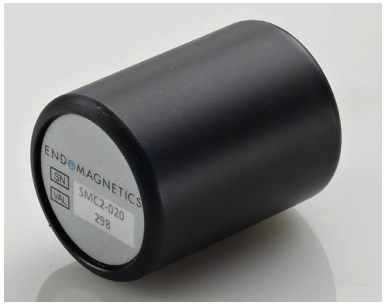
(a)  (b) 

Figure 10: (a) Sensitivity phantom, and (b) Phantom in use with the probe.

NOTE: Make sure that the correct type of sensitivity test phantom is used with a probe. The phantom is designed to fit snugly on the end of the probe. Do not place the probe on to a phantom as it risks falling.

The device must be checked for electrical safety in accordance with your establishment's safety policy, and in any case at least once per year.

6. Cleaning and Disinfecting the Instrument

6.1 Cleaning of the Instrument

⚠ WARNING: The probe assembly must be placed in a new legally marketed single-use sterile sheath before use. After use, remove sheath and discard as a biohazard in accordance with local infection control policy.

6.1.1 Sentimag® Base Unit and footswitch

It is recommended that the Sentimag® base unit, power cable and footswitch are cleaned both immediately before and immediately after use. Only use legally marketed cleaning wipes and cleaning solutions intended for medical devices and indicated as suitable for plastics. Cleaning should be carried out in accordance with manufacturer's instructions and standard hospital procedures. Follow all safety notices.

- Disconnect probe assembly and footswitch from Sentimag® base unit.
- Clean the outside surfaces of the Sentimag® base unit and footswitch using a cleaning wipe or lint-free cloth lightly dampened with a mild water-based detergent in accordance with the manufacturer's instructions.
- Visually inspect all cleaned surfaces for signs of contamination. If contamination is still present, then repeat the cleaning until there is no sign of residue. Additional wipes should be used as necessary.
- Dry or allow to dry in accordance with the cleaning manufacturer's instructions.

☣ **WARNING**: If the Base Unit, power cable or foot switch may have come into contact with biological hazards, then they MUST be cleaned following the procedure set out in Section 5.1.1.

⚠ **CAUTION**: Never clean the instrument or probe using an excessively wet cloth, or by washing it under running water. Do not use pure solvents or other strong cleaning solutions as these may attack and deform the system's plastic components, and

degrade its performance. Avoid ingress of moisture into connectors and apertures. Never immerse the central collar or the probe handle into a cleaning or disinfection solution.

6.1.2 Sentimag® Probe Assembly and Cable

The Sentimag® applied probe assembly (including cable) MUST be cleaned both immediately before and immediately after use. Only use legally marketed cleaning wipes and cleaning solutions intended for medical devices and indicated as suitable for plastics; examples include 70% alcohol-based, enzymatic and quaternary ammonium salts. Cleaning should be carried out in accordance with manufacturer's instructions and standard hospital procedures. Follow all safety notices.

- Clean the outside surfaces of the Sentimag® probe assembly and cable using a cleaning wipe or lint-free cloth lightly dampened with either 70% alcohol, enzymatic or quaternary ammonium salts, in accordance with the manufacturer's instructions.
- Visually inspect all cleaned surfaces for signs of contamination. If contamination is still present, then repeat the cleaning until there is no sign of residue. Additional wipes should be used as necessary.
- Rinse by wiping with a lint-free cloth lightly dampened with distilled water.
- Dry with lint-free cloth or allow to dry in accordance with the cleaning manufacturer's instructions.

⚠ CAUTION: The detachable probe is not suitable for autoclaving or disinfection using formaldehyde, either of which action would result in serious damage to the probe. Autoclaving or formaldehyde-treating the detachable probe will void its warranty.

6.2 High-Level Disinfection of the Probe Head

To facilitate high level disinfection, the Probe Head has been designed as a single piece of PEEK-CLASSIX plastic that extends 11cm from the probe handle. The Sentimag® probe is not suitable for sterilization techniques.

For high-level disinfection of the probe head, use legally marketed medical-grade, low-foaming 2.4% glutaraldehyde solution. Follow the instructions provided by the manufacturer regarding concentration, temperature, contact time and expiration date. Follow all safety notices. Ensure that the solution strength and duration of contact are appropriate for the intended clinical use of the device. Ensure that the disinfectant solution does not enter the probe by making sure that the central black collar and probe handle are not immersed.

- Immerse the probe head into the disinfection solution as shown in Figure 11. The probe can be immersed up to 1cm of the black collar and the probe handle.

- Gently agitate or swirl the probe head in the disinfectant solution, being careful not to allow the disinfection solution to come in contact with the black collar and probe handle. If required, use a clean lint-free cloth to wipe down the probe head, making sure to wipe away from the probe handle towards the distal end.
- Rinse the probe head by filling a basin with sterile water, immerse probe head to same depth as previously and to no more than 1cm away from the central black collar. Gently swirl for 30 seconds and wipe with a lint-free cloth, making sure to wipe away from the probe handle and black central collar and towards the distal end.
- Wipe probe head with a dry sterile gauze/clean lint-free cloth.
- Ensure the probe is dry and examine for damage such as cracks or splitting. If damage is evident, discontinue use and contact your Sentimag supplier's local representative.

Figure 11: Immersion of probe head in disinfection solution

7. Troubleshooting

If the instrument is not working properly, please try the following solutions:

- Turn off the power, wait ten seconds, turn on the power.
- Check the items in Section 7.1 (Troubleshooting Tips) and Section 7.2 (Instrument Error Codes).
- Contact your local distributor for further assistance.

CAUTION: In the unlikely occurrence of the probe becoming hot, all use of the Sentimag® system should cease and the unit sent for Service.

7.1 Troubleshooting Tips

The following is a list of symptoms, and suggestions to try to solve the problem.

Display is not lit

- Check the mains cable is fully inserted into the base unit.
- Check the switch on the rear of the unit is turned on.
- Check the mains outlet switch is turned on.
- Connect the unit to a different mains outlet (one which is known to be working).
- Ask a technician to check the fuses.

Error symbol is displayed

- Note the error code: for interpretation, refer to Instrument Error Codes below.
- Turn off the power, wait ten seconds, turn on the power.

Display does not change

- Turn off the power, wait ten seconds, turn on the power.

'Probe not connected' symbol is displayed

- Check both probe connectors are fully inserted into the correct sockets.
- Disconnect probe, check connectors for dirt or damage, connect probe again.
- Replace probe with a spare (if available).

Footswitch does not work

- Check air hose connector is fully inserted and latched.
- Check footswitch for damage (is there an air-leak?).
- Check plastic tube (is it folded or crushed?).
- Try push-button on base unit to perform balance function.
- Replace footswitch with a spare.

'Failed to balance' symbol is displayed

- Balance again, holding the probe well away from any magnetic or electrically-conducting objects.
- Disconnect probe, check connectors for dirt or damage, connect probe again.
- Replace probe with a spare (if available).
- Switch off power to unit, wait ten seconds, switch back on.

No response to magnetic objects

- Check probe and connectors for damage.
- Replace probe with a spare.

7.2 Instrument Error Codes

On start-up and during normal operation, the instrument performs various self-checks on its internal components. If a problem is detected, the equipment stops operating and the display shows a wrench symbol including an error number:

If the error symbol is displayed, turn off the power, wait ten seconds, turn on the power. If the error is then displayed again, the equipment must be sent for repair. Please contact your local distributer for assistance.

Error code	Meaning
1	Internal communications (no response)
2	Internal communications (out of step)
3	Internal communications (protocol error)
4	Measurement timeout
5	Corrupted settings (start-up)
6	Flash memory failed self-test (start-up)
7	RAM memory failed self-test (start-up)
8	General processing error
9	Firmware hang (microcontroller automatically resets)

Additionally, the unit may display error codes in the range 51-59. The 5 is added to indicate that the “crunch” microcontroller generated the error.

8. Instrument Warranty and Returns

The Supplier warrants the Sentimag®, when purchased new, to be free from defects in materials and workmanship, and will repair or replace, at their discretion, any Sentimag® that, used under proper conditions, exhibits such defects.

Under the terms of this warranty, the product must be returned in the original packaging, transportation prepaid, with a copy of the Proof of Purchase and a Decontamination Certificate (see Section 9) to your local distributor.

☣ **WARNING**: All products must the decontaminated before being placed back in their original packaging.

Contact your local distributor to receive authorisation to return the instrument and enclose a detailed description of the problem.

8.1 Warranty Duration

This warranty is provided to the original purchaser for one year from the date of purchase.

In no event will Endomagnetics Ltd be liable for indirect, incidental or consequential damages; the original user's remedies being limited to repair or replacement of the instrument at the manufacturer's option.

8.2 Particular Exclusion

Unauthorized modification of any part of the Sentimag® or the use or attachment of any peripheral not supplied or specified by Endomagnetics Ltd will void this Warranty.

⚠ **WARNING**: Use only accessories supplied by Endomagnetics Ltd. The use of any non Endomagnetics Ltd supplied accessories will invalidate the warranty.

9. Certificate of Decontamination for returning of Sentimag® components to manufacturer

Endomagnetics Ltd respects the health and safety of its clients and employees, and requests that any product being returned is decontaminated in accordance with the procedure detailed in Section 5. Should you have any questions, please contact your local representative.

⚠ CAUTION: Never clean the instrument or probe using a wet cloth, or by washing it under running water. Avoid ingress of moisture into connectors and apertures.

⚠ CAUTION: Do not use pure solvents or other strong cleaning solutions as these may attack and deform the instrument's plastic components and degrade its performance.

9.1 Decontamination Declaration

Hospital
or Clinic Name: _____

Address: _____

Product Code: _____

Serial Number: _____

Reason For Return: _____

Please mark the appropriate option(s) below:

☐ I certify that I have decontaminated the product as per above.

Decontaminant Used: _____

☐ I certify that the product has <u>not</u> been exposed to any biological materials.

Title: _____ Name: _____

Signature: _____ Date: _____

Telephone: _____ Email: _____

NOTE: Please include a copy of this form with the product being returned.

10. Glossary of Terms and Abbreviations

ABS	Acrylonitrile Butadiene Styrene – the plastic from which the Sentimag® base unit is made.
Balance Function	An electronics-based procedure that results in the base unit control electronics being tuned to optimize the detection capability of the Sentimag®.
Base Unit	The main control electronics, processing, display and power unit for the Sentimag® instrument (see Figures 1 and 2).
Footswitch Assembly	A detachable air-driven switch (see Figure 4) that allows the user to operate the balance function on the Sentimag® base unit without having to use their hands. Rated IPX4.
Instrument	The Endomagnetics Ltd Sentimag® instrument, comprising a base unit, a probe assembly, and an optional footswitch assembly.
LCD	Liquid crystal display.
OEM	Original equipment manufacturer.
Probe Assembly	Applied part consisting of a detachable hand-held probe, cable and connectors (see Figure 3) that the operator uses to detect and locate magnetic materials by moving it towards and away from them and monitoring a change in pitch in an audible signal from the base unit and/or a change in the digital signal on its LCD.

11. Technical Specification

11.1 General Specifications

General

Instrument make / model	Endomagnetics Ltd / Sentimag®
Instrument dimensions (W x H x D)	240mm x 370mm x 210mm
Instrument weight	3.8kg (4.5kg in case)
Operating temperature range	
Instrument	18°C to 32°C (64˚F to 90˚F)
Probe	18°C to 39°C (90˚F to 99˚F)
Storage temperature range	0°C to 40°C (32˚F to 104˚F)
Transportation temperature range	-10°C to 50°C (14˚F to 122˚F)
Operating, Storage and Transportation relative humidity range	20% to 80% non-condensing
Use of device	Less than 2000 meters
Operating, Storage and Transportation atmospheric pressure range	80 kPa to 105 kPa

Instrument Power Supply

Power lead connector	IEC 60320 C13

Power supply voltage	110V to 230V AC 50Hz to 60Hz nominal
Fuse Type (and Rating)	T1AH 250V Ø5x20mm (1 amp)

Instrument Details

Protection against electrical shock	Class I Protectively Earthed
Applied part isolation	Type B
Ingress protection rating	IPX0 (not protected)
Limitation of operation	Parts rated for 5 years lifetime

11.2 Performance and Accuracy

Performance

In the **longitudinal** direction, i.e. parallel to the long axis of the probe, the signal recorded by the Sentimag® decreases approximately exponentially with distance from the tip of the probe.

In the **transverse** direction, i.e. perpendicular to the long axis of the probe, in the plane of the tip of the probe, the signal recorded by the Sentimag® decreases in a Gaussian-like manner with distance from the tip of the probe.

Accuracy

The instrument provides a qualitative measure of the presence of magnetic material in the vicinity of the probe. The signal increases with the amount and proximity of magnetic material.

11.3 Magnetic Field Characteristics

Nature

The Sentimag® is a magnetic susceptometer. It is designed to deliver a small amplitude, time-varying magnetic field via a hand-held probe, and to electronically detect the presence of any magnetic materials in the vicinity of the probe head. It operates on the principle of magnetic susceptibility, wherein different materials respond differently in the presence of an applied magnetic field. The clinically introduced magnetic tracer materials with which the Sentimag® is intended to be used have a very high magnetic susceptibility, several orders of magnitude higher than e.g. water or the human body.

Type

The magnetic field is generated by passing a 10 kHz sinusoidally varying alternating current through a wire coil mounted in the probe.

Intensity

The maximum field intensity at any point on the probe casing is no greater than 251 μT.

Distribution

The magnetic field distribution around the probe head is linearly proportional to the spatial variation in signal, as specified in Performance and Accuracy.

11.4 Electromagnetic Immunity and Separation

<table>
<tr><th colspan="3">Guidance and Manufacturer's Declaration –
Electromagnetic Emissions</th></tr>
<tr><td colspan="3">The Sentimag® is intended for use in the electromagnetic environment specified below. The customer or the user of the Sentimag® should assure that it is used in such an environment.</td></tr>
<tr><th>Emissions Test</th><th>Compliance</th><th>Electromagnetic Environment - Guidance</th></tr>
<tr><td>RF Radiated Emissions
CISPR 11
EN550011
ANDI 63.4</td><td>Group 1
Class A</td><td rowspan="3">The Sentimag® uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby electronic equipment.

There is no known risk of reciprocal interference* posed by Sentimag® with any other equipment during specific investigations or treatments.

The emissions characteristics of the Sentimag® make it suitable for use in industrial areas and hospitals (CISPR 11 class A). If it is used in a residential environment (for which CISPR 11 class B is normally required) the Sentimag® might not offer adequate protection to radio-frequency communication services. The user might need to take mitigation measures, such as relocating or reorienting the equipment.</td></tr>
<tr><td>RF Conducted Emissions
CISPR 11
EN550011
ANDI 63.4</td><td>Group 1
Class B</td></tr>
<tr><td>Voltage Fluctuations / Flicker emissions
IEC 61000-3-3</td><td>Complies</td></tr>
</table>

(*) "Risks of reciprocal interference" means adverse effects on the device caused by instruments present at the time of investigations or treatment, and vice versa.

Guidance and Manufacturer's Declaration – Electromagnetic Immunity			
The Sentimag® is intended for use in the electromagnetic environment specified below. The customer or the user of the Sentimag® should assure that it is used in such an environment.			
Immunity Test	**IEC 60601 Test Level**	**Compliance Level**	**Electromagnetic Environment – Guidance**
Electrostatic Discharge (ESD) IEC 61000-4-2	±4 kV contact ±8 kV air	±4 kV contact ±8 kV air	Floor should be wood, concrete, or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30 %.
Electrical Fast Transient/Burst IEC 61000-4-4	±2 kV for power supply lines ±1 kV for input/output lines	±2 kV for power supply lines Not applicable	Mains power quality should be that of a typical commercial and/or hospital environment.
Surge IEC 61000-4-5	±1 kV line to line ±2 kV line to earth	±1 kV line to line ±2 kV line to earth	Mains power quality should be that of a typical commercial and/or hospital environment.
Voltage dips, short interruptions and voltage variations on power supply IEC 61000-4-11	<5 % *U*T (>95 % dip in *U*T) for 0.5 cycle 40 % *U*T (60 % dip in *U*T) for 5 cycles 70 % *U*T (30 % dip in *U*T) for 25 cycles <5 % *U*T (95 % dip in *U*T) for 5 seconds	<5 % *U*T (>95 % dip in *U*T) for 0.5 cycle 40 % *U*T (60 % dip in *U*T) for 5 cycles 70 % *U*T (30 % dip in *U*T) for 25 cycles 0 % *U*T (100 % dip in *U*T) for 5 seconds	Mains power quality should be that of a typical commercial and/or hospital environment. If the user of the Sentimag® requires continued operation during power mains interruption, it is recommended that the Sentimag® be powered from an uninterruptible power supply.
Note: *U*T is the AC mains voltage prior to application of the test level.			

(continued overleaf)

Guidance and Manufacturer's Declaration – Electromagnetic Immunity			
Immunity Test	**IEC 60601 Test Level**	**Compliance Level**	**Electromagnetic Environment – Guidance**
Power Frequency (50/ 60 Hz) magnetic field IEC 61000-4-8	3 A/m	3 A/m	Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.
Conducted RF IEC 61000-4-6	3 V_{rms} 150 kHz to 80 MHz	3 V_{rms}	Portable and mobile RF communications equipment should be used no closer to any part of the Sentimag® including cables, than the recommended separation distance calculated from the equation appropriate to the frequency of the transmitter.
Radiated RF IEC 61000-4-3	3 V/m 80 MHz to 2.5 GHz	3 V/m	

Recommended separation distance

WARNING: Portable RF communications equipment (including peripherals such as antenna cables and external antennas) should be used no closer than 30 cm (12 inches) to any part of the Sentimag®, including cables specified by the manufacturer. Otherwise, degradation of the performance of this equipment could result.

Field strengths from fixed RF transmitters as determined by an electromagnetic site survey [A] should be less than the compliance level.

Interference may occur in the vicinity of equipment marked with the following symbol:

Note 1: At 80 MHz and 800 MHz, the higher frequency range applies.

Note 2: These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects, and people.

[A] Field strengths from fixed transmitters, such as base stations for radio (cellular/ cordless) telephones and land mobile radio, AM and FM radio broadcast, and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered. If the measured field strength in the location in which the Sentimag® is used exceeds the applicable RF compliance level above, the Sentimag® should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as reorienting or relocating the Sentimag®.

(continued overleaf)

Recommended separation distance between Portable and Mobile RF Communications Equipment and the Sentimag®

The Sentimag® is intended for use in an electromagnetic environment in which radiated RF disturbances are controlled. The customers or the users of the Sentimag® can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and the Sentimag® as recommended below, according to the maximum output power of the communications equipment.

Rated Maximum Output Power of Transmitter in Watts (W)	Separation distance according to frequency of transmitter in meters (m)		
	150 kHz to 80 MHz $d = 2\sqrt{P}$	80 MHz to 800 MHz $d = 2\sqrt{P}$	800 MHz to 2.5GHz $d = 2\sqrt{P}$
0.01	0.30 [A]	0.30 [A]	0.30 [A]
0.1	0.63	0.63	0.63
1	2.00	2.00	2.00
10	6.32	6.32	6.32
100	20.00	20.00	20.00

For transmitters rated at a maximum output power not listed above, the recommended separation distance d in meters (m) can be estimated using the equation, where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer.

Note 1: At 80 MHz and 800 MHz, the separation distance for the higher frequency range applies.

Note 2: These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects, and people.

[A] Portable RF communications equipment (including peripherals such as antenna cables and external antennas) should be used no closer than 30 cm (12 inches) to any part of the Sentimag®, including cables specified by the manufacturer. Otherwise, degradation of the performance of this equipment could result.

Distributed for Endomagnetics by Devicor Medical Products, Inc.

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Website: www.mammotome.com
Email: customerservice@mammotome.com

12. SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

12.1 SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the 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 US (IDE #G140208, **NCT02336737**).

An additional supporting study was conducted in France (NCT01790399) 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 Magtrace™ requiring dilution with saline prior to injection. Note: The French Sentimag Feasibliity Trial is discussed in the Summary of Supplemental Clinical Information section (Section 12.2) because it was only supporting clinical data.

Table 1: 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)

12.1.1 Study Design

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

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

The active control was Technetium 99 labelled 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, i.e.,
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 (δ) = 5%
- Assumed discordance rate = 8%
- Test significance level (α) = 0.05 (1-sided)
- Power (1-β) ≈ 0.85

A minimum of 265 nodes were required for each method. Given that ~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, 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).

1. Clinical Inclusion and Exclusion Criteria

Enrolment 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 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 enrol in the Sentimag® study if they met any of the following exclusion criteria:

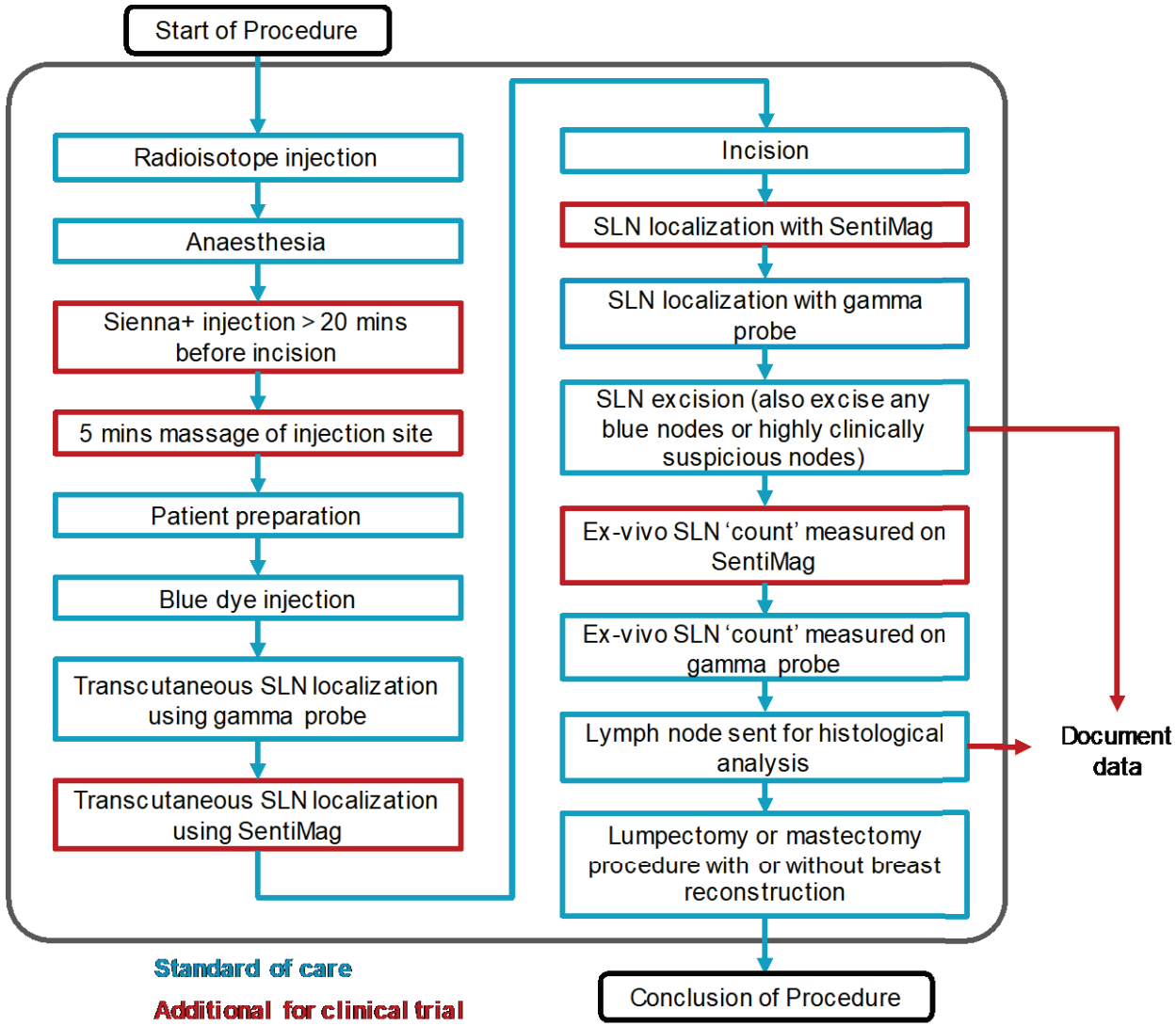
- The subject is pregnant or lactating
- The subject has clinical or radiological evidence of metastatic cancer including palpably abnormal or enlarged lymph nodes
- The subject has a known hypersensitivity to Isosulfan blue dye
- The subject has participated in another investigational drug study within 30 days of scheduled surgery
- Subject has had either a) previous axilla surgery, b) reduction mammoplasty, or c) lymphatic function that is impaired in the surgeon's judgment
- Subject has had preoperative radiation therapy to the affected breast or axilla
- Subject has received a Feraheme® (ferumoxytol) Injection within the past 6 months
- Subject has intolerance or hypersensitivity to iron or dextran compounds or to Magtrace™

- Subject has an iron overload disease
- Subject has pacemaker or other implantable device in the chest wall

2. Study Procedure and Follow-up Schedule

The study procedure flow is depicted in figure 12 below.

Figure 12 : 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 2.

Table 2: Study Visits and Data Collection Overview

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

3. Clinical Endpoints

Primary Safety Endpoint:

To provide evidence of the safety of the Magtrace™ and Sentimag® Magnetic Localization System 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.

12.1.2 Accountability of PMA Cohort

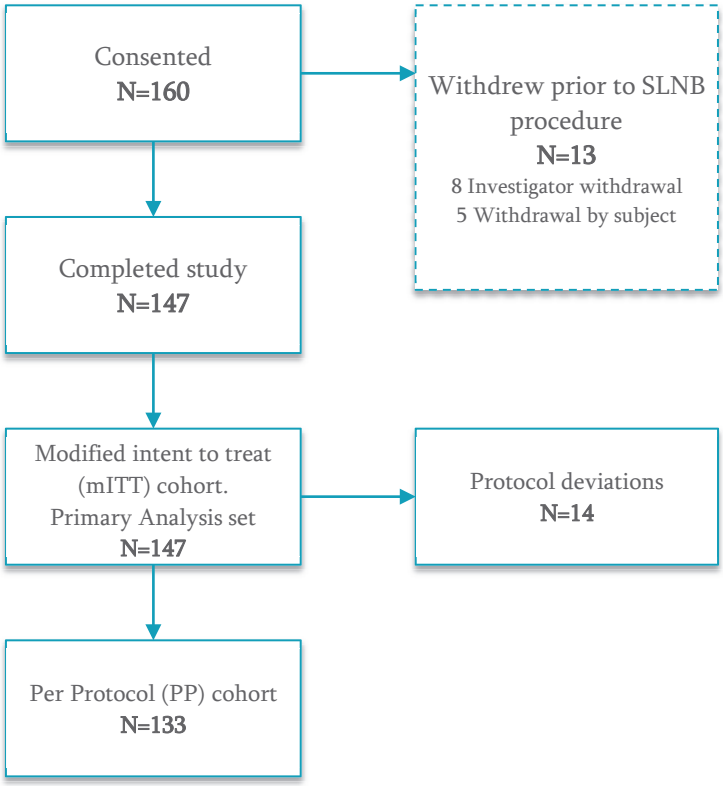
At the time of database lock, of 160 patients enrolled in the PMA study, 147 patients completed the study and are available for analysis. Patient accountability is shown in Figure 13.

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

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



12.1.3 Study Population Demographics and Baseline Clinicopathological Characteristics

Patient demographic characteristics are shown in Table 3 with the patient baseline clinicopathological characteristics given in Table 4.

Table 3: Study Population Demographics

	Overall (N=147)
Race (not mutually exclusive, %)	
American Indian or Alaska Native	0.0%
Asian	4.8 %
Black or African American	7.5%
Pacific Islander	0.0%
White	82.3%
Other	6.1%
Ethnicity (n/N (%))	
Hispanic or Latino	11.6%
Not Hispanic or Latino	88.4%
Mean Age (SD)	61.1 (12.3)
Mean Weight in lbs (SD)	167.1 (38.5)
Mean Height in inches (SD)	63.7 (2.6)
Mean Body Mass Index (BMI Kg/m² (SD))	29.0 (6.9)
Menopausal status	
Premenopausal	19.0%
Perimenopausal	3.4%
Postmenopausal	77.6%

Table 4: 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*

12.1.4 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 5 and 6.

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 (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.

Table 5: 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 6 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 6 events occurring in 6 subjects (4.1%) were assessed as having an undetermined relatedness in relation to Magtrace™. There were 9 serious adverse events in the study. After data analysis, 7 out of the 9 SAEs were unrelated to the Magtrace™, and 2 of the 9 SAEs were found to be undetermined (Bradycardia and Anaphylaxis).

Table 6: 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.*

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

[3] *Cardiac Disorder: Thirty 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 7 to Table 13.

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™ and Sentimag® Magnetic Localization System 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 7: 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 8: The nodal detection rates

	Magtrace™		
Control (Radioisotope and Blue Dye)	Detected	Not Detected	Total
Dectected	326	19	**345 (93.5%)**
Not Detected	22	2	--
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 9: 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 15** malignant nodes table**)**

Table 10: 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 11: 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 12: 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 13: Results of Other Per Node Endpoints

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

Table 14: 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 5 contained micrometastasis. The one node that was not identified by either Control or Magtrace™ but was considered clinically suspicious contained a macrometastasis.

Table 15: Sentinel lymph node detection of malignant nodes - per node

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

One additional positive node (and the one subject with this node) is excluded from analyses discussed above since it did not meet any of the criteria for a sentinel lymph node. This node, subject 06-018, Node 4, was one of two 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.

12.2 SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The supplemental clinical information includes:

1. French Clinical Study NCT01790399
2. Subgroup Analyses of Mastectomy Cohort

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 radiolabelled with Technetium 99m isotope; with or without patent blue dye.

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

Radioisotope (Technetium albumin colloid) was injected according to the standard of care protocol at each site. 45/108 (42%) of patients 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 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 enrol in the French Study if they met any of the following exclusion criteria:

- T3 or T4 tumor (> 5 cm, cutaneous or muscular infiltration, or inflammatory cancer)
- Existence of an axillary adenopathy suspected clinically or in imaging
- Bifocal or multi-focal tumors known before surgery
- History of mammary of axillary surgery
- Metastatic patient

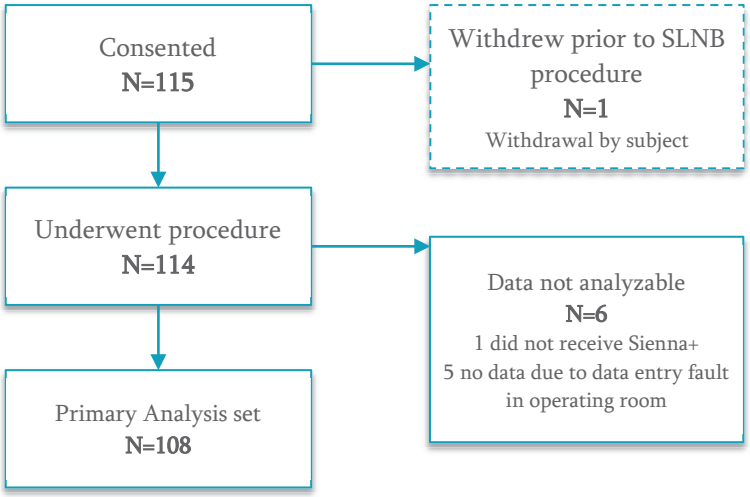
- Patient with a contra-indication to anaesthesia and/or surgery
- Intolerance or hypersensitivity:
    - to iron or dextran or superparamagnetic iron oxide particles
    - to the patent blue dye in centers where it is currently used
- Patient unable to receive a radioactive isotope for excision of the sentinel lymph node
- Allergy to radioactive product
- Iron excess disease
- Cardiac stimulator or any other device implantable in the thoracic wall
- Unable to be medically monitored in the study for geographic, social or mental reasons
- Patient deprived of their freedom or under guardianship
- Pregnant or breast-feeding

H. Patient accountability

One hundred fifteen (115) subjects were enrolled at 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 14.

Figure 14: 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 16.

Table16. Demographic and Baseline Clinicopathologic Characteristics for the French Study Population

	N = 108	%
Age		
≤ 50	29	27
51-69	62	57
≥ 70	17	16
BMI		
Thin	3	3
Normal	44	41
Overweight	40	37
Obese	18	17
Morbidly obese	2	2
Missing	1	
Hormonal status		
Active	26	24
Pre-menopausal	5	5
Menopausal	77	71
Location of the lesion		
Upper inner quadrant	26	24
Upper outer quadrant	62	57
Lower-inner quadrant	5	5
Lower-outer quadrant	9	8
Retro-areolar	5	1
Histology type		
Invasive root carcinoma	96	89
Invasive lobular	9	8
Other	3	3
SBR Grade	37	34
II	58	54
III	13	12
Hormonal receptors		
Estrogen receptors		
Negative	9	8
Positive	99	92

	N = 108	%
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	(0-90)
Missing (#6, #8, #99)	3	

J. Safety & Effectiveness Results

Safety results:

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

Effectiveness results

Table 17: Primary Endpoint Analysis

	Sienna+ 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 18: 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 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 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 (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 19 summarizes the per-patient and per-node endpoints.

Table 19: Per node and per patient lymph node detection rates for Sienna+ and Radioisotope in NCT01790399

	French NCT01790399Study	
	Sienna+ n = 108	Radioisotope with or without blue dye 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% (92.1%, 99.4%)	95.4% (89.5%,98.5%)
Overall per patient concordance % (95% CI)	96.3% (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% (88.4, 99.9)	95.7% (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 sites. The deviations that occurred did not negatively impact the scientific soundness or the data integrity of the clinical study.

L. NCT01790399 Feasibility Safety & Effectiveness Conclusions:

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

1. Subgroup Analyses of Mastectomy Cohort

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

Table 20: 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 below:

Table 21: 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 (HER2) Status (n/N (%))	

Positive	2/43 (4.7%)
Negative	33/43 (76.7%)
Not performed	8/43 (18.6%)

Table 22: 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 23: 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%)

Magnetic Resonance Imaging (MRI) Artifact

After lumpectomy surgery, Magtrace™ can cause image artifacts during magnetic resonance imaging (MRI) near the injection site. These artifacts may be present long-term.

- Information from European sample cases and reports indicate that the artifact persists, often unchanged, for long term.
- The artefact 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 artefacts during Magnetic Resonance Imaging (MRI) of those regions. Some manipulation of scan parameters may be required to compensate for the artifacts. 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 24 below summarises per patient or per breast occurrence of imaging artefacts in mastectomy patients.

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

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 24: Per patient and per breast occurrence of artefact in post-mastectomy MRI

Source	Number of post mastectomy images	Per patient (per breast) occrence of artifact

Krischer et al. (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 2 bilateral= 26 breast cancer cases. • 8 mastectomies • 18 BCS (incl. one after chemotherapy) One subject (PID 15) not interpretable due to breathing artifacts and movement. Therefore 25 breast cancers eligible for analysis: • 8 mastectomies • 17 BCS Bilateral cases were: PID 3 Right mastectomy, left lumpectomy; and PID 17 bilaterallumpectomy	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) (Only 3/5 breasts received MagtraceTM)
Total		0/11 (0/15)

Table 25 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 25 – Type of mastectomy before MRI

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

SentimagIC pivotal study Subject 05-018	Bilateral. Non-skin or nipple sparing	Sub-cutaneous, sub-areolar	None visible
SentimagIC pivotal study Subject 06-030	Skin-sparing	Sub-cutaneous, sub-areolar	None visible

*Subject 05-012 received lumpectomy surgery in the study, but subsequently bilateral mastectomy, after which these MRI scans were obtained.
**Data on the type of mastectomy obtained from the author via a personal communication.

The summary of studies on MRI Artifact is presented in Table 26 to Table 28.

Table 26 (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. 5 ml Retroareolar	n=17 evaluable	13/17 (76.5%)	Not specified	Not specified	Not specified	4/17 (23.5%) Grade 2 - without restriction, 10/17 (58.8%) Grade 1-with restriction, 3/17 (17.6%) Grade 0 – impossible
Aribal 2021	2 ml Sienna+ 3ml Saline. 5 ml Periareolar	n=25	21/25 (84%)	Not specified	Not specified	Not specified	No artifact 4/25(16%) Focal area of signal void artifact (less than 5mm) 10/25 (40%) Segmental area of signal void artifact 3/25(12%) Non diagnostic 8/25(32%)
PostMag Registry (Reference No. ISRCTN85167182) This study is not yet published.	2ml Peritumoral	n=11	10 (91%)	Mean artifact Volume 10 cm^3 Range: 0 cm^3 - 28 cm^3	Yes (18%) No (82%)	Mean 3 months Range: 1 month to 5 months	No Artifacts 1/11 (9%) Minimal Artifacts suitable for diagnosis 6/11 (55%) Significantly impaired, but could be diagnostic 3/11 (25%) Non diagnostic, 1/11 (9%)

Unpublished study	2ml Peritumoral	n=2	1(50%)	Mean artifact Volume 5 cm^3 Range: 0 cm^3 - 10 cm^3	Yes (50%) No (50%)	Not applicable, Magtrace intraoperative followed by MRI	No Artifacts 0/2 (0%) Minimal Artifacts suitable for diagnosis 2/2 (100%) Non diagnostic, significantly impaired 0/2 (0%)
Sentimag IC Study Reference: NCT02336737 IDE No. G140208	2ml Subareolar	147/13	12 (92%)	Mean 68 cm^3 Range 0 cm^3-204 cm^3	Yes (8%) No (92%)	Mean: 10 months, Range: 1 month to 15 months	No Artifacts 1/13 (8%) Minimal Artifacts suitable for diagnosis 4/13 (31%) Significantly impaired but could be diagnostic 5/13 (39%) 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%) Minimal Artifacts suitable for diagnosis 11/14 (78%) Significantly impaired 0/14 (0%) Non diagnostic, 3/14 (21%)

Table 27 (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 Registry (Reference No. ISRCTN85167182) This study is not yet published.	2ml Peritumoral	n=11	10 (91%)	Mean artifact Volume 10 cm^3 Range: 0 cm^3 -28 cm^3	Yes (18%) No (82%)	Mean 3 months Range: 1 month to 5 months	No Artifacts 1/11 (9%) Minimal Artifacts suitable for diagnosis 6/11 (55%) Significantly impaired, but could be diagnostic 3/11 (25%) Non diagnostic, 1/11 (9%)
Unpublished study	2ml Peritumoral	n=2	1(50%)	Mean artifact Volume 5 cm3 Range: 0 cm3 -10 cm3	Yes (50%) No (50%)	Not applicable, Magtrace intraoperative followed by MRI	No Artifacts 0/2 (0%) Minimal Artifacts suitable for diagnosis 2/2 (100%) Non diagnostic, significantly impaired 0/2 (0%)

Table 28 (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. 5 ml Retroareolar	n=17 evaluable	13/17 (76.5%)	Not specified	Not specified	Not specified	3/17 (17.6%) grade 0 – impossible, 10/17 (58.8%) Grade 1-with restriction, 4/17 (23.5%) Grade 2 - without restriction
Aribal 2021	2 ml Sienna+ 3ml Saline. 5 ml Periareolar	n=25	21/25 (84%)	Not specified	Not specified	Not specified	No Artefacts 26/34 (81%) Minimal Artefacts suitable for diagnosis 6/34 (18%) Significantly impaired, but could be diagnostic 1/34 (3%) Non diagnostic, 1/34 (6%)
Sentimag IC Study Reference: NCT02336737 IDE No. G140208	2ml Subareolar	147/13	12 (92%)	Mean 68 cm^3 Range 0 cm^3-204 cm^3	Yes (8%) No (92%)	Mean: 10 months, Range: 1 month to 15 months	No Artifacts 1/13 (8%) Minimal Artifacts suitable for diagnosis 4/13 (31%) Significantly impaired but could be diagnostic 5/13 (39%) 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%) Minimal Artifacts suitable for diagnosis 11/14 (78%) Significantly impaired 0/14 (0%) Non diagnostic, 3/14 (21%)

Published literature studies

Further studies: Seven European studies have been carried out for which the data are published. These are summarized in the Table 29 along with the supporting publications (note that French NCT01790399 Study is the Houpeau study in Table 29).

Table 29: Summary of Published European Studies

Author (reference)	Douek(1)	Thill(2)	Rubio(3)	Ghilli(4)	Houpeau(5)	Pinero(6)	Karakatsanis(7)
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 followed in the MONOS study (Karakatsanis study in Table 29, above) in which 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 three months post-surgery. The first subject had received sub-cutaneous, peri-areolar injection subsequent to which she had undergone skin sparing mastectomy. The position of the stain was towards upper outer quadrant and the size of the stain 1 x 2 cm. The stain had disappeared after three months. The second subject also received sub-cutaneous, peri-areolar injection subsequent to which she underwent classic mastectomy. The position of the stain was also towards upper outer quadrant and the size of the stain 1 x 2 cm. In this case the stain also disappeared after three months. Detail of the cases with staining after mastectomy were obtained from the author.

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 30 to 33 summarize skin staining in patients for a number of studies.

Table 30 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 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 Follow up for 186	n=154 Lumpectomy n=52 mastectomy	35% post-op 0-3 months *"95.6% of patients with discoloration had been*	Yes:75.8% No: 24.2% At 15 months	"*Discoloration was present in 35.5 % of patients post-operatively (0–3 months) and faded progressively in size*	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)**
				treated with breast conserving surgery" (lumpectomy)		*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."*	
Houpeau 2016	5ml SA	108	n=100 lumpectomy n=5 mastectomy n=3 oncoplasty	22 (20.4%) <30days post-operative	Not stated	Not Stated, max follow up 30 days	Unavailable
Ghilli 2015	5ml SA	193	n=184 lumpectomy n=6 bilateral reduction mammoplasty n=2 mastectomy	*"...more than 40% of cases..."*	Yes:91% No: 9% 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 or PT	184 PA 131, PT 53	n=126 lumpectomy n=57 mastectomy no staining in mastectomy patients	Overall: 73/184 (39.9%) PA: 58/131 (44.3%) PT: 15/53 (28.3%) at 3 months	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"* *"Of patients with skin staining, 97% had been treated with BCS."*	(Likert scale was used for assessment.) "*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*

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)**
							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)"*
Karakatsanis 2019	Not specified	n=189	n=129 lumpectomy 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 n=107 mastectomy	47 (15.5%) initial follow-up at 3 months	Yes: 76.6% No: 23.4% 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*	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)
						took 22 and 24 months"	
Wärnberg 2019	5ml RA or PT	n=337 n=177 RA n=163 PT	RA cohort: n=110 lumpectomy n=67 mastectomies. In the PT cohort: n=148 lumpectomy n=15 mastectomies	Lumpectomy + RA injn: 74/110 (67.3%) Lumpectomy + PT injn: 56/148 (37.8%) (p <0.001)	Lumpectomy + RA: Yes: 31.3% No: 68.7% Lumpectomy + PT: Yes: 75.1% No: 24.9%	Analysis based upon N = 130 (74+56) patients with skin staining. "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). 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). Analysing 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, n=43 mastectomy	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 (%)) 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)**
Vural 2019	5ml RA	n=104 underwent analysis	n=89 lumpectomy/oncoplastic n=18 mastectomy	22 (20.4%) at post-operative consultation	Not reported	Not reported	unavailable
Rubio 2020	3 groups of n=45: Group 1: 1ml SA Group 2: 1.5ml SA Group 3: 2ml SA	n=135 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.) *"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"* *"At 6 months follow up, 78.9% of the patients still felt that the skin staining was not a problem."*
PostMag (2020) Registry (Reference No. ISRCTN85167182)	2ml PT	32/32	n=32 Lumpectomy n=0 Mastectomy	12 (37.5%) (immediately post op)	Yes (100%) No (0%)	Mean= 6 months Range=3 months to 9 months	*Unavailable.* *No skin discolouration was observed in any of the subjects at 12 months*

Table 31 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.) 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) Registry (Reference No. ISRCTN85167182)	2ml PT	32/32	n=32 Lumpectomy n=0 Mastectomy	12 (37.5%) (immediately post op)	Yes (100%) No (0%)	Mean= 6 months Range=3 months to 9 months	*Unavailable.* *No skin discolouration 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%) (p <0.001)	Lumpectomy + PT: Yes: 75.1% No: 24.9%	Analysis based upon N = 130 (74+56) patients with skin staining. "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). 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). Analysing 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. n=126 lumpectomy n=57 mastectomy.	PT: 15/53 (28.3%) 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"*	(Likert scale was used for assessment.) "*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*

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)
			no staining in mastectomy patients			*"Of patients with skin staining, 97% had been treated with BCS."*	*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)"*

Table 32 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 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 Follow up for 186	n=154 Lumpectomy n=52 mastectomy	35% post-op 0-3 months *"95.6% of patients with discoloration had been*	Yes:75.8% No: 24.2% 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 %*	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)
				treated with breast conserving surgery" (lumpectomy)		*of patients after a year. Staining remained present in 8.6 % 15 months after the operation, but much smaller and paler."*	
Houpeau 2016	5ml SA	108	n=100 lumpectomy n=5 mastectomy n=3 oncoplasty	22 (20.4%) <30days post-operative	Not stated	Not Stated, max follow up 30 days	Unavailable
Ghilli 2015	5ml SA	193	n=184 lumpectomy n=6 bilateral reduction mammoplasty n=2 mastectomy	*"…more than 40% of cases…"*	Yes:91% No: 9% 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=131 PA	n=126 lumpectomy n=57 mastectomy no staining in mastectomy patients	Overall: 73/184 (39.9%) PA: 58/131 (44.3%) 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"* *"Of patients with skin staining, 97% had been treated with BCS."*	(Likert scale was used for assessment.) "*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*

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)
							noted between the two time points (P = 0·280)"
Karakatsanis 2019	Not specified	n=189	n=129 lumpectomy 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 n=107 mastectomy	47 (15.5%) initial follow-up at 3 months	Yes: 76.6% No: 23.4% 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	n=337 n=177 RA	RA cohort: n=110 lumpectomy n=67 mastectomies.	Lumpectomy + RA injn: 74/110 (67.3%)	Lumpectomy + RA: Yes: 31.3% No: 68.7%	Analysis based upon N = 130 (74+56) patients with skin staining. "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). 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). Analysing 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

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)
							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 n=18 mastectomy	22 (20.4%) at post-operative consulation	Not reported	Not reported	unavailable
Rubio 2020	3 groups of n=45: Group 1: 1ml SA Group 2: 1.5ml SA Group 3: 2ml SA	n=135 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.) *"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"* *"At 6 months follow up, 78.9% of the patients still felt that the skin staining was not a problem.".*

Table 33 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) Registry (Reference No. ISRCTN85167182)	2ml PT	32/32	n=32 Lumpectomy	12 (37.5%) (immediately post op)	Yes (100%) No (0%)	Mean= 6 months Range=3 months to 9 months	*Unavailable.* *No skin discolouration was observed in any of the subjects at 12 months*

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)
Karakatsanis 2019	'Interstitial' Site not specified	n=189	n=129 lumpectomy	Lumpectomy: 42/129 (32.6 %) timepoint not specified No staining in mastectomy group	Not reported	Not reported	unavailable
Wärnberg 2019	5ml RA or PT	n=337 n=177 RA n=163 PT	RA cohort: n=110 lumpectomy In the PT cohort: n=148 lumpectomy	Lumpectomy + RA injn: 74/110 (67.3%) Lumpectomy + PT injn: 56/148 (37.8%) (p <0.001)	Lumpectomy + RA: Yes: 31.3% No: 68.7% Lumpectomy + PT: Yes: 75.1% No: 24.9%	Analysis based upon N = 130 (74+56) patients with skin staining. "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). 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). Analysing 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*
Rubio 2020	3 groups of n=45: Group 1: 1ml SA Group 2: 1.5ml SA Group 3: 2ml SA	n=135 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.) *"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"*

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)
							"At 6 months follow up, 78.9% of the patients still felt that the skin staining was not a problem."

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 retroareolar and peritumoral injections, respectively (p = 0.49). Analysing 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).

MRI SAFETY INFORMATION

The Sentimag is MR Unsafe.

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