Endomagnetics, Inc.

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Magseed Magnetic Marker Localization

A prospective, open label, post marketing study of Magseed and Sentimag in patients undergoing surgical excision of a breast lesion that requires preoperative radiographic localization.

Clinical Investigational Plan Number: US-002
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Version 1.0

Version date: 24th June 2018

Sponsor: Endomagnetics, Inc.

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11 July 2018

Date

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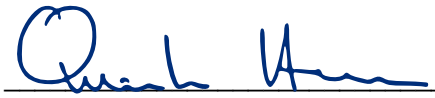

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1 DEFINITIONS

Abbreviation	Definition
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
EDC	Electronic data capture
SAS®	Statistical Analysis System
XML	Extensible markup language

2 STUDY PURPOSE/GOAL

The purpose of this post-marketing study is to provide prospective evidence that the Magseed and Sentimag® is effective for lesion localization in patients undergoing surgical excision of a breast lesion and to summarize measures of product safety and performance.

3 STUDY DESIGN

3.1 STUDY DESIGN OVERVIEW

This is a post-market, prospective, open label, single arm study of Magseed and Sentimag® in patients undergoing surgical excision of a breast lesion.

Eligible subjects have breast lesions requiring excision.

Subjects will have the Magseed marker deployed under imaging guidance up to thirty days prior to surgery.

The Magseed marker will be localized using the Sentimag system during surgery and removed with the lesion.

3.2 DEVICE INTERVENTION

Magseed magnetic marker and Sentimag® surgical guidance system by Endomagnetics, Inc.

3.3 STUDY SUCCESS

The study is not testing a hypothesis and exact 95% confidence intervals will be calculated for the primary endpoint.

3.4 RANDOMIZATION AND TREATMENT MASKING

The study is a non-randomized, single site open label study.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 DATA HANDLING

Magseed Study Data are captured via an Electronic Data Capture System (EDC). Fuel Studio, Inc. is the database development firm responsible for development and management of the EDC system, Clinical Studio. The Clinical Studio database is accessed via an internet connection and a standard web browser. The database is 21CFR Part 11 compliant and all documentation to support the development, specifications and validation of the database is obtained from Fuel Studio, Inc. and maintained in the Project File.

4.1.1 Study Data Collection and Quality Control

All study data are collected by Investigative Site Personnel. The principal investigator will review and approve all study data entered into the database. Data entered into the database are reviewed by the Study Manager for data accuracy, integrity and compliance with the protocol. Data are monitored, per the Monitoring Plan, and other data review include, but is not limited to, the following:

- Missing or ambiguous data
- Missing forms or pages
- Errors in dates
- Protocol deviations
- Adverse device effects
- Device deficiencies
- Inconsistencies
- Alignment with source documentation

4.1.2 Data Queries

The EDC system includes pre-programmed system-generated queries; queries automatically generated by the system after data entry by site personnel, when applicable. Queries may also be created manually by the Magseed Study Manager. Once site personnel address the query, the Study Manager will review the query and determine if the query was addressed adequately. If yes, the Study Manager will resolve / close the query. If not, the query may be re-issued or remain open. All data queries must be resolved / closed prior to analysis of data for decision-making purposes.

4.1.3 Analysis and Closure

Data that will be used for analysis or decision-making purposes will be query-free. Once the designated data are considered query-free and / or “clean”, the Study Manager will request the database or dataset be locked from data entry and a dataset will be generated and exported.

When the study is complete and the final database closure will occur, the Study Manager will ensure the following have been completed:

- Final Subject CRF data are entered into the database
- Data monitoring is completed per the Magseed Monitoring Plan
- All queries are resolved / closed
- The database is closed to data entry

Once the above are designated as complete by the Study Manager, the database will be locked. Datasets will be exported to SAS® using the XML export facility. Imported datasets will be verified against the original database for the first and last patient in each dataset and two additional randomly chosen patients from each dataset.

Upon completion of the clinical study, all study files / data will be provided to Endomagnetics, Inc. for filing / management.

4.2 PRIMARY OBJECTIVE

To provide evidence that the index lesion and Magseed can be successfully retrieved in the initial excised specimen when Magseed and Sentimag® are used as indicated in lumpectomy procedures in patients requiring surgical excision of a breast lesion.

4.3 PRIMARY ENDPOINT

The primary endpoint is the percent retrieval rate of the index lesion and Magseed in the initial excised specimen. This is defined as the number of subjects in whom the index lesion and Magseed are retrieved in the initial excised specimen divided by the total number of subjects undergoing surgery.

4.4 SAFETY ENDPOINTS

Safety will be summarized by reporting rates of device-related adverse events and device-related serious adverse events.

An adverse event is considered **serious** if it meets at least one of the following criteria:

- Led to death
- Led to serious deterioration in the health of the subject that resulted in:
  - A life-threatening illness or injury
  - A permanent impairment of a body structure of a body function
  - In-patient or prolonged hospitalization
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Led to fetal distress, fetal death or a congenital abnormality or birth defect

Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

4.5 OTHER ENDPOINTS

Radiological placement

- Radiologist rated ease of marker placement
- Success rate of Magseed placement (placement accuracy): <5mm to lesion; 5-10mm to lesion; >10 mm to the target.
- Duration of Magseed placement (lesion localization) procedure

Surgical Localization

- Overall re-excision rate
- Re-excision rate necessary to remove the Magseed or targeted lesion
- Surgeon rated ease of localization during surgery
- Duration of lumpectomy procedure

Pathology

- Pathologist rated ease of marker identification and retrieval.
- Positive margin rate (all lesions), see Table 1
- Positive margin rate (cancers), see Table 1

Further surgery (See Table 1)

- Second procedure rate (all lesions)
- Second procedure rate (cancerous lesions)
- Second procedure rate due to localisation device

Table 1 below defines endpoints where a calculation is required:

Endpoint	Definition	Calculation
Positive margin rate (all lesions)	Number of histopathologically positive margins as a proportion of the total number of lesions excised	$= \frac{Positive\ margins}{Total\ lesions\ excised}$
Positive margin rate (cancers)	Number of histopathologically positive margins as a proportion of the total number of cancerous (non-benign) lesions excised*	$= \frac{Positive\ margins}{Total\ cancerous\ lesions\ excised}$
Second procedure rate (all lesions)	Number of second procedures as a proportion of the total number of lesions excised	$= \frac{Second\ procedures}{Total\ lesions\ excised}$

Endpoint	Definition	Calculation
Second procedure rate (cancerous lesions)	Number of second procedures as a proportion of the total number of cancerous (non-benign) lesions excised*	$= \frac{Second\ procedures}{Total\ cancerous\ lesions\ excised}$
Second procedure rate due to localisation device	Number of second procedures necessary to remove the Magseed or the targeted lesion as a proportion of the total number of cancerous (non-benign) lesions excised*	$= \frac{Second\ procs\ to\ remove\ Magseed\ or\ the\ targetted\ lesion}{Total\ cancerous\ lesions\ excised}$

* The total cancerous lesions includes subjects who had cancer but have no residual tumour for example following neo-adjuvant therapy.

5 GENERAL STATISTICAL CONSIDERATIONS

5.1 HYPOTHESIS STATEMENT

Statistical methods are descriptive for this single arm study. Exact 95% confidence intervals will be calculated for the primary endpoint.

5.2 SAMPLE SIZE DETERMINATION

Sample size for this single arm study has been calculated based on the precision of the confidence interval for the primary endpoint, the % retrieval rate. A sample of 100 patients will provide an exact 95% confidence interval[1] with maximum width ±0.092 providing the % retrieval rate is at least 80%. At the anticipated success rate of 90% the confidence interval precision will be ±0.076.

Up to 120 patients will be enrolled to ensure excision data for 100 patients.

5.3 ANALYSIS SETS

All subjects who undergo the lumpectomy with Magseed excision procedure as part of the study will be included in all analyses of safety. Specific endpoints related to Magseed placement and excision will be based on the total number of subjects undergoing the procedure. Protocol violations/deviations will be reviewed prior to analysis and any deemed requiring removal from analysis will be reported with justification.

5.4 POOLING DATA ACROSS CENTERS

This is a single centre study; pooling of data is not necessary.

5.5 SUBJECT DISPOSITION

A detailed description of subject disposition will be provided using a CONSORT diagram and summaries of subjects falling in various subgroups of interest such as: enrolled but

[1] Calculated based on exact confidence intervals using Clopper-Pearson method as expected proportion is high.

not assessed with any study product, discontinued, deaths, withdrawals and study completes. All consented subjects entered in the study will be accounted for in the summary.

5.6 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Baseline CRF data (demographics and breast history) will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables for discrete variables,

5.7 PROCEDURAL DATA SUMMARIES

Procedural CRF data (marker placement and lumpectomy surgery localisation procedure) including the radiologists and surgeons performing the procedures, will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables for discrete variables where appropriate.

5.8 DATA LISTINGS

Full listings will be provided for each section of the CRF (inclusion/exclusion checklist, baseline data, marker placement data, lumpectomy surgery data, pathology data, follow-up/completion data, study exit data, protocol deviations, device observations and device-related adverse events.

5.9 STATISTICAL SOFTWARE

The statistical software package SAS® 9.4 or later version will be used for all the data derivations, summarization, data listings, and statistical analyses.

6 ANALYSIS OF PRIMARY ENDPOINT

6.1 PRIMARY ANALYSIS

Statistical methods are descriptive for this single arm study. The % retrieval rate and exact 95% confidence intervals (Clopper-Pearson) will be calculated for the primary endpoint.

A summary of retrieval failures and reasons will also be reported.

6.1.1 Handling of Missing Data

The products being evaluated in this study are designed to help physicians localize lesions during surgery for breast cancer or excision of other breast lesions. All required information can be obtained during the lumpectomy procedure and missing data for the primary endpoint are not expected to be a concern nor affect the scientific soundness of this study.

If there are missing data (i.e. data for Magseed has not been recorded or has been lost), the primary analysis will assume failure to retrieve. If there are sufficient patients with

missing data then a sensitivity analysis will be carried out with missing data assumed instead to have a magnetic marker detected and retrieved. No other imputations for missing data are planned.

6.2 SUBGROUP ANALYSES

No subgroup analyses are planned. Analyses by gender will not be performed as most subjects are expected to be female.

7 ANALYSIS OF SAFETY

Safety will be summarized by reporting the rates of device-related adverse events and device-related serious adverse events. Events with undetermined relationship will be considered 'related' for the purposes of safety data summarization and reporting.

7.1 ANALYSIS OF ADVERSE EVENTS

Rates of device-related serious adverse events and adverse events will be reported. Any unanticipated adverse device effects (UADEs) will be listed and summarized as appropriate. No formal tests of hypotheses are proposed for the safety endpoints.

8 ANALYSIS OF OTHER ENDPOINTS

Endpoints described in Section 4.5 will be summarized descriptively. For continuous data, means, 95% confidence intervals, medians, standard deviations, sample sizes, minimums, and maximums will be displayed. For binary or categorical data proportions and 95% confidence intervals where applicable will be summarized. Exact confidence intervals will be used where required.

No formal tests of hypotheses are proposed for the other endpoints. Statistical comparisons may be performed for exploratory purposes. No adjustment for multiple comparisons will be made.

9 FURTHER ANALYSES

Further descriptive analyses will be used to look at the timing of surgery. The duration between admission and procedure start for subjects first on the list will be summarized as a continuous variable. The number and cumulative proportion of procedures starting before a given time (8am, 9am, 10am, 11am) will be reported.