FILM-B (Fluorescence Imaging Lymphatic Mapping – Breast)

Clinical Trial Registry Number: NCT03200704

KEY POINTS

Study design: FILM-B is a Level III-2 prospective, open-label, non-inferiority within-subject comparison study of the SPY Portable Handheld Imaging System (SPY-PHI) and SPY AGENT GREEN (indocyanine green for injection, USP) to Technetium-99m (Tc99m) and gamma probe conducted at seven sites in the United States and Canada.

Purpose: To evaluate the safety and effectiveness of SPY-PHI and SPY AGENT GREEN as an intraoperative fluorescence visualization tool in the identification of lymph nodes (LNs) and vessels during lymphatic mapping and sentinel lymph node biopsy (SLNB) procedures in subjects with early-stage breast cancer.

Hypothesis: SPY-PHI and SPY AGENT GREEN would be non-inferior to Tc99m and gamma probe.

Methods: All subjects received an injection of Tc99m either the day before or the morning of surgery and a one-time set of two intradermal peri-areolar injections of 0.05 mL SPY AGENT GREEN (2.5 mg/mL solution; total of 0.25 mg) into the index breast while in the operating room under anesthesia at the start of surgery prior to the SLNB procedure. Two types of Tc99m were used: Tc99m tilmanocept and Tc99m sulfur colloid. Mapping was performed with SPY-PHI, followed by use of the gamma probe. A small number of subjects where lymphatic vessels were occluded or damaged received an additional alternative injection of SPY AGENT GREEN peri-tumorally (three 0.05 mL injections; total of 0.375 mg).

Inclusion	Exclusion criteria
• Age ≥ 18 years	• Known allergy to ICG, iodine, or iodine dyes
• Stage 0 Ductal Carcinoma in Situ (DCIS), IA, IB or IIA undergoing SLNB	• Prior axillary surgery or ipsilateral radiation in the breast(s) planned for this procedure
• Clinically negative nodal status (N0)	• Stage IIB, III or IV
• Negative metastatic involvement (M0)	• Pregnant or lactating
• Subjects of child-bearing potential, must not have been pregnant or lactating and must have had a negative pregnancy test at Baseline	• Participated in another investigational study within 30 days prior to surgery
• Provide informed consent and comply with the protocol	• Any medical condition which in the investigator's opinion would make the subject a poor candidate.

Primary objective:

- To assess the effectiveness of SPY-PHI and SPY AGENT GREEN in the identification of histology-confirmed LNs by determining the proportion of histology-confirmed LNs identified by SPY-PHI and SPY AGENT GREEN compared to the proportion of histology-confirmed LNs identified with Tc99m and gamma probe.

Secondary objectives:

- To evaluate the effectiveness of SPY-PHI and SPY AGENT GREEN and Tc99m and gamma probe in the identification of at least one histology-confirmed LN per subject.
- To evaluate the effectiveness of SPY-PHI and SPY AGENT GREEN as an intraoperative visualization tool in delineation and mapping of lymphatic vessels in the identification of histology-confirmed LNs.
- To confirm the safety of intradermal injection of SPY AGENT GREEN in intraoperative delineation of mapping lymphatic vessels and identification of LNs.

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Results:

Study Population: 153 subjects were screened, 152 subjects were enrolled, and 151 subjects completed the study.

- Five subjects received the alternate injection of SPY AGENT GREEN, and three of these subjects were excluded from the analysis as mapping/SLNB was unsuccessful and they received a full axillary lymph node dissection.
- Therefore, 148 patients (406 lymph nodes) were analyzed and included in the Per-Protocol (PP) and Modified Intent-to-Treat (mITT) populations.
  a. PP population: All subjects that met all the eligibility criteria, received the full dose of tracer/dye, successfully completed the mapping procedure (i.e., had at least one LN detected in-vivo by SPY-PHI and SPY AGENT GREEN or by Tc99m and gamma probe, or had a LN deemed clinically suspicious), and had histology-confirmed LNs.
  b. mITT population: Subjects who received at least one injection of SPY AGENT GREEN, excluding subjects with failed mapping (i.e., received an axillary lymph node dissection) and subjects without histology-confirmed LNs.

Efficacy results: Both the primary and secondary efficacy endpoints were met.

- Primary endpoint:
  a. SPY-PHI and SPY AGENT GREEN identified 89% (360/406; 95% CI, 85%-91%) and Tc99m and gamma probe identified 66%(266/406; 95% CI, 61%-70%) of histology-confirmed lymph nodes in both the PP and mITT populations.
    i. The results show that SPY-PHI and SPY AGENT GREEN is statistically non-inferior to Tc99m and gamma probe (prevalence difference 24.2%; 95% CI, 19%-30%; $p<0.0001$).
- Secondary endpoints:
  a. The per subject LN identification rate for SPY-PHI and SPY AGENT GREEN and for Tc99m and gamma probe was 98% (145/148; 95% CI, 94%-99%) of subjects in both the PP and mITT populations.
  b. Lymphatic vessel mapping with SPY-PHI and SPY AGENT GREEN aided in visualizing 99% (357/360) of the LNs identified by SPY-PHI and SPY AGENT GREEN.

Safety results: The safety outcome was met; the safety of intradermal injection of SPY AGENT GREEN was confirmed. Of the 151 subjects in the safety population, 27 subjects experienced 38 Adverse Events. Of these, 6 were Serious Adverse Events, none of which were related to SPY-PHI or SPY AGENT GREEN. Three events (all mild) in three subjects were suspected to be related to SPY AGENT GREEN, and included skin discoloration, injection site discoloration, and skin necrosis secondary to nipple sparing mastectomy procedure.

Conclusion: The results demonstrate that SPY-PHI and SPY AGENT GREEN is non-inferior to Tc99m and gamma probe in the identification of LNs and vessels during lymphatic mapping and SLNB procedures in subjects with early-stage breast cancer.

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