SILIMED GEL-FILLED MAMMARY IMPLANT

CLINICAL STUDY PROTOCOL:

[redacted]

[redacted]

Current Study Sponsor: Sientra, Inc.
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[redacted]

Study Product: Silimed Gel-Filled Mammary Implant

[redacted]

CONFIDENTIAL

[redacted]

[redacted]

[redacted]

[redacted]

LIST OF ABBREVIATIONS

AE	Adverse Event
CA	Continued Access
CORE	Core Clinical Investigation
CTD	Connective Tissue Disease
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
PMA	Premarket Approval
QOL	Quality-of-Life
SEM	Standard of Measurement
UADE	Unanticipated Adverse Device Effect

1. INTRODUCTION

This document is a protocol for a human research study. This prospective clinical study is designed to document the safety and effectiveness of the Silimed Gel-Filled Mammary Implant (also referred to in this document as the "Implant" or "Implants") as indicated for primary augmentation, primary reconstruction, and/or revision of the female breast. [redacted]

1.1. Silimed Gel-Filled Mammary Implant

[redacted]. The shell is filled with a proprietary silicone gel. The implants are either round or contoured in shape and are available in a range of diameters, profiles (projections), and sizes. The Implants have either smooth or textured shell surfaces.

1.2. Study Overview

Surgical implantation of the Implant is indicated for primary augmentation, primary reconstruction, and/or revision of the female breast. Approximately 1,000 subjects will participate in the Core Clinical Investigation ("CORE Study"). Subjects will be recruited through numerous investigational sites by Investigators throughout the United States. [redacted]

[redacted]

2. STUDY OBJECTIVES

The purpose of the CORE Study is to demonstrate the safety and effectiveness of the Implants as indicated for primary augmentation, primary reconstruction, and/or revision of the female breast.

3. STUDY DESIGN

[redacted]

3.1. Overview of the CORE Clinical Investigation

The CORE study is an open-label, multicenter, prospective clinical investigation designed to evaluate the safety and effectiveness of the Silimed Gel-Filled Mammary Implants. These Implants are indicated for unilateral or bilateral primary augmentation, primary reconstruction, and/or revision of the female breast. This study will enroll approximately 1,000 subjects at 50 primary sites, with approximately 40 subjects per site. [redacted]

[redacted] An agreement with each Investigator will specifically outline the number and type of implant subjects that she/he will enroll. The differences in enrollment mix per Investigator will be based upon the last annual surgical history of the Investigator (e.g., certain sites may specialize in augmentation, reconstruction, or revision). Subjects will be followed for a minimum of 10 years following placement of mammary implant(s).

[redacted]

[redacted]

3.2. Control Group and Randomization Considerations in the CORE Study

In this study, subjects act as their own controls. There are practical implications and limitations to randomization in a study involving a medical device that creates an aesthetic result. If randomization is used to select the style of the implant or manufacturer of the implant for each subject, instead of allowing the Investigator and subject to determine the appropriate choice, a less than optimal outcome may result. Randomization to assign a particular implant to a subject may have a significant negative effect on the outcome of the procedure if the shape/style of the implant is not appropriate for a particular body structure or the subject's preference.

The data obtained at baseline on each subject will be used as the control data. Information from each subject will provide control (baseline) data for physical status, cancer history and status, rheumatologic history and status, medical history and status, and connective tissue history and status. Any changes noted by the physician or reported by the subject in any of these areas will be recorded.

[redacted]

[redacted]

3.3. Study Design and Outcome Measures

All subjects will be screened for eligibility and informed consent will be obtained prior to enrollment in the study. Each subject will be evaluated preoperatively to document baseline status. All subjects will complete the QOL questionnaire. Photographs will be taken during the preoperative visit with additional photographs taken at the 1-year postoperative follow-up visit.

Details of each surgical procedure will be recorded immediately, postoperatively. Subjects are considered study participants once their Implant(s) has/have been placed. Following placement of the Implant, subjects will present for follow-up office visits at 6-10 weeks, 12 months, 24 months, and annually for the remaining 8 years. [redacted]

All secondary treatments and procedures related to the breast, including explant surgery without replacement, will be recorded. Photographs will also be taken prior to and following (6-12 months) any secondary treatment or procedure considered remedial in nature.

All patients will be directed to see a physician if they believe they have a ruptured implant, and these patients will undergo a magnetic resonance imaging (MRI) scan.

Safety of the Implants will be assessed by examining the incidence, severity, method of resolution, and duration for all complications on a per-implant and per-patient basis.

[redacted]

3.4. Safety Endpoints

As stated above, assessment of the safety of the Implants will be based on incidence, severity, method of resolution, and duration for all complications on a per-implant and per-patient basis. The rate of asymptomatic or "silent" rupture will be assessed via MRI at regular intervals in a subset of subjects from the CORE study. Other potential complications of the mammary implant surgery include possible systemic effects (e.g., autoimmune and/or rheumatologic effects) and interference with radiological detection of breast cancer in remaining breast tissues. Safety assessments are described in more detail in the sections that follow.

[redacted]

[redacted]

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[redacted]

[redacted]

[redacted]

3.5. Effectiveness Endpoints

[redacted]

This assessment will incorporate the effects of the following: the initial surgical procedure, adjunctive surgical and medical procedures, complications, and whether the expected benefits of the procedure and the implants have been met. Subject satisfaction data will be

acquired to assess the effects of device explantation, regardless of whether or not the device is replaced.

[redacted]

4. SUBJECT SELECTION AND WITHDRAWAL

4.1. Inclusion Criteria

Subjects are admitted into the study only if all of the following eligibility is true:

1. Female
2. Age limitation specific to the indication:
    - Primary Augmentation: Must be 18 years or older
    - Primary Reconstruction: No age limit
    - Revision: If original surgery was primary reconstruction, then no age limit. If original surgery was primary augmentation, then must be 18 years or older.
3. Adequate tissue available to cover implant(s)
4. Willingness to follow study requirements (informed consent form, follow-up visits)
5. Candidate for primary augmentation, primary reconstruction, or revision [redacted]

[redacted]

[redacted]

4.2. Exclusion Criteria

Subjects are not eligible if any of the following criteria exist:

1. Advanced fibrocystic disease, considered to be pre-malignant without mastectomy
2. Inadequate or unsuitable tissue [redacted]
3. Active infection in the body at the time of surgery
4. Pregnant or lactating
5. Medical condition such as obesity, diabetes, autoimmune disease, chronic lung or severe cardiovascular disease that might result in unduly high surgical risk and/or significant postoperative complications, in the judgment of the Investigator
6. Use of drugs, including any drug that would interfere with blood clotting, that might result in high risk and/or significant postoperative complications
7. Demonstrated psychological characteristics that are unrealistic or unreasonable given the risks involved with the surgical procedure
8. Determination by physical examination that the subject does have any connective tissue/autoimmune disorder, [redacted]

9. Existing carcinoma of the breast without accompanying mastectomy
10. MRI scan is prohibited because of implanted metal device, claustrophobia, or other condition.

4.2.1. Subject Recruiting and Screening

All subjects meeting eligibility requirements that sign an informed consent form and undergo a mammary implantation procedure with a Silimed Gel Filled Mammary Implant are considered study subjects.

4.2.2. Data Collection and Follow-up of Withdrawn Subjects

Subjects are allowed to withdraw from the study at any time and for any reason. Any study subject who misses a scheduled study appointment will be contacted as soon as possible and rescheduled. If a subject does not wish to continue in the study, or if her mammary implant(s) is/are explanted without study implant replacement(s), a reasonable attempt will be made to schedule and collect early termination data. In the event that a study subject withdraws or is lost to follow up, all data collected to that point will be included in the study report and analyzed.

Subjects are required to complete their protocol study visits in a timely manner. The following is the target evaluation window for each time point.

[redacted]

[redacted]

5. STUDY PROCEDURES

[redacted]

5.1. Preoperative/Initial Visit

1. Subject eligibility will be determined. All subjects considering study participation will be entered into the study logbook. If a subject does not wish to participate in the clinical study, the reason is noted on the enrollment log. Only eligible subjects who agree to participate will be issued log numbers and will complete the remaining steps.

2. Demographic information will be collected.

6. Subject Informed Consent will be obtained. [redacted]

7. A physical exam will be performed. Other diagnostic procedures, such as chest x-ray or electrocardiogram may be performed at the discretion of the Investigator.

8. Medical history, including reproductive history, lactation history, breast screening history, and history of all medications taken within the last 3 months will be recorded.

9. For subjects in the CORE Study [redacted], rheumatologic information will be obtained via the Rheumatology Screening Questionnaire as a baseline measurement prior to implant surgery.

10. Detailed breast cancer data will be collected prior to, or at the same time as enrollment. Investigators will have up to 6 months after subject enrollment to provide specific information.

11. Preoperative surgical information will be recorded, including the specific indications (e.g., reconstruction following mastectomy) for the procedure, as well as the proposed procedure (e.g., mastectomy, implantation of a tissue expander, insertion of a mammary implant).

12. Baseline mammography will be performed, as appropriate. Since some of the subjects participating in this study have a history of breast disease or a concern regarding breast disease (prophylactic mastectomy subjects), and will have or had surgery for this condition, they may or may not be a candidate for mammography. The Investigator must discuss this important issue with the subject. Subjects with one or more remaining breasts, or remaining breast tissue, should have a baseline mammogram prior to surgery. [redacted]

13. Subjects will be asked to complete a confidential questionnaire [redacted]

14. Preoperative photos of the breast/chest area will be taken prior to surgery.

[redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

6. STATISTICAL PLAN

6.1. Sample Size, and Subject Drop-Out Considerations

6.1.1. Sample Size and Power Considerations

A sample size of 1,000 subjects for the CORE study was initially chosen to ensure accurate measures of both the safety and effectiveness of the device. [redacted]

[redacted]

To characterize the safety and effectiveness of the device, the prevalence and cumulative incidence of complications will be examined at each visit for each separate subject cohort and for the total population. [redacted]

[redacted]

[redacted]

[redacted]

6.1.2. Subject Drop-Out and Potential Bias

Subjects may discontinue their participation in this study at any time. While it is not possible to predict the reason for dropouts or loss to follow-up, the Sponsor plans to seek final data from subjects who no longer wish to participate in this clinical trial. [redacted]

[redacted]

6.1.3. General Statistical Methods: Hierarchical Models

The data will be analyzed using hierarchical models. Hierarchical models account for correlation in the data (e.g., within sites) by explicitly modeling each "level" of variability. Hierarchical models, also called random effects, mixed, or multilevel models, are well established for continuous measures (Rao 1965, Laird and Ware 1982), binary responses (e.g. Stiratelli et al. 1984, Zeger and Karim 1991), and count data (Lee 1997). Hierarchical models provide an estimate of the population average effect by combining information across individuals, while taking into account correlation within sites. [redacted]

[redacted]

6.1.4. Analysis of Complications

Incidence rates and time course evaluations for complications will be presented using survival analysis. These analyses will be done on both a per-subject and a per-device basis, for each subject cohort and for the total population. [redacted]

6.1.5. Analysis of Effectiveness Measures

The change in QOL measures will be estimated using mixed models, adjusting for the correlation within subjects over time. QOL variables will be transformed before analysis, if necessary, to meet the normality and homogeneity-of-variance assumptions of the mixed model.

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8.4. Administrative Plan to Minimize Risks

[redacted] Sientra, as the current Sponsor has contracted with an independent CRO to continue monitoring of the Study.

[redacted] Risks to the subject population will be minimized by ensuring that the clinical study will be conducted according to IDE regulations. At study initiation Silimed's monitoring plan specifically outlined the review of Investigator credentials, followed by a review by the IRB. Investigators were to have signed an Investigator's Agreement that requires strict adherence to the protocol.

Silimed had a monitoring policy in place that was to ensure no subject is admitted to the study until the investigative site has received IRB approval. No implant surgery can take place until the subject has signed the informed consent.

The site monitors were provided a site monitoring manual that specified periodic audits of patient screening accountability records and source documentation. The case report forms were to be reviewed by the central monitor to ensure protocol compliance.

[redacted]

[redacted]

8.6. Benefits of Breast Prosthesis

There may be quality of life benefits related to breast augmentation and/or reconstruction with mammary implants. The main purpose of these procedures is to restore the appearance of a woman's breast. It has been reported that breast reconstruction with mammary implants has been beneficial in aiding a patient's recovery from breast cancer and reducing emotional stress by helping to return her body to a more natural appearance.

Each woman has her own sense of how she wishes to look and whether she wishes to undergo surgery to restore or augment her breast(s) to achieve this appearance. A study has shown a high degree of satisfaction following breast implant surgery. The study demonstrated that most of these women had a very positive body image, decreased self-consciousness, and heightened self-confidence; an overwhelming majority said they felt better about themselves after surgery; 86% felt the operation was a complete success and 95% said their expectations were met (Young et al. 1994). Another study that surveyed women after mastectomy for cancer reported they felt more balanced, whole, less depressed and glad they had undergone breast reconstruction (Corsten et al. 1992).

Women entering this study may benefit other women by providing safety and efficacy information about the gel-filled mammary implants, including health problems associated with gel-filled mammary implants.

9. DATA HANDLING AND RECORD KEEPING

9.1. Confidentiality

Information from this study will be provided to the Sponsor; it will also be given to the FDA. It may be given to governmental agencies in other countries where the Study device may be considered for approval. Medical records and photographs that identify subjects and the consent form signed by enrolled subjects will be looked at and/or copied for research or regulatory purposes by:

- the Sponsor
- the Sponsor's Clinical Research Organization.

And may also be looked at and/or copied for research or regulatory purposes by:

- the FDA
- other Department of Health and Human Services (DHHS) agencies;
- Government agencies in other countries
- the applicable Institutional Review Board(s)

Confidentiality will be protected as much as possible throughout this study. Medical records may be accessed by the Sponsor's research personnel and reviewed as required by the FDA. Results of data collected will be reported as statistical information only.

The subject's unique identification number will be listed on all clinical study records, including clinical study case report forms and QOL questionnaires.

The possibility exists that clinical records could be obtained by Congress or by a court order. Every effort will be taken by the Sponsor to keep this information confidential. Under certain circumstances this could mean public disclosure of subject surgeries and subsequent loss of subject confidentiality.

9.2. Case Report Forms

CRFs will be completed on all study participants based on the type of visit scheduled. [redacted]

[redacted]

[redacted]

[redacted]

10. STUDY MONITORING

[redacted]

The Medical Monitor's responsibilities include review of the investigational plan, review of adverse reactions or unanticipated adverse device effects, and interpretation of clinical results. The Medical Monitor is qualified by training and qualifications to perform the duties as such.

[redacted]

11. INVESTIGATOR RESPONSIBILITIES AND RECORDS

Investigators selected by the Sponsor will be either board-certified plastic surgeons, surgeons certified in augmentation or reconstruction, or both. The Investigators must also have demonstrated that their facility has the ability to provide the required support personnel to meet the study's objectives.

11.1. Investigator's Responsibilities

Each Investigator must follow the Investigator Agreement [redacted] the investigational plan, and all conditions of IRB approval. A signed Investigator Agreement and written confirmation of IRB approval must be provided to the Sponsor by the Investigator prior to subject enrollment and the start of the study.

The Investigator shall make known to the subjects the nature, expected duration, and purpose of the study, the administration and potential risks of treatment, and available alternative therapy.

Subjects will be informed that their medical records will be subject to review by the Sponsor and its representatives, the Institutional Review Board(s), and the FDA. The subjects shall be informed that they are free to refuse participation in this clinical investigation, and if they participate, that they may withdraw from the study at any time without prejudicing future medical care. Signed Research Subject Information and Consent Forms must be obtained

prior to surgery. The original will be kept by the Investigator and will be reviewed by the Sponsor or its CRO. A copy of the signed informed consent will be given to the subject.

11.2. Investigator Records

Investigators will maintain complete, accurate and current study records, including the following material:

- Correspondence with the Sponsor, the FDA, the IRB, and other Investigators
- Subject records, including Informed Consent documents, copies of Case Report Forms and any supporting documents (e.g., diagnostic reports) and registry enrollment
- Study protocol with dates and reason for deviations that may affect the scientific quality of the study
- Copies of unanticipated adverse device reports

[redacted]

[redacted]

11.4. Protocol Deviations

Deviations from the protocol that may affect the scientific quality of the study or the rights, safety, or welfare of the subjects require prior approval of the Sponsor and the IRB. If deviations are required to protect the subject, the Investigator will notify the Sponsor and the Investigator's IRB within 5 working days that such a deviation has occurred.

11.5. Research Subject Study Packet or IRB Replacement Packet

The Sponsor will provide site specific Research Subject Study Packets to each Investigator to give to the subject during their pre-operative screening visit. This includes, but may not be limited to the following information:

- A sample of the Subject Informed Consent (Research Subject Information and Consent Form)/Incentive Program Table
- Experimental Subject's Bill of Rights

[redacted]

11.7. Informed Consent

Informed consent must be obtained from all subjects to permit their study participation. The consent form must be signed by the subject. [redacted]

11.8. Institutional Review Board (IRB)

The clinical study of the Implants may not begin at any site until Institutional Review Board (IRB) approval is obtained.

Investigators will provide accurate, complete, and current information to their IRB whenever necessary.

Deviations from the protocol that may affect the scientific quality of the study, or the rights, safety, or welfare of the subjects require prior approval of the IRB.

Investigators will report to the Sponsor immediately if, for any reason, their IRB withdraws approval to conduct the investigation. The report will include a complete description of the reason approval was withdrawn.

12. STUDY FINANCES

12.1. Funding Source

Funding for this research study will be provided by the Sponsor.

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