

P020056/S8/A2/C2



FDA CDRH DMC

October 24, 2008

OCT 27 2008

Food and Drug Administration  
Center for Devices and Radiological Health  
PMA Document Mail Center (HFZ-401)  
9200 Corporate Boulevard  
Rockville, MD 20850

Received

**Re: Changes to Post-Approval Study – Reduction of Number of Subjects in Saline Cohort  
PMA P020056/S8/A1  
Natrell® Silicone-Filled Breast Implants**

Dear PMA Staff,

Allergan hereby submits this PMA Supplement to seek approval for changes to the post-approval study for silicone-filled breast implants. Specifically, to reduce the number of subjects in the Saline Breast Implant Cohort of Mentor’s Silicone Gel Breast Implant Follow-up Study (BIFS).

The existence of this PMA submission and the information it contains are considered by Allergan to be confidential. Therefore, the protection afforded to confidential information by all applicable laws including, but not limited to 18 USC 1905, 21 USC 331(j), and 5 USC 552 is hereby claimed.

If you have any questions regarding this submission, please do not hesitate to contact me via telephone at 805-961-5587 or via email at [carrier\\_eric@allergan.com](mailto:carrier_eric@allergan.com).

Sincerely,

Eric Carrier  
Manager, Regulatory Affairs  
Allergan Medical

Enclosures: Three copies

**1. TITLE PAGE**

**BREAST IMPLANT FOLLOW-UP STUDY  
(BIFS)**

|                                   |   |
|-----------------------------------|---|
| <b>PROTOCOL TITLE:</b>            | Breast Implant Follow-up Study: A 10-year Observational Study of the Safety of Allergan Silicone Gel-filled Breast Implants as Compared Both to Saline-Filled Breast Implants and to National Norms |
| <b>PROTOCOL NUMBER:</b>           | BIFS-001  |
| <b>SPONSOR:</b>                   | Allergan  |
| <b>IDE NUMBER:</b>                |   |
| <b>DATE (VERSION):</b>            | September 8, 2008 (version 3.0)   |
| <b>SPONSOR'S MEDICAL OFFICER:</b> |   |

## 2. STUDY CONTACT INFORMATION

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### 3. SYNOPSIS

|  |
|--|
| <p><b>Title of the Protocol: Breast Implant Follow-up Study (BIFS) :</b> A 10-year Observational Study of the Safety of Allergan Silicone Gel-filled Breast Implants as Compared Both to Saline-filled Breast Implants and to National Norms</p>   |
| <p><b>Investigators/Study Centers:</b> Approximately 1,600 study sites will participate in the study.</p>  |
| <p><b>Objectives:</b> The objectives of the study are to compare Allergan silicone breast implants with saline implants or national norms in regard to</p> <ol style="list-style-type: none"><li>1. Long-term safety<ul style="list-style-type: none"><li>• Connective Tissue Diseases (CTD)</li><li>• Rheumatologic signs and symptoms</li><li>• Neurological diseases</li><li>• Cancer (brain, lung, breast, and cervical/vulvar)</li><li>• Suicide or attempted suicide</li><li>• Local complications and the need for reoperations</li></ul></li><li>2. Reproduction, pregnancy outcomes, and lactation<ul style="list-style-type: none"><li>• Pregnancy outcomes</li><li>• Problems related to lactation in subjects who attempted to breastfeed</li><li>• Targeted AEs occurring in offspring</li></ul></li><li>3. Effects on mammography<ul style="list-style-type: none"><li>• Detection of breast cancer</li><li>• Rate of rupture</li></ul></li><li>4. Effects on satisfaction with breasts and quality of life</li><li>5. Compliance with MRI recommendations<ul style="list-style-type: none"><li>• Rupture rate associated with MRI</li></ul></li></ol> |
| <p><b>Statement of Hypothesis to be Tested:</b> The null hypotheses are differentiated based on the rate of safety outcomes in the general population (national norms). For very rare events, the null hypothesis is that women who choose silicone breast implants are no more likely than women in the general population to experience the Target AEs. Tests will be performed at the 0.05 level of significance. For less rare Target AEs, the null hypothesis is that there is no difference in rate between women choosing silicone gel-filled breast implants and women choosing saline-filled breast implants. The comparison of silicone-filled implants and saline-filled implants will also be made for very rare events, but the study is not powered for these comparisons. In each case, the corresponding 2-sided alternative hypothesis is that the rate in the silicone group differs from the rate in the comparator group (national norms or the saline group, depending on the test). Tests will be performed at the 0.10 level of significance in order to reduce the probability of failing to detect a notable safety issue.</p>              |
| <p><b>Planned Sample Size:</b> The study will enroll approximately 54,630 subjects (39,390 subjects with silicone gel-filled breast implants and 15,240 subjects with saline-filled breast implants). Each subject will be followed for 10 years.</p>  |

**Study Design:** BIFS is an observational study comparing targeted safety outcomes of subjects who have received 1 or 2 Allergan silicone-filled breast implants to those of a control group. For adverse events (AEs) occurring between 2.85 per 100,000 person years and 1.2 per 10,000 person-years, national norms will serve as control. For these and other Target AEs, the silicone group will also be compared to subjects who elect to receive 1 or 2 saline-filled breast implants. Data will be collected from the investigator to describe the surgical procedure. Each enrolled subject will provide health information at baseline and by responding to an annual questionnaire for 10 years. Additionally, all silicone implant subjects will return to their surgeons (the Investigators) at years 1, 4, and 10 for a physical exam. Based on these exams, the Investigators will report all local complications. A primary focus of that physical exam will be to evaluate the complications of silicone breast implants. AEs and local complications can also be reported spontaneously throughout the study by the subject or her physician.

**Diagnosis and Key Subject Selection Criteria:** Subjects who have received Allergan silicone breast implants or saline implants will be eligible to participate in the study.

**Inclusion Screening Criteria:**

Subjects must meet all of the following inclusion criteria at the time of surgery:

1. Female, age 18 years or older (age 22 or older for breast augmentation patients)
2. Fluency and literacy in English or Spanish

**Exclusion Screening Criteria:**

Subjects who meet any of the following criteria are not eligible for enrollment in the study:

1. Are transgender
2. If a saline implant patient, have a current or past unilateral or bilateral silicone breast implant
3. Investigator decision that patient is not a suitable candidate for a long-term observational study

**Enrollment Criteria:**

Subjects can be enrolled in the study if they meet all the following enrollment criteria:

1. Have satisfied all the inclusion/exclusion criteria
2. Have completed the surgery
3. Have only one breast implant or have matching breast implants (i.e., either both silicone or both saline) following their qualifying surgery. In the case of silicone the implant(s) must be Allergan.
4. Have signed the informed consent form, documenting agreement to participate in all required follow-up interviews by internet, phone or mail, and authorizing health care providers to release medical records to study personnel and have completed the baseline questionnaire.

**Treatments:** No treatments will be administered by this observational study. The decision to receive a breast implant is made by the patient and her surgeon independent of, and prior to, enrollment into BIFS.

**Criteria for Evaluation:**

**Effectiveness:** Quality of life and satisfaction with breasts will be assessed at baseline, and at years 1, 4, and 10.

**Safety:**

1. Subject self-report of
  - Signs and symptoms and new diagnoses of Target AEs by selecting from itemized lists
  - Complications of implants (i.e., infection, breast pain, capsular contracture, rupture, removal and reoperation)
2. Investigator reports of physical exam results (i.e., local complications) at years 1, 4, and 10 for silicone subjects
3. Spontaneous AE reports
4. Deaths
5. Reproductive outcomes
  - Pregnancy outcomes
  - Problems with lactation
6. Effect of implant on mammography and diagnosis of breast cancer
7. Compliance with MRI recommendations

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## 5. ABBREVIATIONS

|      |   |
|------|---|
| AE   | Adverse Event                             |
| BIFS | Breast Implant Follow-up Study            |
| CRF  | Case Report Form                          |
| CTD  | Connective Tissue Disease                 |
| DSMB | Data and Safety Monitoring Board          |
| EDC  | Electronic Data Capture                   |
| FDA  | Food and Drug Administration              |
| GCP  | Good Clinical Practice                    |
| ICH  | International Conference on Harmonization |
| IRB  | Institutional Review Board                |
| MRI  | Magnetic Resonance Imaging                |

## 6. BACKGROUND INFORMATION

On September 21, 2005, the U.S. Food and Drug Administration (FDA) issued an approvable letter to Inamed (now Allergan) for its premarket application for silicone-filled breast implants. This letter was issued in the context of a long-standing debate between individuals influenced by anecdotal evidence of potential safety concerns and those influenced by the scientific evidence suggesting no significant safety concerns. This debate culminated in the April 2005 meeting of the FDA's General and Plastic Surgery Devices Advisory Panel meeting. A multitude of experts and other interested parties testified on both sides of that debate.

During the Advisory Panel meeting, Inamed presented 4-year, interim clinical trial data from its 10-year uncontrolled Core Study. The Core Study examined rates of diseases, signs and symptoms of targeted diseases, and complications for all subjects. It also evaluated magnetic resonance imaging (MRI) data for possible rupture. Data revealed no noteworthy signal of connective tissue disease (CTD) or cancer, beyond that expected in the general population. In addition, benefits were notable both in breast size change and in the subjects' satisfaction with their implants: at least 85% of subjects in each indication reported being satisfied with their implants at the 4-year follow-up.

In response to public concerns and issues raised by the Advisory Panel, the FDA requested that Allergan perform a research program that would provide postapproval data on safety concerns. These safety concerns include targeted rare events, complication rates, rates of reoperation, silicone subject follow-up with MRI recommendations to check for silent ruptures, reproductive and lactation problems, and health outcomes in offspring conceived subsequent to implantation.

The Breast Implant Follow-up Study (BIFS) is designed to evaluate the long-term safety and long-term benefit of silicone-filled breast implants.

## 7. STUDY OBJECTIVES AND PURPOSE

The objectives of the study are to compare Allergan silicone breast implants with saline implants or national norms in regard to:

- Long-term safety
  - Connective Tissue Diseases (CTD)
  - Rheumatologic signs and symptoms
  - Neurological diseases
  - Cancer (brain, lung, breast, and cervical/vulvar)
  - Suicide or attempted suicide
  - Local complications and the need for reoperations

Appendix A lists the target diagnoses and the background rates as identified in the published literature.

- Reproduction and lactation

- Pregnancy outcomes
- Problems relating to lactation in subjects who attempt to breastfeed
- Targeted AEs occurring in offspring
- Effects on mammography
  - Detection of breast cancer
  - Rate of rupture
- Effects on satisfaction with breasts and quality of life
- Silicone subject compliance with MRI recommendations
  - Rupture rate associated with MRI

Table 7.1 outlines the specific objectives within each of the categories above, and the specific comparator group for each evaluation.

**Table 7.1 BIFS Study Objectives and Comparator Groups**

|   | <b>Specific Issues to be Addressed</b>   | <b>Comparator*</b>                              |
|---|--|---|
| <b>Long Term Safety</b>   |  |   |
| Connective Tissue Disease (CTD)   | <ul style="list-style-type: none"> <li>• What are the types and rates of CTDs reported by women receiving Allergan silicone breast implants</li> </ul>                             | Saline breast implant cohort and national norms |
| Rheumatologic signs and symptoms  | <ul style="list-style-type: none"> <li>• What are the types and rates of rheumatologic signs and symptoms reported by women receiving Allergan silicone breast implants</li> </ul> | Saline breast implant cohort and national norms |
| Neurological diseases   | <ul style="list-style-type: none"> <li>• What are the types and rates of neurological diseases reported by women receiving Allergan silicone breast implants</li> </ul>            | Saline breast implant cohort and national norms |
| Neurological signs and symptoms   | <ul style="list-style-type: none"> <li>• What are the types and rates of neurological signs and symptoms reported by women receiving Allergan silicone breast implants</li> </ul>  | Saline breast implant cohort and national norms |
| Cancer <ul style="list-style-type: none"> <li>• Brain</li> <li>• Lung</li> <li>• Breast</li> <li>• Cervical/vulvar</li> </ul> | <ul style="list-style-type: none"> <li>• What are the types and rates of cancer reported by women receiving Allergan silicone breast implants</li> </ul>                           | Saline breast implant cohort and national norms |

|                                      | <b>Specific Issues to be Addressed</b>  | <b>Comparator*</b>                              |
|--------------------------------------|---|---|
| Suicide or attempted suicide         | <ul style="list-style-type: none"> <li>• What are the rates of suicide and attempted suicide in women receiving Allergan silicone breast implants</li> </ul>  | Saline breast implant cohort and national norms |
| Local complications and reoperations | <ul style="list-style-type: none"> <li>• What are the Kaplan-Meier complication rates over time, including reoperation and removal rates for women receiving Allergan silicone breast implants?</li> <li>• What are the reasons for reoperation over time?</li> </ul> | Saline breast implant cohort                    |
| Reproduction                         | <ul style="list-style-type: none"> <li>• Of those women with Allergan silicone breast implants who attempt to have children, what are the types and rates of reproductive complications?</li> </ul>   | Saline breast implant cohort and national norms |
| Lactation                            | <ul style="list-style-type: none"> <li>• Of those women with Allergan silicone breast implants who attempt to breastfeed, how many are successful?</li> <li>• What are the reported lactation complications?</li> </ul>   | Saline breast implant cohort and national norms |
| Offspring                            | <ul style="list-style-type: none"> <li>• What are the types and rates of congenital deformities of offspring born to women with Allergan silicone breast implants?</li> </ul>   | Saline breast implant cohort and national norms |
| Effects on mammography               | <ul style="list-style-type: none"> <li>• What is the rate of rupture of Allergan silicone breast implants following mammography?</li> <li>• Do the implants interfere with mammography?</li> </ul>  | Saline breast implant cohort                    |

|                            | <b>Specific Issues to be Addressed</b>   | <b>Comparator*</b>           |
|----------------------------|--|------------------------------|
| MRI compliance and results | <ul style="list-style-type: none"> <li>• What is the rate and frequency of MRI screening for rupture in women with Allergan silicone breast implants?</li> <li>• What are the rupture rates based on MRI results?</li> </ul> | None                         |
| <b>Effectiveness</b>       |  |                              |
| Quality of life            | <ul style="list-style-type: none"> <li>• What is the quality of life over time for women with Allergan silicone breast implants?</li> </ul>  | Saline breast implant cohort |
| Satisfaction with breasts  | <ul style="list-style-type: none"> <li>• What is the satisfaction rate over time for women with Allergan silicone breast implants?</li> </ul>  | Saline breast implant cohort |

\* Sources of national comparator data are noted in Appendix A and in the Reference List. Since the reference rates may change over time, the rates used in the final analysis will be described in the final study report.

## 8. STUDY DESIGN

BIFS is an observational study comparing targeted outcomes of 39,390 subjects who elect to receive 1 or 2 Allergan silicone-filled breast implants to those of a control group of 15,240 women receiving saline implants or to national norms. Each enrolled subject will be followed for 10 years. The study will be conducted in approximately 1,600 sites.

Women will be invited to participate at the time the decision to undergo breast implantation has been made. At that time baseline information will be collected. Sites should endeavor to enroll all consecutive women who meet the study eligibility criteria and receive 1 or 2 Allergan silicone implants or 1 or 2 saline implants. Basic demographic information (without personal identifiers) will also be collected on women who are eligible but who do not participate based on their or their surgeons' decisions.

For adverse events (AEs) occurring between 2.85 per 100,000 person-years and 1.2 per 10,000 person-years, the rates in the silicone group will be compared to established national norms. For these and other targeted AEs, the silicone group will also be compared to subjects who elect to receive 1 or 2 saline-filled breast implants. Similarly, the rates of reproductive failure, lactation, and pregnancy outcomes will be compared to the saline group and to national norms. Appendix A outlines the national datasets used to obtain the comparative national norms. Effects of breast implants on mammography

and compliance with MRI screening in the silicone subject population will also be documented.

After the breast implant surgery is complete, the surgeon will provide data on the procedure. All subjects will complete follow-up questionnaires by internet, phone interview or mail annually for ten years. These annual questionnaires will collect information on the targeted AEs, mammography and MRI experience (silicone subjects only), and pregnancy and lactation. Effectiveness as measured by satisfaction with breasts and quality of life will also be assessed. The subject will be asked to notify the study center regarding any local complications, reoperations, and implant removal that occur between the annual surveys. For subjects with silicone implants, a physical exam will be performed by the investigator at years 1, 4, and 10 to assess local complications. Data on unscheduled medical visits will also be collected for key outcomes. If a subject reports signs and symptoms suggesting a Target AE, she will be encouraged to pursue further evaluation.

## **9. INVESTIGATOR SELECTION AND TRAINING**

Investigators will be selected by Allergan based on the following criteria:

- Valid medical license in good standing
- Experience in breast implant surgery
- Allergan Silicone Certified if implanting Allergan silicone implants

## **10. SELECTION AND WITHDRAWAL OF SUBJECTS**

### **10.1 Inclusion Screening Criteria**

Patients must meet all of the following criteria at the time of implant surgery to be eligible for enrollment into the study:

1. Female,
  - a. age 18 years or older who is a candidate for breast reconstruction (primary or revision) with Allergan silicone implants or saline breast implants (controls)OR
  - b. age 22 or older who is a candidate for breast augmentation (primary or revision) with Allergan silicone implants or saline breast implants (controls)
2. Exhibit fluency and literacy in English or Spanish

## 10.2 Exclusion Screening Criteria

Patients who meet any of the following criteria at or prior to implant surgery are not eligible for enrollment in the study:

1. Are transgender
2. If a saline implant patient, have a current or past unilateral or bilateral silicone breast implant
3. Investigator decision that patient is not a suitable candidate for a long-term observational study

## 10.3 Enrollment Criteria

Patients can be enrolled in the study if they meet all the following enrollment criteria:

1. Have satisfied all the inclusion and none of the exclusion criteria
2. Have completed the surgery
3. Have only one breast implant or have matching breast implants (i.e., either both silicone or both saline) following their qualifying surgery. In the case of silicone the device(s) must be Allergan.
4. Have signed the informed consent form, documenting agreement to participate in all required follow-up interviews by internet, phone or mail, and authorizing health care providers to release medical records to study personnel and have completed the baseline questionnaire.

## 10.4 Patients Who Do Not Enroll in BIFS

Sites are expected to enroll consecutive patients who are undergoing breast implantation with an Allergan silicone breast implant or a saline breast implant. Sites will record basic demographic information on the Non-Enrollment Data Form for all women who are invited but do not participate. Reasons for this lack of participation include:

- Women who decline participation for lack of interest
- Women who fail the enrollment criteria

## 10.5 Subject Recruitment and Tracking

Investigative sites will approach qualified patients and will have interested patients sign informed consent for participation in BIFS.

The enrollment period is expected to be completed within a maximum of 2 years. The Enrollment Plan includes detail on methods of patient enrollment and the proportional balance to be achieved in the study sample with regard to national silicone implantation rates, type of implant and race. BIFS administrators will review these enrollment ratios

on a regular basis and will implement various strategies to regain proper balance when necessary.

## **10.6 Subject Retention, Discontinuation, and Minimizing Loss to Follow-up**

### **10.6.1 Subject Retention**

The study will implement multiple strategies to ensure a high level of annual responsiveness. Strategies may include sending annual reminders prior to the scheduled survey window and after missed windows, utilizing email and postal mail communications, and having useful tools available on the BIFS secure website that will encourage subjects to log in and use the website on a regular basis.

### **10.6.2 Subject Discontinuation and Minimizing Loss to Follow-up**

Subjects may discontinue participation at any time during the study. However, all subjects will be strongly encouraged to continue with the study through their 10-year evaluation period. A subject will be discontinued from the study if:

1. She withdraws consent
2. She is lost to follow-up at 10 years

If a subject is lost to follow-up, she will not be considered discontinued until the end of the ten year follow-up period, even if she has not submitted information for a period of time. Numerous efforts will be made to keep track of lost subjects and to re-establish contact. For instance, contact information (phone and mailing address when email contact is lost) will be used, and medical professionals (e.g., implanting surgeon) as well as other personal contacts will be contacted. Further, internet search services and databases will be employed and Federal and state death records will be reviewed regularly to search for subjects who have been unreachable.

Subjects will not be discontinued from the study if the baseline implants are explanted without replacement or if subsequent revision surgery is required, as long as the revision surgery does not result in a change in the implant type from saline to silicone or from silicone to saline. Subjects will not be discontinued even if the manufacturer or style of replacement implant changes, as long as a saline implant is replaced by a saline implant or a silicone implant is replaced by a silicone implant.

## **10.7 Subject Completion**

The subject completes the study if any of the following occurs:

1. The subject completes the annual questionnaire through 10 years following implantation. Completion of each annual questionnaire is not required for a subject to be considered a completer.

2. The subject has subsequent surgery to remove 1 or both of the qualifying baseline breast implants and replaces it/them with different types of implants (e.g. replacing saline with silicone or vice versa). The subject will complete BIFS at the time of the revision surgery.
3. The subject dies.
4. The study terminates.

## 11. STUDY EVALUATIONS

### 11.1 Schedule of Assessments and Evaluations

Table 11.1 presents a flowchart of study assessments and evaluations.

**Table 11.1 Study Assessments and Evaluations**

| Evaluation/Procedure   | Baseline Screening | Post-surgery   | Subject Annual Questionnaire Years 1-10 | Years 1, 4, & 10 Office Visit (Silicone) | Any Time During the Study, as Needed |
|--|--------------------|----------------|---|--|--------------------------------------|
| Informed Consent <sup>1</sup>                                    | X                  |                |   |  |                                      |
| Inclusion/Exclusion Criteria <sup>1</sup>                        | X                  |                |   |  |                                      |
| Enrollment Criteria <sup>1</sup>                                 |                    | X <sup>2</sup> |   |  |                                      |
| Demographics and Lifestyle <sup>1</sup>                          | X                  |                |   |  |                                      |
| Contact Information <sup>3</sup>                                 | X                  |                |   |  | X                                    |
| Satisfaction with Breasts  |                    |                | 1,4,10                                  |  |                                      |
| Quality of Life  | X                  |                | 1,4,10                                  |  |                                      |
| Medical and Reproductive History <sup>3</sup>                    | X                  |                |   |  |                                      |
| Surgical Summary <sup>1</sup>                                    |                    | X              |   |  |                                      |
| Target Adverse Events and Signs & Symptoms <sup>3</sup>          |                    |                | X                                       |  | X                                    |
| Spontaneous Adverse Event Reports <sup>1,3</sup>                 |                    |                |   |  | X                                    |
| Reproductive and Offspring Events and Complications <sup>3</sup> | X                  |                | X                                       |  |                                      |
| Implant Complications, Ruptures, and Reoperations <sup>3</sup>   |                    |                | X                                       |  |                                      |
| Physical Exam <sup>1</sup>                                       |                    |                |   | X  |                                      |
| Study Completion/Early Termination <sup>4</sup>                  |                    |                |   |  | X                                    |

<sup>1</sup>To be provided by site personnel.

<sup>2</sup>The subject terminates screening and is enrolled in the study when her surgery has been completed. The surgery must have been completed in order to be enrolled in the study; follow-up information will not be collected on persons who elect to cancel surgery or for whom surgery was not completed for any reason.

<sup>3</sup>To be provided by the subject.

<sup>4</sup>Subjects choosing to discontinue from BIFS prior to the tenth annual questionnaire may communicate this choice to the BIFS call center to terminate participation.

## **11.2 Description of Assessments and Evaluations**

### **11.2.1 Baseline Information**

After the decision to undergo breast implantation has been made between the patient and her surgeon, and prior to the surgery, the surgeon or other designated site staff will invite the patient to participate in BIFS, explain all study processes and procedures, answer all questions, and provide an opportunity for review and signing of the Informed Consent and Authorization to Release Medical Records. The subject will then be given the Baseline Questionnaire to complete. All demographic and contact information will be obtained prior to surgery.

#### **11.2.1.1 Demographic and Contact Information**

Subjects will provide general background information including, but not limited to:

- Date of birth
- Race
- Socio-economic status
- Educational level

This study requires that a limited number of individuals from the BIFS team have access to contact information for individual subjects. The subjects will provide their contact information along with the names of 2 individuals outside their household who would be able to help the BIFS team locate the subject. The subject will also be asked to provide her Social Security number so that internet search services and databases and Federal and state death records can be reviewed regularly to search for subjects who have been unreachable. Contact information will be confirmed or updated with each annual questionnaire.

All data collection instruments will be available in both English and Spanish.

#### **11.2.1.2 Effectiveness Assessments**

At baseline, a general measure of psychosocial quality of life and satisfaction with breasts will be administered.

### **11.2.1.3 Medical History**

Subjects will be asked to provide basic medical history and will review a pre-established list of clinical signs and symptoms and Target AEs and indicate if they have ever had a physician make a diagnosis of any of the Target AEs or if they have had any of the signs and symptoms in the 3 months prior to surgery.

The baseline medical history will include information on:

- Connective tissue disease
- Rheumatologic diseases
- Neurological diseases
- Neurological and rheumatological signs and symptoms (with a trigger point encouraging the subject to consult her primary care physician for further evaluation)
- Detailed history of all breast-related disease, surgery, and cancer
- Other cancer, specifically lung, brain and cervix/vulva
- Psychological diagnoses such as suicidality or suicide attempts
- Other risk factors (e.g. smoking, alcohol consumption, etc.)

### **11.2.1.4 Reproductive History**

A reproductive history including all pregnancies and their outcomes and a history of lactation will be collected. Subjects will report congenital anomalies and chronic diseases occurring in children born post the implant surgery.

### **11.2.2 Operative Procedure**

Information about the type of implant (silicone or saline) and indication (augmentation, reconstruction, augmentation revision, reconstruction revision) will be recorded following surgery. Additionally, information about the surgical procedure (e.g., incision site, implant location) will also be documented.

### **11.2.3 Annual Self-Administered Subject Questionnaires**

#### **11.2.3.1 Effectiveness Assessments**

During the annual questionnaires at years 1, 4 and 10, a psychosocial quality of life assessment will be administered. In addition, at these timepoints, subjects will respond to questions designed to assess satisfaction with the breasts and implants.

#### **11.2.3.2 Safety Assessments**

Safety will be evaluated by monitoring diagnoses as well as signs and symptoms of the following Target AEs:

- CTD
- Neurological diseases
- Cancer (breast, lung, brain, and cervical/vulvar)
- Suicides and self-reported suicide attempts

For any post-baseline observation, if a subject responds affirmatively to a diagnosis, she will be asked 1) to indicate whether anyone in her immediate blood family (grandparents, parents, siblings or children) has been diagnosed with the same or a similar illness and 2) to provide contact information for the diagnosing physician.

#### **11.2.3.3 Local Complications**

Key local complications will be collected annually via questionnaire. Information to be collected includes:

- Implant complications
- Rupture
- Reoperations

If the device is explanted during a subject's participation in the study, the investigator will be strongly encouraged to return the device to Allergan for evaluation.

#### **11.2.3.4 Pregnancy, Lactation and Offspring Data**

Pregnancy outcomes will be evaluated through subject self-report (currently pregnant, live birth, miscarriage, stillbirth, ectopic pregnancy and fetal death). Information will also be collected on any congenital anomalies and diseases of offspring conceived after qualifying surgery. The health of all offspring conceived after the qualifying breast implant surgery will be reexamined with each annual questionnaire.

#### **11.2.4 Other Information Collected Annually**

##### **11.2.4.1 Contact Information**

At each annual questionnaire, each subject will also be asked to confirm or update the current contact information for herself and her designated secondary contacts.

##### **11.2.4.2 Mammography and MRI Screening**

Information on any mammography conducted during the previous year, and the results including number of views needed to complete the exam, will be obtained during the annual survey. In addition, in the silicone population, information on any MRI conducted during the previous year will be obtained, including the reason the patient scheduled the screening.

If any rupture or suspected rupture is identified by MRI, the BIFS study center will attempt to collect information to confirm the rupture.

#### **11.2.5 Physical Exam**

For subjects with silicone implants, a physical exam will be conducted at years 1, 4, and 10 to assess local complications.

#### **11.2.6 Unscheduled Reports**

##### **11.2.6.1 Adverse Events**

A primary focus of this safety study is the set of Target AEs. However, for purposes of completeness, subjects and Investigators will have the opportunity to report any troubling AEs contemporaneously, either by means of the BIFS website or by calling the BIFS study center. Subjects and Investigators will be trained to report an AE (an undesirable sign, symptom, or condition) that is new or significantly worsened since their baseline surgery.

The adverse event report will also include event start and stop date, severity, action taken, and outcome. Events that resulted in death will be identified by the investigators and by BIFS study center responsible for investigating death records for subjects who are lost to follow-up.

When signing the BIFS informed consent form, subjects will grant permission for the BIFS study center to contact health-care professionals (oncologists, primary care physicians, specialists) during the study, as necessary, to collect needed information from follow-up visits triggered by subject self-report of Target AEs, signs or symptoms.

#### **11.2.6.2 Subsequent Surgery and Local Complications/New Medical Conditions**

General information about implant complications, rupture and reoperations will be collected both from the subject and from the Investigator at any time using the Report a Subsequent Surgery or Medical Condition (Subject) or Report a Subsequent Surgery or Local Complication (Investigator).

If the device is explanted during a subject's participation in the study, the investigator will be strongly encouraged to return the device to Allergan for evaluation.

#### **11.2.6.3 Mortality**

Deaths reported by physicians will be documented. Additionally, every attempt will be made to ascertain the status of subjects who have not responded to the annual questionnaires. The subject's surgeon/investigator will be contacted. Federal and state death records will be reviewed regularly to search for subjects who have been unreachable. If attempts to reach the subject are unsuccessful, the BIFS study center may communicate with the individuals from the subject's approved contact list to ascertain the subject's status. If a death is reported, the date and city of the death will be collected, if possible, in order to verify the report. When necessary, hospital or other medical records will be obtained to ascertain the cause of death.

## **12. METHODS OF DATA COLLECTION AND MONITORING**

Clinical sites will enter CRF data into the secure, Internet-based electronic data capture (EDC) system on the BIFS website. Whenever possible, subjects will also use this system to enter their own questionnaire data. Subjects who have no access to the Internet can respond to the entire panel of questionnaires via telephone. Trained telephone interviewers will be available for extended business hours to collect data on behalf of the subject. Additionally, paper questionnaires will be sent in the mail if neither the Internet nor the telephone are viable tools for a particular subject. A list of the CRFs is provided in Appendix B.

## **13. STATISTICAL METHODS**

### **13.1 Study Hypotheses**

The null hypotheses are differentiated based on the rate of safety outcomes in the general population (national norms). For very rare events, the null hypothesis is that women who choose silicone breast implants are no more likely than women in the general population to experience the Target AEs. Tests will be performed at the 0.05 level of significance. For less rare Target AEs, the null hypothesis is that there is no difference in rate between women choosing silicone gel-filled breast implants and women choosing saline-filled breast implants. The comparison of silicone-filled implants and saline-filled implants will also be made for very rare events, but the study is not powered for these comparisons. In each case, the corresponding 2-sided alternative hypothesis is that the rate in the silicone group differs from the rate in the comparator group (national norms or the saline group, depending on the test). Tests will be performed at the 0.10 level of significance in order to reduce the probability of failing to detect a notable safety issue.

### **13.2 Sample Size**

The determination of sample size for BIFS is based on 2 objectives. The first objective is to determine whether AEs with incidence rates in the range of 2.85 per 100,000 person-years to <1.2 per 10,000 person-years have an incidence rate in silicone-filled implant subjects that is at least twice as high as in the normative population. To address this objective, sample size for subjects receiving silicone implants was calculated to achieve at least 80% power for a 1-sided test to detect a relative risk of 2 (to 5.70 per 100,000 person-years) for an AE with a baseline incidence rate based on national norms as low as 2.85 per 100,000 person-years. The baseline fixed normal incidence rate of 2.85 per 100,000 person-years was selected to give adequate power for the smallest baseline incidence rate in the range of Target AEs of interest; 2.85 per 100,000 person-years is the normative rate for scleroderma, as provided by the agency.

The appropriate total person years of follow-up needed to address this objective is approximately 317,983 person-years and yields 80% power for the 1-sided test. Calculations were performed using the Fisher's exact test. This study plans to follow each subject for 10 years post implant. The number of subjects depends on the assumed rate of loss to follow-up over 10 years. Based on the minimum acceptable loss to follow-up rate as suggested by the FDA, the overall loss to follow-up rate is assumed to be 35% calculated as a loss of 3.5% of the original cohort per year. Given this rate, the number of subjects in the silicone cohort needed to obtain approximately 317,983 person-years of follow-up is approximately 39,390. The incidence rates of the aforementioned events in silicone-filled subjects will also be compared to the rates in saline-filled implant subjects, although such comparisons will be underpowered and considered secondary relative to the main comparisons in this study.

The second objective for BIFS is to determine whether AEs with incidence rates of at least 1.2 per 10,000 person-years (including local complications, mammography and

lactation issues, and some AEs listed in Appendix A) have an incidence rate in silicone-filled implant subjects that is at least twice as high as in subjects with saline-filled implants. To address this objective, sample size was calculated to achieve at least 80% power for a 1-sided test at the 0.05 level to detect a relative risk of 2.0 (to 2.4 per 10,000 person-years) for an AE with a baseline incidence rate of 1.2 per 10,000 person-years in a cohort that receives silicone implants compared to a control group that receives saline-filled implants. The total number of person-years needed for the control cohort is approximately 124,240. Based on an overall loss to follow-up rate of 35% (with attrition at 3.5% of the original sample per year), the number of control subjects needed to obtain approximately 124,240 person-years of follow-up is approximately 15,240.

### **13.3 Analysis Populations**

#### **13.3.1 Safety Population**

All subjects who are enrolled in this study according to the enrollment criteria will be included in the Safety Populations.

In this study, subjects will be enrolled and will be used as the basis of some statistical summaries. Additionally, some summaries may be based on the individual implants surgically placed into the subjects at the time of enrollment. Assuming that a subject received 2 implants upon enrollment, it is possible for one implant to be removed and replaced while the other implant remains in place. In this event, the explanted device would no longer be enrolled in the study, but the subject and the remaining implant would still be enrolled in the study. However, the subject and the remaining implant would be removed from the study and considered to be completers if the revision surgery used a different type of implant (silicone or saline) from the original implant.

#### **13.3.2 Data and Safety Monitoring Board and FDA Reviews**

The Data and Safety Monitoring Board (DSMB) will consist of 1 statistician, 2 board-certified plastic surgeons who are not otherwise affiliated with the study, and 1 clinical trial ethicist. The mission of the DSMB is to ensure the continuing safety of the study subjects throughout the clinical trial. Secondly, the DSMB will monitor enrollment and follow-up rates and study conduct. Their initial meeting will be organizational and will occur prior to the first visit of the first subject. Meetings will be held periodically to review enrollment, study progress, and interim safety data reports. Throughout the enrollment period, the DSMB will receive quarterly reports with enrollment, follow-up and safety data and, if warranted, will convene a meeting or take other appropriate action to address inadequate progress in achieving enrollment and follow-up goals. These reports will also include clarification of any action that was taken to enhance enrollment overall or for a particular implant group or demographic segment. After the enrollment period is complete, the DSMB will receive annual reports with interim study results, including follow-up rates, prior to the scheduled DSMB meeting.

The FDA will also review study status and study conduct. The primary goals of the FDA reviews will be to confirm 1) that patient enrollment is proceeding satisfactorily; 2) that both implant groups are enrolling at appropriate relative rates; 3) that there is no noteworthy imbalance between the demographic makeup of the study sample and that of the population of women receiving implants; and 4) that follow-up rates are consistent with goals. These reports will also include a description of any action taken to enhance enrollment overall or for a particular demographic segment. Information will be provided to the FDA approximately 3 months following the first visit of the first subject, and quarterly thereafter until such time that the FDA designates a different reporting schedule.

Both the DSMB and the FDA will provide guidance to the BIFS team, if important concerns are identified.

## **14. HUMAN SUBJECTS PROTECTION**

### **14.1 Ethics**

Compliance with GCP guidelines for the conduct and monitoring of this clinical trial will occur through observation of the ethical and regulatory requirements presented in ICH E6, GCP: Consolidated Guideline. By signing this protocol, the investigator agrees to adhere to these requirements. The study (protocol, informed consent, advertisements, subject information sheets, and Investigator credentials) must be reviewed and approved by the IRB. Changes to the protocol will be initiated by the Sponsor and must be approved by the IRB.

The investigators and institutions affiliated with this study will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source documents.

### **14.2 Good Clinical Practice and IRB Review**

BIFS will not begin at any site until the site's Institutional Review Board (IRB) has granted approval. In many cases, sites will use a central IRB for this review process. IRB approval also is required prior to use of any study announcement. Investigators will provide accurate, complete, and current information to the IRB(s) whenever requested or necessary. The investigator is required to provide all active IRBs with updates on study participation on at least an annual basis, depending upon the IRB's requirements.

#### **14.2.1 Informed Consent**

Informed consent must be obtained from each study subject before any study related procedures are performed. When signing the Authorization for Release of Medical Information, subjects will grant permission for the BIFS study center to contact health-

care professionals (oncologists, primary care physicians, specialists) during the study, as necessary, to collect needed information triggered by subject self-report of targeted symptoms or AEs. Informed consent forms will be provided in both English and Spanish.

The following items must be completed:

- The subject must sign and concurrently date the informed consent prior to completing her baseline questionnaire and surgery.
- The investigator or designee (person rendering consent) must sign and concurrently date the informed consent prior to surgery.
- Subjects must be literate in English or Spanish. If a patient is unable to read in either of these languages, then the patient will not be enrolled in the study.
- The original signed and dated informed consent must be kept in the subject's medical chart or in a study file.
- A copy of the signed informed consent must be provided to the subject.
- Any changes to the informed consent must be approved by the Sponsor prior to consenting any study subject using the revised or altered form.

#### **14.2.2 Confidentiality**

Ensuring subject confidentiality is an important component of this study. For internal identification, tracking, and monitoring purposes, subjects' initials and pre-assigned subject identification numbers will be listed on all paper and electronic clinical study records. Special care will be taken to separate an individual's personal identifying information from the data contained in the clinical database. A very limited number of BIFS staff will have access to the data that link subjects to their clinical data.

It will be necessary to communicate with women whose implant status is not public knowledge, possibly even within the context of their own home. The subject will be asked to confirm acceptable modes of communication to ensure the level of confidentiality that she deems fit. Allergan will take exceptional efforts to keep all individuated subject information confidential. However, under certain rare circumstances public disclosure of subject information and subsequent loss of subject confidentiality is possible. For instance, clinical records and information could be obtained by Congress or by a court order.

### **14.3 Disclosure of Data**

Individual subject data will be held in strictest confidence. Results reported from this study will not include any personal identifiers. If data are made available for use by the scientific community, each data record would be de-identified, making it impossible to link data to a particular subject.

## **15. ADMINISTRATION**

Allergan will serve as the Sponsor and will be responsible for clinical trial oversight and guidance.

Allergan or its designee will be responsible for the clinical operations activities. Responsibilities include selecting qualified investigators; ensuring that IRB approvals are obtained and that all participating IRBs and the FDA are promptly informed of significant new information about the study; staffing a clinical call center to keep up with site questions and other needs; conducting monitoring visits on a for-cause basis; ensuring that the proper records are being maintained and that study procedures and all applicable FDA regulations are being followed; verifying quality data; and preparing clinical reports of the results of the study.

### **15.1 Medical Monitor**

The medical monitor's responsibilities include review of the protocol, review of unanticipated adverse device events, and interpretation of clinical results. The medical monitor is qualified by training and experience to perform these duties as described.

### **15.2 Clinical Quality Assurance**

The secure, Internet-based EDC system provides validation checks that are designed to issue an immediate alert when a questionable value has been entered into the system. In this way, the veracity of the initial data entry is enhanced, and subsequent data queries are minimized.

**APPENDIX A: TABLE OF TARGET DIAGNOSES BEING CAPTURED IN BIFS**

This table contains information that has been collected to date regarding normative rates and is illustrative of the approach that is being taken. It is expected that the information will change with time. Changes to this table will be made to reflect changes in the literature. However, rather than amend the protocol to reflect those changes, the final study report will contain the updated information.

| <b>Target Diagnoses</b>   | <b>Rates</b>  |
|---|---|
| <b>Cancer</b>   |   |
| Brain Cancer  | 5.4 per 100,000 women <sup>1</sup>  |
| Breast Cancer (including Paget's disease and malignant nipple neoplasms) <sup>1</sup> | 129.1 per 100,000 women during 2000-2003<br>134.0 per 100,000 for white women<br>118.0 per 100,000 for black women<br>89.0 per 100,000 for Hispanic women <sup>1</sup>  |
| Cervical/vulvar Cancer<br>(from CDC Wonder)   | Cervix Uteri → 11.8 per 100,000 <sup>2</sup><br>Vulvar → 2.4 per 100,000 <sup>2</sup>   |
| Cervix Uteri, age adjusted<br>(from SEER fact sheets) <sup>1</sup>                    | All Races 8.8 per 100,000<br>White 8.5 per 100,000<br>Black 11.5 per 100,000<br>Asian/Pacific Islander 8.2 per 100,000<br>American Indian/<br>Alaska Native+ 7.2 per 100,000<br>Hispanic~ 14.2 per 100,000  |
| Vulva Cancer, age adjusted<br>(from SEER fact sheets) <sup>1</sup>                    | All Races 2.2 per 100,000<br>White 2.3 per 100,000<br>Black 1.9 per 100,000<br>Asian/Pacific Islander 0.8 per 100,000<br>American Indian/<br>Alaska Native+ ^ per 100,000<br>Hispanic~ 1.6 per 100,000  |
| Lung Cancer   | 48.9 per 100,000 women <sup>2</sup><br><br>(from SEER fact sheets) <sup>1</sup><br>All Races 52.3 per 100,000<br>White 54.7 per 100,000<br>Black 53.1 per 100,000<br>Asian/Pacific Islander 27.3 per 100,000<br>American Indian/<br>Alaska Native+ 33.8 per 100,000<br>Hispanic~ 24.0 per 100,000 |

| Target Diagnoses  | Rates  |
|---|--|
| <b>Congenital and Neonatal Anomalies and Diseases<br/>(of offspring born subsequent to implant surgery)</b>   |  |
| Esophageal disorders  | 1.7 per 10,000 live births <sup>3</sup>  |
| Congenital malformations  | 232.6 to 810.2 per 10,000 live births <sup>3</sup>   |
| Pyloric stenosis  | 1 to 3 per 1000;<br>17 per 10,000 live births <sup>3</sup>   |
| Other congenital anomalies and diseases   | Varied   |
| <b>Connective Tissue Disease/Disorders</b><br>Excluded based on genetic causal factors:   |  |
| <ul style="list-style-type: none"> <li>• Larsen's syndrome</li> <li>• Ehlers-Danlos</li> <li>• Marfan Syndrome</li> <li>• Ochronosis (autosomal recessive)</li> </ul> |  |
| Behcet's syndrome<br><br>Behcet's is seen more often in the Middle East than in the United States. Males present with Behcet's more frequently than females.          | International Incidence of Behçet Disease <sup>4, 5, 6</sup><br>*Country Incidence and Prevalence rates per 100,000:<br>Turkey - 80 to 370 prevalence<br>Iran - 16 to 100 incidence <sup>5</sup><br>Iran - 345/60 million prevalence<br>Japan - 13.5 to 20 prevalence<br>Saudi Arabia - 13 to 20 prevalence<br>Germany - 1.6 to 2 prevalence<br>England - 0.64 |
| Chronic fatigue syndrome (CFS)  | 180 per 100,000 persons (95% confidence interval, 0-466 per 100,000 persons) <sup>7</sup><br><br>A study of the Seattle area estimated that CFS affects between 75 and 265 people per 100,000 population <sup>8</sup>  |
| Connective tissue disorder (Not Otherwise Specified)/Undifferentiated connective tissue disorder (UCTD)   |  |
| CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia)  | The incidence of CREST syndrome has not been identified specifically, since this nomenclature is not used consistently. <sup>9</sup>   |
| Cutis laxa  | Rare. Congenital forms are more common than acquired. <sup>10</sup>  |

| Target Diagnoses  | Rates  |
|---|--|
| <b>Connective Tissue Disease/Disorders (cont)</b>         |  |
| Dermatomyositis / Polymyositis                            | 5 to 10 per 1,000,000 <sup>11</sup>  |
| Eosinophilic fasciitis                                    |  |
| Facial hemiatrophy/Romberg disease                        |  |
| Fibromyalgia  | Prevalence is 3.4% of women <sup>12</sup>  |
| Lupus and lupus-like syndrome                             | 1.8 to 7.6 per 100,000<br>5.6 per 100,000 <sup>13</sup><br>2.5 per 100,000 in women <sup>14</sup>  |
| Mixed connective tissue disease                           | Incidence rates are difficult to obtain because of overlapping clinical features with lupus, scleroderma, and polymyositis <sup>15</sup>   |
| Morphoea  | The annual age and sex adjusted incidence rate per 100,000 population was 2.7 (95% confidence interval 2.1, 3.3). The incidence rate increased significantly over the 33 years ( $p = 0.0037$ ) on an average of 3.6% per year. <sup>16, 17</sup><br>3.4 cases per million adults to 2.7 cases per 100,000.<br>Female-to-male ratio of 3-4:1. <sup>18</sup>  |
| Periarteritis   | <b>See POLYARTERITIS NODOSA</b>  |
| Polyarteritis nodosa (PAN)<br>Also known as periarteritis | Incidence is about 0.2 – 0.8 per 100,000.<br>Overall incidence of primary systemic vasculitides (PSVs) involving medium- or small-sized blood vessels [PAN, Wegener's granulomatosis (WG), and Churg-Strauss Syndrome] is around 19.8 per million. 19<br><br>Incidence ranges from 0.7 to 1.8 per 100,000 population. PAN affects men more than women in an approximate ratio of 2:1. 20<br><br>Disease process more commonly occurs in the fourth to seventh decades of life. |

| Target Diagnoses   | Rates   |
|--|---|
| <b>Connective Tissue Disease/Disorders (cont)</b>                |   |
| Polymyalgia rheumatica   | <p>53.7 per 100,000 <sup>21</sup></p> <p>The incidence rate of polymyalgia rheumatica for the population 50 years and older is approximately 3 times higher than that of giant cell arteritis <sup>22</sup></p> <p>In almost 40-50% of the cases it is associated with polymyalgia rheumatica <sup>19</sup></p>   |
| Relapsing polychondritis (RPC)                                   | RPC has an estimated incidence of 3-5 cases/million <sup>23, 24</sup>   |
| Rheumatoid arthritis (RA)  | <p>70 per 100,000 annually. Both incidence and prevalence of rheumatoid arthritis are two to three times greater in women than in men. <sup>25</sup></p> <p>The overall age- and sex-adjusted annual incidence of RA among Rochester, Minnesota, residents &gt; or = 18 years of age was 44.6/100,000 population (95% confidence interval 41.0-48.2 <sup>26</sup></p> |
| <p>Scleroderma (SSc)</p> <p>Also known as Systemic sclerosis</p> | <p>0.2 - 2 per 100,000 <sup>27, 28, 29</sup></p> <p>SSc is a rare disease. The limited form of SSc (lSSc) has a strong female predominance, with a female-to-male ratio of ~10:1.30</p>   |
| Sjogren's syndrome   | <p>Female:Male ~ 9:1, onset around 40-50 years. Incidence 4 per 100,000 <sup>31</sup></p> <p>3.9 per 100,000 population (95% confidence interval, 2.8-4.9) <sup>32</sup></p>  |

| Target Diagnoses   | Rates  |
|--|--|
| <b>Connective Tissue Disease/Disorders (cont)</b>                  |  |
| Temporal Arteritis (Giant cell arteritis (GCA); cranial arteritis) | <p>The incidence rate of GCA for the population 50 years and older ranges from 0.49 to 27 per 100,000 <sup>22</sup></p> <p>The incidence rate of Giant cell arteritis (GCA) for the Icelandic population 50 years and older was 27/100,000 (36/100,000 and 18/100,000 for women and men, respectively) <sup>33</sup></p> <p>In Southern Europe and Israel, the incidence is lower than 12 per 100,000 in the population aged 50 years and older. GCA is uncommon in patients under 50 years of age <sup>19</sup></p> <p>In almost 40-50% of the cases it is associated with polymyalgia rheumatica <sup>19, 34</sup></p> |
| Wegener's granulomatosis   | <p>Wegener's granulomatosis (WG) strikes one in every 30,000 to 50,000 people - has its peak in the 4th or 5th decade of life. M:F ~ 1:1. <sup>35</sup></p> <p>Incidence is about 0.2 to 0.8 per 100,000. Overall incidence of primary systemic vasculitides (PSVs) involving medium- or small-sized blood vessels [PAN, Wegener's granulomatosis (WG), and Churg-Strauss Syndrome] is around 19.8 per million. <sup>19</sup></p>  |
| <b>Neurological Diseases, Signs, and Symptoms</b>                  |  |
| Multiple-sclerosis   | <p>3.6 to 6.2 per 100,000. Studies indicate that incidence rates are fairly stable across specific geographic regions. <sup>36</sup></p> <p>F:M ~ 2:1. Studies from Northern Europe, North America, Southern Australia, and Southern NZ indicate higher incidence rates of &gt; 30 per 100,000. Typical onset of disease occurs between 15 and 50 years of age. <sup>37</sup></p>  |
| Other, to be determined  |  |

| Suicides and Suicide Attempts   | Rates  |
|---------------------------------|--|
| Suicides                        | 3.3 per 100,000 (females only, all races, age adjusted) <sup>38</sup><br>5.35 per 100,000 (females only, all races, age adjusted, see below) <sup>39</sup><br>10.6 per 100,000 <sup>40</sup> |
| Suicide attempts (unsuccessful) | Estimates range from 8 to 25 suicide attempts per every one suicide death. Females report attempting suicide 3 times as often as men. <sup>40</sup>  |

Note: All Target diagnoses with rates between 2.85/100,000 person-years and <1/10,000 will be compared to national norms.

<sup>1</sup> Surveillance Epidemiology and End Results (SEER) by NCI; [www.seer.cancer.gov](http://www.seer.cancer.gov).

<sup>2</sup> Cancer Registry Public Information Data: 1999-2002, WONDER On-line Database. United States Department of Health and Human Services, National Program of Cancer Registries, Centers for Disease Control and Prevention. November 2005.

<sup>3</sup> National Birth Defects Prevention Network; [www.nbdpn.org](http://www.nbdpn.org).

<sup>4</sup> <http://www.emedicine.com/med/topic218.htm>

<sup>5</sup> Kaklamani VG, Vaiopoulos G, Kaklamani PG. *Behcet's Disease*. Semin Arthritis Rheum 1998 Feb;27(4):197-217.

<sup>6</sup> Shimizu T, Ehrlich GE, Inaba G, Hayashi K. *Behcet disease (Behcet syndrome)*. Semin Arthritis Rheum 1997 May;8(4):223-260.

<sup>7</sup> Reyes M, Nisenbaum R, et al. *Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas*. Archives of Internal Medicine 2003;163:1530-6.

<sup>8</sup> <http://www.cdc.gov/ncidod/diseases/cfs/about/demographics.htm>

<sup>9</sup> <http://www.emedicine.com/med/topic88.htm>

<sup>10</sup> <http://www.emedicine.com/med/topic93.htm>

<sup>11</sup> Washington University School of Medicine in St. Louis, MO, Department of Neurology website accessed on May 1, 2005 at [www.neuro.wustl.edu/neuromuscular/alfindex.htm](http://www.neuro.wustl.edu/neuromuscular/alfindex.htm).

<sup>12</sup> Wolfe F, Ross K, Anderson J, et al. *The prevalence and characteristics of fibromyalgia in the general population*. Arthritis & Rheumatism 1995 Jan;38(1):19-28.

<sup>13</sup> Uramoto KM, Michet CJ, Thumboo J, et al. *Trends in the incidence and mortality of systemic lupus erythematosus, 1950 – 1992*. Arthritis Rheum 1999 Jan;42(1):46-50.

<sup>14</sup> Michet CJ, McKenna CH, Elveback LR, et al. *Epidemiology of systemic lupus erythematosus and other connective tissue disease in Rochester, Minnesota, 1950 through 1979*. Mayo Clin Proc. 1985;60:105-13.

<sup>15</sup> Kim P, Grossman JM. *Treatment of mixed connective tissue disease*. [Rheum Dis Clin North Am](http://www.medscape.com/viewarticle/41444). 2005 Aug;31(3):549-65, viii.

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<sup>17</sup> Peterson LS, Nelson AM, Su WP. *Classification of morphea (localized scleroderma)*. Mayo Clin Proc. 1995;70:1068-76.

<sup>18</sup> <http://www.emedicine.com/med/topic3132.htm>

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**APPENDIX B: LIST OF CASE REPORT FORMS****Participant Forms**

- **Baseline Questionnaire**
  - Participant Profile
  - Demographics and Lifestyle
  - Quality of Life & Breast Satisfaction
  - Medical and Reproductive History
  - Signs and Symptoms Checklist
- **Annual Questionnaire**
  - Lifestyle Update
  - Target Adverse Events
  - Reproductive, Offspring & Lactation Events
  - Supplemental Offspring Health Report
  - Implant Complications
  - Assessments of Reoperation
  - Assessments of Implant Removal
  - Signs and Symptoms Checklist
  - Mammogram Experience
- **Quality of Life and Breast Satisfaction Questionnaire**
- **MRI Status Check**
- **Report a Subsequent Surgery or Medical Condition (Participant)**

**Site Forms**

- **Patient Activation**
- **Excluded Patient Data**
- **Surgical Summary**
  - **Revision Surgery Implant Details**
- **Update Contact Information (Investigator)**
- **Investigator Follow-Up Form**

**Call Center Forms**

- **MRI Results**
- **Mammography Results**
- **Completion & Discontinuation Form**