CONFIDENTIAL

The following contains confidential, proprietary information
which is the property of Allergan

Study Title:	Breast Implant Follow-up Study: A Long-term Observational Study of the Safety of Allergan Silicone Gel-filled Breast Implants as Compared Both to Saline-filled Breast Implants and to National Norms
Protocol Number:	BIFS-001 Amendment 5
Protocol Date:	August 21, 2015
Product Name:	NATRELLE® Silicone Gel-filled Breast Implants
Development Phase:	Post-approval
Sponsor:	Allergan, Inc 2525 Dupont Drive Irvine, California 92612 Telephone (714) 246-4500
Manufacturer:	Allergan Medical
Safety Reporting:	Fax: 877 (605)-4524 Email: medical_safety@allergan.com

Names and contact information of Allergan study personnel are provided in the supplementary Study Contacts page.

INVESTIGATOR SIGNATURE PAGE

Study Title: Breast Implant Follow-up Study: A Long-term Observational Study of the Safety of Allergan Silicone Gel-filled Breast Implants as Compared Both to Saline-filled Breast Implants and to National Norms

Protocol Number: BIFS-001 Amendment 5

Protocol Date: August 21, 2015

Product Name: Allergan Silicone Gel-filled Breast Implants

Investigator:

Study Location:

I agree to:

- Implement and conduct this study diligently and in strict compliance with this protocol, good clinical practices (GCP), and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, and I agree to all aspects.

Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date

RETURN TO ALLERGAN

Synopsis

NUMBER AND TITLE OF STUDY:
Breast Implant Follow-up Study: A Long-term Observational Study of the Safety of Allergan Silicone Gel-filled Breast Implants as Compared Both to Saline-filled Breast Implants and to National Norms

DEVELOPMENT PHASE: Post-approval

STUDY CENTERS: At least 38 US centers for the BIFS and 410 arms, up to 982 sites for the National Breast Implant Registry (NBIR) arm

NUMBER OF SUBJECTS: Approximately 54,630 subjects were originally enrolled including 39,390 subjects with NATRELLE® Silicone-filled Breast Implants (Styles 10, 15, 20, 40, 45, 110, 115, and 120, hereafter referred to as Round Responsive implants) and 15,240 subjects with saline implants. Under Amendment 5, approximately 2,245 of these subjects will continue in the Breast Implant Follow-Up Study (BIFS) arm, including 2,000 subjects with silicone gel-filled breast implants and 245 subjects with saline implants. The remaining subjects will continue in the US National Breast Implant Registry (NBIR) arm until the NBIR is established. When the NBIR is established, follow-up of reoperations will continue under the NBIR. In addition, approximately 530 subjects with NATRELLE® Highly Cohesive Anatomically Shaped Silicone-filled Breast Implants (hereafter referred to as Style 410 implants) will be enrolled in a 410 arm under Amendment 5. Therefore, approximately 2,775 subjects (2,000 Round Responsive, 530 Style 410, and 245 saline) will be followed up under this amendment.

OBJECTIVES:
The objectives of the study are to compare Round Responsive and Style 410 implants with saline implants or national norms in regard to:

1) Long-term safety
   - Connective Tissue Diseases (CTD)
   - Rheumatologic and neurologic signs and symptoms
   - Cancer (lung and breast)
   - Suicide or attempted suicide
   - Local complications and the need for reoperations
2) Reproduction, pregnancy outcomes, and lactation
   - Pregnancy outcomes
   - Problems related to lactation in subjects who attempt to breastfeed
   - Target adverse events (AEs) occurring in offspring
3) Effects on mammography
   - Detection of breast cancer
   - Rate of rupture
4) Effects on satisfaction with breasts and psychosocial well-being
5) Silicone subject compliance with magnetic resonance imaging (MRI) recommendations
   - Rupture rate associated with MRI

STUDY DESIGN:
This is a prospective observational study comparing targeted safety outcomes of subjects who elect to receive 1 or 2 Round Responsive implants or 1 or 2 Style 410 implants to national norms or those of a control group of women receiving saline breast implants. For AEs occurring at less than 55 events per 10,000 person-years, national norms will serve as a 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.

After the breast implant surgery is complete, the surgeon will provide data on the procedure. Each enrolled subject will provide health information at baseline. Subjects in the BIFS and 410 arms will respond to an annual

questionnaire for 10 years and complete the Satisfaction with Breasts and Psychosocial Well-Being modules of the BREAST-Q at years 1, 4, and 10. Additionally, silicone implant subjects in the BIFS and 410 arms 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 gel-filled breast implants. AEs and local complications can also be reported spontaneously throughout the study by the subject or her physician. Under Amendment 5, subjects in the NBIR arm will only return to their surgeons as needed for reoperations, which will be reported by the investigator.

Under Amendment 5, the focus of BIFS-001 will change from detecting differences in the rates of very rare adverse events to local complications, reoperation, implant removal, and rare adverse events in order to satisfy postapproval requirements for both Round Responsive and Style 410 implants. The change in study focus will be accompanied by a reduction in the sample size from approximately 54,630 to approximately 2,245 (approximately 2,000 subjects with round silicone gel-filled implants and 245 subjects with saline implants). These subjects will provide adequate data to assess endpoints that are not considered device specific, such as rare adverse events, and support the safety of Round Responsive and Style 410 implants. In addition, these subjects will provide data on device-specific endpoints, such as local complications, mammography results, MRI results, and effectiveness following implantation with Round Responsive implants. To collect data on device-specific endpoints for Style 410 implants, an additional 530 subjects (250 augmentation, 80 revision-augmentation, 150 reconstruction, and 50 revision-reconstruction subjects) implanted with Style 410 implants will be enrolled in a 410 arm.

Cluster sampling will be used to select subjects to remain in the BIFS arm under Amendment 5. A sample of all sites with at least 30 enrolled subjects with Round Responsive implants will be randomly selected. Under Amendment 5, all subjects at these sites who meet the continuation criteria will continue in the BIFS arm through year 10. The remaining subjects will continue in the NBIR arm until the NBIR is established. At least 38 investigational sites will be selected randomly in the initial cluster sample. Additional sites will be selected at random until 2,000 subjects with Round Responsive implants and 245 subjects with saline implants have been identified for the BIFS arm. If a site is selected with more than 200 subjects who are eligible for the BIFS arm, 200 subjects will be randomly selected from this site to continue in the BIFS arm, and the remaining Round Responsive subjects will continue in the NBIR arm. In addition, approximately 530 subjects with Style 410 implants will be enrolled in the 410 arm under Amendment 5.

DIAGNOSIS AND CRITERIA FOR INCLUSION, EXCLUSION, ENROLLMENT, AND CONTINUATION:

Subjects who have received Allergan silicone gel-filled breast implants or saline implants will be eligible to participate in the study.

INCLUSION:

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 subjects)
2) Exhibit fluency and literacy in English or Spanish

EXCLUSION:

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

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

ENROLLMENT:

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 (ie, both Round Responsive, both Style 410, or both saline) following their qualifying surgery. In the case of silicone, the device(s) must be manufactured by Allergan.

4) Be free of all target diseases at baseline (410 arm only)
5) 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

CONTINUATION CRITERIA BIFS ARM ONLY):

Subjects are eligible to continue in the BIFS arm under Amendment 5 if they meet all of the following criteria:

1) Have complete baseline and years 1, 2, 3, and 4 follow-up questionnaires available (including the Satisfaction with Breasts and Psychosocial Well-Being modules of the BREAST-Q)
2) Meet all enrollment criteria, specifically the minimum age requirements for silicone implants (18 or older for reconstruction subjects and 22 or older for augmentation subjects), and were free of all target diseases at baseline
3) Are enrolled at a site that is selected in the cluster sampling to continue in the BIFS arm under Amendment 5

TEST PRODUCT AND MODE OF ADMINISTRATION:

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

DURATION OF STUDY: up to 10 years of follow-up after device implantation

RESPONSE MEASURES:

Effectiveness:

The BREAST-Q Satisfaction with Breasts and Psychosocial Well-Being modules 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 (ie, infection, breast pain, capsular contracture, rupture, removal, and reoperation)
2) Investigator reports of physical exam results (ie, local complications) at years 1, 4, and 10
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

STATISTICAL METHODS:

Sample Size Calculation:

For subjects continuing in the BIFS arm under Amendment 5, the event rate of lung cancer was chosen to use in the sample size calculation because it is the rarest disease among the revised study endpoints, based on published rates available at the time of the amendment. As a result, the study will also provide adequate power to detect a doubling of other study outcomes, which are less rare than lung cancer.

A random sample of approximately 1,720 silicone subjects, from the current silicone population enrolled in BIFS-001 will provide approximately 80% power to detect a doubling of the rate of lung cancer which is estimated at 52.7 events per 100,000 person years (SEER, 2005-2009). This calculation uses a 1-sided 5% exact binomial test of the null hypothesis proportion of 0.000527, against an alternative proportion of 0.001054, with a total of 17,195 person-years accumulated over a total of 10 years of follow-up per subject. The calculation was done using Proc Power in SAS version 9.3. Assuming a drop-out rate of 5% of the original BIFS arm annually from years 4 to 10 (so that the cumulative drop-out rate is 35% at year 10), a total random sample of 2,000 silicone subjects from the current silicone population enrolled in BIFS-001 is planned.

A control group of approximately 210 subjects with saline implants will provide approximately 81% power to detect a doubling of event rates in the breast implant cohort as small as 55 events per 10,000 person-years. This corresponds to a null hypothesis proportion of 0.0055 in the control group, and an alternative proportion of 0.011 in the silicone implant group. This calculation uses a 1-sided Fisher's test of the difference between 2 sample proportions, with alpha = 0.05. It assumes that the control group and silicone group provide a total of 2,100 person-years and 17,195 person-years, respectively, over a total of 10 years of follow-up per subject. The calculation was done using Proc Power in SAS version 9.3. Assuming a drop-out rate of 5% of the original BIFS arm annually from years 4 to 10 (so that the cumulative drop-out rate is 35% at year 10), a total random sample of 245 saline subjects from the current saline population enrolled in BIFS-001 is planned.

To allow for 35% drop-out at the end of the 10-year study, 530 subjects with Style 410 implants will be enrolled including 250 augmentation, 80 revision-augmentation, 150 reconstruction, and 50 revision-reconstruction subjects. A sample of 163 augmentation subjects at year 10 will provide a prevision of ± 4.4% to estimate the occurrence of capsular contracture, based on the capsular contracture rate of 9.2% observed in augmentation subjects in Study 410 Core at year 10 and a 95% CI (normal approximation) for binomial proportions. A sample of 98 reconstruction subjects at year 10 will provide a prevision of ± 7.0 % to estimate the occurrence of capsular contracture, based on the capsular contracture rate of 14.5% observed in augmentation subjects in Study 410 Core at year 10 and a 95% CI (normal approximation) for binomial proportions. A sample of 52 revision-augmentation subjects at year 10 will provide a prevision of ± 8.8% to estimate the occurrence of capsular contracture, based on the capsular contracture rate of 11.9% observed in augmentation subjects in Study 410 Core at year 10 and a 95% CI (normal approximation) for binomial proportions. A sample of 33 revision-reconstruction subjects at year 10 will provide a prevision of ± 15.1% to estimate the occurrence of capsular contracture, based on the capsular contracture rate of 26.8% observed in augmentation subjects in Study 410 Core at year 10 and a 95% CI (normal approximation) for binomial proportions.

Effectiveness:
Breast satisfaction and psychosocial well-being will be summarized at baseline and at years 1, 4, and 10, and will be compared between the BIFS arm and a sample of subjects ineligible to remain in the BIFS arm at the end of the study. In addition, for each indication a mixed effect model will be used to estimate the changes from baseline within each implant group and the differences between implant groups for breast satisfaction and psychosocial well-being. The change from baseline will be modeled with fixed effects for implant group, time, and baseline score as a covariate. Effectiveness measures will be analyzed separately for subjects with Round Responsive and Style 410 implants.

Safety:
Two analysis populations will be used to assess safety: the primary safety population and the safety population. The primary safety population will include only those subjects selected for the BIFS arm under Amendment 5 and the 410 arm. Analyses will include all data collected for up to 10 years. The safety population will include all subjects who are enrolled in BIFS-001. Analysis of the safety population will use all data from the primary safety population as well as subjects' data up to the date the central Institutional Review Board (IRB) approves Amendment 5 for subjects not selected for the BIFS arm. This analysis will only be performed for the first annual report after implementing Amendment 5. Additionally, a sample of subjects ineligible to remain in the BIFS arm will be randomly selected from all ineligible subjects before finalizing the BIFS arm. At the end of the study, this sample will be compared with the primary safety population on rates of selected complications (rupture, deflation, reoperation, removal without replacement, removal with replacement, and capsular contracture).

Under Amendment 5, the null hypotheses are differentiated based on the rate of safety outcomes in the general population (national norms). For rare events (< 55/10,000 person-years), the null hypothesis is that women who choose silicone gel-filled breast implants are no more likely than women in the general population to experience the Target AEs. Tests will be performed at the 1-sided 0.05 level of significance. For less rare Target AEs (≥ 55/10,000 person-years), 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 gel-filled implants and saline-filled implants will also be made for 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 2-sided 0.10 level of significance in order to reduce the probability of failing to detect a notable safety issue.

Table 1: Schedule of Visits and Procedures

	BIFS and 410 Arms					NBIR Arm
Study Period	**Baseline Screening**	**Post-surgery**	**Subject Annual Questionnaire (Years 1 to 10)**	**Office Visits (Years 1, 4, and 10; Silicone Only)**	**Any Time During the Study, as Needed**	**Any Time until the NBIR is Established, as Needed**
Informed Consent[a]	X					
Inclusion/Exclusion Criteria[a]	X					
Enrollment Criteria		X[b]				
Demographics and Lifestyle[a]	X					
Contact Information[c]	X		X	X	X	
Satisfaction with Breasts[c]	X		Years 1, 4, and 10			
Psychosocial Well-Being	X		Years 1, 4, and 10			
Medical and Reproductive History[c]	X					
Surgical Summary[a]		X				
Target Adverse Events and Signs & Symptoms[a,c]			X	X	X	
Spontaneous Adverse Events Reports[a,c]			X	X	X	
Reproductive and Offspring Events and Complications[c]	X		X			
Implant Complications, Ruptures, and Reoperations[a,c]			X	X	X	
Mammography and MRI Screening[c]			X			
Physical Exam[a]				X		
Study Completion/Early Termination[d]					X	
NBIR Reoperations[a]						X

BIFS = Breast Implant Follow-up Study; MRI = magnetic resonance imaging; NBIR = US National Breast Implant Registry

[a] To be recorded by site personnel

[b] 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

[c] To be provided by the subject

[d] Subjects choosing to discontinue from the study prior to the last annual questionnaire may communicate this choice to the BIFS-001 call center to terminate participation

Table of Contents

List of Tables

1.0 Abbreviations and Terms

Abbreviation/Term	Definition
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
GEE	Generalized estimating equations
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MRI	Magnetic resonance imaging
NBIR	US National Breast Implant Registry
Round Responsive implants	NATRELLE® Silicone-filled Breast Implants (Styles 10, 15, 20, 40, 45, 110, 115, and 120)
Style 410 implants	NATRELLE® Highly Cohesive Anatomically Shaped Silicone-filled Breast Implants (Styles FX, FF, FM, FL, MX, MF, MM, ML, LX, LF, LM, and LL)

2.0 Background and Clinical Rationale

2.1 Background

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 gel-filled breast implants (hereafter referred to as Round Responsive 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 implant 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 visit.

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

On February 20, 2013, the FDA issued Allergan an approval letter for its premarket application for NATRELLE® Highly Cohesive Anatomically Shaped Silicone-filled Breast Implants Style 410 Breast Implants (Styles FM, FF, MM, and MF, hereafter referred to as Style 410 implants) under PMA P040046. Under approval condition 3, Allergan agreed to a follow-up study of Style 410 breast implants to assess their clinical performance under general conditions of use in the postmarket environment. Additionally, Allergan agreed to be a stakeholder in the US National Breast Implant Registry (NBIR). The NBIR is intended to be a surveillance tool to track patient safety and real-world outcomes associated with breast implants used for aesthetic or reconstructive purposes. With the addition of the NBIR to study breast implant safety, Amendment 5 will reduce the sample size of BIFS-001 to focus on less rare adverse events (AEs). Under this new study design, a subset of subjects will remain in BIFS-001 for follow-up and evaluation of less rare AEs and local complications through 10 years after implantation, per the objectives of Study BIFS-001 (BIFS arm).

Therefore, Amendment 5 will enroll new subjects implanted with anatomically shaped silicone gel-filled breast implants in a 410 arm to assess device-specific endpoints, such as local complications, mammography results, MRI results, and effectiveness. The subjects with Round

Responsive implants will provide adequate data to assess endpoints that are not considered device-specific, such as rare adverse events, as well as endpoints that are device-specific. A single cohort of subjects with saline breast implants (enrolled in the BIFS arm) will serve as a control for both round and anatomically shaped breast implants. All subjects who are not enrolled in the BIFS or 410 arms will compose the NBIR arm, which only contributes data through investigator reports of reoperation while the NBIR is being constructed.

2.2 Clinical Rationale

The purpose of this study is to evaluate the long-term clinical performance of Round Responsive and Style 410 implants under general conditions of use in the postmarket environment. Subjects implanted with Round Responsive or Style 410 implants will be compared to national norms, to subjects implanted with NATRELLE® saline implants, or both to assess the relationship between silicone gel-filled breast implants and certain relatively rare, systemic diseases, such as lung cancer. The open-label study design will provide information on risks, such as implant removal with replacement, and benefits, such as subject satisfaction and psychosocial well-being, associated with Round Responsive or Style 410 implants in the postmarket environment. Subject compliance with MRI recommendations will also be assessed.

3.0 Study Objectives and Clinical Hypothesis

3.1 Study Objectives

The objectives of the study are to compare Round Responsive and Style 410 implants with saline implants or national norms in regard to:

- Long-term safety
  - Connective Tissue Diseases (CTD)
  - Rheumatologic and neurologic signs and symptoms
  - Cancer (lung and breast)
  - Suicide or attempted suicide
  - Local complications and the need for reoperations

The Target AE diagnoses and the background rates as identified in the published literature are provided in Attachment 13.1.

- Reproduction, pregnancy outcomes, and lactation
  - Pregnancy outcomes
  - Problems related to lactation in subjects who attempt to breastfeed
  - Target AEs occurring in offspring
- Effects on mammography
  - Detection of breast cancer
  - Rate of rupture
- Effects on satisfaction with breasts and psychosocial well-being
- Silicone subject compliance with MRI recommendations
  - Rupture rate associated with MRI

Table 2 outlines the specific objectives within each of the categories above, and the specific comparator group for each evaluation.

Table 2: Study Objectives and Comparator Groups

Endpoint	Question	Comparator[a]	Device Specific
Long-term Safety			
Connective Tissue Disease (CTD)	What are the types and rates of CTDs reported by women receiving Allergan silicone gel-filled breast implants?	Saline breast implant cohort and national norms	No
Rheumatologic signs and symptoms	What are the types and rates of rheumatologic signs and symptoms reported by women receiving Allergan silicone gel-filled breast implants?	Saline breast implant cohort	No
Neurologic signs and symptoms	What are the types and rates of neurological signs and symptoms reported by women receiving Allergan silicone gel-filled breast implants?	Saline breast implant cohort	No
Cancer	What are the rates of breast and lung cancer reported by women receiving Allergan silicone gel-filled breast implants?	Saline breast implant cohort and national norms	No
Suicide or attempted suicide	What are the rates of suicide and attempted suicide in women receiving Allergan silicone gel-filled breast implants?	Saline breast implant cohort and national norms	No
Local complications and reoperations	What are the Kaplan-Meier complication rates over time, including reoperation and removal rates for women receiving Allergan silicone gel-filled breast implants? What are the reasons for reoperation over time?	Saline breast implant cohort	Yes
Reproduction	Of those women with Allergan silicone gel-filled breast implants who attempt to have children, what are the types and rates of reproductive complications?	Saline breast implant cohort	No

Endpoint	Question	Comparator[a]	Device Specific
Lactation	Of those women with Allergan silicone gel-filled breast implants who attempt to breastfeed, how many are successful? What are the reported lactation complications?	Saline breast implant cohort	No
Congenital deformities	What are the types and rates of congenital deformities of offspring born to women with Allergan silicone gel-filled breast implants?	Saline breast implant cohort and national norms	No
Effects on mammography	What is the rate of rupture of Allergan silicone gel-filled breast implants following mammography? Do the implants interfere with mammography?	Saline breast implant cohort	Yes
MRI compliance and results	What is the rate and frequency of MRI screening for rupture in women with Allergan silicone gel-filled breast implants? What are the rupture rates based on MRI results?	None	Rupture rates only
Effectiveness			
Psychosocial well-being	What is the psychosocial well-being over time for women with Allergan silicone gel-filled breast implants?	Saline breast implant cohort	Yes
Satisfaction with breasts	What is the satisfaction rate over time for women with Allergan silicone gel-filled breast implants?	Saline breast implant cohort	Yes

[a] Sources of national comparator data are provided in Attachment 13.1. Since the reference rates may change over time, the rates used in the final analysis will be described in the final statistical analysis plan.

3.2 Clinical Hypothesis

The clinical hypothesis is that subjects implanted with silicone gel-filled breast implants will not have a higher incidence of Target AEs than subjects implanted with saline-filled breast implants or national norms.

4.0 Study Design

4.1 Structure

BIFS-001 is a prospective observational study comparing targeted safety outcomes of subjects who elect to receive 1 or 2 Round Responsive or Style 410 breast implants to those of a control group of women receiving saline implants or to national norms. Each subject in the BIFS and 410 arms will be followed for 10 years after implantation of the original study device. Each subject who continues in the NBIR arm under Amendment 5 will be followed for reoperations until the NBIR is established. At that time, subjects will be followed for reoperations under the NBIR.

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 Round Responsive implants, 1 or 2 Style 410 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 AEs occurring at less than 55 events per 10,000 person-years, the rates for subjects with silicone implants will be compared to established national norms and to subjects who elect to receive 1 or 2 saline-filled breast implants. For other target AEs, Round Responsive and Style 410 implants will also be compared to saline breast implants. The national datasets used to obtain the comparative national norms are provided in Attachment 13.1. Similarly, the rates of reproductive failure, lactation, and pregnancy outcomes will be compared to the saline group.

After the breast implant surgery is complete, the surgeon will provide data on the procedure. All subjects in the BIFS and 410 arms will complete follow-up questionnaires by internet, phone interview, or mail annually for 10 years. These annual questionnaires will collect information on the target AEs, mammography experience, MRI experience (silicone subjects only), and pregnancy and lactation. Effectiveness, as measured by satisfaction with breasts and psychosocial well-being, will be assessed at years 1, 4, and 10. The subject will be asked to notify the call center regarding any local complications, reoperations, and implant removal that occur between the annual surveys. For subjects with Round Responsive or 410 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. Subjects in the NBIR arm will only contribute data through investigator reports of reoperation.

Study BIFS-001 originally enrolled approximately 54,630 subjects (39,390 with Round Responsive implants and 15,240 with saline implants). Approximately 2,245 of these subjects (2,000 Round Responsive subjects and 245 saline subjects) will continue in the BIFS arm under Amendment 5. The remaining subjects will continue in the NBIR arm until the NBIR is established. Subjects who continue in the BIFS arm will be selected based on cluster sampling. A sample of all sites with at least 30 enrolled subjects with Round Responsive implants will be randomly selected. All subjects enrolled at these sites who meet the continuation criteria in

Section 5.6 will be selected to continue in the BIFS arm. A total of 38 investigational sites will be selected in the initial cluster sample, with additional sites selected at random until 2,000 subjects with Round Responsive implants and 245 subjects with saline implants who are eligible to continue in the BIFS arm have been identified. If a selected site has more than 200 subjects with Round Responsive implants who are eligible to continue in the BIFS arm, a random sample of 200 eligible subjects will be selected to continue in the BIFS arm, and the remaining silicone subjects will continue in the NBIR arm. In addition, approximately 530 subjects with Style 410 implants will be enrolled in the 410 arm under Amendment 5 (250 augmentation, 80 revision-augmentation, 150 reconstruction, and 50 revision-reconstruction subjects). Therefore, under Amendment 5, BIFS-001 will include 2,775 subjects (2,000 Round Responsive, 530 Style 410, and 245 saline).

No information regarding study outcomes will be used to select study sites or to screen subjects to continue in the BIFS arm under Amendment 5. Before finalizing the BIFS arm, baseline and demographic characteristics will be evaluated to confirm that the subjects selected to continue in the BIFS arm under Amendment 5 are representative of both the total original study population and a sample of subjects not eligible to remain in the BIFS arm. For this analysis, primary indication (augmentation or reconstruction), age, race, body mass index, smoking status, implant size, implant location, and implant surface type will be compared. If clinically meaningful differences (rather than simply statistically significant differences) are observed, the above methodology will be repeated to create a new random sample. If a third sample is required, the sample that is most representative among the 3 will be selected.

4.2 Duration

The study will span 3 years for recruitment and 10 years of follow-up for the BIFS Arm and 14 months of recruitment and 10 years of follow-up for the 410 arm (Table 3). Due to overlap between the arms, the entire study will span approximately 19 years. Each subject's participation will encompass up to 10 years of follow-up after device implantation.

Table 3: Detailed BIFS-001 Study Timeline

	Time from FDA Approval of BIFS-001	
Activity	**BIFS Arm**	**410 Arm**
Subject Recruitment	**N/A – Complete**	14 months
Subject Follow-Up	6 years (remaining)	10 years
Database Lock	6 months	6 months
Final Report Submission	6 months	6 months
Total Duration	7 years from FDA Approval	12 years 2 months from FDA Approval

BIFS = Breast Implant Follow-up; FDA = Food and Drug Administration; N/A = not applicable

4.3 Treatment Groups and Treatment Regimen

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

4.3.1 Study Treatment

NATRELLE® Silicone Gel-filled Breast Implants (Styles 10, 15, 20, 40, 45, 110, 115, and 120)

Commercially available NATRELLE® Highly Cohesive Anatomically Shaped Silicone-filled Breast Implants (Styles FX, FF, FM, FL, MX, MF, MM, ML, LX, LF, LM, and LL)

4.3.2 Control Treatments

Saline-Filled Breast Implants

4.3.3 Methods for Blinding

Blinding does not apply to this study.

4.4 Prohibited Medications/Treatments

Surgery to remove 1 or both of the qualifying baseline breast implants and replace it/them with different types of implants (eg, switching between saline and silicone or between Round Responsive and Style 410) will result in the subject being withdrawn from the study.

4.5 Data Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will consist of 1 statistician, 2 board-certified plastic surgeons, and 1 clinical trial ethicist. The mission of the DSMB is to ensure the continuing safety of the study subjects throughout the clinical trial. Secondarily, the DSMB will monitor enrollment (both the original enrollment and enrollment of the 410 arm) 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 both enrollment periods, the DSMB will receive annual 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 any scheduled DSMB meeting.

The FDA will also review study status and study conduct. These reports will also include a description of any action taken to enhance enrollment overall or for a particular demographic segment. Information was provided to the FDA approximately 3 months following the first visit of the first subject, and quarterly thereafter until all subjects had completed the year 2 visit. Under Amendment 5, information will be provided annually.

Both the DSMB and the FDA will provide guidance to the BIFS-001 team if important concerns are identified.

5.0 Study Population

5.1 Number of Subjects

Approximately 54,630 subjects were originally enrolled, including 39,390 subjects implanted with Round Responsive implants and 15,240 subjects implanted with saline breast implants. Approximately 2,245 of these subjects will continue in the BIFS arm under Amendment 5, including 2,000 subjects with Round Responsive implants and 245 subjects with saline implants. All remaining subjects will continue in the NBIR arm until the NBIR is established, at which point they will be followed by the NBIR. Under Amendment 5, no more than 200 subjects with Round Responsive implants will be enrolled in the BIFS arm at each investigational site.

Under Amendment 5, an additional 530 subjects with Style 410 implants will be enrolled in the 410 arm (250 augmentation, 80 revision-augmentation, 150 reconstruction, and 50 revision-reconstruction subjects). No more than 53 subjects will be enrolled in the 410 arm at each investigational site.

5.2 Study Population Characteristics

Subjects who have received Allergan silicone gel-filled breast implants or saline implants will be eligible to participate in the study.

5.3 Inclusion Screening Criteria

Subjects 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

5.4 Exclusion Screening Criteria

Subjects 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 subject, have a current or past unilateral or bilateral silicone gel-filled breast implant
3) Investigator decision that subject is not a suitable candidate for a long-term observational study

5.5 Enrollment Criteria

Subjects 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 (ie, both Round Responsive, both Style 410, or both saline) following their qualifying surgery. In the case of silicone, the device(s) must be manufactured by Allergan.
4) Are free of all target diseases at baseline (410 arm only)
5) 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

5.6 Continuation Criteria (BIFS Arm Only)

Subjects are eligible to continue in the BIFS arm under Amendment 5 if they meet all of the following criteria:

1) Have complete baseline and years 1, 2, 3, and 4 follow-up questionnaires available (including the Satisfaction with Breasts and Psychosocial Well-Being modules of the BREAST-Q)
2) Meet all enrollment criteria, specifically the minimum age requirements for silicone implants (18 or older for reconstruction subjects and 22 or older for augmentation subjects), and were free of all target diseases at baseline
3) Are enrolled at a site that is selected in the cluster sampling to continue in the BIFS arm under Amendment 5

6.0 Procedures

6.1 Procedures to be Performed

The study visits and procedures to be performed are described in Table 1.

6.1.1 Subjects Who Do Not Enroll in BIFS-001

Before Amendment 5, sites were expected to enroll consecutive subjects who were undergoing breast implantation with a Round Responsive implant or a saline breast implant. Sites were to record basic demographic information on the Non-enrollment Data Form for all women who were invited but did not participate. Reasons for this lack of participation included:

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

Under Amendment 5, no data will be collected from women who are invited but do not participate.

6.1.2 Baseline Information

After the decision to undergo breast implantation has been made between the subject and her surgeon, and prior to the surgery, the surgeon or other designated site staff will invite the subject to participate in the study, explain all study processes and procedures, answer all questions, and provide an opportunity for review and signing of the Informed Consent Form 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.

6.1.2.1 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-001 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-001 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.

6.1.2.2 Effectiveness Assessments

At baseline, BREAST-Q Satisfaction with Breasts and Psychosocial Well-Being modules will be administered.

6.1.2.3 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 (eg, smoking, alcohol consumption)

6.1.2.4 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 after the implant surgery.

6.1.3 Operative Procedure

Information about the type of implant (Round Responsive, Style 410, or saline) and indication (augmentation, reconstruction, augmentation revision, reconstruction revision) will be recorded following surgery. Additionally, information about the surgical procedure (eg, incision site, implant location) will also be documented.

6.1.4 Annual Self-Administered Subject Questionnaires

6.1.4.1 Effectiveness Assessments

During the annual questionnaires, the BREAST-Q Satisfaction with Breasts and Psychosocial Well-Being questionnaires will be administered at years 1, 4, and 10.

6.1.4.2 Safety Assessments

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

- CTD
- Rheumatologic and neurologic signs and symptoms
- Cancer (lung and breast)
- 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.

6.1.4.3 Local Complications

Key local complications will be collected annually via subject questionnaire as well as via Investigator Follow-Up Form. 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.

6.1.4.4 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). The ability of the baby to suckle and

any complications of breastfeeding will be reported by the subject. 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 re-examined with each annual questionnaire.

6.1.5 Other Information Collected Annually

6.1.5.1 Contact Information

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

6.1.5.2 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 subject scheduled the screening.

If any rupture or suspected rupture is identified by MRI, the BIFS-001 call center will attempt to collect information to confirm the rupture.

6.1.6 Physical Exam

For subjects with Round Responsive and 410 implants, a physical exam will be conducted at years 1, 4, and 10 to assess local complications; Target AEs and signs and symptoms; spontaneous AE reports; and implant complications, ruptures, and reoperations.

6.1.7 NBIR Reoperations

Subjects in the NBIR arm will only return for follow-up as needed for reoperations. The investigator will report the reason for the reoperation and details of the procedure(s). Once the NBIR is established, data from future reoperations for the NBIR arm will be collected under the NBIR.

6.2 Unscheduled Visits

6.2.1 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-001 website or by calling the BIFS-001 call center. Subjects and investigators will be trained to report any undesirable sign, symptom, or condition that occurs during their participation in the study as an AE.

The report of an adverse event will also include event start and stop date, severity, action taken, and outcome, as applicable. Events that resulted in death will be identified by the investigators and by the BIFS-001 call center responsible for investigating death records for subjects who are lost to follow-up.

When signing the BIFS-001 informed consent form, subjects will grant permission for the BIFS-001 call center to contact healthcare 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.

6.2.2 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 Subsequent Surgery or Medical Condition Report (Participant) Form or Investigator Follow-Up Form.

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.

6.2.3 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-001 call 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.

6.3 Study Completion

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

1) A subject in the BIFS or 410 arm 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 (eg, changing between saline and silicone or between Round Responsive and Style 410). The subject will complete the study at the time of the revision surgery
3) The subject dies
4) The study terminates

The NBIR arm will complete the study once the NBIR is established.

6.4 Early Discontinuation of Subjects

The study will implement multiple strategies to ensure a high level of annual responsiveness. Strategies 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-001 secure website that will encourage subjects to log in and use the website on a regular basis.

Subjects may discontinue participation at any time during the study. However, all subjects will be strongly encouraged to continue with the study through their entire 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 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 (eg, implanting surgeon) as well as other personal contacts will be contacted. Further, internet search services and databases may 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 between saline and silicone or between Round Responsive and Style 410.

7.0 Response Measures and Summary of Data Collection Methods

7.1 Effectiveness Measures

The effectiveness measures are the BREAST-Q Satisfaction with Breasts and Psychosocial Well-Being modules.

7.2 Safety Measures

Safety measures include subject and investigator reports of CTD, cancer (lung and breast, including breast implant interference with mammography and delay of breast cancer detection), suicide/attempted suicide, rheumatologic and neurologic signs and symptoms, local complications, reoperation, implant removal with and without replacement, reproductive complications, pregnancy outcomes, lactation complications, and congenital deformities (see list in Section 8.2.2). Subjects and investigators may also report other cancers, CTDs, and neurological diseases.

7.3 Summary of Methods of Data Collection

Clinical sites will enter case report form (CRF) data into the secure, internet-based electronic data capture (EDC) system on the BIFS-001 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 to collect data on behalf of the subject.

8.0 Statistical Procedures

A separate statistical analysis plan will be written and finalized prior to the clinical database lock.

Both descriptive statistics and inferential statistics will be used to summarize results. Categorical variables will be summarized using counts and percentages. Continuous data will be summarized using the mean, standard deviation, median, minimum, and maximum. Data that are highly skewed will be reported using the median, 25th and 75th percentiles, and the minimum and maximum values. A combination of 1-tailed tests at the 5% level of significance and 2-sided 90% CIs will be used for inferential testing.

Every attempt will be made to collect complete data and limit the occurrence of missing data. Due to the descriptive nature of all analyses, no imputation of missing data will be performed.

8.1 Analysis Populations

Statistical summaries and analyses will be based on 2 safety populations:

- Primary safety population: all subjects who are selected in the BIFS and 410 arms under Amendment 5. Analyses of the primary safety population will include data collected over the entire duration of the study.
- Safety population: all subjects who are enrolled in BIFS-001. Analyses of the safety population will use all data from the primary safety population as well as subjects' data up to the date the central Institutional Review Board (IRB) approves Amendment 5 for subjects not selected for the BIFS arm. This safety analysis using the safety population will only be performed for the first annual report after implementing Amendment 5.

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.

In addition, a sample of subjects not eligible to remain in the BIFS arm, the "sample of ineligible subjects" population, will be randomly selected to include at least 2000 silicone ineligible subjects and 245 saline ineligible subjects. To ensure consistent sampling, the sample will be selected from the same sites in which subjects have been randomly selected to remain in the BIFS arm. As stated in Section 4.1, before finalizing the BIFS arm, baseline and demographic characteristics will be evaluated to confirm that the subjects selected to continue in the BIFS arm under Amendment 5 are representative of both the total original study population and the sample of ineligible subjects.

8.2 Collection/Derivation of Safety and Effectiveness Assessments

8.2.1 Effectiveness Variables

Effectiveness variables (breast satisfaction and psychosocial well-being) are collected at baseline and years 1, 4, and 10 by administering the BREAST-Q Augmentation pre-operative questions, BREAST-Q Augmentation post-operative questions, BREAST-Q Reconstruction pre-operative questions, or BREAST-Q Reconstruction post-operative questions, as applicable.

The subjects will be asked 2 sets of questions corresponding to 2 of the BREAST-Q domains: (1) Satisfaction with Breasts, and (2) Psychosocial Well-being. A separate summary score will be calculated for each set of questions. In general, the summary score is computed by summing the score for each response in the set of questions. The specific questions and number of questions differ based on pre-operative and post-operative and based on whether the subject is an Augmentation subject or a Reconstruction subject.

8.2.2 Safety Variables

Safety variables are collected at baseline, on all annual questionnaires, and at any scheduled or unscheduled visits by asking the subject if they have a new diagnosis of any of the safety variables below. Confirmation by the diagnosing physician will be sought for any diseases reported by the subject.

Safety variables include the following:

- CTDs
  - Chronic fatigue syndrome
  - Fibromyalgia
  - Rheumatic polymyalgia
  - Rheumatoid arthritis
  - Undifferentiated connective tissue disorder
- Cancer
  - Lung
  - Breast
- Suicide/attempted suicide
- Rheumatologic and neurologic signs and symptoms
- Complications and Reoperations
  - Time to first rupture (Silicone)
  - Time to first deflation (Saline)
  - Time to first complication
  - Time to first reoperation
  - Time to first removal without replacement
  - Time to first removal with replacement
- Time to the first of each of the following complications reported by the investigator:
  - Bruising
  - Capsular contracture (Baker Grade III or IV)
  - Capsule calcification

  - Delayed wound healing
  - Hematoma
  - Hypertrophic/abnormal scarring
  - Implant deflation
  - Implant extrusion
  - Implant malposition
  - Implant palpability/visibility
  - Infection
  - Irritation/inflammation
  - Loss of nipple sensation
  - Loss of skin sensation
  - Lymphadenopathy
  - Lymphedema
  - Nipple paresthesia/hypersensitivity
  - Pneumothorax
  - Seroma
  - Skin paresthesia/hypersensitivity
  - Skin rash
  - Suspected rupture
  - Tenderness
  - Tissue or skin necrosis
  - Wrinkling/rippling
- Time to the first of each of the following complications reported by the subject:
  - Breast infection
  - Breast pain
  - Capsular contracture (Baker grade III or IV)
  - Saline implant deflation
  - Silicone implant rupture
- Reproductive complications
- Lactation complications
- Congenital deformities
- Potential of breast implant interference with mammography and delay of breast cancer detection
- MRI Compliance

Subjects and investigators may also report other cancers, CTDs, and neurological diseases.

8.3 Hypothesis and Methods of Analysis

8.3.1 Effectiveness Analyses

The Satisfaction with Breasts and Psychosocial Well-Being modules of the BREAST-Q questionnaire will be summarized at baseline and years 1, 4, and 10 for subjects with both a baseline and follow-up assessment at the appropriate timepoint, using both safety populations.

For each indication a mixed effect model will be used to estimate the within implant-group changes from baseline and the between implant-group differences for breast satisfaction and

psychosocial well-being. The adjusted mean changes for each implant group and the comparison between silicone and saline at years 1, 4, and 10, along with the 2-sided 95% CIs and p-value will be reported.

In addition, the effectiveness analyses will be performed at the end of the study in the population of "sample of ineligible subjects", using the last observed outcomes. Results will be compared with those from the BIFS arm. Further analysis may be performed to adjust imbalances observed in baseline and demographic characteristics.

Effectiveness analyses will be performed separately for Round Responsive and Style 410 implants.

8.3.2 Safety Analyses

For the analysis of CTDs and cancers (lung and breast), the null hypotheses are differentiated based on the rates in the general population (national norms). For target AEs with an incidence < 55 events per 10,000 person-years, the null hypothesis is that women who choose silicone gel-filled breast implants are no more likely than women in the general population to experience the Target AEs. Tests will be performed at the 1-sided 0.05 level of significance, with 2-sided 90% exact CIs around the observed rate reported. If data are available, rates will be adjusted for age and race, otherwise crude rates will be reported.

For target AEs with a rate of ≥ 55 per 10,000 person years, the null hypothesis is that there is no difference in the target AE rate between women choosing silicone gel-filled breast implants and women choosing saline-filled breast implants. 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 2-sided 0.10 level of significance in order to reduce the probability of failing to detect a notable safety issue.

Differences in rates of rheumatologic and neurologic signs and symptoms for subjects with silicone gel-filled and saline-filled breast implants will be assessed using logistic regression. Analysis of complications and reoperations will be investigated at the implant level and the subject level. Time to endpoints will be summarized using the Kaplan-Meier method, Cox-Proportional hazards model, or both.

The overall number and frequency of reproductive complications and lactation complications will be summarized by implant group. For reproductive complications, subjects in the enrolled safety population who become pregnant will be used for the analysis. For lactation complications subjects in the enrolled safety population who had a live birth during the study will be used. For each reproductive and lactation complication, the difference between the silicone and saline groups will be estimated using a generalized estimating equations (GEE) approach. To account for repeated measurements within a subject, an exchangeable correlation structure will be used. The odds ratio of silicone vs. saline and associated 90% CIs will be reported.

Congenital deformities for all children born during the study, in the silicone and saline groups, will be summarized and compared to each other using a GEE approach with a 1-sided 0.05 level of significance. A logit link and binomial distribution will be used. To account for subjects having multiple births, an exchangeable correlation structure will be used.

Data collected on mammography and MRI compliance will be summarized by implant group using descriptive statistics, with no formal statistical inference.

For device-specific endpoints (as defined in Table 2), analyses will be provided separately for Round Responsive implants, Style 410 implants, and saline implants. For endpoints that are not device specific, analyses will use data from Round Responsive and saline implants. For the endpoints, descriptive analyses will be provided for Style 410 implants.

Safety analyses will be performed in both the primary safety population and the safety population as appropriate. Additionally, at the end of the study, rates of selected complications (rupture, deflation, reoperation, removal without replacement, removal with replacement, and capsular contracture) will be compared between the primary safety population and the sample of ineligible subjects.

8.4 Sample Size Calculation

For subjects continuing in the study arm under Amendment 5, the event rate of lung cancer was chosen to use in the sample size calculation because it is the rarest disease among the revised study endpoints, based on published rates available at the time of the amendment. As a result, the study will also provide adequate power to detect a doubling of other study outcomes, which are less rare than lung cancer.

A random sample of approximately 1,720 silicone subjects from the current silicone population enrolled in BIFS-001 will provide approximately 80% power to detect a doubling of the rate of lung cancer which is estimated at 52.7 events per 100,000 person years (SEER, 2005-2009). This calculation uses a 1-sided 5% exact binomial test of the null hypothesis proportion of 0.000527, against an alternative proportion of 0.001054, with a total of 17,195 person-years accumulated over a total of 10 years of follow-up per subject. The calculation was done using Proc Power in SAS version 9.3. Assuming a drop-out rate of 5% of the original BIFS arm annually between years 4 to 10 (so that the cumulative dropout rate at year 10 is 35%), a total random sample of 2,000 silicone subjects from the current silicone population enrolled in BIFS-001 is planned.

A control group of 210 subjects with saline implants will provide approximately 81% power to detect a doubling of event rates in the breast implant cohort as small as 55 events per 10,000 person-years. This corresponds to a null hypothesis proportion of 0.0055 in the control group, and an alternative proportion of 0.011 in the silicone implant group. This calculation uses a 1-sided Fisher's test of the difference between 2 sample proportions, with alpha = 0.05. It assumes that the control group and silicone group provide a total of 2,100 person-years and 17,195 person-years, respectively, over a total of 10 years of follow-up per subject. The calculation was done using Proc Power in SAS version 9.3. Assuming a drop-out rate of 5% of

the original BIFS arm annually between years 4 to 10 (so that the cumulative dropout rate at year 10 is 35%), a total random sample of 245 saline subjects from the current saline population enrolled in BIFS-001 is planned.

To allow for 35% drop-out at the end of the 10-year study, 530 subjects with Style 410 implants will be enrolled including 250 augmentation, 80 revision-augmentation, 150 reconstruction, and 50 revision-reconstruction subjects. A sample of 163 augmentation subjects at year 10 will provide a prevision of ± 4.4% to estimate the occurrence of capsular contracture, based on the capsular contracture rate of 9.2% observed in augmentation subjects in Study 410 Core at year 10 and a 95% CI (normal approximation) for binomial proportions. A sample of 98 reconstruction subjects at year 10 will provide a prevision of ± 7.0 % to estimate the occurrence of capsular contracture, based on the capsular contracture rate of 14.5% observed in augmentation subjects in Study 410 Core at year 10 and a 95% CI (normal approximation) for binomial proportions. A sample of 52 revision-augmentation subjects at year 10 will provide a prevision of ± 8.8% to estimate the occurrence of capsular contracture, based on the capsular contracture rate of 11.9% observed in augmentation subjects in Study 410 Core at year 10 and a 95% CI (normal approximation) for binomial proportions. A sample of 33 revision-reconstruction subjects at year 10 will provide a prevision of ± 15.1% to estimate the occurrence of capsular contracture, based on the capsular contracture rate of 26.8% observed in augmentation subjects in Study 410 Core at year 10 and a 95% CI (normal approximation) for binomial proportions.

8.5 Interim Analyses

Descriptive summaries will be provided to FDA in periodic progress reports as the study progresses. The first summary provided after Amendment 5 will include analyses of the primary safety population and the safety population. All following reports will only include analyses of the primary safety population.

9.0 Materials

9.1 Study Treatment

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

9.2 Other Study Supplies

The investigational site is responsible for routine supplies related to device administration and follow-up visits (eg, antiseptics, drapes, gloves, gauze, anesthesia, ice packs, blood pressure cuff, internet connection for electronic CRF completion).

10.0 Study Administration Procedures

BIFS-001 will not begin at any site until the site's IRB has granted approval.

Investigators will be selected by Allergan based on criteria such as:

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

10.1 Subject Entry Procedures

10.1.1 Overview of Entry Procedures

Prospective subjects as defined by the criteria in Sections 5.3 and 5.4 (inclusion/exclusion criteria) will be considered for entry into the study.

Screening procedures include:

- Informed Consent
- Evaluation of inclusion/exclusion criteria
- Collection of demographic and lifestyle information
- Collection of contact information
- Collection of psychosocial well-being and satisfaction with breasts
- Collection of medical and reproductive history
- Collection of reproductive and offspring events and complications

Following the surgery, a surgical summary will be collected, and the subject will be enrolled when they meet the enrollment criteria defined in Section 5.5.

The Enrollment Plan, which includes details on methods of subject enrollment and the proportional balance to be achieved in the study sample with regard to national silicone implantation rates, type of implant, and race, applied only during the original enrollment, not to new enrollment of the 410 arm. During the original enrollment period, BIFS-001 administrators reviewed these enrollment ratios on a regular basis and implemented various strategies to regain proper balance when necessary.

10.1.2 Informed Consent and Subject Privacy

During the original enrollment period for BIFS-001, which was completed within 3 years, investigative sites approached qualified subjects and had interested subjects sign informed consent for participation.

Informed consent for the 410 arm will proceed as follows. As was performed during the original enrollment period, the surgeon or other designated site staff will invite the subject to participate in the study, explain all study processes and procedures, answer all questions, and provide an opportunity for review and signing of the Informed Consent Form and Authorization to Release Medical Records.

Subjects continuing in the BIFS and NBIR arms under Amendment 5 will be notified of changes to the clinical study protocol with a patient notification form.

10.2 Pregnancy

If a female in the BIFS or 410 arm becomes pregnant during the study, the investigator will notify Allergan and report the pregnancy on her next annual questionnaire. The subject will continue to be followed as part of the study population.

11.0 Adverse Events

An AE is defined as any undesirable sign, symptom, or condition that occurs during a subject's participation in the study. Subjects will report AEs on annual questionnaires. Investigators will report AEs on CRFs for scheduled or unscheduled visits. Events that resulted in death will be identified by the investigators and by the BIFS-001 call center responsible for investigating death records for subjects who are lost to follow-up.

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-001 call 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.

12.0 Administrative Issues

12.1 Protection of Human Subjects

12.1.1 Compliance with Informed Consent Regulations

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-001 call 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 subject is unable to read in either of these languages, then the subject 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 form must be provided to the subject
- Any changes to the informed consent form must be approved by Allergan before any study subject is consented using the revised or altered form

12.1.2 Compliance with IRB Regulations

BIFS-001 will not begin at any site until the site's 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.

12.1.3 Compliance with Good Clinical Practice

Compliance with Good Clinical Practice (GCP) guidelines for the conduct and monitoring of this clinical trial will occur through observation of the ethical and regulatory requirements presented in International Conference on Harmonization (ICH) E6, GCP: Consolidated Guideline, as applicable. 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 Allergan 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.

12.2 Subject Confidentiality and Privacy

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-001 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.

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.

12.3 Labeling, Packaging, Storage, and Return of Study Devices

No treatments will be administered by this observational study. The decision to receive a breast implant is made by the subject and her surgeon independent of, and prior to, enrollment into BIFS-001.

12.4 Monitoring by Allergan

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 address 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.

The Medical Safety Physician's responsibilities include review of the protocol, coding of Target AEs, and interpretation of clinical results. The Medical Safety Physician is qualified by training and experience to perform these duties as described.

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.

13.0 Attachments

13.1 Target Diagnosis Normative Rates

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.

Target Diagnoses	Rates[1]	
Cancer		
Breast Cancer (including Paget's disease and malignant nipple neoplasms)[2]	All Races	124.3 per 100,000 women [2]
Lung Cancer	All Races	52.7 per 100,000 women[3]
Congenital and Neonatal Anomalies and Diseases (of offspring born subsequent to implant surgery)		
Esophageal disorders	1.7 per 10,000 live births[4]	
Congenital malformations	232.6 to 810.2 per 10,000 live births[4]	

Target Diagnoses	Rates[1]
Pyloric stenosis	1 to 3 per 1000; 17 per 10,000 live births[4]
Other congenital anomalies and diseases	Varied
Connective Tissue Disease/Disorders	
Chronic fatigue syndrome (CFS)	180 per 100,000 persons (95% confidence interval, 0-466 per 100,000 persons)[5] A study of the Seattle area estimated that CFS affects between 75 and 265 people per 100,000 population[6]
Connective tissue disorder (Not Otherwise Specified)/Undifferentiated connective tissue disorder	
Fibromyalgia	Prevalence is 3.4% of women[7]
Polymyalgia rheumatica	53.7 per 100,000[8] The incidence rate of polymyalgia rheumatica for the population 50 years and older is approximately 3 times higher than that of giant cell arteritis[9] In almost 40-50% of the cases it is associated with polymyalgia rheumatica[10]
Rheumatoid arthritis (RA)	70 per 100,000 annually. Both incidence and prevalence of rheumatoid arthritis are two to three times greater in women than in men.[11] The overall age- and sex-adjusted annual incidence of RA among Rochester, Minnesota, residents > or = 18 years of age was 44.6/100,000 population (95% confidence interval 41.0-48.2[12]
Suicides and Suicide Attempts	
Suicides	3.3 per 100,000 (females only, all races, age adjusted)[13] 5.35 per 100,000 (females only, all races, age adjusted, see below)[14] 10.6 per 100,000[15]
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.[15]

CFS = chronic fatigue syndrome; RA = rheumatoid arthritis

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

[2] SEER 18 registries 2005-2009: http://seer.cancer.gov/statfacts/html/breast.html#incidence-mortality

[3] SEER 18 registries 2005-2009: http://seer.cancer.gov/statfacts/html/lungb.html#incidence-mortality

[4] National Birth Defects Prevention Network; www.nbpdn.org.

[5] Reyes M, Nisenbaum R, et al. *Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas*. Archives of Internal Medicine 2003;163:1530-6.

[6] http://www.cdc.gov/ncidod/diseases/cfs/about/demographics.htm

[7] 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.

[8] Cohen MD, Ginsburg WW. *Polymyalgia rheumatica*. Rheum Dis Clin North Am. 1990 May;16(2):325-39.

[9] Meskimen S, Cook TD, Blake RL Jr. *Management of Giant Cell Arteritis and Polymyalgia Rheumatica.* Am Fam Physician [serial online] 2000 Apr 1;61(7):2061-8, 2073. Available from the American Academy of Family Physicians, Leawood, KS. Accessed May 02, 2006.

[10] Gonzales-Gay, M Garcia-Porrus, C: *Epidemiology of the vasculitides.* Rheum Dis Clin North Am. 2001 Nov; 27(4): 729-49. Review.

[11] As reported on the Johns Hopkins Arthritis website at http://www.hopkinsarthritis.org/arthritis-info/psoriatic-arthritis/

[12] Doran MF, Pond GR, Crowson CS, O'Fallon WM, Gabriel SE. *Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period.* Arthritis Rheum. 2002 Mar;46(3):625-31.
[13] National violent Death Reporting System; www.cdc.gov/mmwr/preview/mmwrhtml/mm5415a1.htm
http://www.cdc.gov/ncipc/factsheets/suifacts.htm
[14] WISQARS Injury Mortality Reports, online database from the www.cdc.gov website
[15] "In Harm's Way: Suicide in America." *NIH Publication No. 03-4594.* Printed January 2001; Revised May 2003. Available from the National Institute of Mental Health, Bethesda, MD. Accessed May 2, 2006.

13.2 Protocol Amendment Summary

Version Date/ Amend. No.	Changes to Protocol
08/21/15 Amendment 5	• Protocol format was changed to make it consistent with current Allergan standard operating procedures • Added Style 410 implant sizes approved by FDA • Added a cluster sampling procedure and justification to reduce sample size • Added enrollment, follow-up, and analysis of Style 410 breast implants • Added Table 3 Detailed BIFS-001 Study Timeline • Added the NBIR arm and follow-up procedures • The protocol was reworded to move the focus of the study from very rare Target AEs to less rare Target AEs and other events • Clarified that Satisfaction with Breasts and Psychosocial Well-Being modules of the BREAST-Q questionnaire will be used to assess effectiveness • Added a clinical rationale and clinical hypothesis • Clarified safety and effectiveness measures • Clarified procedures to report lactation data • Clarified and updated statistical analyses to reflect changes in study design • Updated target diagnosis normative rates for lung and breast cancer to more recent data • The attachment "List of CRFs" was removed

ALLERGAN

Protocol BIFS-001 Amd 5

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
21-Aug-2015 11:00 GMT-07	Hardas_Bhushan	Clinical Development Approval