SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Gel-Filled Mammary Prosthesis
Device Trade Name:	Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants
Device Procode:	FTR
Applicant's Name and Address:	Allergan, Inc. 71 South Los Carneros Road Goleta, California 93117
Date(s) of Panel Recommendation:	Not Applicable
Premarket Approval Application (PMA) Number:	P040046
Date of FDA Notice of Approval:	February 20, 2013
Expedited:	Not Applicable

II. INDICATIONS FOR USE

Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants are indicated for women for the following uses (procedures):

- Breast Augmentation for women at least 22 years old. Breast augmentation includes primary breast augmentation to increase the breast size, as well as revision surgery to correct or improve the result of a primary breast augmentation surgery.

- Breast Reconstruction. Breast reconstruction includes primary reconstruction to replace breast tissue that has been removed due to cancer or trauma or that has failed to develop properly due to a severe breast abnormality. Breast reconstruction also includes revision surgery to correct or improve the result of a primary breast reconstruction surgery.

III. CONTRAINDICATIONS

Breast implant surgery should not be performed in:

- Women with active infection anywhere in the body.
- Women with existing cancer or pre-cancer of their breast who have not received adequate treatment for those conditions

- Women who are currently pregnant or nursing

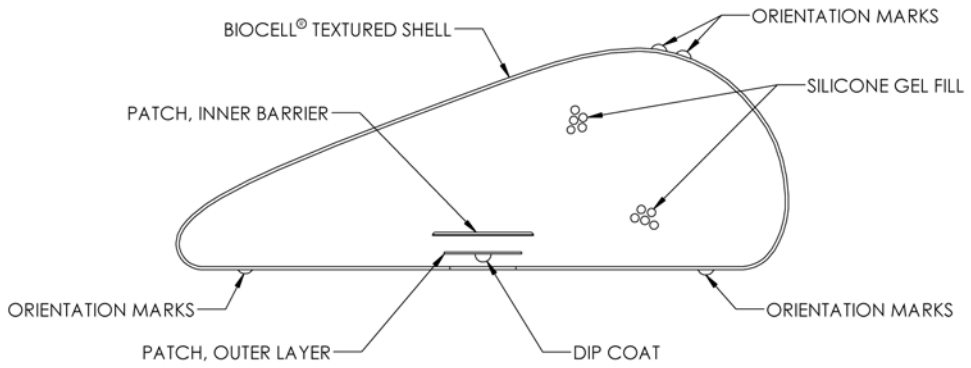
IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants labeling.

V. DEVICE DESCRIPTION

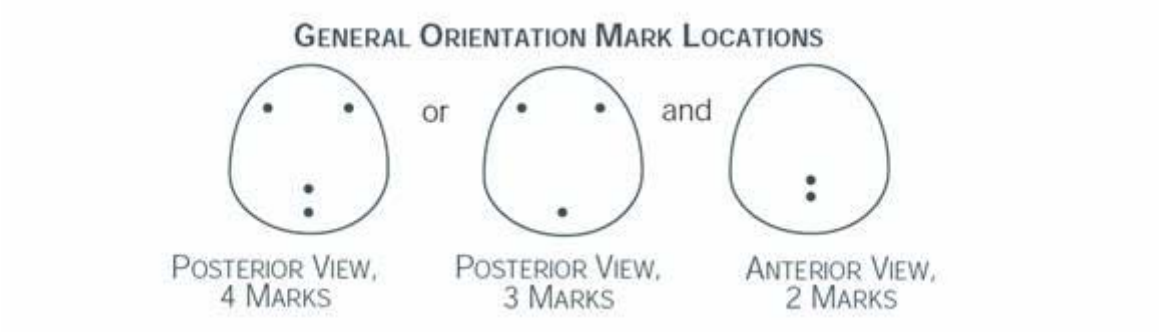
Each Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implant consists of a single-lumen, shaped, textured (BIOCELL®) elastomer surface shell, with a patch positioned on the posterior side and filled with a highly cohesive silicone gel. Orientation marks are attached to the implant shell. The implants are provided dry-heat sterilized with a 5-year shelf life from the date of sterilization. Figure 1 shows a diagram of the implant.

Figure 1: Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implant



The orientation marks are circular silicone elastomer dots located on the anterior and posterior surfaces of the implant to assist in aligning the implant vertically in the pocket. There are 2 orientation marks present on the anterior side of the implant in the lower pole. Depending on the style, there are either 3 or 4 orientation marks on the posterior surface of the implant. (The smaller and/or shorter styles may only have the 3 marks). An illustration of the orientation marks are shown in Figure 2 below.

Figure 2: General Orientation Mark Locations

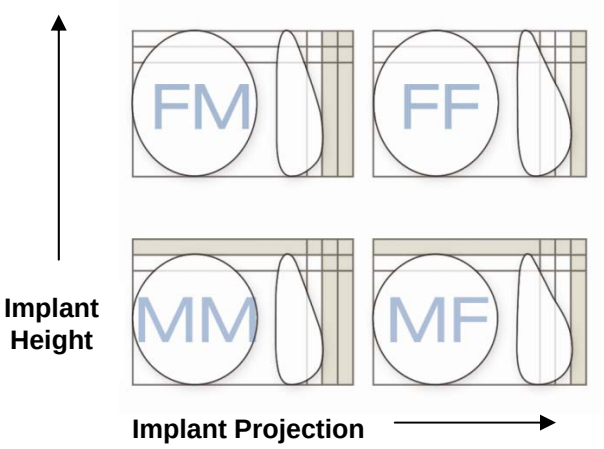


The principal features distinguishing this style from Allergan's previously approved Natrelle Silicone-Filled Breast Implants (P020056) are the:

- More cohesive silicone gel fill
- Device shape (Figure 3)
- Range of shapes and sizes (Table 1)
- Presence of orientation marks (Figure 2)

Figure 3 shows the device shapes and the profiles of the implants.

Figure 3: Profiles Available for Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants



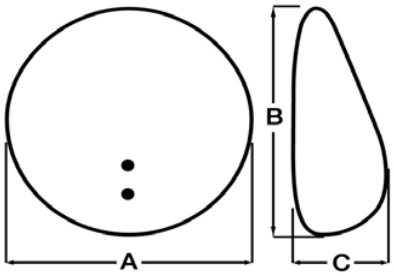


Table 1 below shows the Allergan styles that are approved. All approved implants are shaped and BIOCELL® textured, with shell thicknesses of 0.018-0.060 inches. Table 2 shows the general device materials for the shell, patch, and gel components.

Table 1: Approved Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants

Style Number	Profiles		Volume (cc)	Number of Sizes
	Height	Projection		
410FM	Full	Moderate	205-670	11
410FF	Full	Full	185-740	12
410MM	Moderate	Moderate	160-450	9
410MF	Moderate	Full	140-640	13

Table 2: Device Materials

Component	Material
Shell, inner/outer layers	Dimethyl/Diphenyl Silicone Elastomer
Shell, barrier layer	Dimethyl/Diphenyl Silicone Elastomer
Shell, textured layer	Dimethyl/Diphenyl Silicone Elastomer
Patch assembly	Dimethyl Silicone Elastomer and Dimethyl/Diphenyl Silicone Elastomer
Silicone adhesive	Dimethyl Silicone Elastomer
Gel	Dimethyl Silicone Gel: Base and Crosslinker; Platinum Cure (78% silicone oil by weight extractable by hexane)

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for augmentation or reconstruction of the breast with silicone-filled breast implants. Alternative procedures include undergoing no treatment, wearing an external prosthesis inside the woman's brassiere, transferring tissue from other parts of the body (autologous tissue transfer procedure or flap procedure), or placement of saline-filled breast implants. Each alternative has its own advantages and

disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Silicone-filled breast implants are pre-amendment devices that have been used since 1963. The Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants are similar to the pre-amendment silicone-filled breast implants with the major difference being that the Natrelle® Highly Cohesive devices are shaped devices filled with a more cohesive gel. Over 600,000 of the current Natrelle® 410 design have been produced and sold outside the United States in 24 countries since 1993. Allergan's Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants have not been withdrawn from any foreign market for any reason relating to the safety and effectiveness of the device.

On September 8, 2000, Allergan received approval to begin the Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implant Pivotal clinical study (referred to as the Pivotal or Core study below). The Pivotal Study is the primary clinical data set in this PMA. Two additional clinical studies, Continued Access and Continued Access Reconstruction/Revision (CARE), provided further access and information in the U.S.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Reoperation (additional surgeries)
- Implant Removal with or without Replacement
- Implant Rupture
- Capsular Contracture
- Swelling
- Implant Malposition or Displacement
- Breast Pain
- Ptosis
- Infection including toxic shock syndrome
- Breast/Skin Sensation Changes
- Nipple Complications
- Seroma/Fluid Accumulation
- Delayed Wound Healing
- Hematoma
- Hypertrophic Scarring
- Asymmetry
- Redness
- Wrinkling/Rippling

- Skin Rash
- Bruising
- Extrusion of Implant
- Implant Palpability/Visibility
- Gel Fracture
- Irritation
- Tissue/Skin Necrosis
- Upper Pole Fullness
- Capsule Calcification
- Lymphadenopathy
- Lymphedema
- Palpable Orientation mark
- Pneumothorax
- Scarring
- Breastfeeding difficulties
- Calcium deposits
- Breast tissue atrophy/chest wall deformity
- Connective Tissue Disease (CTD)
- CTD signs and symptoms
- Neurological Disease
- Neurological Signs and Symptoms
- Cancer
- Lymphoma
- Suicide
- Potential Effects on Offspring

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL CLINICAL STUDIES

The preclinical studies are divided into 6 sections: chemistry, toxicology, mechanical testing, modes and causes of device failure, magnetic resonance imaging phantom study, and shelf life.

A. Chemistry Data

1. Extent of Crosslinking

Shell and Patch Materials - The physical strength (tensile strength) and elasticity (elongation at failure) of the shell and patch materials are results of the extent of crosslinking achieved during the vulcanization process. The physical properties of cured samples of all elastomer lots used for breast implant shells and

patches are measured to ensure they meet or exceed pre-established material specifications prior to being released for use in the manufacture of the devices.

This testing demonstrated the extent of crosslinking of the elastomers used in the device shell is sufficient to assure all shells meet a specification of a minimum 3.0 lb break force and 380% elongation.

Gel Materials - Using penetrometer testing, every lot of gel received by Allergan is tested to ensure that the extent of crosslink density conforms to predetermined specifications prior to being released for use in the manufacture of breast implants. In addition, every batch of mixed gel is penetrometer tested to ensure that the penetration conforms to predetermined specifications.

The penetrometer testing on mixed gel lots occurs during the manufacture of every lot of Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants produced by Allergan. Penetrometer samples are obtained from the same batch that is used to fill the implants. The uniformity of the crosslink density across all lots of gel used is thus ensured by conducting penetrometer testing on every batch of mixed gel prior to filling the devices, for each breast implant lot produced. All lots of gel used in the implants have an extent of crosslinking sufficient to achieve the internal penetrometer specification.

2. Extractables

Finished sterilized devices were analyzed for extractables. Table 3 provides the amounts of various low molecular weight components present in the subject device. The techniques used to detect these components include solvent extraction followed by gas chromatography, using both a mass spectrometer (GC-MS) and a flame ionization detector (GC-FID), and by gel permeation chromatography.

The highest level of extracts was isolated using n-hexane as the extracting solvent. Table 3 also lists the concentration of the various oligosiloxanes quantified from hexane extract. Polydimethyl cyclic siloxanes (PDMS) from cyclic dimethyl oligo siloxanes (D_4–D_{21}) were detected and analyzed from extracts of both the shell and gel; polydimethyl linear oligosiloxanes from L_5 to L_{18} were detected in hexane extracts of the gel and shell that had been exposed to gel. Identification of the various low molecular weight components was performed by matching the elution time of the component of the extract with analytical standards, or in some cases extrapolation of the data obtained from these standards. Standards for linear and cyclic polydimethyl siloxanes are commercially available; however, because there are no commercially available standards for diphenyl oligosiloxanes (diphenyl siloxanes or mixed dimethyl diphenyl siloxanes), it is not possible to determine the level of these compounds in the extracts.

Table 3: Concentrations of Low Molecular Weight Silicone Components Detected (in ppm by component weight)

Identification	Molecular Weight (amu)	Gel (ppm)	Implant Shell & Patch (ppm)
D3	222	ND<10	ND<0.1
D4	296	10	ND<0.1
D5	370	8	2
D6	444	46	2
D7	518	35	4
D8	592	23	3
D9	666	17	3
D10	740	63	43
D11	814	88	66
D12	888	52	41
D13	962	59	11
D14	1036	90	16
D15	1110	130	21
D16	1184	127	25
D17	1258	193	25
D18	1332	207	27
D19	1406	240	30
D20	1480	267	34
D21	1554	283	33
L1	236	ND<10	ND<0.1
L2	310	ND<10	ND<0.1
L3	384	ND<10	ND<0.1
L4	458	ND<10	ND<0.1
L5	532	TR<1	ND<0.1
L6	606	2	ND<0.1
L7	680	13	0
L8	754	3	0
L9	828	4	1
L10	902	8	3
L11	976	43	25
L12	1050	15	6
L13	1124	5	8
L14	1198	26	10
L15	1272	30	14
L16	1346	28	61
L17	1420	100	70
L18	1494	97	64

ND = Not Detected (at limit indicated); TR = Trace (at limit indicated)

The extractables testing results are comparable to results seen in previously approved breast implant devices.

3. Volatiles

Analysis for volatiles present in the shell and patch material showed that the maximum exposure possible from implant residuals for isopropyl alcohol to be 201.1 µg and for xylene to be 337.2 µg. Analysis for volatiles present in gel was not necessary because the gel materials do not contain any organic solvents. The volatiles testing results are comparable to results seen in previously approved breast implant devices.

4. Heavy Metals

Complete metal analyses were provided on the individual components of the device. The metal concentrations obtained from the atomic absorption of digested device materials are shown in Table 4 below.

Table 4: Concentrations of Metal Contents Detected (in ppm)

Metal	Atomic Weight (amu)	Gel	Shell (Inner and Outer Layers)	Shell (Barrier Layer)	Patch
Antimony	121.76	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Arsenic	74.92	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Barium	137.33	1	1	1	2
Beryllium	9.01	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Cadmium	112.41	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Calcium	40.08	ND (<10)	ND (<10)	ND (<10)	ND (<10)
Chromium	52.00	0.2	0.3	0.4	1.8
Cobalt	58.93	ND (<0.2)	ND (<0.2)	ND (<0.2)	ND (<0.2)
Copper	63.55	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Iron	55.84	1.2	ND (<0.1)	0.2	8.7
Lead	207.19	0.3	ND (<0.2)	ND (<0.2)	ND (<0.2)
Magnesium	24.30	ND (<10)	ND (<10)	ND (<10)	ND (<10)
Manganese	54.94	ND (<0.05)	ND (<0.05)	ND (<0.05)	0.15
Mercury	200.59	ND (<1)	ND (<1)	ND (<1)	ND (<1)
Molybdenum	95.94	ND (<0.5)	ND (<0.5)	ND (<0.5)	ND (<0.5)
Nickel	58.69	ND (<0.2)	ND (<0.2)	1	0.7
Potassium	39.10	ND (<1)	ND (<1)	8	1
Selenium	78.96	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Silver	107.87	ND (<0.1)	ND (<0.1)	0.2	ND (<0.1)
Sodium	22.99	ND (<10)	ND (<10)	ND (<10)	ND (<10)
Thallium	204.38	ND (<1)	ND (<1)	ND (<1)	ND (<1)
Vanadium	50.94	ND (<0.4)	ND (<0.4)	ND (<0.4)	ND (<0.4)
Zinc	63.40	0.22	0.12	ND (<0.05)	3.9

ND = Not Detected (at limit indicated)

In addition, complete catalyst metal analyses were provided on the individual components of the device. The metal concentrations obtained from the atomic absorption of digested device materials are shown in Table 5 below.

Table 5: Concentrations of Catalyst Metals Detected (in ppm by component weight)

Identification	Atomic Weight (amu)	PQL (ppm)	Gel (ppm)	Implant Shell (ppm)	Patch (ppm)	Total (ppm)
Tin	118.71	0.01	0.06	0.05	6.60	0.077
Platinum	195.08	0.01	4.00	3.30	2.60	3.95

The heavy metal analysis results are comparable to results seen in previously approved breast implant devices.

As a note, platinum is a metal used as a catalyst in the manufacture of the shell and gel components of silicone breast implants. The small amounts of platinum remaining in the product following manufacturing may enter the body, either by diffusing through the intact shell (i.e., through gel bleed) or through an implant rupture. Based on a review of the gel bleed testing, the published literature on this topic, as well as the biocompatibility testing and clinical data on the device, FDA concluded that the platinum contained in breast implants is in the zero oxidation state, which has the lowest toxicity and, thus, does not pose a significant risk to women with silicone breast implants. FDA has posted a Backgrounder on its website, which provides a brief summary of some of the key scientific studies on platinum and silicone gel-filled breast implants (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/UCM064040)

5. Silicone Filler (Silica)

X-ray diffraction studies on the elastomer shell confirmed that the silica used as reinforcing filler material is in the amorphous form, not in crystalline form.

B. Toxicology Data

Allergan provided toxicology data, including pharmacokinetic analysis information, immunotoxicity determinations, reproductive toxicology/teratology and carcinogenicity data regarding the breast implant device. Style 410 Silicone-Filled Breast Implant, the subject of this PMA, was subjected to toxicological risk assessment and concluded to be chemically identical to breast implant Styles 10, 20, 40, 45, 110, and 120 devices which were approved for marketing via P020056. As the Style 410 device gel is constructed from the same silicone materials and uses the same manufacturing methods as the devices that are the subject of P020056, all biocompatibility testing completed for Style 10, 20, 40, 45, 110, and 120 devices was also considered to be applicable to the Style 410 device.

1. Pharmacokinetic Studies

A literature review was completed regarding the pharmacokinetics of silicone elastomers, gel, fluids, and low molecular weight compounds. The reviewed literature included 63 published journal articles and publicly available Dow Corning studies. These studies examined aspects of the Absorption, Distribution, Metabolism or Elimination (ADME) of silicone fluid and low molecular weight silicones. Pharmacokinetic studies of silicone were also reviewed as part of the evaluation performed by the Committee on the Safety of Silicone Breast Implants, Institute of Medicine (IOM). The literature indicates that silicone materials appear to have low mobility, typically remaining where implanted, and eliciting only a local response. The IOM concurs with this perspective stating that the depots of gel, whether free or in implants, remain predominantly where they are implanted.

To independently assess the potential for distribution of silicone post-implantation, a pharmacokinetics study of the silicone gel used in Allergan's Silicone-Filled Breast Implants was performed. The study design consisted of 3 Fischer F-344 female rats that were subcutaneously implanted with approximately 3.4 grams of C^{14} radiolabeled silicone gel for 30 days. After dosing, the rats were housed in individual glass metabolism chambers, which allowed separate collection of carbon dioxide, potential expired volatile chemicals, feces and urine. Blood was drawn throughout the study period. Low amounts of the radiolabel were collected in blood (0.0190% of dose), or were measured cumulatively in expired air (0.0004% of dose), feces (0.0186% of dose) and urine (0.0005% of dose). In regard to individual tissues, the liver, muscle and skin had the highest counts (0.0122%, 0.0055% and 0.0020% of the implanted dose, respectively). The vast majority of the gel remained at the implantation site (~100% of dose), thus demonstrating that the gel was encapsulated, with minimal movement away from the site of implantation. The data are similar to the observations reported in the published scientific literature. The results are comparable to results seen in previously approved breast implant devices.

2. General Toxicity Evaluations

Cytotoxicity

Cytotoxicity testing using mouse L929 cells in the ISO agarose overlay method was conducted in parallel on silicone gel from the previously approved Style 110 breast implant and the current Style 410 breast implant device. Concurrent control groups included a negative control (HDPE) and a positive control (latex). For the acceptance criteria, the negative control must have been a grade of 0 (reactivity none), the positive control must have produced a zone of lysis (reactivity moderate, to severe), and the three monolayers exposed to the test article showed no greater than a grade of 2 (reactivity mild). In the agarose overlay assessment, the negative and positive control groups performed as anticipated, validating the tests. Both products were found to be non-cytotoxic in that neither device showed evidence of causing cell lysis or toxicity.

Minimum essential medium (MEM) extracts of test articles representative of the silicone elastomers and gel materials used in the Style 410 device were also evaluated for cytotoxic effects on mouse L929 fibroblast cells. Shells were extracted at 120cm^2/20-mL extraction medium, while all other remaining components were extracted at 4 g/20-mL extraction medium. Samples were extracted at 37ºC for 24-hours. Cultures containing test material extract medium were incubated at 37ºC for 48-hours. Cells were examined for lysis and changes in cell morphology or cell death following 24- and 48-hours exposure. The results showed that the test articles consisting of the silicone gel filling, shell (also referred to as barrier), patch, adhesive, and orientation marks (same material as patch) met the acceptance criterion of being non-cytotoxic.

3. **Irritation**

Saline, sesame seed oil, polyethylene glycol (PEG), and alcohol in saline (1:10) extracts of test articles representative of the silicone elastomers and gel materials used in the Style 410 gel-filled device were evaluated for irritation in rabbits. Test articles were extracted at the USP-specified ratio of 60 cm^2/20-mL extract solution. Resulting test article extracts composed of the silicone gel filling, shell, patch, adhesive and orientation marks (same material as patch) were injected subcutaneously (individually or as composite samples) at the USP-specified volume and observed for erythema and edema. For the acceptance criterion, the mean macroscopic scores for test implants were compared to mean scores of the control sites. The requirements of the test were met if the difference between test and control score means (macroscopic) was not greater than 1.0. The results showed that none of the test article extracts were irritants.

4. **Acute Systemic Toxicity**

Saline, sesame seed oil, PEG, and alcohol in saline (1:10) extracts of test articles representative of the silicone elastomers and gel materials used in the Style 410 gel-filled devices were evaluated for acute systemic toxicity in mice. Test articles were extracted at the USP-specified ratio of 60 cm^2/20-mL extract solution. Resulting test article extracts composed of the silicone gel fill, shell, patch, adhesive and orientation marks (same material as patch) were then injected intravenously or intraperitoneally into mice (individually or as composite samples) at the USP-specified volumes. Animals were observed for abnormal clinical signs and mortality. If during the observation period, none of the mice treated with the individual test extract exhibited a significantly greater reaction than the corresponding control mice, the test extract met the test requirements. The results showed that none of the test article extracts were toxic.

5. **Hemocompatibility**

Test article (2 g) representative of the silicone elastomers and gel materials used in the Style 410 gel-filled devices was added to 10 mL 0.9% sodium chloride USP solution (SC) to determine whether direct contact with the test article would cause hemolysis *in vitro*. For the acceptance criteria, an average hemolytic index of the triplicate test samples was compared to the negative control. A hemolytic index of

2% or less was considered to be nonhemolytic. Whole rabbit blood (0.2 mL) was added to the test article in SC. A negative control (SC) and USP Purified Water (PW) positive control were similarly prepared but without the test article. Samples examined spectrophotometrically at 545 nm showed a hemolysis value of 0% indicating that the test article was not hemolytic. In a second study, test article (13 g) representative of the silicone elastomers and gel materials used in the Style 410 gel-filled devices was extracted with 65 mL SC at 121ºC for 1 hour to determine whether indirect contact with leachables from the test article would cause hemolysis *in vitro*. Whole rabbit blood (0.2mL) was added to 10 mL of the test article SC extract. A negative control (SC) and PW positive control were similarly prepared but without the test article. Samples examined spectrophotometrically at 545 nm showed a hemolysis value of 0% indicating that the test article was not hemolytic.

6. Pyrogenicity

Test article (39.4 g) representative of the silicone elastomers and gel material used in the Style 410 gel-filled devices was extracted with 197 mL of SC at 121ºC for 1 hour, and then allowed to cool to 37ºC. Three rabbits each received a single intravenous injection of the test extract via the marginal ear vein at 10 mL/kg body weight. Rectal temperatures were measured and recorded at 30-minute intervals between 1 and 3 hours after injection. The test article met the USP criteria because no single animal showed an increase of 0.5ºC or more above its baseline temperature. The test article was determined to be non-pyrogenic.

7. Immunology

Test articles representative of the silicone elastomers and gel material used in the Style 410 gel-filled devices were evaluated for immunotoxicity and dermal sensitization.

- Immunotoxicity – In 5 separate studies, female B6C3F1 mice were subcutaneously implanted for 28-days with 1) 1, 2, or 3 cc silicone gel, 2) 56.52 mm^2, 113.04 mm^2, or 226.08 mm^2 silicone shell, 3) 56.52 mm^2, 113.04 mm^2, or 226.08 mm^2 leaf valve and overlay assembly materials, 4) 56.52 mm^2, 113.04 mm^2, or 226.08 mm^2 patch and overlay assembly material, or 5) 150.8 mm^2, 301.6 mm^2, or 452.4 mm^2 diaphragm valve and plug assembly materials. The immunological parameters evaluated at sacrifice on study Day 29 included: absolute body weight and body weight gain, absolute and relative spleen and thymus weights, thymus histopathology, hematological measurements (e.g., RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet number, WBC, WBC differential), spleen IgM antibody response to the T-dependent antigen, T cell and T cell subsets and B cell enumeration, mixed leukocyte response (MLR) to allogeneic spleen cells, and natural killer (NK) cell activity. For the acceptance criteria, animals were assessed for signs of toxicity.

  In the silicone gel evaluation, there were no statistically significant differences between the test article and control groups for the immunologic assays.

Exposure to the silicone shell also did not affect the immunological functions of the study animals. Although there was a statistically significant increase in the antibody-forming response observed between groups in the study, this was considered related to the historically low response of the control group, as compared to an actual change in activity due to test article exposure.

In the leaf valve and overlay assembly evaluation, the functional ability of the immune system was also not affected, with the possible exception of the percentage of eosinophils, which increased in the low dose group. It was considered, however, that the increase was related to a low percentage of eosinophils in the sham control animals, and no significant increase was seen in the absolute number of eosinophils.

In the diaphragm valve and plug assembly evaluation, the functional ability of the immune system was also not affected, with the possible exception of natural killer cells (NK), which decreased in the low and middle dose groups and increased in the high dose group. It was considered, however, that the physical size and number of implants employed may have contributed to the effects observed in NK activity.

In the patch and overlay evaluation, although some changes were observed in spleen cell number and spleen cell populations, exposure to the test article was concluded to not have adversely affected the functional ability of the immune system.

In conclusion, the data indicate that the test articles did not adversely affect the immune system.

- Sensitization – Saline and sesame seed oil extracts of the silicone shell (60 cm^2/20 mL extraction solution) were used to evaluate the sensitization potential in Hartley Albino guinea pigs by the Magnusson and Kligman method. Positive and negative controls included DNCB and ethanol, respectively. Scoring grades of 1 or greater in the test group generally indicated sensitization, provided that grades of less than 1 were observed on the control animals. The results following induction and challenge showed that the test articles were not irritants or sensitizers.

  In a second study, a complete device was subdivided to expose both inner and outer surfaces and then extracted in cottonseed oil or saline at 121ºC for 1-hour. Other experimental conditions were as described above. The results following induction and challenge showed that the test article (composite sample) was not an irritant or sensitizer.

8. Mutagenicity

Test articles representative of the silicone elastomers and gel material used in the Style 410 gel-filled devices were evaluated for mutagenicity using several standard mutagenicity and genotoxicity assays.

- Bacterial Mutagenicity (Ames Test) – Saline, ethanol, and/or DMSO extracts of silicone elastomer shell, gel, and leaf valve assemblies were evaluated for bacterial mutagenicity in the presence and absence of metabolic activation. Bacterial tester strains included TA98, TA100, TA1535, TA1537, and TA1538.

  For DMSO extract of the test articles (as individually submitted materials), 6 doses were tested, from 2.50 µL to 100 µL per plate. The results showed that the test articles did not cause a positive increase in the number of histidine revertants per plate in any of the tester strains either in the presence or absence of microsomal enzymes prepared from Arochlor-induced rat liver homogenate.

  For ethanol extracts a complete device was apportioned and then tested. Shell test material was extracted at 70ºC for 24 hours at a ratio of 120 cm^2/20 mL ethanol, while gel and leaf valve assembly test materials were extracted at a ratio of 4 g/20 mL ethanol. Other experimental conditions were as described above. The results showed that the test articles did not cause a positive increase in the number of histidine revertants per plate in any of the tester strains either in the presence or absence of microsomal enzymes prepared from Arochlor-induced rat liver homogenate.

  Additional testing of a complete device (slit open to expose inner and outer surfaces) was completed using saline and DMSO and an extraction ratio of 4 g/20 mL extract. Other experimental conditions were as described above. Under the conditions of this study, both saline and DMSO extracts of the test article (complete device) were concluded to be negative in the Salmonella Ames test for mutagenicity.

- CHO/HGPRT Forward Mutation Assay – Ethanol extracts of elastomer and gel test articles were evaluated for mutagenicity with the CHO/HGPRT Forward Mutation Assay in the presence and absence of metabolic activation. The extracts were prepared by extracting the elastomer shell, gel, and leaf valve assembly in ethanol at 70ºC for 24 hours. The shell test materials were extracted at a ratio of 120 cm^2/20 mL ethanol, while the gel and leaf valve assembly were extracted at a ratio of 4 g/20 mL ethanol. Equal volumes of the individual extracts were combined and reduced to 20% of the initial composite volume by evaporation. Mutation assays were performed with and without S9 metabolic activation. In each assay, 5 dose levels were used that included 1.0, 2.5, 5.0, 7.5, and 10.0 µL/mL. The test material was not toxic in either mutation assay at any concentration tested. The mutant frequencies of

treated cultures varied randomly with dose within the range acceptable for background mutant frequencies, i.e., 0-15 x 10^{-6}. The results showed that the test articles were negative for inducing forward mutations at the HGPRT locus in CHO cells with and without S9 metabolic activation.

- *In Vitro* Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in CHO Cells – Ethanol extracts of elastomer and gel test articles were evaluated for mutagenicity in the presence and absence of metabolic activation. The extracts from silicone shell, gel and leaf valve assembly were prepared individually from the test articles in ethanol and were mixed in equal amounts. Replicate cultures of CHO cells were incubated with 1.25 to 5.00 µL/mL of the combined extracts in a 10-hour aberrations assay, with 5.00 to 10.0 µL/mL in a 20-hour aberrations assay under non-activation conditions, and with 1.25 to 10.0 µL/mL in a 10-hour aberrations assay with metabolic activation. No significant increase in cells with chromosomal aberrations was observed at the concentrations analyzed; thus the test articles (shell, gel, and leaf valve assembly) were considered negative for inducing chromosomal aberrations in CHO under both non-activation and activation conditions.

- Mouse Lymphoma Mutagenicity Assay – Saline and DMSO extracts of a complete device were tested in the L5178Y/$TK^{+/-}$ Mouse Lymphoma Mutagenesis Assay in the presence and absence of metabolic activation. The test article was slit open to expose the inner and outer surfaces and extracted at a ratio of 4 g/20 mL extraction medium. The dose levels for mutagenesis ranged from 6.3 to 100 µL/mL for the saline test article and 0.63 to 10 µL/mL for the DMSO test article in both the non-activated and metabolically activated cultures. Under the conditions of this study, saline and DMSO extracts of the test articles were concluded to be negative for mutagenesis.

- Unscheduled DNA Synthesis Assay – Saline and DMSO extracts of a complete device were tested in the Unscheduled DNA Synthesis Assay using primary cultures of rat hepatocytes. The test article was slit open to expose the inner and outer surfaces and extracted at a ratio of 4 g/20 mL extraction medium. The test articles extracts were tested and fully evaluated at 5 dose levels ranging from 6.3 to 100 µL/mL for the saline extract and 0.63 to 10 µL/mL for the DMSO extract. The results of the UDS assay indicate that under the test conditions, neither the saline nor the DMSO extracts of the test article induced a significant increase in the mean number of net nuclear grain counts, i.e., indication of DNA synthetic activity, at any dose level in isolated rat hepatocytes, and therefore, the test article was considered to be negative in this study.

- Cell Transformation Assay – Saline and DMSO extracts of a complete device were tested in the BALB/3T3 cell transformation assay in the presence and absence of metabolic activation. The test article was slit open to expose the inner and outer surfaces and extracted at a ratio of 4 g/20 mL extraction

medium. The assays were conducted with a 3 day exposure in the non-activated test system and with a 4-hour exposure in the metabolically activated system. The dose levels evaluated were 12.5, 25, 50 and 100 µL for the saline test article extract and 1.25, 2.5, 5 and 10 µL for the DMSO extract. No increases in transformation frequency were observed relative to the negative controls in either the activated or non-activated test systems with either extract.

9. Muscle Implantation

Test articles representative of the silicone elastomers used in the shell, patch and overlay system, and diaphragm valve and plug assembly used in the Style 410 gel-filled devices were evaluated for irritation in 90 day muscle implantation studies conducted in New Zealand White rabbits. Test article implantation sites were macroscopically and microscopically assessed, with comparison to a low-density polyethylene control. The gross observations were classified as either non-reactive or slightly reactive, and the microscopic observations were given an overall toxicity rating of zero for each test article. For the acceptance criterion, the mean macroscopic scores for test implants were compared to mean scores of the control sites. The requirements of the test were met if the difference between test and control score means (macroscopic) was not greater than 1.0. The results showed that the test articles were non-toxic.

10. Subchronic Toxicity

Test articles representative of the silicone elastomers used in the shell, patch and overlay system, leaf valve and overlay system, diaphragm valve and plug assembly, and gel material used in the Style 410 gel-filled devices were evaluated in 90 day toxicity studies. Female Fischer 344 rats were evaluated for mortality, body weight, clinical chemistry, hematology, organ weights, organ/body weight or brain weight ratios, and tissue histopathology. For the acceptance criterion, the animals were assessed for toxicity. The histopathological findings at the implant site were those typically associated with the implantation of test article and included fibrous encapsulation. The histological findings in non-implant, distant site tissues were considered typical for the animals at their age and occurred in similar frequency and severity among the control and implanted groups. The results demonstrated that the test articles did not produce subchronic toxicity in rats.

11. Chronic Toxicity and Carcinogenicity

Test articles representative of the silicone elastomers used in the shell, patch and overlay system, leaf valve and overlay system, diaphragm valve and plug assembly, and gel material used in the Style 410 gel-filled devices were subcutaneously implanted in female Fisher 344 rats. The elastomers were pulverized prior to implantation. For the acceptance criterion, the animals were assessed for toxicity. No evidence of systemic toxicity or carcinogenicity, other than solid state tumorigenicity, was observed in association with the test articles. The incidence and type of histologic findings other than those related to the presence of a foreign body reaction were typical of Fischer 344 rats and were not considered test article related. Encapsulation of pulverized low-density polyethylene control or elastomer test article varied somewhat from that of the gel due to their differing physical characteristics.

Whereas the connective tissue septa penetrated between separate pulverized polyethylene or elastomeric particles, the connective tissue septa surrounded but did not penetrate the gel. As previously stated, solid state tumorgenicity was observed in the studies. This is a typical finding for this type of study, as it is a known rodent-specific response to the implantation of materials.

With respect to solid state tumorigenicity, important discussion may be found in ISO 10993-3, Annex C (informative) – Role of implantation carcinogenicity studies, §C.1 a-f, §C.2 – The process and rationale of decision, and §C.3 – Carcinogenicity studies performed as implantation tests. Importantly, in §C.2 it is noted that representatives from European, Japanese, and U.S regulatory bodies agreed that no decision on carcinogenic risk has been made on the basis of solid state carcinogenesis alone. In the few examples known, where decisions on carcinogenic risk were made using solid state carcinogenesis results, there had always been supporting data, such as mutagenicity data. Noteworthy, the current test articles were negative for mutagenicity testing (Salmonella Reverse Mutation Assay (Ames test), CHO/HGPRT Forward Mutation Assay, Chromosome Aberration Frequencies in CHO cells, Mouse Lymphoma Mutagenicity Assay, Unscheduled DNA Synthesis Assay, and a Cell Transformation Assay, all with and without microsomal activation), and the US FDA has previously determined that bacterial mutagenesis, mammalian mutagenesis, and DNA damage had been adequately addressed. Such foreign body reactions resulting in solid state tumorigenicity have long been documented in the literature (cf. Oppenheimer BS, Oppenheimer ET Stout AP (1948) Sarcomas induced in rats by implanting cellophane. *Proc. Soc. Exp. Biol. Med.*, **67** (33); Bischoff F, Bryson G (1964) Carcinogenesis through solid state surfaces. Prog. Exp. Tumor Res. 5: 85-133; and, Brand KG, Johnson KH, Buoen LC, Golberg L (1976) Foreign body tumorigenesis. *Critical Reviews in Toxicology*, 4(4): 353-394) and are discussed extensively in IARC Monographs Volume 74, Surgical implants and other foreign body reactions, §4B.22.1 and 5B.4.1.

12. Reproductive Toxicology

A literature review was completed regarding reproductive and developmental toxicity studies on silicone elastomers, gel, fluids, and low molecular weight compounds. The reviewed literature included 33 published journal articles and publicly available Dow Corning studies. The literature indicated that the silicone materials are neither reproductive nor developmental toxins.

In addition, a 2-generation reproductive toxicology study was performed evaluating the elastomer materials used in gel-filled devices. The test article, gel-exposed patched shells, was pulverized and subcutaneously implanted in F_0 generation female Sprague-Dawley rats of the test article group at a dose of 2 g/kg. The control female animals underwent a sham control surgery. F_0generation female rats were then mated and allowed to deliver their litters (F_1generation pups). F_1 generation offspring were evaluated during the lactation period. At the time of weaning, sufficient numbers of F_1 generation male and female rats in both the

control and test article groups were selected to continue on in the study. Those animals not selected were sacrificed.

Subsequently, the female F_1 generation animals in the test article group were implanted with the test article at a dose of 2 g/kg and the female control animals underwent a sham surgery. Upon reaching maturity, some F_1 generation male and female adult animals were sacrificed to evaluate reproductive organs and selected endocrine tissues. The majority of the F_1 generation male and female rats were mated. The F_1 generation females were allowed to deliver their litters (F_2 generation pups). F_2 generation offspring were evaluated throughout the lactation period, and then the dams and pups were sacrificed.

The resulting mating indices demonstrated that the F_0 generation and F_1 generation animals in both the test article and the sham control groups were capable of successful mating and subsequent delivery of live pups. Furthermore, there were no significant histological differences observed between the test article and sham control groups with respect to the reproductive organs and selected endocrine tissues of male and female F_1 generation rats. Overall, there were no biologically significant differences observed between the control and implanted groups in any of the adult F_0 generation and F_1 generation parental parameters or F_1 generation and F_2 generation offspring parameters evaluated as part of this 2 consecutive generation reproductive toxicity study.

13. Developmental Toxicity (Teratology)

Test articles representative of the silicone elastomers used in the Style 410 device were evaluated in 3 separate studies. In the first, the gel material was subcutaneously implanted between the scapula of female CD Sprague-Dawley rats. The animals were exposed to either 0.62, 7.28 or 14.79 g/kg test article. In a second study, 2 g of pulverized complete device materials representative of the Style 410 device (0.3 to 1.0 mm particle size) were implanted subcutaneously in the dorsal area of the back. In a third study, 2 g of pulverized test materials representative of the patch materials used in the Style 410 device were also implanted subcutaneously in the dorsal area of the back. Treated females were mated, and litters were evaluated between Days 20 and 25 (depending on study) of gestation. For all studies, there were no biologically significant differences observed between the controls and the implanted groups for the maternal dam and fetal pup parameters evaluated, including pregnancy rates, dam organ weights, and fetal survival, weight, sex and morphological development. The results showed that the gel and pulverized patch/gel/shell material did not produce developmental effects.

C. Mechanical Data

This section includes a summary of the fatigue, gel bleed, and gel cohesion testing that Allergan provided in support of establishing the safety of their product.

1. Fatigue Rupture

Implants (125 cc) with the LF profile (Style 410LF) were chosen for fatigue testing as representative of Allergan's Highly Cohesive product line. Although the LF profile is not proposed in this application, the surface area of the 125 cc implants with the LF profile is less than the surface areas of the implants proposed in this PMA; therefore, the 125 cc implants with the LF profile represent a worst case for fatigue testing. All implants tested were final, sterilized versions with the minimum allowable radial shell thickness. The test set-up consisted of a uniaxial test fixture of parallel plates. Testing was performed under ambient laboratory conditions in air. The applied cyclic loads ranged from 10 to 55 lbs. Testing was performed at 1 Hz for all applied loads. A minimum of 3 implants for each style was tested for each load level. Runout was defined as 6.5 million cycles. The resulting endurance load level was 10 lbs. As expected, based on the test set-up, all fatigue failure modes were radial tears. FDA believes that these data demonstrated that the Allergan product can withstand physiological static loading and in-vivo cyclic loading. . In addition, the results are comparable to the results seen in approved breast implants.

2. Gel Bleed

Allergan provided testing to identity the gel bleed constituents (including the platinum species [or other catalysts]), the rate that the gel constituents bleed out, and how that rate changes over time. Allergan's test method, which was designed to mimic in-vivo exposure to silicone gel-filled breast implants, involved the incubation of smooth implants in bovine serum at 37ºC. At specific timepoints, samples of the solution were withdrawn for analysis for low molecular weight (LMW) silicones and platinum. The results indicated that the diffusion of measured constituents essentially ceased by 90 days and that measurable amounts of silicones from D4 to D21 and from MD2M to MD19M diffused into the serum over that period.

Through 90 days immersion of the Style 410 devices (125 gm size) in bovine serum, the cumulative amount of LMW observed silicone release was 470 μg and the observed rate of total LMW silicone gel bleed leveled off at approximately 13 $ng/cm^2/day$. This suggests that the total cumulative LMW silicones released through 10 years for even the largest of Allergan's Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants (775 gm) would be less than 23.7 mg in this physiologically relevant model. This represents less than 0.003% of the total weight of the silicone in the implant, indicating that over 99% of the LMW silicones and platinum stayed in the implant.

With regard to the health consequences of gel bleed, the literature has reported small quantities of LMW silicone compounds, as well as platinum (in zero oxidation state), have been found to diffuse ("bleed") through an intact implant shell.[i,ii] The evidence is mixed as to whether there are any clinical consequences

associated with gel bleed. For instance, studies on implants implanted for a long duration have suggested that such bleed may be a contributing factor in the development of capsular contracture[ii] and lymphadenopathy.[iii] However, evidence against gel bleed being a significant contributing factor to capsular contracture and other local complications is provided by the fact that there are similar or lower complication rates for silicone gel-filled breast implants than for saline-filled breast implants. Saline-filled breast implants do not contain silicone gel and, therefore, gel bleed is not an issue for those products. Furthermore, toxicology testing has indicated that the silicone material used in the Allergan implants does not cause toxic reactions in test animals. It should also be noted that studies reported in the literature have demonstrated that the low concentration of platinum contained in breast implants is in the zero oxidation (most biocompatible) state.[iv,v,vi,vii] The overall body of available evidence supports that the low level of gel bleed for Allergan's product is of no clinical consequence. In addition, the results are comparable to the results seen in approved breast implants.

3. Gel Cohesivity

Gel cohesivity and penetration testing assess the cohesive and cure characteristics of silicone gel, respectively. Gel cohesivity testing was performed as per ASTM F703 (cone/pendant method) using gel from final finished product. Of the 289 samples tested, the average pendant length was 0.0 cm (range of 0.0-0.8cm), which meets the ASTM F703 specification of <4.5cm. Gel penetration testing was performed as per an Allergan test method involving measurement of the penetration of a plunger into in-process gel in a jar. All samples passed Allergan's internal penetration specification.

D. Modes and Causes of Device Failure

Rupture

Allergan provided numerous test reports and other information to characterize modes and causes of failure of their device for a range of in-vivo times, such as failure analyses of retrieved devices (i.e., retrieval study), physical property testing, assessment of manufacturing processes and surgical techniques that may impact rupture, and a review of the explant literature.

The primary set of modes and causes of rupture data was a retrieval study that involved 2,390 explanted Style 410 devices (IDE and Worldwide returns) that were returned to the Allergan Device Analysis Laboratory. Of the devices returned, 512 were categorized as failed devices. The samples analyzed were explanted anywhere from time 0 (damaged during the implantation procedure and, thus, not implanted) to over 10 years after implantation. For these 512 explants, the failure modes were surgical instrument damage (n=267); unidentified openings (n=208); surgical impact (n=16); manufacturing (n=14); and fold flaw (n=7). FDA determined that these data

are adequate to characterize the modes and causes of rupture through approximately 10 years. See Section XI below for more details.

Gel Fracture

Gel fracture, or a fissure, or crack, in the gel, has been reported in the Natrelle 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants. About 16.2% (n=386) of the 2,390 explanted Style 410 devices (IDE and Worldwide returns) that were returned to the Allergan Device Analysis Laboratory implants showed signs of gel fracture. Manipulation during explantation may have caused additional fractures. The occurrence of gel fracture was low, and it was noted that the rupture rate did not increase with the reported gel fractures. While there were no clinical consequences of gel fractures seen in the study, any clinical consequences of gel fracture will be investigated further in the post-approval studies.

E. Magnetic Resonance Imaging (MRI) Phantom Study

1. MRI Use for Rupture Detection

Allergan provided data showing that MRI remained a definitive tool for diagnosing the rupture/intact status of their highly cohesive implants.

Allergan performed an *in vitro* phantom MRI study using both Natrelle® Silicone-Filled Breast Implants (P020056) and their implant with a more cohesive gel, Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast implants. This *in vitro* study was designed to determine if there were significant differences in rupture detection based on the differences in the two gel types used in the two different styles of implants.

The comparative study was conducted on 40 implants (20 style 410 and 20 round approved silicone implants) of differing sizes. Fine-line ruptures were created at specific points using a scalpel. Ruptures were not opened or manipulated further. Two implants were randomly suspended in each container in agar and subjected to MRI. Each implant contained 0 to 4 ruptures of 2 cm size on the anterior region (front of the implant) and 0 to 4 ruptures on the peripheral edge placed in specified quadrants of the implant according to a SAS randomization table. Images were collected, stored on CD, and read in a blinded fashion by two MRI expert physician reviewers. The presence or absence of a rupture in each quadrant on the anterior or peripheral region of the implant was determined and declared to be positive if at least 1 of the 2 reviewers identified it. Sensitivity was determined by the number of positively identified quadrants with ruptures per total with each style of implant. Specificity was determined by the number of quadrants without ruptures correctly identified per total negative quadrants. Data collected on both types of implants was compared and is summarized in the Table 6 below.

Table 6 : Comparative Study Results For Rupture Diagnosis

	Number of Correctly identified quadrants with or without a rupture per total (%)	
	Style 410	**Approved Round**
Sensitivity*	40/82 (49%)	47/82 (57%)
Specificity**	54/78 (69%)	52/78 (66%)

* Number or percent of correctly identified ruptures per total quadrants with ruptures; 95% confidence interval for 410 = 37.6 to 68.2 and for Approved Round= 45.9 to 68.2
** Number or percent of correctly identified quadrants without rupture per total quadrants without rupture; 95% confidence interval for 410= 57.8 to 79.2 and for Approved Round= 55.1 to 76.9

Allergan concluded that no significant difference was observed in the sensitivity or specificity of MRI detection of fine-line ruptures in this study and that this *in vitro* study indicates that the detection of fine line ruptures in the 410 device with a more cohesive silicone gel is comparable to that for the approved silicone implants

2. MRI Use for Gel Fracture Detection With and Without Implant Rupture

Allergan clarified that gel fracture and implant rupture can be distinguished on MRI, using either 1.5T or 3.0T, and that gel fracture will not mask rupture. Testing showed that although air voids and/or shell deformation can be identified at both 1.5T and 3.0T, when a rupture to the shell is introduced, the air in the void dissipates through the rupture and the fracture is no longer visible under either setting. The only imaging signature present is that of a distinguishable shell rupture.

In the clinical study, gel fracture was seen within the intact shell due to excessive compressive forces, where, upon release of the force, the gel sections may not immediately return to their original position. *In vitro*, gel fracture results in a fissure with an air void with or without a distortion in the shape of the implant. Imaging via MRI identified this gel fracture and air void as dark shaded areas within the implant. Conversely, imaging of shell rupture by MRI are recognized as an inverted loop, subcapsular line, linguini sign, or extracapsular silicone without intracapsular sign.

F. Shelf Life Data

Allergan's shelf life testing was performed on representative devices (gel cohesion, tension set, shell/patch joint strength, ultimate elongation, and break force) and the package (thermoform dye penetration and peel seal strength). Validated accelerated test results were the primary set of data used to establish the shelf life of the Allergan product. All device and package testing met the acceptance criteria set in the protocol. Accordingly, the data supported a 5-year shelf life for the Allergan product.

X. SUMMARY OF THE ALLERGAN STYLE 410 CORE STUDY

Allergan performed a clinical pivotal study to establish a reasonable assurance of safety and effectiveness of the Natrelle® Style 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants for breast augmentation, reconstruction and/or revision in the US under IDE # G000201. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were implanted between February 5, 2001 and February 28, 2002. The database for this PMA reflected data collected through September 8, 2009.

The Allergan Style 410 Core Study is a prospective, 10-year, multicenter, single arm observational clinical study conducted across 47 investigational sites in 941 women undergoing breast augmentation, reconstruction and revision operations. Patients are serially followed at 4 weeks, 6 months, 1 year, and annually thereafter through 10 years. A subset of patients was consented to receive MRIs at years 1, 3, 5, 7, and 10 years to screen for silent breast implant rupture. There were originally 2 patient cohorts—those screened for silent rupture by MRI and those who were not screened for silent rupture by MRI. On May 27, 2008, the study protocol was revised to include MRI evaluations for those patients not originally consented to receive periodic scheduled MRIs (known as non-MRI patients) who are MRI-eligible and consent to undergo MRI at Years 7 and 10. The results through 7-year patient follow-up are reported, and the study remains ongoing.

Key aspects of the protocol are as follows:

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the Core study was limited to patients who met the following inclusion criteria:

- Female, age 18 years or older
- Patient presents with one or more of the following conditions:
    i. **Primary breast augmentation** (i.e., no previous breast implant surgery) indicated for the following:
        - Patient dissatisfaction with size or shape of breast (e.g., mammary hypoplasia)
        - Asymmetry
        - Ptosis
        - Aplasia

ii. **Primary breast reconstruction** (i.e., no previous breast implant surgery other than implantation of tissue expanders or contralateral augmentation for asymmetry) indicated for the following:
    - For affected breast(s):
        - Mastectomy for cancer
        - Prophylactic mastectomy
        - Breast trauma (resulting in mastectomy)
    - For the unaffected (contralateral) breast
        - Contralateral asymmetry (may be performed on the date of the mastectomy or the date when permanent implants are placed in the reconstructed breast)

iii. **Breast implant revision surgery** (i.e., removal and replacement of breast implants) indicated for the following:
    - Previous augmentation or reconstruction with silicone-filled or saline-filled breast implants

- Adequate tissue available to cover implants
- Patients at MRI designated sites must be willing to undergo MRI at their 1, 3, 5, 7, and10-year follow-up visits (serial MRI). The patient must be eligible for MRI (for example, no implanted metal or metal devices and no history of severe claustrophobia that may make her ineligible for MRI).
- Patient is willing to follow all study requirements, including agreeing to attend all required follow-up visits, and accepts the risks involved as indicated by signing and dating (at the same time as the signature) the study Patient Informed Consent prior to surgery

Patients were <u>not</u> permitted to enroll in the Core study if they met any of the following exclusion criteria:

- Advanced fibrocystic disease considered to be premalignant without accompanying subcutaneous mastectomy
- Existing carcinoma of the breast, without mastectomy
- Abscess or infection in the body at the time of enrollment
- Pregnant or nursing
- Have any disease, including uncontrolled diabetes (e.g., Hb AIc > 8%), that is clinically known to impact wound healing ability
- Show tissue characteristics that are clinically incompatible with mammoplasty, such as tissue damage resulting from radiation, inadequate tissue, compromised vascularity or ulceration
- Have, or under treatment for, any condition that may constitute an unwarranted surgical risk (e.g., unstable cardiac or pulmonary problems)
- Show psychological characteristics that may be incompatible with the surgical procedure and the prosthesis, such as inappropriate attitude or motivation (e.g., body dysmorphic disorder)
- Are not willing to undergo further surgery for revision, if medically required

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 4 weeks, 6 months, 1 year, and annually through 10 years. Patient medical histories and baseline clinical data were collected preoperatively. Rupture is assessed for patients who have scheduled MRIs serially throughout the study. The follow-up schedule is shown in Table 7 below:

Table 7: Follow-up Schedule of Core Clinical Study

Data Collected[A]	**Enrollment**	**Prior to Explant**	**0-4 wks**	**6 mo**	**1 yr**	**2 yr**	**3 yr**	**4 yr**	**5 yr**	**6 yr**	**7 yr**	**8 yr**	**9 yr**	**10 yr**
Eligibility/ Screening	x													
Scheduled Visit			x	x	x	x	x	x	x	x	x	x	x	x
Quality of Life Questionnaire	x				x	x								
Activities and Lifestyle Index	x				x	x		x		x		x		x
MRI Central Reviewer Reading[B]		x			x		x		x		x			x
MRI Investigational Site Reading[B]		x			x		x		x		x			x
Documentation Photographs	x				x									

[A] Complications/treatment, secondary procedures, explants, connective tissue diseases, breast cancer diagnoses, unanticipated adverse events, and discontinuation information were collected any time throughout the study as applicable.

[B] Originally there were two cohorts, an MRI cohort that underwent serial MRI at 1, 3, 5, 7, and 9 years, and a non-MRI cohort that did not undergo serial MRIs. On May 27, 2008, FDA approved a protocol revision so that non-MRI patients who were MRI-eligible and consented would also receive MRI evaluations at the 7 and 10 year follow-up time points.

3. Clinical Endpoints

Safety assessments include local complication rates (e.g., infection, capsular contracture), implant-related complications (e.g., wrinkling, asymmetry), device failure (e.g., implant rupture, gel fracture), and reasons for reoperation and implant removal. A qualitative analysis is performed on patients who experience a systemic condition (e.g., connective tissue disease), breast cancer, or other adverse event.

Effectiveness assessments include change in breast size (augmentation patients only), patient and physician satisfaction with outcome (augmentation,

reconstruction and revision patients), and quality of life (QoL) (augmentation and reconstruction patients). QoL is comprised of measures of self-esteem, body image and general health outcome.

4. Prespecified Analysis Plan

All statistical methods were established prior to conducting the analyses. All patients implanted with the study device contributed to the analyses. Descriptive statistics, appropriate to the type of variable and scale of measurement, were provided. All analyses were performed separately for each indication cohort, except where noted below.

All safety outcomes were summarized descriptively, separately by cohort. For key outcomes, Kaplan-Meier product limit survival analyses were performed and the cumulative risk of first occurrence reported. For each reported follow-up timepoint, the complication rate estimate is provided along with the associated 95% confidence interval. Effectiveness and survey-based outcomes were summarized descriptively, separately by cohort. An analysis of potential risk factors that are related to key safety outcomes was performed using multiple logistic regression.

If a primary study implant for augmentation or reconstruction is removed and replaced with another device ("secondary implant"), data continue to be gathered on the secondary study implant, adhering to the patient's same ongoing study schedule as for the primary implant. However data collected on these secondary implants are not included in the primary analysis with the exception of patient quality of life and satisfaction. Outcomes following replacement surgery are presented in the Revision cohorts identified as Revision-Augmentation and Revision-Reconstruction. For patients having all study implants removed without replacement, the patient is followed by telephone follow-up on the same follow-up schedule to track development and/or duration of adverse events.

For patients enrolled into the study for one side only (i.e. unilaterally) who later receive a study device on the contralateral side, all by-patient analyses are performed based on the surgery date for the patient's first implant. All by-implant analyses are based on the separate implant surgery dates for each device.

The rate of rupture in the MRI cohort was calculated as a Kaplan-Meier rate with censoring at the time of last MRI. If a patient had no MRI assessments, she was considered censored immediately after implantation. The numerator for this Kaplan-Meier calculation included both explant-confirmed ruptures and unconfirmed but suspected ruptures (suspected due to imaging or physical exam). In addition, if a patient had a symptomatic rupture, this patient was included in the numerator and the implant was considered ruptured at the time of the symptomatic rupture. For the non-MRI cohort in the Core Study, the rupture rate was calculated using the same methodology at the timepoints when MRI screening was performed.

B. Accountability of PMA Cohort

At the time of database lock, of 941 patients enrolled in the PMA study, 656 patients are available for analysis at the 7-year follow-up timepoint. Taking into account patients who died or had all study devices removed without replacement with other study devices, follow-up compliance was 76.4%.

1. Augmentation, Reconstruction and Revision Cohorts

The study consists of 941 patients of which data are available through 7 years. The study is divided into four cohorts including 492 primary augmentation patients, 156 revision-augmentation patients, 225 primary reconstruction patients and 68 revision-reconstruction patients. The 7-year follow-up rates by cohort are 74.9% (356) for augmentation, 81.3% (152) for reconstruction, 73.8% (104) for revision augmentation, and 77.2% (44) for revision reconstruction. Tables 8 through 11 below provide a tabulation of patient compliance with study visits.

To assess the representativeness of the responder results to those patients who did not provide data, additional analyses were performed for cohorts having less than an 80% rate of patient follow-up at 7 years. These analyses are described in section c.

Table 8: Patient Accountability for the Augmentation Cohort

	0-4 weeks	6 months	1 year	2 years	3 years	4 years	5 years	6 years	7 years
Theoretically Due	492	492	492	492	492	492	492	492	492
Deaths	0	0	0	0	0	0	0	0	0
Explant-Related Discontinuations	0	1	2	6	7	9	10	13	17
Replacement with non-study device	0	0	1	5	5	7	8	11	13
Unknown replacement status	0	1	1	1	2	2	2	2	4
Expected	492	491	490	486	485	483	482	479	475
Actual Evaluated	492	473	466	436	422	409	390	350	356
Lost-to-Follow-Up	0	18	24	50	63	74	92	129	119
% Follow-Up	100%	96.3%	95.1%	89.7%	87.0%	84.7%	80.9%	73.1%	74.9%

Table 9: Patient Accountability for the Reconstruction Cohort

	0-4 weeks	6 months	1 year	2 years	3 years	4 years	5 years	6 years	7 years
Theoretically Due	225	225	225	225	225	225	225	225	225
Deaths	0	0	0	2	6	10	13	15	15
Explant-Related Discontinuations	0	4	5	5	9	14	17	22	23
Replacement with non-study device	0	4	4	4	7	12	15	20	21
Unknown replacement status	0	0	1	1	2	2	2	2	2
Expected	225	221	220	218	210	201	195	188	187
Actual Evaluated	225	209	215	200	191	181	175	156	152
Lost-to-Follow-Up	0	12	5	18	19	20	20	32	35

% Follow-Up	100%	94.6%	97.7%	91.7%	91.0%	90.0%	89.7%	83.0%	81.3%

Table 10: Patient Accountability for the Revision-Augmentation Cohort

	0-4 weeks	**6 months**	**1 year**	**2 years**	**3 years**	**4 years**	**5 years**	**6 years**	**7 years**
Theoretically Due	156	156	156	156	156	156	156	156	156
Deaths	0	0	0	0	0	0	0	0	0
Explant-Related Discontinuations	0	1	4	6	9	11	11	13	15
Replacement with non-study device	0	1	4	6	9	11	11	13	14
Unknown replacement status	0	0	0	0	0	0	0	0	1
Expected	156	155	152	150	147	145	145	143	141
Actual Evaluated	156	146	145	137	127	117	117	108	104
Lost-to-Follow-Up	0	9	7	13	20	28	28	35	37
% Follow-Up	100%	94.2%	95.4%	91.3%	86.4%	80.7%	80.7%	75.5%	73.8%

Table 11: Patient Accountability for the Revision-Reconstruction Cohort

	0-4 weeks	**6 months**	**1 year**	**2 years**	**3 years**	**4 years**	**5 years**	**6 years**	**7 years**
Theoretically Due	68	68	68	68	68	68	68	68	68
Deaths	0	0	0	1	1	1	2	2	2
Explant-Related Discontinuations	0	0	0	2	4	6	7	8	9
Replacement with non-study device	0	0	0	2	3	4	4	5	6
Unknown replacement status	0	0	0	0	1	2	3	3	3
Expected	68	68	68	65	63	61	59	58	57
Actual Evaluated	68	64	64	59	59	54	52	48	44
Lost-to-Follow-Up	0	4	4	6	4	7	7	10	13
% Follow-Up	100%	94.1%	94.1%	90.8%	93.7%	88.5%	88.1%	82.8%	77.2%

2. MRI Cohorts

A total of 316 patients were originally enrolled in the MRI sub-study of the Core study to screen for silent breast implant rupture. This includes 150 primary augmentation patients, 45 revision augmentation patients, 96 primary reconstruction patients and 25 revision-reconstruction patients. As previously stated, FDA approved a protocol revision on May 27, 2008 so that *all* enrolled patients—both the MRI and non-MRI cohorts—who were MRI-eligible and consented would undergo MRI evaluations at the 7-year and 10-year follow-up time points. Therefore, the number of patients theoretically due at the 7-year timepoint was changed to 317 primary augmentation patients, 88 revision-augmentation patients, 146 primary reconstruction patients and 39 revision-reconstruction patients. The 7-year MRI compliance rate in the MRI cohort was 69.6% for the augmentation cohort, 81.6% for the revision augmentation cohort, 67.2% for the reconstruction cohort and 83.3% for the revision reconstruction cohort. Tables 12 through 15 below present patient accounting for the MRI cohort.

Table 12: Patient Accountability for MRI Evaluations – Augmentation

	1 year	3 years	5 years	7 years (MRI cohort)	7 years (Non-MRI cohort)
Theoretically Due	150	150	150	150	167
Deaths	0	0	0	0	0
Discontinued Due to Claustrophobia/ Metal-Implanted Devices	0	0	1	2	0
Explant-Related Discontinuations	0	2	5	13	3
Expected	150	148	144	135	164
Actual Evaluated	124	127	119	94	120
Lost-to-Follow-Up	26	21	25	41	44
% Follow-Up	82.7%	85.8%	82.6%	69.6%	73.2%

Table 13: Patient Accountability for MRI Evaluations – Revision-Augmentation

	1 year	3 years	5 years	7 years	7 years (Non-MRI cohort)
Theoretically Due	45	45	45	45	43
Deaths	0	0	0	0	0
Discontinued Due to Claustrophobia/ Metal-Implanted Devices	0	2	2	2	0
Explant-Related Discontinuations	0	3	4	5	2
Expected	45	40	39	38	41
Actual Evaluated	37	33	31	31	30
Lost-to-Follow-Up	8	7	8	7	11
% Follow-Up	82.2%	82.5%	79.5%	81.6%	73.2%

Table 14: Patient Accountability for MRI Evaluations – Reconstruction

	1 year	3 years	5 years	7 years	7 years (Non-MRI cohort)
Theoretically Due	96	96	96	96	50
Deaths	0	4	6	6	0
Discontinued Due to Claustrophobia/ Metal-Implanted Devices	0	3	4	3	0
Explant-Related Discontinuations	8	16	22	29	0
Expected	88	73	64	58	50
Actual Evaluated	80	64	56	39	37
Lost-to-Follow-Up	8	9	8	19	13
% Follow-Up	90.9%	87.7%	87.5%	67.2%	74.0%

Table 15: Patient Accountability for MRI Evaluations – Revision-Reconstruction

	1 year	3 years	5 years	7 years	7 years (Non-MRI cohort)
Theoretically Due	25	25	25	25	14
Deaths	0	0	0	0	0
Discontinued Due to Claustrophobia/ Metal-Implanted Devices	0	0	0	0	0
Explant-Related Discontinuations	1	2	4	7	2
Expected	24	23	21	18	12
Actual Evaluated	23	23	19	15	4
Lost-to-Follow-Up	1	0	2	3	8
% Follow-Up	95.8%	100%	90.5%	83.3%	33.3%

C. Study Population Demographics and Baseline Parameters

Demographic information for the Core Study with regard to race is as follows: 92% were Caucasian, 3% were Hispanic, 2% were Asian, 2% were African American, and 1% were other. The median age at surgery was 36 years for primary augmentation patients, 44 years for revision-augmentation patients, 48 years for primary reconstruction patients, and 52 years for revision-reconstruction patients. Approximately 65% of the Pivotal Study patients were married, and approximately 82% had some college education. Table 16 below presents the study population demographics at baseline by cohort.

Table 16: Patient Demographics by Cohort

	All Cohorts	Augmentation (n = 492)	Reconstruction (n = 225)	Revision-Augmentation (n = 156)	Revision-Reconstruction (n = 68)	MRI (n=316)	Non-MRI (n=625)
Race:							
Caucasian	91.5%	90.5%	90.7%	94.9%	94.1%	92.1%	91.2%
Hispanic	3.0%	4.0%	0.4%	2.6%	4.4%	0.9%	4.0%
Asian	2.3%	3.0%	3.1%	0.0%	0.0%	2.8%	2.1%
African American	1.5%	0.8%	4.0%	0.6%	0.0%	1.6%	1.4%
Other	1.3%	1.6%	0.9%	0.6%	1.5%	1.3%	1.3%
Not Provided	0.4%	0.0%	0.9%	1.3%	0.0%	1.3%	0
Median Age[A]	40	36	48	44	52	42	40
Median BMI (Range)	21.1 (15.8-42.8)	20.6 (15.8 - 33.3)	22.6 (17.1 - 41.6)	21.0 (16.0 - 36.4)	22.4 (18.1 - 42.8)	21.3 (16.0-36.4)	21.1 (15.8-42.8)
Married	65.1%	59.8%	71.6%	69.2%	73.5%	69.0%	63.2%
College Education[B]	81.8%	81.7%	81.8%	80.8%	85.3%	82.6%	81.4%

[A] at time of surgery

[B] includes some college education, college graduates, post college education

With respect to surgical baseline factors in the Core study, for primary augmentation patients, the most frequently used devices were full height with moderate projection (49.3%), the most common incision site was inframammary (86.8%), and the most frequent site of placement was submuscular (84.3%). The majority of patients (79.1%) enrolled for augmentation and the remaining patients enrolled for cosmetic augmentation with accompanying conditions as follows: 10.6% asymmetry, 6.7% ptosis, and 3.7% aplasia.

For revision-augmentation patients, the most frequently used devices were full height with full projection (37.1%), the most common incision site was inframammary (76%), and the most frequent site of placement was submuscular (71.6%).

For primary reconstruction patients, the most frequently used devices were full height with full projection (40.1%), the most common incision site was the mastectomy scar (75%), and the most frequent site of placement was submuscular (87.6%).

For revision-reconstruction patients, the most frequently used devices were full height with full projection (62.5%), the most common incision site was mastectomy scar (54%), and the most frequent site of placement was submuscular (91.9%).

Table 17: Surgical Baseline Factors by Cohort

	All Cohorts	**Augmentation (n = 983)**	**Reconstruction (n = 354)**	**Revision-Augmentation (n = 310)**	**Revision-Reconstruction (n = 112)**
Style Number					
410FM	38.3%	49.3%	23.4%	31.3%	8.9%
410FF	30.8%	21.9%	40.1%	37.1%	62.5%
410MM	19.9%	21.9%	14.7%	22.9%	10.7%
410MF	10.9%	6.9%	21.8%	8.7%	17.9%
Placement Site[A]					
Submuscular	83.2%	84.3%	87.6%	71.6%	91.9%
Subglandular	14.0%	15.7%	0.3%	28.4%	2.7%

[A] Other placement sites included subcutaneous and subtissue flap

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on data from 941 patients enrolled in the Core study of which 656 patients were available for the 7-year evaluation. The overall 7-year cumulative complication rates, reasons for reoperation, and reasons for implant removal for this study are presented below in Tables 18 to 20. Details describing cumulative risk at each follow-up assessment point for first occurrence of each complication are detailed in Tables 21 to 50. Other clinical safety outcomes are described in section d below.

a. 7-year Cumulative Complication Rates

The 7-year, by-patient, cumulative Kaplan-Meier (KM) risk rates of first occurrence (95% confidence interval) of complications are shown in Table 18 below. For details on the cumulative risk at each follow-up assessment point for first occurrence of each of the listed complications, refer to Tables 21 to 50.

Table 18: 7-year Cumulative Complication Rates by Cohort

KM Rates through 7 Years[a, b]		Primary Augmentation[c]	Revision-Augmentation[d]	Primary Reconstruction[e]	Revision-Reconstruction[f]
		N=492	N=156	N=225	N=68
Any complication (including reoperation)		31.0% (27.0, 35.5)	47.7% (39.9,56.2)	53.0% (46.5, 59.8)	57.2% (45.7,69.2)
Any reoperation		22.4% (18.8, 26.6)	37.7% (30.3, 46.2)	45.2% (38.7, 52.1)	38.6% (27.9, 51.7)
Implant removal with or without replacement		12.6% (9.8, 16.1)	23.6% (17.4, 31.5%)	29.3% (23.6, 36.0)	28.6% (19.0, 41.6)
Implant removal without replacement		1.2% (0.5, 2.9)	3.6% (1.5, 8.4)	5.3% (2.9, 9.7)	1.9% (0.3, 12.4)
Implant removal with replacement		11.5% (8.9, 14.9)	21.3% (15.4, 29.1)	25.2% (19.7, 31.8)	27.2% (17.8, 40.2)
Asymmetry		0.8% (0.3, 2.2)	5.7% (2.9, 11.0)	10.3% (6.8, 15.4)	14.8% (8.0, 26.7)
Breast pain		2.7% (1.5, 4.7)	3.0% (1.1, 7.7)	4.7% (2.5, 8.8)	4.8% (1.6, 14.3)
Breast/skin sensation changes		1.5% (0.7, 3.1)	0	0	0
Bruising		0.4% (0.1, 1.6)	0.6% (0.1, 4.5)	0	1.5% (0.2, 10.0)
Capsular contracture III/IV		6.1% (4.2, 8.9)	8.7% (5.0, 14.8)	10.7% (7.1, 15.9)	21.6% (13.1, 34.4)
Delayed wound healing		1.1% (0.4, 2.6)	1.3% (0.3, 5.1)	0.5% (0.1, 3.3)	2.9% (0.7, 11.3)
Gel Fracture		0.2% (0. 1.5)	0	0	0
Hematoma		1.1% (0.4, 2.5)	2.0% (0.6, 6.0)	1.0% (0.3, 4.0)	0
Hypertrophic scarring/ scarring		1.1% (0.5, 2.7)	2.7% (1.0, 7.1)	4.8% (2.6, 8.7)	3.2% (0.8, 12.3)
Implant extrusion		0.4% (0.1, 1.6)	1.5% (0.4, 5.8)	0.9% (0.2, 3.7)	0
Implant malposition		2.9% (1.7, 4.9)	7.0% (3.8, 12.6)	3.6% (1.7, 7.4)	4.8% (1.6, 14.3)
Implant palpability/visibility		0.3% (0.0, 1.9)	1.4% (0.3, 5.4)	0.5% (0.1, 3.3)	1.5% (0.2, 10.3)
Implant rupture	MRI cohort	11.3% (6.7, 18.7)	8.9% (2.9, 25.2)	10.3% (4.7, 21.7)	21.1% (8.4, 47.1)
	Non-MRI cohort	6.9% (3.8, 12.4)	16.1% (8.0, 30.9)	8.9% (3.8, 20.1)	0
Infection		1.7% (0.8, 3.4)	2.1% (0.7, 6.3)	4.8% (2.6, 8.7)	6.9% (2.6, 17.7)
Nipple complications		1.3% (0.6, 2.9)	0	0.5% (0.1, 3.3)	1.7% (0.2, 11.2)
Ptosis		1.9% (1.0, 3.8)	0	0	0
Redness		0.7% (0.2, 2.0)	0	0.9% (0.2, 3.7)	4.9% (1.6, 14.7)
Seroma		1.3% (0.6, 2.9)	3.3% (1.2, 8.6)	2.1% (0.8, 5.5)	6.2% (2.4, 15.8)
Skin Rash		0.5% (0.1, 1.9)	0	0	0
Swelling		3.5% (2.1, 5.8)	2.7% (1.0, 7.2)	3.8% (1.9, 7.5)	3.2% (0.8, 12.4)
Tissue/Skin Necrosis		0	0	0.5% (0.1, 3.2)	1.5% (0.2, 10.0)
Upper pole fullness		0	1.4% (0.4, 5.5)	4.2% (2.2, 7.8)	1.5% (0.2, 10.1)
Wrinkling/Rippling		0.7% (0.2, 2.0)	3.7% (1.5, 8.9)	3.1% (1.4, 6.8)	7.7% (3.3, 17.4)
Other complications[g]		1.3% (0.6, 2.9)	1.5% (0.4, 5.8)	4.4% (2.3, 8.3)	1.7% (0.2, 11.4)

[a] Includes reports of only ≥ moderate severity for all complications except for reoperation, implant removal, implant extrusion, implant rupture, and pneumothorax

[b] There were no reports of the following complications: capsule calcification, irritation, lymphadenopathy, lymphedema, palpable orientation mark, pneumothorax

[c] 143 primary augmentation patients experienced at least one complication

[d] 70 revision-augmentation patients experienced at least one complication

[e] 116 primary reconstruction patients experienced at least one complication

[f] 38 revision-reconstruction patients experienced at least one complication

[g] Other complications include complications such as joint swelling, implant movement, bottoming out, tear in the capsule, skin indentation, and synmastia

b. Main Reasons for Reoperation

The main reasons for reoperation through 7 years are shown in Table 19 below.

Table 19: Main Reasons for Reoperations through 7 Years

Reasons for Reoperation through 7 Years[a]	Primary Augmentation N=128 Reoperations in 102 Patients	Revision-Augmentation N=70 Reoperations in 55 Patients	Primary Reconstruction N=129 Reoperations in 97 Patients	Revision-Reconstruction N=31 Reoperations in 25 Patients
Asymmetry	4 (3.1%)	4 (5.7%)	9 (7.0%)	2 (6.5%)
Biopsy	10 (7.8%)	8 (11.4%)	7 (5.4%)	1 (3.2%)
Breast cancer	4 (3.1%)	0	2 (1.6%)	0
Breast pain	1 (0.8%)	3 (4.3%)	3 (2.3%)	0
Breast tissue contour deformity	2 (1.6%)	0	5 (3.9%)	0
Capsular contracture	13 (10.2%)	9 (12.9%)	16 (12.4%)	7 (22.6%)
Delayed wound healing	4 (3.1%)	1 (1.4%)	0	3 (9.7%)
Gel Fracture	1 (0.8%)	0	0	0
Hematoma/seroma	12 (9.4%)	3 (4.3%)	3 (2.3%)	1 (3.2%)
Implant extrusion	1 (0.8%)	1 (1.4%)	2 (1.6%)	0
Implant malposition	15 (11.7%)	11 (15.7%)	16 (12.4%)	3 (9.7%)
Implant palpability/visibility	0	1 (1.4%)	0	0
Implant rupture (suspected)	8 (6.3%)	6 (8.6%)	7 (5.4%)	1 (3.2%)
Infection	4 (3.1%)	4 (5.7%)	9 (7.0%)	3 (9.7%)
Necrosis	0	0	1 (0.8%)	0
Nipple complications (unplanned)	1 (0.8%)	0	0	2 (6.5%)
Patient request for style/size change	21 (16.4%)	6 (8.6%)	12 (9.3%)	3 (9.7%)
Ptosis	11 (8.6%)	6 (8.6%)	6 (4.7%)	0
Scarring/hypertrophic scarring	15 (11.7%)	7 (10.0%)	28 (21.7%)	1 (3.2%)
Wrinkling	1 (0.8%)	0	3 (2.3%)	2 (6.5%)

[a] The reoperation rate excludes planned secondary surgeries. If more than one reason for a given reoperation was reported, the following hierarchy was used to determine a primary reason for that reoperation: rupture; gel fracture; infection; capsular contracture; extrusion, necrosis, hematoma/seroma; delayed wound healing; breast pain; implant malposition; wrinkling; palpability/visibility; asymmetry; breast tissue contour deformity; ptosis; scarring; nipple complications; device injury/iatrogenic; breast cancer mass; biopsy; and patient request for style/size change.

c. Main Reasons for Implant Removal

The main reasons for implant removal through 7 years are shown in Table 20 below.

Table 20: Main Reasons for Implant Removal through 7 Years

Reasons for Implant Removal through 7 Years[a]	Primary Augmentation N=99 Explants in 56 Patients	Revision-Augmentation N=60 Explants in 34 Patients	Primary Reconstruction N=87 Explants in 61 Patients	Revision-Reconstruction N=28 Explants in 18 Patients
Asymmetry	6 (6.1%)	5 (8.3%)	10 (11.5%)	1 (3.6%)
Biopsy	1 (1.0%)	0	0	0
Breast cancer	0	0	1 (1.2%)	0
Breast pain	1 (1.0%)	3 (5.0%)	4 (4.6%)	0
Breast tissue contour deformity	4 (4.0%)	0	1 (1.2%)	0
Capsular contracture	8 (8.1%)	12 (20.0%)	13 (14.9%)	6 (21.4%)
Delayed wound healing	0	0	0	1 (3.6%)
Gel fracture	1 (1.0%)	0	0	0
Hematoma/seroma	4 (4.0%)	0	2 (2.3%)	0
Implant extrusion	1 (1.0%)	1 (1.7%)	2 (2.3%)	0
Implant malposition	4 (4.0%)	6 (10.0%)	9 (10.3%)	2 (7.1%)
Implant palpability/visibility	0	2 (3.3%)	0	0
Implant rupture (suspected)	8 (8.1%)	8 (13.3%)	5 (5.8%)	1 (3.6%)
Infection	3 (3.0%)	4 (6.7%)	6 (6.9%)	3 (10.7%)
Patient request for style/size change	46 (46.5%)	16 (26.7%)	26 (29.9%)	7 (25.0%)
Ptosis	10 (10.1%)	2 (3.3%)	2 (2.3%)	0
Scarring/hypertrophic scarring	0	1 (1.7%)	0	0
Wrinkling	1 (1.0%)	0	5 (5.8%)	4 (14.3%)

[a] If more than one reason for a given implant removal was reported, the following hierarchy was used to determine a primary reason for that removal: rupture; gel fracture; infection; capsular contracture; extrusion; necrosis; hematoma/seroma; delayed wound healing; breast pain; implant malposition; wrinkling; palpability/visibility; asymmetry; breast tissue contour deformity; ptosis; scarring; nipple complications; device injury/iatrogenic; breast cancer mass; biopsy; and patient request for style/size change.

d. Other Clinical Safety Outcomes

Below is a summary of clinical findings from the Core study with regard to anaplastic large cell lymphoma, connective tissue disease (CTD), CTD signs and symptoms, cancer, lactation complications, reproductive complications and suicide. These issues, along with others, will be further evaluated beyond 7 years as part of an Allergan postapproval study of a large number of patients followed through 10 years.

CTD Diagnoses

Three primary augmentation patients (0.6%) were reported to have a new diagnosis. One had a diagnosis of sclerosis/scleroderma at 1 month post-implantation, one had a diagnosis of mitochondrial myopathy at 69 months post-

implantation, and one had a positive ANA-specific diagnosis at 77 months after implantation. Two revision-augmentation patients (1.3%) were reported to have a new diagnosis of fibromyalgia (at 46 months) and Hashimoto thyroiditis (at 30 months). There were 2 primary reconstruction patients (0.9%) who reported CTDs through 7 years. One patient had a new diagnosis of alopecia at 7 months after implantation and rheumatoid arthritis at 25 months after implantation. The other patient had fibromyalgia 27 months after implantation. No revision-reconstruction patients had new diagnoses of a CTD through 7 years. It cannot be determined whether or not these CTD diagnoses were caused by the implants because there was no comparison group of similar women without implants.

CTD Signs and Symptoms

In the Core study, self-reported signs and symptoms were collected in the categories of General, Gastrointestinal, Neurological, Urinary, Global, Pain, Fatigue, Fibromyalgia, Joint, Muscular, Skin, and Other. For primary augmentation patients, at 6 years statistically significant increases after accounting for age were found for the symptom categories of Joint, Muscular, and Skin. Statistically significant increases after accounting for age were found for revision-augmentation patients in the Gastrointestinal symptom category and for primary reconstruction patients in the Pain symptom category at 6 years. For revision-reconstruction patients, no significant increases were found.

The Core Study was not designed to evaluate the cause and effect associations because there is no comparison group of women without implants, and because other contributing factors, such as medications and lifestyle/exercise, were not studied. Therefore, it cannot be determined whether this increase was due to the implants or not, based on the Core Study. However, a patient should be aware that she may experience an increase in these symptoms after receiving breast implants.

Cancer

There were 3 primary augmentation patients (0.7%) with a new diagnosis of breast cancer through 7 years in the Allergan Core Study. There was a 3.6% benign breast disease rate and a 0.7% malignant breast disease rate through 7 years. In primary augmentation patients, there was 1 report of skin cancer and 1 report of renal cell cancer. One primary augmentation patient who was pregnant at the time of implantation gave birth to a child who later developed histiocytosis. For revision-augmentation patients there was one patient (0.8%) with a new diagnosis of breast cancer through 7 years. There was an 8% benign breast disease rate and a 0.8% malignant breast disease rate through 7 years. There was 1 patient report of bladder cancer and 1 patient report of multiple myeloma.

There were 11 primary reconstruction patients (6.1%) with recurrence of breast cancer through 7 years in the Core Study. There was a 5% benign breast disease

rate and a 6% malignant breast disease rate through 7 years. There was 1 report of non-Hodgkin's lymphoma and 1 report of uterine cancer. For revision-reconstruction patients, there was 1 report (1.5%) of recurrence of breast cancer through 7 years. There was a 1.5% malignant breast disease rate through 7 years. There were no reports of other cancers such as brain, respiratory, or cervical/vulvar in primary reconstruction or revision-reconstruction patients.

Lactation Complications

Ten (23%) of the 44 primary augmentation patients who attempted to breastfeed following breast implantation in the pivotal study through 7, years experienced difficulty with breastfeeding. The most common difficulty was mastitis. For the 3 revision-augmentation patients who attempted to breastfeed after receiving breast implants, 1 (33%) had difficulty breast feeding due to inadequate milk production. Two of the 225 primary reconstruction patients attempted to breastfeed following breast implantation in the pivotal study through 7 years and did not experience any difficulties. No revision-reconstruction patients attempted to breastfeed after receiving breast implants.

Reproduction Complications

Seventeen (3.5%) of the primary augmentation patients in the Allergan Pivotal study reported a reproduction problem though 7 years, most commonly miscarriage. Two (1.3%) revision-augmentation patients experienced a reproduction problem (miscarriage and hysterectomy) through 7 years. One (0.4%) primary reconstruction patient reported a reproduction problem through 7 years. One (1.5%) revision-reconstruction patient experienced a reproduction problem through 7 years.

Suicide

There were no reports of suicide in the Core study.

Anaplastic Large Cell Lymphoma

No patients in the pivotal study were reported with this diagnosis through 7 years.

Cases of anaplastic large cell lymphoma (ALCL) have been reported globally in patients with breast implants from all manufacturers distributed in the US, including those of silicone, saline, textured, and smooth design. Style 410 implants have been marketed outside the US in the last twenty years with over half a million units sold.

As of August 1, 2012 there have been two cases of ALCL reported from outside of the US in patients with Style 410 implants. Both cases occurred in patients that were not a part of controlled clinical studies and had a history of breast cancer prior to having breast implants.

The details of these 2 cases are as follows:

Case 1:

A 55-year-old Australian patient with a history of right ductal carcinoma in situ was treated with lumpectomy and radiation therapy in 1995. In 1998, the patient had recurrent right breast cancer and was reconstructed with a latissimus dorsi flap with a breast implant of unknown type or manufacturer.

In February 2006, the patient's right breast implant was replaced with an Allergan Style 410 device. In November, 2010, a lump was discovered in the right breast implant capsule and thought to be benign. The patient had no systemic symptoms.

In March 2011, the patient's breast implant was removed, found to be ruptured, and replaced with a new Allergan Style 410 implant. A capsulotomy with removal of the associated lump in the capsule was also performed. The lump in the capsule was diagnosed as CD30+, ALK negative ALCL. CT scan, bone marrow biopsy and PET scan were negative for lymphoma.

The patient had her breast implant removed prior to receiving chemotherapy and radiation therapy, and has subsequently been disease free.

Case 2:

A 51-year-old Australian patient with a history of right infiltrating ductal carcinoma was treated by lumpectomy and radiation therapy in 1997. The patient did not have reconstruction after lumpectomy but elected to have bilateral breast augmentation in 2003 with Allergan Style 410 implants.

In 2011, an ultrasound examination performed for right breast erythema showed moderate periprosthetic fluid collection. There were no findings on the mammogram performed at the time.

In April 2012, the patient presented with an acutely swollen right breast, periprosthetic fluid collection, and cellulitis. There were no systemic symptoms. The patient was treated with antibiotics and several aspirations. The clinical site reported aspiration of purulent periprosthetic fluid that demonstrated malignant cells on cytology that were CD30 positive, CD15 positive, ALK negative, and LCA negative--consistent with a diagnosis of ALCL. Cellulitis and clinical symptoms improved with antibiotic treatment, and a follow-up mammogram was negative.

The implant was removed in May 2012, and the patient is currently undergoing chemotherapy.

e. Cumulative Risk for First Occurrence of Each Complication at Each Follow-Up Assessment Point

The cumulative risk for first occurrence of each complication at each follow-up assessment point is presented in Tables 21 through 50 below. The Kaplan-Meier risk rates are presented by cohort for the 4-week, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, and 7-year assessment points.

Any Complication

Table 21: Cumulative Risk of First Occurrence of Any Complication

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	6.1% (4.3, 8.7)	5.1% (2.6, 10.0)	8.5% (5.5, 12.9)	14.7% (8.2, 25.6)
6 months	10.2% (7.9, 13.3)	15.4% (10.6, 22.1)	25.0% (19.8, 31.2)	23.7% (15.2, 35.7)
1 year	13.6% (10.8, 16.9)	20.6% (15.0, 27.8)	31.7% (26.0, 38.2)	34.2% (24.2, 46.8)
2 years	16.9% (13.9, 20.6)	25.8% (19.6, 33.5)	37.1% (31.2, 43.8)	40.3% (29.6, 53.0)
3 years	19.7% (16.4, 23.6)	30.6% (23.9, 38.6)	42.2% (36.0, 49.0)	41.8% (31.0, 54.5)
4 years	21.5% (18.0, 25.4)	34.8% (27.8, 43.0)	46.5% (40.1, 53.3)	47.9% (36.7, 63.4)
5 years	24.4% (20.8, 28.5)	38.5% (31.2, 46.8)	47.9% (41.5, 54.7)	51.0% (39.7, 63.4)
6 years	28.0% n(24.1, 32.3)	43.8% (36.1, 52.2)	51.4% (45.0, 58.2)	55.6% (44.1, 67.7)
7 years	31.0% (27.0, 35.5)	47.7% (39.9, 56.2)	53.0% (46.5, 59.8)	57.2% (45.7, 69.2)

Reoperation

Table 22: Cumulative Risk of First Occurrence of Reoperation

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	2.1% (1.1, 3.8)	1.3% (0.3, 5.0)	0.9% (0.2, 3.5)	0.0%
6 months	4.1% (2.7, 6.3)	7.1% (4.0, 12.4)	13.5% (9.6, 18.7)	7.5% (3.2, 17.0)
1 year	7.6% (5.6, 10.4)	14.2% (9.6, 20.7%)	22.4% (17.5, 28.5)	11.9% (6.2, 22.5)
2 years	10.8% (8.3, 13.9)	18.8% (13.4, 25.9)	28.9% (23.4, 35.3)	21.0% (13.0, 32.9)
3 years	12.7% (10.0, 16.0)	22.2% (16.4, 29.7)	33.1% (27.3, 39.7)	21.0% (13.0, 32.9)
4 years	13.8% (11.0, 17.2)	26.4% (20.1, 34.3)	36.9% (30.9, 43.7)	27.1% (18.0, 39.5)
5 years	16.5% (13.4, 20.2)	30.1% (23.4, 38.1)	39.9% (33.7, 46.7)	30.1% (20.6, 42.7)
6 years	19.6% (16.3, 23.5)	34.5% (27.4, 42.9)	43.0% (36.7, 49.9)	34.9% (24.8, 47.8)
7 years	22.4% (18.8, 26.6)	37.7% (30.3, 46.2)	45.2% (38.7, 52.1)	38.6% (27.9, 51.7)

Implant Removal with or without Replacement

Table 23: Cumulative Risk of First Occurrence of Implant Replacement/Removal

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.4% (0.1, 1.6)	0.0%	0.5% (0.1, 3.1)	0.0%
6 months	2.1% (1.1, 3.8)	3.9% (1.7, 8.4)	5.4% (3.1, 9.3)	4.5% (1.5, 13.2)
1 year	3.1% (1.9, 5.1)	7.1% (4.0, 12.4)	9.4% (6.2, 14.1)	6.0% (2.3, 15.1)
2 years	4.6% (3.0, 6.9)	9.1% (5.5, 14.8)	13.6% (9.7, 18.9)	13.5% (7.3, 24.4)
3 years	5.4% (3.7, 7.9)	11.1% (7.1, 17.3)	17.4% (13.0, 23.1)	15.1% (8.4, 26.2)
4 years	6.5% (4.6, 9.2)	15.4% (10.5, 22.2)	20.3% (15.5, 26.3)	16.6% (9.5, 28.0)
5 years	8.1% (6.0, 11.0)	18.2% (12.9, 25.5)	22.8% (17.8, 29.1)	19.7% (12.0, 31.6)
6 years	10.3% (7.8, 13.5)	22.0% (16.1, 29.7)	27.1% (21.6, 33.7)	23.1% (14.6, 35.3)
7 years	12.6% (9.8, 16.1)	23.6% (17.4, 31.5)	29.3% (23.6, 36.0)	28.6% (19.0, 41.6)

Implant Removal without Replacement

Table 24: Cumulative Risk of First Occurrence of Implant Removal (without Replacement)

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.0%	0.0%	0.5% (0.1, 3.2)	0.0%
6 months	0.0%	0.7% (0.1, 4.5)	1.4% (0.4, 4.2)	0.0%
1 year	0.0%	1.3% (0.3, 5.2)	1.9% (0.7, 4.9)	0.0%
2 years	0.2% (0.0, 1.5)	2.0% (0.7, 6.1)	2.4% (1.0, 5.6)	0.0%
3 years	0.5% (0.1, 1.8)	2.0% (0.7, 6.1)	2.9% (1.3, 6.4)	0.0%
4 years	0.7% (0.2, 2.1)	3.6% (1.5, 8.4)	4.6% (2.4, 8.8)	0.0%
5 years	0.7% (0.2, 2.1)	3.6% (1.5, 8.4)	4.6% (2.4, 8.8)	1.9% (0.3, 12.4)
6 years	0.9% (0.4, 2.5)	3.6% (1.5, 8.4)	4.6% (2.4, 8.8)	1.9% (0.3, 12.4)
7 years	1.2% (0.5, 2.9)	3.6% (1.5, 8.4)	5.3% (2.9, 9.7)	1.9% (0.3, 12.4)

Asymmetry

Table 25: Cumulative Risk of First Occurrence of Asymmetry

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.4% (0.1, 1.6)	0.7%(0.1, 4.5)	1.3% (0.4, 4.1)	2.9% (0.7,11.3)
6 months	0.6% (0.2, 1.9)	2.6%(1.0, 6.8)	3.7% (1.9, 7.2)	4.4% (1.5,13.1)
1 year	0.8% (0.3, 2.2)	2.6% (1.0, 6.8)	5.6% (3.2, 9.6)	4.4% (1.5,13.1)
2 years	0.8% (0.3, 2.2)	2.6% (1.0, 6.8)	7.5% (4.7,12.0)	9.4% (4.3,19.7)
3 years	0.8% (0.3, 2.2)	3.3% (1.4, 7.8)	8.5% (5.5,13.2)	9.4% (4.3,19.7)
4 years	0.8%(0.3, 2.2)	4.8% (2.3, 9.9)	9.6% (6.3,14.5)	9.4% (4.3,19.7)
5 years	0.8% (0.3, 2.2)	5.7% (2.9,11.0)	9.6% (6.3,14.5)	13.0% (6.7,24.4)
6 years	0.8% (0.3, 2.2)	5.7% (2.9,11.0)	9.6% (6.3,14.5)	14.8% (8.0,26.7)
7 years	0.8% (0.3, 2.2)	5.7% (2.9,11.0)	10.3% (6.8,15.4)	14.8% (8.0,26.7)

Breast Pain

Table 26: Cumulative Risk of First Occurrence of Breast Pain

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.8% (0.3, 2.2)	0.6% (0.1, 4.5)	0.0%	1.5% (0.2, 10.0)
6 months	1.0% (0.4, 2.4)	1.3% (0.3, 5.1)	0.0%	1.5% (0.2, 10.0)
1 year	1.2% (0.6, 2.7)	1.3% (0.3, 5.1)	1.0% (0.2, 3.8)	1.5% (0.2, 10.0)
2 years	1.2% (0.6, 2.7)	1.3% (0.3, 5.1)	2.5% (1.0, 5.8)	3.1% (0.8, 11.9)
3 years	1.5% (0.7, 3.0)	1.3% (0.3, 5.1)	3.0% (1.3, 6.5)	3.1% (0.8, 11.9)
4 years	1.7% (0.8, 3.4)	2.1% (0.7, 6.3)	4.1% (2.1, 8.0)	4.8% (1.6,14.3)
5 years	2.2% (1.2, 4.0)	2.1% (0.7, 6.3)	4.1% (2.1, 8.0)	4.8% (1.6,14.3)
6 years	2.7% (1.5, 4.7)	3.0% (1.1, 7.7)	4.7% (2.5, 8.8)	4.8% (1.6,14.3)
7 years	2.7% (1.5, 4.7)	3.0% (1.1, 7.7)	4.7% (2.5, 8.8)	4.8% (1.6,14.3)

Bruising

Table 27: Cumulative Risk of First Occurrence of Bruising

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.4% (0.1, 1.6)	0.6% (0.1, 4.5)	0.0%	1.5% (0.2, 10.0)
6 months	0.4% (0.1, 1.6)	0.6% (0.1, 4.5)	0.0%	1.5% (0.2, 10.0)
1 year	0.4% (0.1, 1.6)	0.6% (0.1, 4.5)	0.0%	1.5% (0.2, 10.0)
2 years	0.4% (0.1, 1.6)	0.6% (0.1, 4.5)	0.0%	1.5% (0.2, 10.0)
3 years	0.4% (0.1, 1.6)	0.6% (0.1, 4.5)	0.0%	1.5% (0.2, 10.0)
4 years	0.4% (0.1, 1.6)	0.6% (0.1, 4.5)	0.0%	1.5% (0.2, 10.0)
5 years	0.4% (0.1, 1.6)	0.6% (0.1, 4.5)	0.0%	1.5% (0.2, 10.0)
6 years	0.4% (0.1, 1.6)	0.6% (0.1, 4.5)	0.0%	1.5% (0.2, 10.0)
7 years	0.4% (0.1, 1.6)	0.6% (0.1, 4.5)	0.0%	1.5% (0.2, 10.0)

Capsular Contracture

Table 28: Cumulative Risk of First Occurrence of Capsular Contracture

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.0%	0.0%	0.0%	0.0%
6 months	0.8% (0.3, 2.2)	1.3% (0.3, 5.1)	2.3% (1.0, 5.5)	3.0% (0.8, 11.6)
1 year	1.0% (0.4, 2.5)	3.9% (1.8, 8.6)	3.3% (1.6, 6.7)	9.2% (4.2, 19.3)
2 years	1.5% (0.7, 3.1)	5.3% (2.7, 10.4)	6.2% (3.7, 10.5)	10.8% (5.3, 21.3)
3 years	2.1% (1.2, 3.9)	5.3% (2.7, 10.4)	7.3% (4.5, 11.8)	10.8% (5.3, 21.3)
4 years	3.1% (1.8, 5.1)	6.9% (3.7, 12.4)	8.9% (5.7, 13.8)	12.5% (6.4, 23.4)
5 years	4.0% (2.5, 6.3)	6.9% (3.7, 12.4)	10.1% (6.6, 15.2)	16.0% (8.9, 27.7)
6 years	5.3% (3.5, 7.9)	6.9% (3.7, 12.4)	10.7% (7.1, 15.9)	19.6% (11.6, 32.1)
7 years	6.1% (4.2, 8.9)	8.7% (5.0, 14.8)	10.7% (7.1, 15.9)	21.6% (13.1, 34.4)

Delayed Wound Healing

Table 29: Cumulative Risk of First Occurrence of Delayed Wound Healing

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.6% (0.2, 1.9)	0.7% (0.1, 4.5)	0.0%	2.9% (0.7, 11.3)
6 months	0.8% (0.3, 2.2)	1.3% (0.3, 5.1)	0.5% (0.1, 3.3)	2.9% (0.7, 11.3)
1 year	0.8% (0.3, 2.2)	1.3% (0.3, 5.1)	0.5% (0.1, 3.3)	2.9% (0.7, 11.3)
2 years	0.8% (0.3, 2.2)	1.3% (0.3, 5.1)	0.5% (0.1, 3.3)	2.9% (0.7, 11.3)
3 years	0.8% (0.3, 2.2)	1.3% (0.3, 5.1)	0.5% (0.1, 3.3)	2.9% (0.7, 11.3)
4 years	0.8% (0.3, 2.2)	1.3% (0.3, 5.1)	0.5% (0.1, 3.3)	2.9% (0.7, 11.3)
5 years	0.8% (0.3, 2.2)	1.3% (0.3, 5.1)	0.5% (0.1, 3.3)	2.9% (0.7, 11.3)
6 years	1.1% (0.4, 2.6)	1.3% (0.3, 5.1)	0.5% (0.1, 3.3)	2.9% (0.7, 11.3)
7 years	1.1% (0.4, 2.6)	1.3% (0.3, 5.1)	0.5% (0.1, 3.3)	2.9% (0.7, 11.3)

Gel Fracture

Table 30: Cumulative Risk of First Occurrence of Gel Fracture

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.0%	0.0%	0.0%	0.0%
6 months	0.0%	0.0%	0.0%	0.0%
1 year	0.2% (0.0, 1.5)	0.0%	0.0%	0.0%
2 years	0.2% (0.0, 1.5)	0.0%	0.0%	0.0%
3 years	0.2% (0.0, 1.5)	0.0%	0.0%	0.0%
4 years	0.2% (0.0, 1.5)	0.0%	0.0%	0.0%
5 years	0.2% (0.0, 1.5)	0.0%	0.0%	0.0%
6 years	0.2% (0.0, 1.5)	0.0%	0.0%	0.0%
7 years	0.2% (0.0, 1.5)	0.0%	0.0%	0.0%

Hematoma

Table 31: Cumulative Risk of First Occurrence of Hematoma

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.8% (0.3, 2.2)	1.3% (0.3, 5.0)	0.0%	0.0%
6 months	0.8% (0.3, 2.2)	1.3% (0.3, 5.0)	0.5% (0.1, 3.3)	0.0%
1 year	0.8% (0.3, 2.2)	1.3% (0.3, 5.0)	0.5% (0.1, 3.3)	0.0%
2 years	0.8% (0.3, 2.2)	2.0% (0.6, 6.0)	0.5% (0.1, 3.3)	0.0%
3 years	0.8% (0.3, 2.2)	2.0% (0.6, 6.0)	1.0% (0.3, 4.0)	0.0%
4 years	0.8% (0.3, 2.2)	2.0% (0.6, 6.0)	1.0% (0.3, 4.0)	0.0%
5 years	1.1% (0.4, 2.5)	2.0% (0.6, 6.0)	1.0% (0.3, 4.0)	0.0%
6 years	1.1% (0.4, 2.5)	2.0% (0.6, 6.0)	1.0% (0.3, 4.0)	0.0%
7 years	1.1% (0.4, 2.5)	2.0% (0.6, 6.0)	1.0% (0.3, 4.0)	0.0%

Hypertrophic/Abnormal Scarring

Table 32: Cumulative Risk of First Occurrence of Hypertrophic/Abnormal Scarring

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.0%	0.0%	0.5% (0.1, 3.2)	0.0%
6 months	0.0%	0.7% (0.1, 4.5)	3.2% (1.6, 6.7)	0.0%
1 year	0.2% (0.0. 1.5)	0.7% (0.1, 4.5)	3.7% (1.9, 7.3)	1.5% (0.2, 10.3)
2 years	0.4% (0.1, 1.7)	2.7% (1.0, 7.1)	4.2% (2.2, 7.9)	1.5% (0.2, 10.3)
3 years	0.9% (0.3, 2.3)	2.7% (1.0, 7.1)	4.2% (2.2, 7.9)	1.5% (0.2, 10.3)
4 years	0.9% (0.3, 2.3)	2.7% (1.0, 7.1)	4.2% (2.2, 7.9)	3.2% (0.8, 12.3)
5 years	1.1% (0.5, 2.7)	2.7% (1.0, 7.1)	4.8% (2.6, 8.7)	3.2% (0.8, 12.3)
6 years	1.1% (0.5, 2.7)	2.7% (1.0, 7.1)	4.8% (2.6, 8.7)	3.2% (0.8, 12.3)
7 years	1.1% (0.5, 2.7)	2.7% (1.0, 7.1)	4.8% (2.6, 8.7)	3.2% (0.8, 12.3)

Implant Extrusion

Table 33: Cumulative Risk of First Occurrence of Implant Extrusion

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.2% (0.0, 1.5)	0.0%	0.0%	0.0%
6 months	0.4% (0.1, 1.6)	0.7% (0.1, 4.5)	0.5% (0.1, 3.2)	0.0%
1 year	0.4% (0.1, 1.6)	0.7% (0.1, 4.5)	0.9% (0.2, 3.7)	0.0%
2 years	0.4% (0.1, 1.6)	0.7% (0.1, 4.5)	0.9% (0.2, 3.7)	0.0%
3 years	0.4% (0.1, 1.6)	0.7% (0.1, 4.5)	0.9% (0.2, 3.7)	0.0%
4 years	0.4% (0.1, 1.6)	0.7% (0.1, 4.5)	0.9% (0.2, 3.7)	0.0%
5 years	0.4% (0.1, 1.6)	1.5% (0.4, 5.8)	0.9% (0.2, 3.7)	0.0%
6 years	0.4% (0.1, 1.6)	1.5% (0.4, 5.8)	0.9% (0.2, 3.7)	0.0%
7 years	0.4% (0.1, 1.6)	1.5% (0.4, 5.8)	0.9% (0.2, 3.7)	0.0%

Implant Malposition

Table 34: Cumulative Risk of First Occurrence of Implant Malposition

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.2% (0.0, 1.4)	0.0%	0.0%	0.0%
6 months	0.6% (0.2, 1.9)	2.6% (1.0, 6.8)	0.9% (0.2, 3.7)	1.5% (0.2, 10.1)
1 year	1.5% (0.7, 3.0)	4.6% (2.2, 9.4)	2.4% (1.0, 5.6)	3.0% (0.8, 11.4)
2 years	1.9% (1.0, 3.6)	4.6% (2.2, 9.4)	2.4% (1.0, 5.6)	3.0% (0.8, 11.4)
3 years	2.1% (1.1, 3.9)	5.3% (2.7, 10.3)	2.9% (1.3, 6.3)	3.0% (0.8, 11.4)
4 years	2.3% (1.3, 4.2)	6.0% (3.2, 11.3)	2.9% (1.3, 6.3)	3.0% (0.8, 11.4)
5 years	2.3% (1.3, 4.2)	6.0% (3.2, 11.3)	2.9% (1.3, 6.3)	4.8% (1.6, 14.3)
6 years	2.3% (1.3, 4.2)	6.0% (3.2, 11.3)	2.9% (1.3, 6.3)	4.8% (1.6, 14.3)
7 years	2.9% (1.7, 4.9)	7.0% (3.8, 12.6)	3.6% (1.7, 7.4)	4.8% (1.6, 14.3)

Implant Palpability/Visibility

Table 35: Cumulative Risk of First Occurrence of Implant Palpability/Visibility

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.0%	0.0%	0.0%	0.0%
6 months	0.0%	0.0%	0.5% (0.1, 3.3)	0.0%
1 year	0.0%	0.7% (0.1, 4.6)	0.5% (0.1, 3.3)	1.5% (0.2, 10.3)
2 years	0.0%	0.7% (0.1, 4.6)	0.5% (0.1, 3.3)	1.5% (0.2, 10.3)
3 years	0.0%	1.4% (0.3, 5.4)	0.5% (0.1, 3.3)	1.5% (0.2, 10.3)
4 years	0.0%	1.4% (0.3, 5.4)	0.5% (0.1, 3.3)	1.5% (0.2, 10.3)
5 years	0.0%	1.4% (0.3, 5.4)	0.5% (0.1, 3.3)	1.5% (0.2, 10.3)
6 years	0.0%	1.4% (0.3, 5.4)	0.5% (0.1, 3.3)	1.5% (0.2, 10.3)
7 years	0.3% (0.0, 1.9)	1.4% (0.3, 5.4)	0.5% (0.1, 3.3)	1.5% (0.2, 10.3)

Implant Rupture – Overall (i.e. silent and symptomatic breast implant rupture confirmed with implant explantation)

Table 36: Cumulative Risk of First Occurrence of Implant Rupture – Overall

	Augmentation[a]	Revision-Augmentation[b]	Reconstruction[c]	Revision-Reconstruction[d]
4 weeks	0.0%	0.0%	0.0%	0.0%
6 months	0.0%	0.0%	0.0%	0.0%
1 year	0.0%	0.0%	0.0%	0.0%
2 years	0.4% (0.0, 2.4%)	1.1% (0.2, 7.8)	0.0%	0.0%
3 years	1.8% (0.7, 4.2)	3.5% (1.1, 10.5)	1.6% (0.4, 6.2)	0.0%
4 years	4.7% (2.8, 8.0)	4.8% (1.8, 12.3)	5.8% (2.8, 11.8)	0.0%
5 years	6.2% (3.9, 9.8)	10.1% (5.2, 19.3)	8.4% (4.6, 15.0)	11.1% (3.7, 30.6)
6 years	6.2% (3.9, 9.8)	11.5% (6.1, 21.0)	8.4% (4.6, 15.0)	11.1% (3.7, 30.6)
7 years	8.8% (5.9, 12.9)	13.0% (7.2, 22.8)	9.5% (5.3, 16.5)	15.6% (6.1, 36.5)

[a] 23 patients with ruptures (26 implants): 13 silent in MRI cohort, 8 silent and 2 symptomatic in Non-MRI cohort

[b] 10 patients with ruptures (12 implants): 2 silent and 1 symptomatic in MRI cohort, 5 silent and 2 symptomatic in Non-MRI cohort

[c] 11 patients with ruptures (11 implants): 6 silent in MRI cohort, 5 silent in Non-MRI cohort

[d] 4 patients with ruptures (4 implants): 3 silent and 1 symptomatic in MRI cohort

Implant Rupture – MRI Cohort

Table 37: Cumulative Risk of First Occurrence of Implant Rupture – MRI Cohort

	Augmentation[a]	Revision-Augmentation[b]	Reconstruction[c]	Revision-Reconstruction[d]
4 weeks	0.0%	0.0%	0.0%	0.0%
6 months	0.0%	0.0%	0.0%	0.0%
1 year	0.0%	0.0%	0.0%	0.0%
2 years	0.0%	0.0%	0.0%	0.0%
3 years	2.2% (0.7, 6.7)	2.7% (0.4, 17.7)	3.0% (0.8, 11.4)	0.0%
4 years	3.0% (1.1, 7.8)	2.7% (0.4, 17.7)	3.0% (0.8, 11.4)	0.0%
5 years	6.3% (3.2, 12.1)	5.7% (1.4, 20.8)	8.0% (3.4, 18.1)	15.0% (5.1, 39.6)
6 years	6.3% (3.2, 12.1)	5.7% (1.4, 20.8)	8.0% (3.4, 18.1)	15.0% (5.1, 39.6)
7 years	11.3% (6.7, 18.7)	8.9% (2.9, 25.2)	10.3% (4.7, 21.7)	21.1% (8.4, 47.1)

[a] 13 silent rupture, none symptomatic.
[b] 2 silent rupture, 1 symptomatic
[c] 6 silent rupture, 0 symptomatic
[d] 3 silent rupture, 1 symptomatic

Implant Rupture – Non-MRI Cohort

Table 38: Cumulative Risk of First Occurrence of Implant Rupture – Non-MRI Cohort

	Augmentation[a]	Revision-Augmentation[b]	Reconstruction[c]	Revision-Reconstruction
4 weeks	0.0%	0.0%	0.0%	0.0%
6 months	0.0%	0.0%	0.0%	0.0%
1 year	0.0%	0.0%	0.0%	0.0%
2 years	0.7% (0.1, 4.5)	2.0% (0.3, 13.1)	0.0%	0.0%
3 years	1.3% (0.3, 5.2)	4.1% (1.0, 15.2)	0.0%	0.0%
4 years	6.2% (3.3, 11.5)	6.3% (2.1, 18.4)	8.9% (3.8, 20.1)	0.0%
5 years	6.2% (3.3, 11.5)	13.6% (6.3, 27.9)	8.9% (3.8, 20.1)	0.0%
6 years	6.2% (3.3, 11.5)	16.1% (8.0, 30.9)	8.9% (3.8, 20.1)	0.0%
7 years	6.9% (3.8, 12.4)	16.1% (8.0, 30.9)	8.9% (3.8, 20.1)	0.0%

[a] 8 silent rupture, 2 symptomatic
[b] 5 silent rupture, 2 symptomatic
[c] 5 silent rupture, 0 symptomatic

Infection

Table 39: Cumulative Risk of First Occurrence of Infection

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.4% (0.1, 1.6)	0.0%	1.4% (0.4, 4.1)	1.5% (0.2, 10.0)
6 months	1.2% (0.6, 2.7)	1.3% (0.3, 5.1)	2.3% (1.0, 5.4)	3.0% (0.7, 11.3)
1 year	1.5% (0.7, 3.0)	1.3% (0.3, 5.1)	2.7% (1.2, 6.0)	4.5% (1.5, 13.3)
2 years	1.5% (0.7, 3.0)	1.3% (0.3, 5.1)	3.7% (1.9, 7.4)	4.5% (1.5, 13.3)
3 years	1.5% (0.7, 3.0)	1.3% (0.3, 5.1)	4.3% (2.2, 8.0)	4.5% (1.5, 13.3)
4 years	1.5% (0.7, 3.0)	2.1% (0.7, 6.3)	4.8% (2.6, 8.7)	4.5% (1.5, 13.3)
5 years	1.7% (0.8, 3.4)	2.1% (0.7, 6.3)	4.8% (2.6, 8.7)	4.5% (1.5, 13.3)
6 years	1.7% (0.8, 3.4)	2.1% (0.7, 6.3)	4.8% (2.6, 8.7)	4.5% (1.5, 13.3)
7 years	1.7% (0.8, 3.4)	2.1% (0.7, 6.3)	4.8% (2.6, 8.7)	6.9% (2.6, 17.7)

Nipple Complications (i.e. loss of nipple sensation, nipple hypersensitivity/paresthesia and other nipple related observation)

Table 40: Cumulative Risk of First Occurrence of Nipple Complications

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.2% (0.0, 1.5)	0.0%	0.0%	0.0%
6 months	0.4% (0.1, 1.6)	0.0%	0.5% (0.1, 3.3)	0.0%
1 year	0.6% (0.2, 1.9)	0.0%	0.5% (0.1, 3.3)	0.0%
2 years	0.8% (0.3, 2.2)	0.0%	0.5% (0.1, 3.3)	1.7% (0.2, 11.2)
3 years	1.1% (0.4, 2.5)	0.0%	0.5% (0.1, 3.3)	1.7% (0.2, 11.2)
4 years	1.3% (0.6, 2.9)	0.0%	0.5% (0.1, 3.3)	1.7% (0.2, 11.2)
5 years	1.3% (0.6, 2.9)	0.0%	0.5% (0.1, 3.3)	1.7% (0.2, 11.2)
6 years	1.3% (0.6, 2.9)	0.0%	0.5% (0.1, 3.3)	1.7% (0.2, 11.2)
7 years	1.3% (0.6, 2.9)	0.0%	0.5% (0.1, 3.3)	1.7% (0.2, 11.2)

Breast/Skin Sensation Changes (i.e. skin hypersensitivity, paresthesia, loss of skin sensation)

Table 41: Cumulative Risk of First Occurrence of Breast/Skin Sensation Changes

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.8% (0.3, 2.2)	0.0%	0.0%	0.0%
6 months	0.8% (0.3, 2.2)	0.0%	0.0%	0.0%
1 year	1.0% (0.4, 2.5)	0.0%	0.0%	0.0%
2 years	1.3% (0.6, 2.8)	0.0%	0.0%	0.0%
3 years	1.3% (0.6, 2.8)	0.0%	0.0%	0.0%
4 years	1.3% (0.6, 2.8)	0.0%	0.0%	0.0%
5 years	1.3% (0.6, 2.8)	0.0%	0.0%	0.0%
6 years	1.5% (0.7, 3.1)	0.0%	0.0%	0.0%
7 years	1.5% (0.7, 3.1)	0.0%	0.0%	0.0%

Ptosis

Table 42: Cumulative Risk of First Occurrence of Ptosis

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.0%	0.0%	0.0%	0.0%
6 months	0.2% (0.0, 1.5)	0.0%	0.0%	0.0%
1 year	0.2% (0.0, 1.5)	0.0%	0.0%	0.0%
2 years	0.6% (0.2, 2.0)	0.0%	0.0%	0.0%
3 years	0.9% (0.3, 2.3)	0.0%	0.0%	0.0%
4 years	0.9% (0.3, 2.3)	0.0%	0.0%	0.0%
5 years	0.9% (0.3, 2.3)	0.0%	0.0%	0.0%
6 years	1.4% (0.6, 3.0)	0.0%	0.0%	0.0%
7 years	1.9% (1.0, 3.8)	0.0%	0.0%	0.0%

Redness

Table 43: Cumulative Risk of First Occurrence of Redness

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.2% (0.0, 1.5)	0.0%	0.5% (0.1, 3.2)	2.9% (0.7, 11.3)
6 months	0.4% (0.1, 1.6)	0.0%	0.5% (0.1, 3.2)	2.9% (0.7, 11.3)
1 year	0.4% (0.1, 1.6)	0.0%	0.9% (0.2, 3.7)	2.9% (0.7, 11.3)
2 years	0.4% (0.1, 1.6)	0.0%	0.9% (0.2, 3.7)	2.9% (0.7, 11.3)
3 years	0.4% (0.1, 1.6)	0.0%	0.9% (0.2, 3.7)	2.9% (0.7, 11.3)
4 years	0.4% (0.1, 1.6)	0.0%	0.9% (0.2, 3.7)	2.9% (0.7, 11.3)
5 years	0.7% (0.2, 2.0)	0.0%	0.9% (0.2, 3.7)	2.9% (0.7, 11.3)
6 years	0.7% (0.2, 2.0)	0.0%	0.9% (0.2, 3.7)	4.9% (1.6, 14.7)
7 years	0.7% (0.2, 2.0)	0.0%	0.9% (0.2, 3.7)	4.9% (1.6, 14.7)

Seroma/Fluid Accumulation

Table 44: Cumulative Risk of First Occurrence of Seroma/Fluid Accumulation

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.8% (0.3, 2.2)	0.0%	0.9% (0.2, 3.5)	2.9% (0.7, 11.3)
6 months	0.8% (0.3, 2.2)	0.7% (0.1, 4.5)	0.9% (0.2, 3.5)	4.4% (1.5, 13.1)
1 year	0.8% (0.3, 2.2)	0.7% (0.1, 4.5)	0.9% (0.2, 3.5)	4.4% (1.5, 13.1)
2 years	0.8% (0.3, 2.2)	0.7% (0.1, 4.5)	1.4% (0.5, 4.3)	4.4% (1.5, 13.1)
3 years	0.8% (0.3, 2.2)	1.4% (0.4, 5.5)	1.4% (0.5, 4.3)	4.4% (1.5, 13.1)
4 years	0.8% (0.3, 2.2)	1.4% (0.4, 5.5)	1.4% (0.5, 4.3)	6.2% (2.4, 15.8)
5 years	1.1% (0.4, 2.5)	1.4% (0.4, 5.5)	1.4% (0.5, 4.3)	6.2% (2.4, 15.8)
6 years	1.3% (0.6, 2.9)	2.3% (0.7, 7.1)	1.4% (0.5, 4.3)	6.2% (2.4, 15.8)
7 years	1.3% (0.6, 2.9)	3.3% (1.2, 8.6)	2.1% (0.8, 5.5)	6.2% (2.4, 15.8)

Skin Rash

Table 45: Cumulative Risk of First Occurrence of Skin Rash

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.2% (0.0, 1.4)	0.0%	0.0%	0.0%
6 months	0.2% (0.0, 1.4)	0.0%	0.0%	0.0%
1 year	0.2% (0.0, 1.4)	0.0%	0.0%	0.0%
2 years	0.2% (0.0, 1.4)	0.0%	0.0%	0.0%
3 years	0.2% (0.0, 1.4)	0.0%	0.0%	0.0%
4 years	0.2% (0.0, 1.4)	0.0%	0.0%	0.0%
5 years	0.2% (0.0, 1.4)	0.0%	0.0%	0.0%
6 years	0.5% (0.1, 1.9)	0.0%	0.0%	0.0%
7 years	0.5% (0.1, 1.9)	0.0%	0.0%	0.0%

Swelling

Table 46: Cumulative Risk of First Occurrence of Swelling

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	1.6% (0.8, 3.2)	1.3% (0.3, 5.0)	1.3% (0.4, 4.1)	1.5% (0.2, 10.0)
6 months	1.6% (0.8, 3.2)	1.9% (0.6, 5.9)	2.3% (1.0, 5.4)	1.5% (0.2, 10.0)
1 year	1.6% (0.8, 3.2)	1.9% (0.6, 5.9)	2.3% (1.0, 5.4)	1.5% (0.2, 10.0)
2 years	1.6% (0.8, 3.2)	1.9% (0.6, 5.9)	2.8% (1.3, 6.1)	1.5% (0.2, 10.0)
3 years	1.6% (0.8, 3.2)	1.9% (0.6, 5.9)	3.3% (1.6, 6.8)	1.5% (0.2, 10.0)
4 years	1.6% (0.8, 3.2)	1.9% (0.6, 5.9)	3.8% (1.9, 7.5)	3.2% (0.8, 12.4)
5 years	2.1% (1.1, 3.9)	2.7% (1.0, 7.2)	3.8% (1.9, 7.5)	3.2% (0.8, 12.4)
6 years	2.6% (1.5, 4.6)	2.7% (1.0, 7.2)	3.8% (1.9, 7.5)	3.2% (0.8, 12.4)
7 years	3.5% (2.1, 5.8)	2.7% (1.0, 7.2)	3.8% (1.9, 7.5)	3.2% (0.8, 12.4)

Tissue/Skin Necrosis

Table 47: Cumulative Risk of First Occurrence of Tissue/Skin Necrosis

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.0%	0.0%	0.5% (0.1, 3.2)	1.5% (0.2, 10.0)
6 months	0.0%	0.0%	0.5% (0.1, 3.2)	1.5% (0.2, 10.0)
1 year	0.0%	0.0%	0.5% (0.1, 3.2)	1.5% (0.2, 10.0)
2 years	0.0%	0.0%	0.5% (0.1, 3.2)	1.5% (0.2, 10.0)
3 years	0.0%	0.0%	0.5% (0.1, 3.2)	1.5% (0.2, 10.0)
4 years	0.0%	0.0%	0.5% (0.1, 3.2)	1.5% (0.2, 10.0)
5 years	0.0%	0.0%	0.5% (0.1, 3.2)	1.5% (0.2, 10.0)
6 years	0.0%	0.0%	0.5% (0.1, 3.2)	1.5% (0.2, 10.0)
7 years	0.0%	0.0%	0.5% (0.1, 3.2)	1.5% (0.2, 10.0)

Upper Pole Fullness

Table 48: Cumulative Risk of First Occurrence of Upper Pole Fullness

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.0%	0.0%	1.3% (0.4, 4.1)	0.0%
6 months	0.0%	0.7% (0.1, 4.5)	3.2% (1.5, 6.6)	1.5% (0.2, 10.1)
1 year	0.0%	0.7% (0.1, 4.5)	3.7% (1.8, 7.2)	1.5% (0.2, 10.1)
2 years	0.0%	0.7% (0.1, 4.5)	4.2% (2.2, 7.8)	1.5% (0.2, 10.1)
3 years	0.0%	1.4% (0.4, 5.5)	4.2% (2.2, 7.8)	1.5% (0.2, 10.1)
4 years	0.0%	1.4% (0.4, 5.5)	4.2% (2.2, 7.8)	1.5% (0.2, 10.1)
5 years	0.0%	1.4% (0.4, 5.5)	4.2% (2.2, 7.8)	1.5% (0.2, 10.1)
6 years	0.0%	1.4% (0.4, 5.5)	4.2% (2.2, 7.8)	1.5% (0.2, 10.1)
7 years	0.0%	1.4% (0.4, 5.5)	4.2% (2.2, 7.8)	1.5% (0.2, 10.1)

Wrinkling/Rippling

Table 49: Cumulative Risk of First Occurrence of Wrinkling/Rippling

	Augmentation	Revision-Augmentation	Reconstruction	Revision-Reconstruction
4 weeks	0.0%	0.0%	0.0%	1.5% (0.2, 10.0)
6 months	0.0%	0.0%	0.5% (0.1, 3.2)	3.0% (0.7, 11.3)
1 year	0.0%	0.7% (0.1, 4.6)	0.5% (0.1, 3.2)	6.0% (2.3, 15.2)
2 years	0.2% (0.0, 1.5)	2.7% (1.0, 7.1)	1.9% (0.7, 5.1)	7.7% (3.3, 17.4)
3 years	0.7% (0.2, 2.0)	2.7% (1.0, 7.1)	2.5% (1.0, 5.8)	7.7% (3.3, 17.4)
4 years	0.7% (0.2, 2.0)	2.7% (1.0, 7.1)	2.5% (1.0, 5.8)	7.7% (3.3, 17.4)
5 years	0.7% (0.2, 2.0)	2.7% (1.0, 7.1)	2.5% (1.0, 5.8)	7.7% (3.3, 17.4)
6 years	0.7% (0.2, 2.0)	2.7% (1.0, 7.1)	3.1% (1.4, 6.8)	7.7% (3.3, 17.4)
7 years	0.7% (0.2, 2.0)	3.7% (1.5, 8.9)	3.1% (1.4, 6.8)	7.7% (3.3, 17.4)

Other Complications

Table 50: Cumulative Risk of First Occurrence of Other Complications

	Augmentation[a]	Revision-Augmentation[b]	Reconstruction[c]	Revision-Reconstruction[d]
4 weeks	0.2% (0.0, 1.5)	0.0%	0.9% (0.2, 3.5)	0.0%
6 months	0.2% (0.0, 1.5)	0.0%	0.9% (0.2, 3.5)	0.0%
1 year	0.6% (0.2, 1.9)	0.7% (0.1, 4.6)	2.3% (1.0, 5.5)	0.0%
2 years	0.6% (0.2, 1.9)	0.7% (0.1, 4.6)	2.3% (1.0, 5.5)	0.0%
3 years	0.6% (0.2, 1.9)	0.7% (0.1, 4.6)	3.9% (2.0, 7.6)	1.7% (0.2, 11.4)
4 years	1.1% (0.5, 2.6)	1.5% (0.4, 5.8)	4.4% (2.3, 8.3)	1.7% (0.2, 11.4)
5 years	1.3% (0.6, 2.9)	1.5% (0.4, 5.8)	4.4% (2.3, 8.3)	1.7% (0.2, 11.4)
6 years	1.3% (0.6, 2.9)	1.5% (0.4, 5.8)	4.4% (2.3, 8.3)	1.7% (0.2, 11.4)
7 years	1.3% (0.6, 2.9)	1.5% (0.4, 5.8)	4.4% (2.3, 8.3)	1.7% (0.2, 11.4)

[a] Joint swelling (1 patient), implant moving (1 patient), crease below breast (1 patient), double bubble phenomenon (1 patient), bottoming out (2 patients), Mondors (1patient)
[b] Tear capsule (1 patient), implant not-adhered (1 patient)
[c] Residual dipadystrophy (1 patient), implant displacement (1 patient), focal herniation (1 patient), indentation (2 patients), pleurisy & pneumonitis (1 patient), upper pole hollowness (1 patient), insufficient lateral and anterior projection (1 patient), symmastia (1 patient)
[d] Symmastia (1 patient)

2. Effectiveness Results

The analysis of effectiveness was based on the 656 evaluable patients at the 7-year timepoint. Effectiveness assessments include change in breast size (augmentation patients only), patient and physician satisfaction with outcome (augmentation, reconstruction and revision patients), and quality of life (QoL) (augmentation and reconstruction patients). QoL is comprised of measures of self-esteem, body image and general health outcomes assessed at baseline and years 1 and 2 only. Change in breast size was assessed by cup/circumferential chest size measurements. Patient satisfaction was based on a 5-point scale assessment of satisfaction with their implants at the time of follow-up visits. The QoL measures were from the Rosenberg Self Esteem Scale, the Body Esteem Scale, the SF-36 and the Rowland Expectation Scale.

Primary Augmentation Patients

For primary augmentation patients, 469 (95%) of the original 492 patients had a breast measurement within 18 months of surgery. Of these 469 patients, 38% increased by 1 cup size; 53.5% increased by 2 cup sizes; 5.5% increased by more than 2 cup sizes; and 2.8% had no increase or decrease due to correction of congenital asymmetry or change in shape without change in size.

Of the original 492 patients, 354 (72.0%) provided a satisfaction rating at 7 years after implantation. Of these 354 patients, 87.3% indicated that they were definitely satisfied with their breast implants, 9.0% indicated they were somewhat satisfied, 1.4% indicated that they were neither satisfied nor dissatisfied, 0.3% were indicated they were somewhat dissatisfied, and 2.0% indicated they were definitely dissatisfied.

Physician satisfaction with patient results was rated in 351 cases (71.3%) at 7 years. Physicians reported being definitely satisfied with the breast implants in 91.7% of cases, somewhat satisfied in 5.4% of cases, neither satisfied nor dissatisfied in 1.1% of cases, somewhat dissatisfied in 0.6% of cases and definitely dissatisfied in 1.1% of cases.

For primary augmentation patients, prior to implantation, scores on the SF-36 Scale, which measures mental and physical health, were significantly higher than the general female population. There were no significant changes after 2 years.

Scores on the Rosenberg Self-Esteem Scale and on the Body Esteem scale also generally showed no significant changes at 2 years. However, body esteem related to sexual attractiveness improved significantly after implantation, and on the Rowland Expectation instrument, patients showed significant improvement in "self image," "social relations," and "daily living."

Primary augmentation patients also had significantly improved satisfaction with specific aspects of their breasts after 2 years, including satisfaction with breast size, shape, feel, and how well they matched.

Revision-Augmentation Patients

Revision-augmentation patients did not undergo a measurement of breast cup size change because they were undergoing replacement of an existing implant.

Of the original 156 revision-augmentation patients, 101 (64.7%) patients provided a satisfaction rating at 7 years. Of these 101 patients, 80.2% indicated they were definitely satisfied with their breast implants, 10.9% indicated that they were somewhat satisfied, 5.0% indicated that they were neither satisfied nor dissatisfied, 3.0% indicated they were somewhat dissatisfied, and 1.0% indicated that they were definitely dissatisfied.

Physician satisfaction with patient results was rated in 100 cases (64.1%) at 7 years. Physicians reported being definitely satisfied with the breast implants in 80.0% of cases, somewhat satisfied in 12.0% of cases, neither satisfied nor dissatisfied in 3.0% of cases, and somewhat dissatisfied in 5.0% of cases.

Revision-augmentation patients did not undergo a quality of life assessment.

Primary Reconstruction Patients

Of the original 225 primary reconstruction patients, 149 (66.2%) provided a satisfaction rating at 7 years after implantation. Of these 149 patients, 74.5% indicated that they were definitely satisfied with their breast implants, 20.8% indicated that they were somewhat satisfied, 2.7% indicated that they were neither satisfied nor dissatisfied, 1.3% indicated that they were somewhat dissatisfied, and 0.7% indicated that they were definitely dissatisfied.

Physician satisfaction with patient results was rated in 149 cases (66.2%) at 7 years. Physicians reported being definitely satisfied with the breast implants in 80.5% of cases, somewhat satisfied in 14.1% of cases, neither satisfied nor dissatisfied in 3.4% of cases, somewhat dissatisfied in 0.7% of cases, and definitely dissatisfied in 1.3% of cases.

For primary reconstruction patients, prior to implantation, scores on the SF-36 Scale, which measures mental and physical health, were for the most part

significantly higher than the general female population. At 2 years, the only significant decrease was in the subscale "reported health transition." There were no significant changes on the Rosenberg Self-Esteem Scale and on the Body Esteem scale at 2 years. On the Rowland Expectation instrument, patients showed a significant positive change in "improve well-being."

Primary reconstruction patients also had significantly improved satisfaction with specific aspects of their breasts after implantation, such as the size, shape, feel, and how well they matched.

Revision-Reconstruction Patients

Of the original 68 revision-reconstruction patients, 43 (63.2%) provided a satisfaction rating at 7 years after implantation. Of these 43 patients, 62.8% indicated that they were definitely satisfied with their breast implants, 30.2% indicated that they were somewhat satisfied, 4.7% indicated that they were neither satisfied nor dissatisfied, and 2.3% indicated that they were definitely dissatisfied.

Physician satisfaction with patient results was rated in 43 cases (63.2%) at 7 years. Physicians reported being definitely satisfied with the breast implants in 67.4% of cases, somewhat satisfied in 23.3% of cases, neither satisfied nor dissatisfied in 4.7 % of cases, somewhat dissatisfied in 2.3 % of cases, and definitely dissatisfied in 2.3% of cases.

Revision-reconstruction patients did not undergo a quality of life assessment.

3. Subgroup Analyses

a. Detection of Breast Implant Rupture

Implant rupture was identified from 3 sources:

- Physician Exam
- Evidence of Rupture observed by the physician upon reoperation or device explant
- Devices identified as ruptured (from options being ruptured, indeterminate, unreadable film, no evidence of rupture) via MRI for those patients participating in the serial MRI portion of this study

No implant ruptures were suspected by either ultrasound or mammography.

Detection of Breast Implant Rupture: Physician Exam

In some cases, implant ruptures were suspected based on physician exam. The implants were either confirmed to be ruptured upon explant, confirmed as non-ruptured upon explant, or confirmed as non-ruptured on MRI and not explanted. Table 51 includes information by cohort.

Table 51: Resolution of Rupture Suspected Based on Physician Exam

	Suspected Rupture based on Physician Exam	Rupture Confirmed on Explant	Non-Rupture Confirmed on Explant	Non-Ruptured Assessed on MRI
Augmentation	3	2	0	1
Revision-Augmentation	4	3	1	0
Reconstruction	1	0	1	0
Revision-Reconstruction	2	1	0	1

Detection of Breast Implant Rupture: MRI

Through 7 years, 180 patients had pre-explant MRIs and subsequent device explantation. Ninety-one (91) of these patients underwent MRI as part of the MRI cohort, while 89 obtained MRI based on their symptoms. An analysis of device status upon explant was used to evaluate MRI sensitivity and specificity and is provided in Table 52. Sensitivity is the MRI's success in correctly identifying ruptured implants, and specificity is the success in correctly identifying non-ruptured implants.

Table 52: MRI Sensitivity and Specificity for Implant Rupture

	Rupture Confirmed on Explant	Non-Rupture Confirmed on Explant
MRI showed rupture	15	4
MRI Indeterminate	0	6[a]
MRI showed no rupture	6[b]	149
MRI Sensitivity		
Best Case	94% (70%, 100%)	
Worst Case[a]	71% (48%, 89%)	
MRI Specificity		
Best Case	97% (93%, 99%)	
Worst Case	94% (89%, 97%)	

[a] The 6 cases of indeterminate MRI results were included in the "MRI Showed Rupture"/"Non-Rupture Confirmed on Explant" cell for the calculation of worst case specificity.
[b] In 5 of these cases, more than 2 years elapsed between the time of MRI and device explants, increasing the possibility that the rupture occurred between MRI and explant These 5 cases are used in the calculation of worst case sensitivity.

b. Risk Factor Analysis

In the Core study, the most notable risk factor analysis finding was that larger device size is a risk factor for reoperation (p = 0.0001), with a hazard ratio of 1.16 (95% CI: 1.08, 1.25) per 50cc increase in size. This result was observed in the pooled Augmentation/Revision-Augmentation cohort. Note that this result is robust to a statistical multiplicity adjustment for at least 500 comparisons. Note also that device size was not significantly associated with reoperation for patients electing size/style change (p= 0.2549). This increases the clinical significance of the above association of device size with reoperation.

There was a similar finding of an association between device size and implant replacement/removal (p = 0.0016) with a hazard ratio of 1.17 (95% CI: 1.06, 1.28) in the pooled Augmentation/Revision-Augmentation cohort. Other nominally significant findings from the Core study are not reported here because they are not robust to adjustment for multiplicity.

c. Comparison of Lost to Follow-up and Evaluated Patients

In order to confirm that results for evaluated patients are representative of those who are lost to follow-up (LTFU), these two groups were compared on a wide range of baseline characteristics and key complications, and on their last observed patient satisfaction responses. Out of the 23 variables compared across the 4 cohorts, statistically significant differences were observed in a small number of comparisons. There were two findings which were robust to multiple comparisons. These were that Augmentation LTFU patients were more likely to have the FF, FM and MF styles as compared to the MM style and that they were also more likely to have had a periareolar incision site. Note that comparisons between LTFU patients and completers were not made for the Reconstruction cohort as follow-up was greater than 80%.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

After enrollment into Allergan's Core study was completed, additional patients were enrolled under 2 continued access studies, the Continued Access (CA) study and the Continued Access Reconstruction/Revision Expansion (CARE) study.

The Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implant is provided in a range of profiles and sizes. Although only 4 profiles were evaluated in the Core study, a larger range of profiles were made available through the CA and CARE studies. Table 53 lists the profile numbers studied in the Core, CA, and CARE studies:

Table 53: Profiles Evaluated in the Clinical Studies

	FF	FL	FM	FX	LF	LL	LM	LX	MF	ML	MM	MX
Core	x		x						x		x	
CA	x	x	x	x	x	x	x	x	x	x	x	x
CARE	x	x	x	x	x	x	x	x	x	x	x	x

In the CA study, there were 6,601 patients who received 12,786 devices. Of the 12,786 devices, 9,872 (77.2%) were devices with profiles evaluated in the Core study (i.e., FF, FM, MF, and MM). Of the 4 profiles cited, MM had the lowest patient experience with 1,601 devices implanted across all 4 study cohorts.

In the CARE study, there were 8,761 patients who received 15,058 devices. Of the 15,058 devices, 6,167 (41%) were devices with profiles evaluated in the Core study. Of the 4 profiles, FM had the lowest patient experience with 771 devices implanted across all 3 study cohorts.

A. CA Study

The purpose of the CA study is to provide participating surgeons with additional experience with the Natrelle Highly Cohesive device. The CA study approval was limited to 60 institutions and 80 patients per month with a total of 4,320 patients at the time of database closure. As this is an ongoing study, CA patients are still being enrolled. However, enrollment into the CA study ceased on the date of FDA Notice of Approval. The CA study patients have been enrolled under the same enrollment criteria and study design as for the Core study with the following exceptions:

1. CA study patients were not required to participate in the serial MRI portion of the study;
2. CA study patients had to sign a CA study informed consent.

The 7-year by patient cumulative complication rates for the Continued Access Study is presented by cohort in Table 54 below.

Table 54: 410 Continued Access Clinical Study – Summary of 7-year Risk Rates for Specific Complications

KM Rates through 7 Years[a, b]	Primary Augmentation[c] N=4534	Revision-Augmentation[d] N=670	Primary Reconstruction[e] N=978	Revision-Reconstruction[f] N=419
Any complication (including reoperation)	25.7% (23.3, 28.3)	42.6% (37.8, 47.9)	52.2% (47.8, 56.8)	51.3% (44.8, 58.1)
Any reoperation	18.4% (16.3, 20.7)	33.0% (28.6, 37.8)	42.0% (37.5, 46.7)	37.9% (32.1, 44.4)
Implant removal with or without replacement	9.3% (7.8, 11.1)	20.6% (16.8, 25.1)	24.6% (20.6, 29.3)	25.0% (19.8, 31.3)
Implant removal without replacement	1.2% (0.8, 1.8)	1.9% (0.9, 4.2)	5.7% (3.6, 8.9)	6.1% (3.6, 10.4)
Implant removal with replacement	8.2% (6.7, 9.9)	19.3% (15.6, 23.7)	21.2% (17.3, 25.9)	20.5% (15.7, 26.5)
Asymmetry	1.2% (0.9, 1.7)	2.2% (1.2, 4.0)	14.0% (10.9, 17.8)	10.5% (6.6, 16.3)
Breast pain	3.0% (2.1, 4.3)	4.6% (3.0, 7.1)	6.4% (4.5, 9.1)	4.3% (2.5, 7.3)
Breast/skin sensation changes	0.2% (0.1, 0.4)	0	0.1% (0.0, 0.9)	0.3% (0.0, 1.9)
Bruising	0.1% (0.0, 0.2)	0.5% (0.1, 1.4)	0.1% (0.0, 0.8)	0
Capsular contracture III/IV	6.4% (5.0, 8.1)	7.8% (5.5, 11.0)	14.1% (10.9, 18.1)	13.9% (9.7, 19.7)
Capsule Calcification	0.2% (0.0, 1.1)	0	0	0
Delayed wound healing	0.3% (0.2, 0.5)	0.8% (0.3, 2.3)	1.6% (1.0, 2.7)	1.0% (0.3, 3.1)
Gel Fracture	0.1% (0.0, 0.2)	0	0	0.5% (0.1, 3.3)
Hematoma	0.6% (0.3, 1.0)	1.2% (0.5, 2.4)	0.2% (0.1, 0.9)	1.3% (0.5, 3.1)
Hypertrophic scarring/ scarring	1.0% (0.7, 1.4)	1.9% (1.0, 3.5)	5.0% (3.3, 7.6)	1.9% (0.8, 4.8)
Implant extrusion	0.1% (0.0, 0.4)	0.5% (0.2, 1.5)	1.3% (0.6, 2.7)	2.7% (1.4, 5.1)
Implant malposition	3.5% (2.8, 4.5)	5.7% (3.9, 8.3)	5.0% (3.5, 7.1)	5.7% (3.0, 10.5)
Implant palpability/visibility	0.5% (0.2, 1.1)	1.9% (0.9, 4.0)	1.5% (0.6, 3.6)	0.5% (0.1, 2.0)
Infection	0.6% (0.4, 0.9)	2.0% (0.7, 5.5)	3.0% (2.0, 4.5)	4.5% (2.3, 8.7)
Irritation	0.1% (0.0, 0.3)	0	0.1% (0.0, 0.9)	0.6% (0.2, 2.6)
Lymphadenopathy	0	0.2% (0.0, 1.6)	0	0
Lymphedema	0	0	0.7% (0.2, 1.9)	0
Nipple complications	0.7% (0.5, 1.0)	0.8% (0.3, 1.9)	0.8% (0.4, 1.8)	0.9% (0.3, 2.6)
Ptosis	0.8% (0.5, 1.2)	1.1% (0.4, 2.9)	0.3% (0.0, 2.0)	0
Redness	0.3% (0.2, 0.6)	0.9% (0.4, 2.3)	3.1% (1.6, 6.0)	2.6% (1.1, 6.2)
Seroma	1.3% (0.7, 2.3)	1.5% (0.7, 3.1)	1.0% (0.5, 2.2)	2.4% (1.2, 4.9)
Skin Rash	0.2% (0.1, 0.4)	0.2% (0.0, 1.1)	0.4% (0.1, 1.1)	0.5% (0.1, 2.0)
Swelling	1.8% (1.2, 2.8)	3.0% (1.4, 6.6)	2.6% (1.2, 5.4)	2.5% (1.1, 5.5)
Tissue/Skin Necrosis	0.1% (0.0, 0.4)	0	0.6% (0.2, 1.5)	0.9% (0.2, 3.5)
Upper pole fullness	0.1% (0.0, 0.4)	0.5% (0.1, 1.9)	0.6% (0.3, 1.5)	0.6% (0.1, 2.4)
Wrinkling/Rippling	0.7% (0.3, 1.5)	3.9% (2.4, 6.2)	4.6% (2.9, 7.5)	5.7% (3.3, 9.9)
Other complications[g]	0.7% (0.3, 1.5)	3.6% (1.9, 6.7)	4.5% (2.8, 7.1)	4.1% (1.9, 8.5)

[a] Includes reports of only ≥ moderate severity for all complications except for reoperation, implant removal, implant extrusion, implant rupture, and pneumothorax

[b] There were no reports of the following complications: palpable orientation mark and pneumothorax

[c] 659 primary augmentation patients experienced at least one complication

[d] 217 revision-augmentation patients experienced at least one complication

[e] 368 primary reconstruction patients experienced at least one complication

[f] 158 revision-reconstruction patients experienced at least one complication

[g] Other complications include complications such as joint swelling, bottoming out, tear in the capsule, skin indentation, and synmastia

B. CARE Study

The CARE study was designed to provide participating surgeons access to the Natrelle® Highly Cohesive device for revision and reconstruction patients and to provide additional information regarding the Natrelle Highly Cohesive device. Enrollment is limited to 175 patients per month. Enrollment into the CARE study began October 31, 2005 and is ongoing. However, enrollment into the CARE study ceased on the date of FDA Notice of Approval. CARE study patients have been enrolled under a protocol that differs from the Core and Continued Access study protocols in that:

1. There is no primary augmentation cohort;
2. The follow-up intervals are 1, 2, 5, 7 and 10 years;
3. Serial MRI occurs at 2, 5, and 10 years post-implantation.

The overall 2-year by patient cumulative complication rates for the CARE Study is presented by cohort in Table 55 below.

Table 55: 410 CARE Clinical Study – Summary of 2-year Risk Rates for Specific Complications

KM Rates through 2 Years[a, b]		Revision-Augmentation[c] N=1700	Primary Reconstruction[d] N=5304	Revision-Reconstruction[e] N=1757
Any complication (including reoperation)		26.6% (24.3, 29.2)	30.8% (29.2, 32.3)	29.7% (27.3, 32.2)
Any reoperation		22.0% (19.8, 24.4)	25.1% (23.7, 26.6)	24.5% (22.3, 26.9)
Implant removal with or without replacement		12.6% (10.8, 14.6)	15.2% (14.0, 16.5)	16.2% (14.3, 18.3)
Implant removal without replacement		2.5% (1.8, 3.6)	4.4% (3.7, 5.1)	4.0% (3.0, 5.2)
Implant removal with replacement		10.6% (9.0, 12.4)	11.4% (10.4, 12.5)	12.9% (11.2, 14.9)
Asymmetry		2.6% (1.8, 3.6)	4.1% (3.5, 4.8)	3.8% (2.9, 5.0)
Breast pain		2.0% (1.3, 2.9)	1.9% (1.5, 2.5)	1.7% (1.1, 2.6)
Breast/skin sensation changes		0	0.1% (0.0, 0.3)	0.1% (0.0, 0.6)
Bruising		0.1% (0.0, 0.5)	0.1% (0.0, 0.3)	0
Capsular contracture III/IV		4.1% (3.1, 5.4)	3.1% (2.6, 3.8)	3.0% (2.2, 4.1)
Capsule Calcification		0	0.0% (0.0, 0.3)	0.2% (0.0, 0.7)
Delayed wound healing		1.0% (0.6, 1.7)	1.2% (0.9, 1.6)	1.3% (0.8, 2.1)
Hematoma		0.4% (0.2, 0.9)	0.6% (0.4, 0.9)	1.1% (0.7, 1.8)
Hypertrophic scarring/ scarring		1.3% (0.8, 2.1)	0.9% (0.6, 1.3)	0.9% (0.5, 1.5)
Implant extrusion		0.6% (0.3, 1.3)	1.4% (1.0, 1.8)	0.9% (0.5, 1.6)
Implant malposition		4.5% (3.5, 5.9)	2.4% (1.9, 3.0)	4.2% (3.2, 5.4)
Implant palpability/visibility		0.6% (0.3, 1.1)	0.4% (0.3, 0.7)	0.3% (0.1, 0.8)
Implant Rupture	MRI cohort	2.3% (0.6, 9.0)	1.4% (0.4, 5.5)	2.1% (0.5, 8.0)
	Non-MRI cohort	1.0% (0.1, 7.0)	1.9% (0.6, 5.7)	0.9% (0.1, 6.1)
Infection		2.3% (1.6, 3.2)	3.9% (3.3, 4.6)	4.8% (3.8, 6.2)
Irritation		0.1% (0.0, 0.5)	0.0% (0.0, 0.2)	0
Lymphadenopathy		0	0	0.1% (0.0, 0.5)
Lymphedema		0	0.1% (0.1, 0.3)	0.1% (0.0, 0.5)
Nipple complications		0.4% (0.2, 0.9)	0.2% (0.1, 0.4)	0.2% (0.1, 0.7)
Pneumothorax		0.1% (0.0, 0.5)	0	0.1% (0.0, 0.5)
Ptosis		0.4% (0.2, 1.0)	0	0
Redness		0.7% (0.4, 1.4)	1.6% (1.2, 2.0)	1.5% (1.0, 2.4)
Seroma		2.6% (1.8, 3.6)	1.3% (0.9, 1.7)	2.0% (1.4, 2.9)
Skin Rash		0.2% (0.1, 0.7)	0.5% (0.3, 0.8)	0.2% (0.1, 0.7)
Swelling		0.6% (0.3, 1.3)	0.6% (0.4, 1.0)	1.5% (0.9, 2.3)
Tissue/Skin Necrosis		0.3% (0.1, 0.8)	0.7% (0.5, 1.1)	0.5% (0.2, 1.0)
Upper pole fullness		0.2% (0.0, 0.7)	0.1% (0.0, 0.2)	0.2% (0.1, 0.7)
Wrinkling/Rippling		1.0% (0.6, 1.8)	0.6% (0.4, 0.9)	0.9% (0.5, 1.5)
Other complications[f]		0.6% (0.3, 1.3)	1.1% (0.8, 1.5)	1.2% (0.7, 2.0)

[a] Includes reports of only ≥ moderate severity for all complications except for reoperation, implant removal, implant extrusion, implant rupture, and pneumothorax

[b] There were no reports of the following complications: gel fracture and palpable orientation mark

[c] 342 revision-augmentation patients experienced at least one complication

[d] 1135 primary reconstruction patients experienced at least one complication

[e] 408 revision-reconstruction patients experienced at least one complication

[f] Other complications include complications such as joint swelling, bottoming out, tear in the capsule, skin indentation, and synmastia

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness outcomes demonstrate that the majority of patients who underwent a measurement of breast cup size change (augmentation cohort only), report an increase in bra cup-size by at least 1 cup size. The majority of patients who provided Quality of Life assessments at the 7-year assessment point had favorable results. The majority of patients who provided a satisfaction rating at 7 years indicated that they were satisfied with their breast implants. The majority of physicians who provided a satisfaction rating at 7 years reported being satisfied with the breast implants.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory studies as well as data collected in the pivotal clinical study conducted to support PMA approval as described above.

Cumulative risk of complications through 7-year follow-up of pivotal study patients demonstrated that 31% of primary augmentation patients experienced complications, 48% of revision-augmentation patients experienced complications, 53% of primary reconstruction patients experienced complications, and 57% of revision-reconstruction patients experienced complications. The most common complications through 7 years were reoperation and implant removal with or without replacement in all study cohorts.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in the clinical study conducted to support PMA approval as described above.

Additional factors to be considered in determining probable risks and benefits for the Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implant device included: the active and deliberate search/documentation of adverse events in the pivotal study, single arm pivotal study design, lacking individual patient success criteria, good patient follow-up through 7 years, the *availability of* alternative treatments, patient-centric assessments, and risk mitigation with device use by trained surgeons in patients with informed consent.

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for females for Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implant indicated for females for the following uses (procedures):

- Breast Augmentation for women at least 22 years old. Breast augmentation includes primary breast augmentation to increase the breast size, as well as revision surgery to correct or improve the result of a primary breast augmentation surgery.
- Breast Reconstruction. Breast reconstruction includes primary reconstruction to replace breast tissue that has been removed due to cancer or trauma or that has failed to develop properly due to a severe breast abnormality. Breast reconstruction also includes revision surgery to correct or improve the result of a primary breast reconstruction surgery.

D. **Overall Conclusions**

Based on the totality of the evidence, there is reasonable assurance of safety and effectiveness when the Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implant is used as labeled. Despite frequent local complications and adverse outcomes, the benefits and risks of breast implants are sufficiently well understood for women to make informed decisions about their use.

Breast augmentation and breast reconstruction using breast implants is an aesthetic procedure. Not only are there different reasons for obtaining breast implants among the women studied, there is variable perception of benefit by each individual patient.

XIV. CDRH DECISION

CDRH issued an approval order on February 20, 2013. The final conditions of approval cited in the approval order are described below.

1. PMA Core Study

At the time of approval, all patients in the PMA Core study have completed their 10 year follow-up, i.e. the last patient was enrolled to the study on February 28, 2002. Therefore, Allergan must submit a final study report for the Premarket Core Study within 90 days of their receipt of the approval order. Allergan must submit the final report as a PAS study report to the PMA and in addition submit a supplement to the IDE referencing the final report is being submitted for P040046.

2. Natrelle 410 Full and Moderate height/projection Breast Implant Continued Access Study (Natrelle 410 CAS)

Per Natrelle 410 Full and Moderate height/projection Breast Implant Continued Access Study protocol version dated August 17, 2012 (e-mail), the Natrelle 410 CAS will consist of the continued follow-up, for 5-years post-implantation, of approximately 3,500 subjects who were enrolled before the date of approval in the 410 Continued Access and 410 Continued Access Revision/Reconstruction Expansion clinical studies. All safety and effectiveness endpoints evaluated premarket will continue to be studied through 5-years of follow-up. Descriptive statistics will be provided. Additional analyses will be performed as per protocol version dated August 17, 2012. Allergan is also required to conduct Device Explant Analyses for all devices retrieved from women enrolled in the Natrelle 410 CAS as outlined in the protocol version dated June 8, 2012.

On an annual basis and until the completion of 5 year follow-up, Allergan must submit, a PAS progress report to FDA that includes: patient compliance, a summary of findings for all study endpoints, and results of the device explant analyses for devices explanted within this study.

3. Natrelle 410 Breast Implant US Post-Approval Study (Natrelle 410 US-PAS)

Per Natrelle 410 US Post-approval Study protocol version dated August 16, 2012 (e-mail), this study is a newly enrolled cohort study in the US. The purpose of this study is to evaluate the long-term clinical performance of Natrelle 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants under general conditions of use in the postmarket environment. The study will enroll 2,287 women receiving Natrelle 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants and 300 women receiving Natrelle Saline implants as the comparison group. Study subjects will be followed annually for 10 years. Data will be collected on the following safety endpoints: connective tissue diseases (CTDs), rheumatologic and neurologic signs and symptoms, cancer (lung and breast, including the potential of breast implant interference with mammography and delay of breast cancer detection), suicide/attempted suicide, local complications (including infection, rupture; including rupture rate following mammography), reoperation and implant removal, reproductive complications in women who attempt to have children, lactation complications, and congenital deformities. The effectiveness will be assessed by participants' responses to questions addressing their satisfaction with the breast implants and psychosocial well-being.

Data are to be collected via annual patient questionnaires. For the patients who receive Natrelle 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants, there will also be physician evaluations at years 1, 5, and 10. Descriptive statistics will be provided for the studied endpoints. In addition, the association between the studied endpoints and the approved device will be assessed as per protocol version dated August 16, 2012. Allergan is also required to conduct Device Explant Analyses for all devices retrieved from women enrolled in the Natrelle 410 US-PAS per protocol version dated

June 8, 2012. Allergan must report results of these explant analyses in the post-approval study Annual Report.

Allergan also agrees to participate as a stakeholder in developing the National Breast Implants Registry and to contribute data from their Natrelle 410 US Post-Approval Study to the Registry upon its implementation. They should be advised that because the establishment of the National Breast Implants Registry is currently in progress, this condition of approval will be labeled as "Study Pending" upon further notification from the FDA. Under this agreement, Allergan must submit interim reports every 6 months that include: (1) activities that Allergan undertakes for the development of the National Breast Implant Registry; (2) US sales data for the Natrelle 410 breast implants; and (3) US implant data for the Natrelle 410 breast implants.

Otherwise, Allergan's reporting requirements for the Natrelle 410 US-PAS are as follows:
On a quarterly basis, they must submit a report to FDA that includes: (1) the number enrolled by subjects receiving studied device versus enrolled in comparison group; (2) the number enrolled by indication (primary augmentation, revision-augmentation, primary reconstruction, revision-reconstruction) for subjects receiving studied device; (3) the number enrolled by race/ethnicity; (4) the enrollment rates versus the stated goals; (5) the reason why eligible patients were not enrolled into the study; and (6) the follow-up rates versus the stated goals. FDA will inform Allergan when quarterly reports are no longer necessary.

In addition, every 6 months for the first 2 years and then annually, thereafter, Allergan is to submit a progress report that includes: (1) the status of patient enrollment as it compares to the stated goals; (2) the status of the race/ethnicity distribution as it compares to the stated goals; (3) detailed patient and device accounting; (4) the reasons why eligible patients were not enrolled into the study; (5) the follow-up rates versus the stated goals; and (6) a summary of findings for all study endpoints.

Allergan must update their patient and physician labeling to reflect 5 and 10-year Natrelle 410 US-PAS study findings, as soon as these data are available, as well as any other time point deemed necessary by FDA, if significantly new information from this study becomes available.

4. Allergan Silicone Breast Implants and Case-control Studies

In order to evaluate the rare endpoints, FDA approves Allergan's proposal to conduct case-controlled studies using data that is already collected in countries where the device has been on the market for years. Per Allergan Silicone Breast Implants and Case-control Study protocols version dated August 3, 2012 (e-mail), the purpose of the Allergan Silicone Breast Implants and Case-control Studies is to evaluate the association between Natrelle 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants and five rare disease outcomes (rare connective tissue diseases, rare neurological diseases,

brain cancer, cervical/vulvar cancer and lymphoma). These studies will be conducted in the United Kingdom and will enroll a total of 7,500 cases and 4,000 controls. For each of the five rare disease outcomes, 1,500 cases will be enrolled and compared to the controls on the history of the implantation of Natrelle silicone gel-filled breast implants.

Every 6 months for the first 2 years and then annually, Allergan must submit a report to FDA that includes: (1) the number enrolled by cases and controls; (2) the enrollment rate versus the stated goal. FDA will inform Allergan when quarterly reports are no longer necessary. In addition, within 3 months of the completion of subject enrollment and data collection, Allergan must submit a final Allergan Silicone Breast Implants and Case-control study report that includes the results and conclusions of the Allergan Silicone Breast Implants and Case-control studies.

5. Focus Group Study

Per the Focus Group Study protocol version dated September 7, 2012, the purpose of the Focus Group Study is to evaluate the augmentation and reconstruction patient labeling. This will involve an independent group obtaining responses from patients on the format and content of the approved labeling. Upon completion of the focus group study, Allergan must submit a Final Report of the Focus Group Study findings and suggested revision of patient and physician labeling based on those findings.

6. In addition to the studies listed above, Allergan must conduct non-PAS Device Explant Analyses for all Natrelle 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants that are retrieved in the commercial setting outside the post-approval studies, as per explant analysis protocol version dated June 8, 2012. On an annual basis, Allergan must report the results of these Device Explant Analyses in the PMA Annual Reports.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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