Five-Year Follow-Up Data from the U.S. Clinical Trial for Sientra's U.S. Food and Drug Administration–Approved Silimed® Brand Round and Shaped Implants with High-Strength Silicone Gel

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Background: In March of 2012, the U.S. Food and Drug Administration approved Sientra's application for premarket approval for its Silimed brand silicone gel implants, based on data from the largest silicone gel breast implant study to date. This was the first approval for shaped silicone gel breast implants. This article presents the results of Sientra's study through 5 years.
Methods: Sientra's study is an ongoing, 10-year, open-label, prospective, multicenter clinical study designed to assess the safety and effectiveness of Sientra's implants in patients undergoing augmentation and reconstruction. A total of 1788 subjects were implanted with 3506 implants, including 1116 primary augmentation, 363 revision-augmentation, 225 primary reconstruction, and 84 revision-reconstruction subjects. Physical evaluations and complications were recorded at each visit. Effectiveness was measured by postimplantation bra cup size and assessment of subject satisfaction and quality of life. Of the 1788 subjects, 571 underwent magnetic resonance imaging to assess silent rupture. Safety endpoints were analyzed using the Kaplan-Meier method.
Results: Across all cohorts, the risk of rupture was 1.8 percent (95 percent CI, 1.2 to 2.6 percent), the risk of capsular contracture (Baker grade III/IV) was 9.0 percent (95 percent CI, 7.6 to 10.6 percent), and the risk of reoperation was 23.8 percent (95 percent CI, 21.8 to 26.0 percent). Over 99 percent of surgeons reported satisfaction with the postoperative results, and subject satisfaction remained high 5 years after implantation.
Conclusion: The 5-year results of Sientra's study continue to provide a comprehensive safety and effectiveness profile of Sientra's portfolio of Silimed brand shaped and round implants. (*Plast. Reconstr. Surg.* 130: 973, 2012.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.

Founded in 2007, Sientra is a U.S. company headquartered in Santa Barbara, California, that acquired substantially all of the North American assets of Silimed. The Sientra portfolio of Silimed brand silicone gel breast implants has been manufactured and distributed worldwide outside of North America for almost 15 years. Silimed is the third largest global manufacturer of silicone implantable devices. With over 33 years of experience, Silimed has a long record of safety and quality manufacturing that strictly complies with regulatory stan-

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dards and requirements from multiple government agencies, including the U.S. Food and Drug Administration, the Brazilian National Health Surveillance Agency, and the European Medical Device Directive. Each Sientra Silicone Gel Breast Implant is composed of a low-bleed, barrier-type silicone elastomer shell, which is thin and soft, and filled with clear, high-strength silicone gel. The cohesive gel fill aids the shape retention characteristics of the implants (Fig. 1). The silicone gel fill is 100 percent medical grade silicone from Applied Silicone Corporation, a U.S. silicone supplier (Santa Paula, Calif.) with over 25 years of experience manufacturing the highest quality silicone materials exclusively for use in critical long-term implants and medical products. The "high-strength" gel, as defined by Applied Silicone Corporation, is a two-part system of pure silicone polymers designed for use to fabricate medical devices where cohesiveness, good mechanical strength, and resiliency are desired. Applied Silicone's manufacturing and quality systems are based on U.S. Food and Drug Administration Good Manufacturing Practices and are also ISO 9001:2008 certified.

Sientra's breast implant portfolio has a wide spectrum of designs to satisfy a variety of patient needs. The implants have either a round or shaped profile, with either a smooth or textured surface (Fig. 2), and three different projections (low, moderate, and high) to support a personalized aesthetic result. Silimed's proprietary texturing technology does not use sodium chloride and does not use the "lost salt" method[1] that includes rinsing salt crystals from the surfaces of implant shells. Finally, there are three implant footprints/bases to allow for a proportional relationship of the implant base to the patient chest wall dimensions.

On March 9, 2012, the U.S. Food and Drug Administration approved Sientra's premarket approval application to market the Silimed brand portfolio of silicone gel breast implants, based on their review of the prospective study data for the largest pivotal silicone gel breast implant study to date. This approval also marked the first U.S. Food and Drug Administration approval for a shaped gel breast implant. The 5-year experience reported here is based on Sientra's pivotal study data.

SUBJECTS AND METHODS

Study Design

Sientra's study is an ongoing, 10-year, open-label, prospective, multicenter clinical study designed to assess safety and effectiveness in 1788 subjects implanted with 3506 Sientra Silicone Gel Breast Implants. The study encompasses four types of subject indications (1116 primary augmentation subjects, 363 revision-augmentation subjects, 225 primary reconstruction subjects, and 84 revision-reconstruction subjects).

All subjects were scheduled to return for follow-up examinations at 6 to 10 weeks, at 1 year, and ongoing annually through 10 years postoperatively. A subgroup of subjects (magnetic resonance imaging cohort) were scheduled to have magnetic resonance imaging scans to screen for silent rupture, beginning at year 3, and continuing every other year through 10 years. This subgroup consisted of 571 total subjects from all of the four cohorts. As a condition of approval, all subjects are included in the magnetic resonance imaging cohort. Adverse events and complications were recorded at all visits and each was assessed on a severity scale of 1 to 5. Complications that were very mild (score of 1) or mild (score of 2) in severity were not included in the analysis. Effectiveness was measured by preimplantation to post-

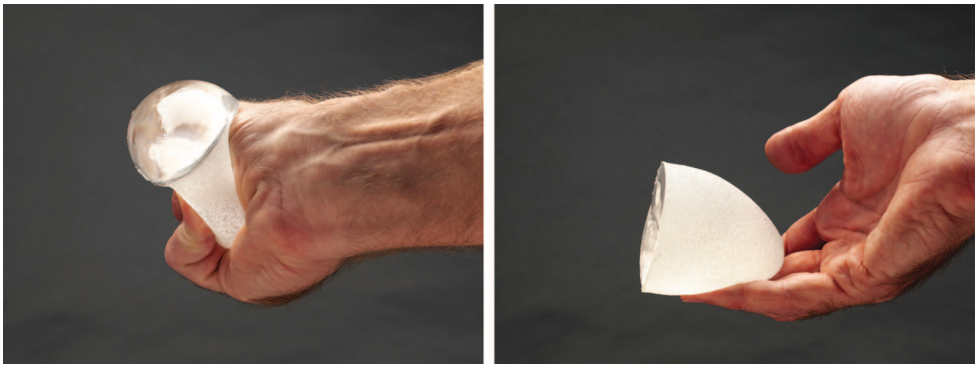

Fig. 1. Photographs of a Sientra textured gel breast implant cut in half under applied pressure (*left*) and then after the pressure is released (*right*), demonstrating the strong gel cohesivity and shape retention characteristics of the implants.

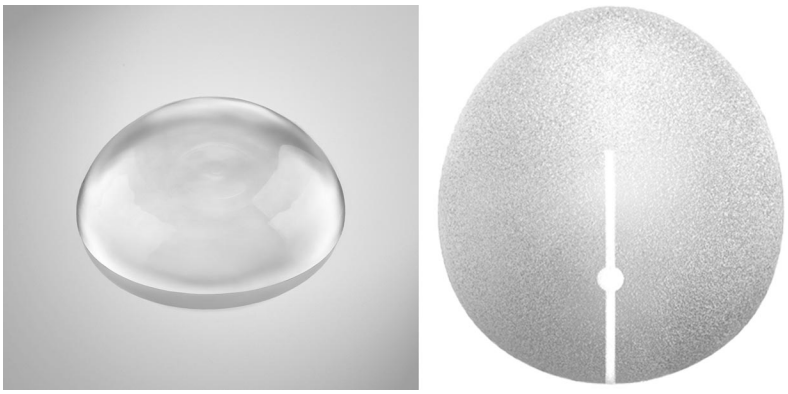

Fig. 2. A Sientra round, smooth silicone gel breast implant (*left*) and a Sientra textured, shaped silicone gel breast implant (*right*).

implantation bra/cup sizes and changes in subject satisfaction and quality of life. All subjects provided informed consent to participate in the U.S. Food and Drug Administration–approved study and the study's protocol underwent review and institutional review board approval.

Subjects

The study's protocol dictated subject enrollment under stringent inclusion and exclusion criteria.[2] Enrollment in the study was limited to female patients who were willing to follow study requirements; were undergoing implantation for augmentation, reconstruction, or revision; and were at least 18 years old for primary or revision augmentation surgery. There was no age limit for primary or revision reconstruction. Patients were not permitted to enroll in the study if they met any of the following exclusion criteria: advanced fibrocystic disease (considered to be premalignant without mastectomy); inadequate or unsuitable tissue; active infection in the body at the time of surgery; pregnant or lactating; any medical condition such as obesity, diabetes, autoimmune disease, chronic lung or severe cardiovascular disease that might result in unduly high surgical risk and/or significant postoperative complications; patient use of drugs (including any drug that would interfere with blood clotting) that might result in high risk and/or significant postoperative complications; demonstrated psychological characteristics that are unrealistic or unreasonable given the risks involved with the surgical procedure; determination by physical examination that the subject has any connective tissue/autoimmune disorder (e.g., systemic lupus erythematosus, discoid lupus, or scleroderma); existing carcinoma of the breast without accompanying mastectomy; and prohibition of magnetic resonance imaging scanning (because of implanted metal device, claustrophobia, or other condition).

Data Collection and Statistical Analysis

The clinical study data were collected on standardized case report forms and underwent double data entry into a validated clinical database. These data were used to conduct safety and effectiveness analyses. The assessment of safety was based on the incidence of subject complications, including device ruptures and adverse effects. The cumulative incidence of first events among primary implants was estimated based on Kaplan-Meier risk rates (1 minus the complication-free survival rate) along with 95 percent confidence intervals. These were calculated using Proc LifeTest in SAS (SAS Institute, Inc., Cary, N.C.). In addition, the reasons for all reoperations (not simply the first experienced by the patient) and number of events at each investigational site were analyzed to provide a frequency distribution. Effectiveness analyses include a comparison of preimplantation to postimplantation bra cup sizes to assess anatomical change, and changes in subject satisfaction.

Rupture was analyzed using data from the magnetic resonance imaging cohort. These 571 subjects constitute the largest pivotal trial magnetic resonance imaging cohort to date. The magnetic resonance imaging scans were reviewed by a local radiologist and then by a blinded central expert radiologist. The worst-case rupture status from either local or central radiologist was used in the analysis (i.e., if either radiologist indicated a possible rupture, that subject was conservatively reported as ruptured in the database).

This article presents safety and effectiveness results through 5 years of follow-up. Data will con-

tinue to be analyzed at regular study intervals through 10 years.

RESULTS

Subject and Surgical Characteristics

Analysis of demographic data reported that the median subject age at the time of surgery was 38 years, the majority of subjects were Caucasian and married, and the most commonly reported household income exceeded $80,000. The median height and weight across the four cohorts was 5 feet 5 inches and 128 pounds, respectively, at enrollment. In addition, at the time of enrollment, the majority of study subjects had completed some college education, with 43 percent holding at least a bachelor degree and more than 8 percent having completed postgraduate level education. Table 1 describes the demographic profile of Sientra's study population.

The device distribution included in the study was comprehensive. Table 2 describes the distribution within each of the enrollment indications. Round devices were implanted more often than shaped devices. Among the augmentation cohorts, the inframammary approach was used most frequently, whereas the mastectomy or other scar approach was most common among the reconstruction cohorts. The use of submuscular placement was consistently more common than subglandular placement across all cohorts.

Safety Experience

Table 3 summarizes the complication rates for various complications in each of the four study cohorts (i.e., primary augmentation, revision-augmentation, primary reconstruction, and revision-reconstruction) through 5 years after surgery. Overall, across all cohorts by subject, the risk of rupture is 1.8 percent, the risk of capsular contracture is 9.0 percent, and the risk of reoperation is 23.8 percent. It should be noted that complications in the reconstruction cohort include subjects who underwent radiation therapy. Radiation may contribute to increased complication rates in this cohort.[3] Other local complications not listed in Table 3 (e.g., delayed wound healing, hematoma) occurred at a risk rate of less than 2 percent in all cohorts.

Table 4 and Figure 3 summarize the reoperation rates across all four subject cohorts. There were 483 reoperations in 387 subjects through 5 years (i.e., 21.6 percent of subjects underwent at least one reoperation). The most common reasons for reoperation were style/size change (19.0 percent), capsular contracture (17.6 percent), and asymmetry (9.5 percent). Figure 4 shows that over half of the reoperations were performed for cosmetic reasons.

Table 1. Demographic Data by Indication

	Primary Augmentation	Revision-Augmentation	Primary Reconstruction	Revision-Reconstruction
No. of subjects	1116	363	225	84
Median age, yr	36	42	46	51
Median height	5 ft 5 in	5 ft 5 in	5 ft 5 in	5 ft 5 in
Median weight, lb	125	126	140	140
Marital status, %				
Married	57.4	59.8	63.1	70.2
Single	28.4	25.3	20.9	16.7
Divorced	11.3	11.6	11.6	7.1
Other (e.g., widowed)	2.9	3.3	4.4	6.0
Race/ethnicity, %				
Caucasian	90.9	93.1	90.7	95.2
Hispanic	3.3	1.9	4.4	1.2
Asian	2.6	2.2	0.4	0.0
Other	3.2	2.8	4.4	3.6
Income, %				
<$40,000	21.6	20.1	31.1	25.0
$40,000–$80,000	28.5	22.3	22.2	17.9
≥$80,000	32.5	38.8	28.9	29.8
Not provided	17.4	18.7	17.8	27.4
Education, %				
Less than high school	0.7	1.1	2.2	1.2
High school	16.8	18.7	31.6	28.6
Some college	33.0	26.2	23.1	28.6
College graduate	35.8	41.3	27.1	26.2
Postgraduate	8.4	7.2	8.0	7.1
Not provided	5.4	5.5	8.0	8.3

Table 2. Device and Surgical Characteristics by Indication

Characteristic	Primary Augmentation	Revision-Augmentation	Primary Reconstruction	Revision-Reconstruction
No. of implants, no. (%)	2230 (63.6%)	725 (20.7%)	412 (11.8%)	139 (4.0%)
Device distribution, %				
Smooth round	57.8	46.9	45.9	40.3
Textured round	30.8	39.2	41.7	47.5
Textured shaped	11.5	13.9	12.4	12.2
Device placement, %				
Subglandular	42.9	39.3	27.2	8.6
Submuscular	57.1	60.7	72.8	89.9
Other	0	0	0	1.4*
Incision site, %				
Periareolar	33.5	33.4	17.0	6.5
Inframammary	61.6	60.6	28.4	33.8
Mastectomy or other scar	0.0	0.3	45.1	55.4
Other (e.g., transaxillary)	4.8	5.8	9.5	4.3
Incision size, %				
0–3 cm	22.0	19.3	15.8	10.1
3–6 cm	67.5	68.1	36.9	29.5
6–9 cm	10.4	12.6	47.3	60.4
Not provided	0.1	0.0	0.0	0.0
Pocket irrigation, %				
No	7.3	8.7	3.9	8.6
Yes	92.7	91.3	96.1	91.4
Antibiotics only	41.2	37.0	61.1	63.0
Anesthetic only	6.2	4.8	2.5	1.6
Other solutions/combinations (e.g., antibiotic, povidone-iodine, steroid solutions)	52.6	58.2	36.4	35.4

*One revision-reconstruction subject had bilateral implants placed during a subcutaneous mastectomy.

Table 3. Risk of Complications by Cohort*

Local Complication	Primary Augmentation (95% CI)	Revision-Augmentation (95% CI)	Primary Reconstruction (95% CI)	Revision-Reconstruction (95% CI)
Asymmetry	1.2 (0.7–2.0)	2.5 (1.2–4.9)	10.9 (7.1–16.6)	14.4 (7.6–26.5)
Breast mass/cyst/lump	1.7 (1.0–2.8)	0.8 (0.2–3.1)	3.3 (1.3–7.8)	4.9 (1.6–14.7)
Breast pain	0.9 (0.4–1.6)	1.6 (0.7–3.8)	4.0 (1.9–8.2)	3.6 (0.9–14.4)
Capsular contracture	8.8 (7.2–10.8)	7.9 (5.4–11.6)	10.6 (7.0–16.0)	10.9 (5.1–22.6)
Hypertrophic/abnormal scarring	0.9 (0.5–1.8)	1.7 (0.7–4.0)	3.0 (1.2–7.1)	2.9 (0.7–11.3)
Implant extrusion	0.1 (0.0–0.7)	0.9 (0.3–2.9)	2.2 (0.8–6.0)	—
Implant malposition	1.9 (1.2–2.9)	4.8 (2.8–8.0)	3.9 (1.8–8.0)	6.6 (2.8–15.3)
Infection	0.8 (0.4–1.6)	1.5 (0.6–3.6)	5.2 (2.9–9.2)	1.2 (0.2–8.3)
Nipple sensation changes	3.4 (2.4–4.7)	2.3 (1.1–4.8)	1.4 (0.3–5.6)	—
Rupture				
Overall	2.0 (1.3–3.2)	1.5 (0.6–3.8)	1.4 (0.4–5.4)	—
MRI cohort only	4.2 (2.6–6.7)	2.8 (0.9–8.4)	2.4 (0.3–15.7)	—
Ptosis	2.6 (1.8–3.9)	3.3 (1.7–6.2)	2.1 (0.8–5.4)	—
Redness	0.5 (0.2–1.2)	0.6 (0.2–2.5)	2.6 (1.1–6.2)	—
Seroma/fluid, accumulation	0.7 (0.3–1.4)	1.6 (0.7–3.9)	2.5 (1.0–5.9)	1.2 (0.2–8.4)
Swelling	0.8 (0.4–1.6)	0.3 (0.1–2.4)	1.6 (0.5–4.8)	—
Upper pole fullness	0.1 (0.0–0.8)	—	1.5 (0.4–6.3)	—
Wrinkling/rippling	1.0 (0.6–1.9)	3.0 (1.6–5.5)	1.8 (0.6–5.5)	1.4 (0.2–9.6)

CI, confidence interval.
*Data are presented from a by-subject Kaplan-Meier analysis.

Almost half of the explant procedures (n = 386 implants) were performed because of a requested change in style/size (46.4 percent). The next most common reason was capsular contracture (10.9 percent). Of the 386 explants, 75.6 percent were replaced.

Additional Safety Analyses

Given the almost equal distribution of smooth and textured implants within the study population (53 and 47 percent, respectively), secondary analyses were conducted to compare the rate of occurrence of capsular contracture for smooth ver-

Table 4. Risk of Reoperation by Subject and by Cohort

Reoperations	Primary Augmentation (95% CI)	Revision-Augmentation (95% CI)	Primary Reconstruction (95% CI)	Revision-Reconstruction (95% CI)
Any reoperation, %	16.6 (14.4–19.0)	29.7 (24.9–35.0)	42.7 (36.0–50.0)	47.8 (36.8–60.2)
Reoperation with explantation (with or without replacement), %	8.7 (7.1–10.6)	17.3 (13.5–22.0)	31.0 (24.9–38.1)	38.6 (27.9–51.6)

CI, confidence interval.

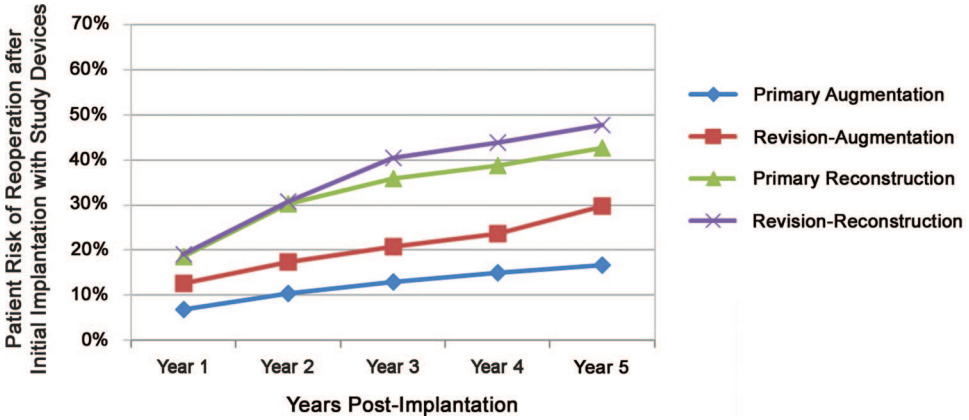

Fig. 3. Risk of reoperation.

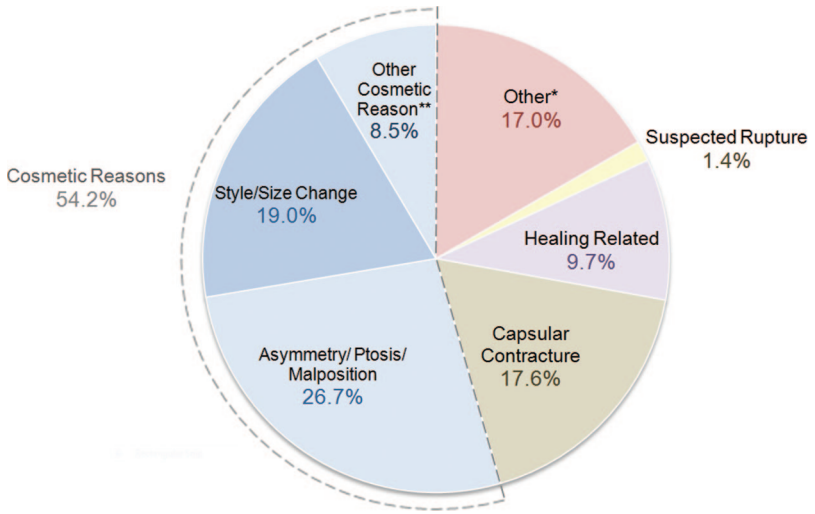

Fig. 4. Reasons for reoperation (all cohorts combined). *Other includes infection (4.3 percent), pain (1.9 percent), nipple related (2.1 percent), breast cancer (1.2 percent), mass/lump/cyst (3.7 percent), skin related (0.2 percent), trauma (0.2 percent), unknown (3.1 percent), and other (0.2 percent). **Other cosmetic reason includes wrinkling/rippling (3.1 percent), palpability/visibility (0.4 percent), upper pole fullness (0.2 percent), and scarring/hypertrophic scarring (4.8 percent).

sus textured implants. Although the overall risk rate of capsular contracture was 6.7 percent (by implant), the risk of capsular contracture for smooth implants was 10.0 percent (95 percent confidence interval, 8.6 to 11.7 percent), and the risk rate for textured implants was 3.0 percent (95 percent confidence interval, 2.2 to 4.0 percent).

In addition, the distribution of some key safety endpoints was examined across sites. Specifically, an analysis was performed to determine which three sites had the highest occurrence of rupture, capsular contracture, and reoperation. Regarding rupture, although most of the 36 sites experienced no ruptured implants, the three highest sites col-

lectively enrolled only 12 percent of the total study subjects and accounted for over half (60 percent) of the patients with rupture. Examining capsular contracture, the three highest sites collectively enrolled only 18 percent of the total study subjects and accounted for almost half (46 percent) of all patients with capsular contracture. For reoperations, the three highest sites enrolled approximately one-fourth (24 percent) of all the study subjects and contributed over one-third (36 percent) of the patients with reoperations. Interestingly, the site with the highest incidence of these three key safety endpoints was not consistent across the endpoints (i.e., the site that contributed the most ruptures did not also contribute the most capsular contractures).

Effectiveness Experience

At the completion of the implant surgery across all cohort indications, over 99 percent of surgeons reported their satisfaction with the results. Furthermore, within the primary augmentation cohort, almost 60 percent of the subjects increased their bra cup size by at least 1.5 cup sizes. Figure 5 depicts the satisfaction levels of the surgeons and the subjects following implantation. Primary augmentation, revision-augmentation, and primary reconstruction subjects collectively reported the highest satisfaction with their increased feeling of femininity. Revision-reconstruction subjects highly valued the way that the breast implants made their clothes fit better, above all other satisfaction questions.

DISCUSSION

The U.S. Food and Drug Administration approved Sientra's Silimed brand portfolio of silicone gel breast implants on March 9, 2012. The round and shaped breast implants, which have been available on all continents and in over 70 countries for almost 15 years, are now available in the United States for primary and revision breast augmentation in women at least 22 years old and for primary and revision breast reconstruction in women of any age. U.S. Food and Drug Administration approval of these breast implants was based on clinical data through 3 years from a 10-year, open-label, prospective, multicenter clinical study. The study included data from almost 1800 subjects implanted with 3506 Sientra Silicone Gel Breast Implants, making it the largest pivotal U.S. breast implant study to date. This article presents updated results of Sientra's clinical study through 5 years of follow-up.

Consistent with the 3-year study results,[2,4] the 5-year results of Sientra's study continue to support the safety and effectiveness of Sientra's Silicone Gel Breast Implants and provide evidence of high satisfaction rates in women for all implantation indications (i.e., augmentation, reconstruction, and revision).

Furthermore, complication rates for Sientra's breast implants remain low through 5 years, consistent with the literature establishing the safety of silicone gel breast implants in general.[5–11] Similarly, consistent with the 3-year study results,[2,4] patient choice continues to be the most common reason for reoperation. In fact, over half of the reoperations performed were attributable to cosmetic reasons, with the most common reason being patient request for style/size change. Furthermore, implant removal (with or without replacement) continues to be

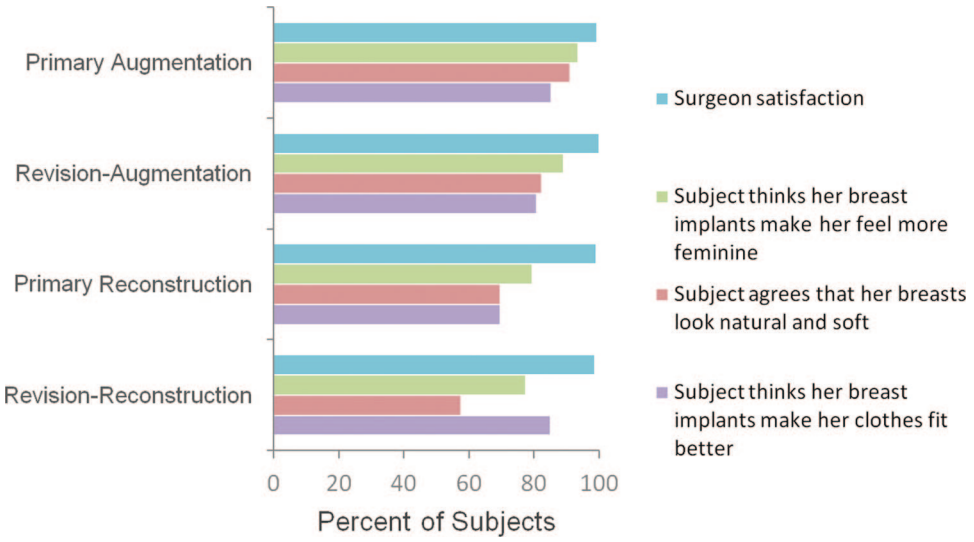

Fig. 5. Surgeon and subject satisfaction.

higher in the reconstruction cohorts compared with the augmentation cohorts.[11,12] In addition, almost half of the explant procedures (implant removals) were performed because of a patient's request for style/size change.[2,4]

The most common complication in the primary and revision-augmentation subjects was capsular contracture, whereas the most common complication in the primary and revision-reconstruction cohort was asymmetry. However, capsular contracture rates remain relatively low across all four subject cohorts. The 5-year Kaplan-Meier risk of capsular contracture within the primary and revision-augmentation cohorts was 8.8 and 7.9 percent, respectively. This is lower than the corresponding primary and revision-augmentation 4-year rates reported by both Mentor (8.8 and 19.9 percent[13]) and Allergan (13.2 and 17.0 percent[14]). Sientra's rates are reported through 5 years; therefore, this is not intended to be a direct comparison with other manufacturers' reported results. Given the shorter follow-up time of 4 years reported, and the fact that the other two manufacturers' study results and Sientra's study results are not designed to be compared directly, as the protocols and study cohorts are not identical, no scientifically valid comparisons can be made. This information is provided to more broadly illustrate the safety profile of Sientra breast implants.

Further analyses of capsular contracture rates reported in smooth and textured Sientra implants indicate that the risk of capsular contracture is over three times lower for textured implants (3.0 percent) versus smooth implants (10.0 percent). This suggests, as other articles have hypothesized,[15] that textured implants may reduce the risk of capsular contracture. However, further analyses controlling for other variables (e.g., pocket irrigation and implant placement) should be conducted to better understand this potential correlation.

Given the large study sample size and the fact that procedures and surgical approach were not standardized across sites, information about surgical techniques was collected as part of the study. This provided an opportunity to identify whether the rate of occurrence of certain complications may be influenced by surgical technique. For example, when examining implant rupture, 60 percent of the reported ruptures occurred at only three of the 36 study sites. However, these three sites contributed only 12 percent of the total study enrollment. In the case of capsular contracture, three of the 36 investigational sites contributed almost half of the reported occurrences of capsular contracture. These three sites contributed 18 percent of the total study enrollment. These two examples suggest that the rate of occurrence of some complications may be impacted by surgical technique (e.g., incision size and implant placement) and highlight the need for further research on the correlation between surgical technique and outcomes.

Based on information reported to the U.S. Food and Drug Administration and found in the medical literature, women with breast implants may have a very small but increased risk of developing anaplastic large cell lymphoma, a rare type of non-Hodgkin lymphoma.[16,17] However, in the Sientra study, no occurrences of anaplastic large cell lymphoma (or any cases of lymphoma) have been reported in any of the study subjects. The U.S. Food and Drug Administration, the industry, and the scientific community continue to collaborate to study this possible association.

In addition, the overall cancer and connective tissue disease results in this study have not produced any evidence to support correlation between Sientra breast implants and an increase in cancer or connective tissue disease diagnosis, which reinforces the conclusion made by other studies that there is no increased risk of cancer or connective tissue disease diagnosis for women with silicone gel breast implants.[5,6,18–21]

To examine the long-term safety and effectiveness of Sientra's implants, the study will continue through 10 years after implantation. In addition, as part of the conditions of premarket approval, Sientra is conducting a separate dual-design post-approval study intended to address specific post-market questions regarding the long-term clinical performance of Sientra's Silicone Gel Breast Implants under general conditions of use[4] to further the scientific knowledge base of silicone-gel breast implants.

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