Results from the MemoryGel Post-approval Study

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Background: The approval of Mentor MemoryGel Breast Implants in November 2006 was conditional on conducting a 10-year study designed to collect long-term experience in US women with MemoryGel Breast Implants, known as the MemoryGel Post-Approval Study.

Methods: This prospective, observational 10-year follow-up study used a current cohort design that began in 2007, which included both MemoryGel Breast Implant participants and concurrent saline controls to assess rheumatologic and neurologic signs and symptoms. The protocol was amended in 2015, which limited the scope of further data collection for the study to only secondary procedure/re-operation data for MemoryGel participants.

Results: Primary augmentation (n = 6743), revision augmentation (n = 2071), primary reconstruction (n = 1763), and revision reconstruction (n = 557) participants were enrolled in the Re-operation Phase Safety Set. Kaplan-Meier−estimated 10-year cumulative incidence of re-operation and explantation on a participant-level were 10.5% and 4.2% (primary augmentation), 14.1% and 7.7% (revision augmentation), 20.8% and 12.8% (primary reconstruction), and 25.0% and 16.6% (revision reconstruction).

Conclusions: The Re-operation Phase of the post-approval study addressed the Kaplan-Meier implant removal and re-operation rates over time, and provided the reasons for re-operation over time. Overall, no significant new hazards, increased risk, or unexpected adverse events were identified in the MemoryGel Post-Approval Study Re-operation Phase Safety Set. (Plast Reconstr Surg Glob Open 2021;9:e3402; doi: 10.1097/GOX.0000000000003402; Published online 26 March 2021.)

INTRODUCTION

On November 17, 2006, the US Food and Drug Administration (FDA) approved Mentor’s MemoryGel silicone gel-filled breast implants for use in women 22 years and older who are undergoing primary or revisional breast augmentation and all women undergoing primary or revisional breast reconstruction surgery. The approval was conditional on Mentor conducting a 10-year study designed to collect long-term experience in US women with MemoryGel Breast Implants. The MemoryGel Post-approval Study (MemoryGel PAS) was intended to satisfy one element of FDA’s post-approval requirements.

METHODS

Original Phase

MemoryGel PAS (NCT00756652) began by using a current cohort design of the first 41,900 women receiving Mentor’s MemoryGel Breast Implants from the time the study commenced, with 10 years of follow-up, before an amendment in its first year to change from mandatory to voluntary enrollment. The study was initiated in 2007, and enrollment was completed in October 2008. In the Original Phase, there were 1000 saline breast implant participants enrolled from the participating surgeons’ practices who served as concurrent controls. Exclusion criteria included the presence of an active infection anywhere in the body, existing breast cancer or pre-cancer of the breast without adequate treatment for those conditions, and currently pregnant or nursing. Baseline data were collected from the participant using survey methodology. Data on operative characteristics were collected from the surgeon. Follow-up data were collected from the participant by a combination of mail, internet, and telephone survey methodologies annually for years 1–10, and on an interim/unscheduled basis from the surgeons, as needed, for key local complications and results of MRI evaluations (MemoryGel participants only), and results from rheumatological or neurological referral evaluations (MemoryGel and saline participants). Additionally, the surgeon was expected to see the MemoryGel participants at year 1, a second time during years 4–6, a third time during years 9–10, and at unscheduled/interim visits. All local

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complications, including reasons for re-operation, with or without removal, and reasons for removal, reported by the participant or diagnosed by the surgeon were recorded during these visits. Owing to low participant follow-up, questionnaire response rates experienced in the study—which were addressed during a 2011 FDA advisory panel hearing—the Original Phase of the MemoryGel PAS was closed and the Re-operation Phase was initiated in November 2014.

Re-operation Phase

Understanding that the low follow-up rate would limit interpretation of the data, the FDA—in collaboration with other key stakeholders, including the American Society of Plastic Surgeons, breast implant manufacturers, and patient representatives—investigated innovative alternative approaches to collect long-term data on silicone gel breast implants, including the use of registries such as the National Breast Implant Registry. As part of the results of those efforts, the MemoryGel PAS protocol was amended to specifically limit the scope of further data collection to only secondary procedure/re-operation data. There were no longer requirements for scheduled office visits or annual participant questionnaires, which included the collection of data on conditions and diseases such as connective tissue disease, rheumatological signs and symptoms, and neurological disease. Saline implant participants were not to have data collected under the amended protocol and therefore they were exited from any further study participation.

The cumulative incidence of explantation and re-operation for women with MemoryGel Breast Implants was estimated based on physician evaluations for the MemoryGel participants using Kaplan-Meier methodology to estimate the time to the first occurrence of the complication or re-operation. Participants enrolled only in the Original Phase of the study were either censored according to their last follow-up or withdrawal from the Original Phase. Those also enrolled in the Re-operation Phase Safety Set were censored at the withdrawal from the Re-operation Phase. The data for the Kaplan-Meier analysis used the follow-up and re-operation/explantation reports from the entire data set of the 41,452 participants in the Original Phase, with follow-up and additional re-operations/explantations reported on the 11,101 participants in the Re-operation Phase Safety Set. Those with no post-operative follow-up were excluded from the Kaplan-Meier analysis. If a re-operation participant had multiple events, then the date of the first event was used to calculate the cumulative incidence. Ninety-five percent confidence intervals were computed. In addition, the relative frequency of reasons for re-operation were computed for all study participants with or without scheduled follow-up visits.

RESULTS

Approximately 1700 centers participated in the Original Phase of the study and enrollment included 41,452 MemoryGel participants (n = 26,173 primary augmentation, n = 8382 revision augmentation, n = 5023 primary reconstruction, n = 1761 revision reconstruction, n = 113 unknown indication) and 1039 saline participants. Of those, 752 study investigators and 11,101 MemoryGel participants (n = 6685 primary augmentation, n = 2029 revision augmentation, n = 1794 primary reconstruction, n = 566 revision reconstruction, n = 27 unknown indication) were included in the Re-operation Phase Safety Set. Overall, 74.1% of women in the Re-operation Phase Safety Set of the study completed their 10-year follow-up. Demographics and operative characteristics from women included in both the Original and Re-operation Phase Safety Set are provided in Table 1. Women in the 2 groups were of similar age with those enrolled in the Re-operation Phase Safety Set being slightly older (42.1 versus 40.3 years) with the majority in both groups being White of not Hispanic origin (79.4% of Original Phase versus 85.0% of Re-operation Phase Safety Set). Operative characteristics were comparable between the 2 groups with the majority from both the Original and Re-operation Phase Safety Set made up of primary augmentation participants (63.1% and 60.2%, respectively), undergoing sub-muscular placement of the implant (77.6% and 81.6%, respectively) with smooth implants (92.9% and 91.2%, respectively).

Kaplan-Meier—estimated 10-year cumulative incidence of re-operation (Table 2) and explantation (Table 3) were determined. The estimated cumulative incidence of re-operation and explantation were lowest in the primary augmentation cohort: 10.5% and 4.2% for all re-operations and explantations, respectively. When excluding patient-requested re-operations and explantations for size-change, those rates decrease to 8.9% and 2.5%. The estimated cumulative incidence of re-operation and explantation were highest in the revision reconstruction cohort: 25.0% and 16.6% for all re-operations and explantations, respectively. When excluding patient-requested re-operations and explantations for size change, those rates decrease to 22.3% and 13.7%. Among those in the Re-operation Phase Safety Set who underwent a re-operation, the most frequently reported reasons for re-operation by indication were participant-requested size change in primary augmentation and revision augmentation participants (19.1% and 16.9%, respectively), and asymmetry (18.6% and 18.3%, respectively) in primary reconstruction and revision reconstruction participants (Table 4).

DISCUSSION

This study was originally envisioned to collect and examine additional long-term safety data on women with MemoryGel Breast Implants. However, due to insufficient follow-up and lack of confirmed diagnosis by board-certified specialists in regard to connective tissue disease, rheumatological, and neurological signs and symptoms, the focus of the study was amended. The Re-operation Phase of the study aimed to address the Kaplan-Meier implant removal and re-operation rates over time and provide the reasons for re-operation over time. The focus on tracking re-operations and removals—thought to represent more clinically significant complications—mirrors the adverse event capture framework of many of the breast implant registries worldwide. Overall, no significant new hazards, increased risks, or unexpected adverse events were
Critical Limitations of the MemoryGel PAS Original Phase

Partial results from the Original Phase have been previously referenced by Coroneos, whose analysis was critiqued by Ashar, Colwell & Mehrara, Swanson, and others. As stated in the FDA Update on the Safety of Silicone Gel-Filled Breast Implants from June 2011 authored by the Center for Devices and Radiological Health and US FDA, the lower-than-expected follow-up rates prevent a meaningful analysis of the study endpoints from the Original Phase, including local complications, connective tissue disease, neurological disease, potential effects on offspring of women with breast implants, potential effects on reproduction and lactation, cancer, suicide, rupture, potential interference of breast implants with mammography, and participant compliance with recommendations for MRI follow-up, for which the study was originally intended. In addition to the low follow-up rates, meaningful interpretation of data from the Original Phase is significantly limited by lack of adjustment for differences between study population and the general population in demographic characteristics and risk factors related to adverse reproductive and offspring outcomes and a lack of board-certified neurologist or rheumatologist confirmation of cases of neurological and connective tissue disease (which, as previous studies have identified in the MemoryGel PAS Re-operation Phase Safety Set).

Table 1. Demographics and Operative Characteristics

| Variable                                      | Large PAS (N = 41,452) | Re-op Phase Safety Set (N = 11,101) |
|-----------------------------------------------|------------------------|------------------------------------|
| Age (mean ± SD), n                           | 40.3 ± 11.44, 41,263  | 42.1 ± 11.47, 11,077               |
| Race, n (%)                                   |                        |                                    |
| White, not of Hispanic origin                | 32,201/40,563 (79.4%)  | 9299/10,964 (85.0%)                |
| White, of Hispanic origin                    | 4122/40,563 (10.2%)    | 847/10,964 (7.7%)                  |
| Black, not of Hispanic origin                | 890/40,563 (2.2%)      | 200/10,964 (1.8%)                  |
| Black, of Hispanic origin                    | 146/40,563 (0.4%)      | 21/10,964 (0.2%)                   |
| Asian, Asian American, Pacific Islander      | 1873/40,563 (4.6%)     | 312/10,964 (2.9%)                  |
| Native American or Alaskan Native            | 306/40,563 (0.8%)      | 69/10,964 (0.6%)                   |
| Other (specify)                              | 1025/40,563 (2.5%)     | 198/10,964 (1.8%)                  |
| Indication: participant-level, n (%)         |                        |                                    |
| Primary augmentation                         | 26173/41,452 (63.1%)  | 6685/11,101 (60.2%)                |
| Primary reconstruction                       | 5023/41,452 (12.1%)    | 1794/11,101 (16.2%)                |
| Revision augmentation                        | 8382/41,452 (20.2%)    | 2029/11,101 (18.3%)                |
| Revision reconstruction                      | 1761/41,452 (4.2%)     | 566/11,101 (5.1%)                  |
| Unknown indication                           | 113/41,452 (0.3%)      | 27/11,101 (0.2%)                   |
| Implant placement: right, n (%)              |                        |                                    |
| Sub-glandular                                | 7799/40,275 (19.4%)    | 1847/10,750 (17.2%)                |
| Sub-muscular                                 | 31262/40,275 (77.6%)   | 8769/10,750 (81.6%)                |
| Other                                        | 1214/40,275 (3.0%)     | 134/10,750 (1.2%)                  |
| Implant placement: left, n (%)               |                        |                                    |
| Sub-glandular                                | 7765/40,114 (19.4%)    | 1837/10,691 (17.2%)                |
| Sub-muscular                                 | 31147/40,114 (77.6%)   | 8719/10,691 (81.6%)                |
| Other                                        | 1202/40,114 (3.0%)     | 135/10,691 (1.3%)                  |
| Implant style                                |                        |                                    |
| Smooth                                       | 38,510/41,452 (92.9%)  | 10,129/11,101 (91.2%)              |
| Textured                                     | 2552/41,452 (6.2%)     | 889/11,101 (8.0%)                  |
| Mixed                                        | 38/41,452 (0.1%)       | 9/11,101 (0.1%)                    |
| Not available                                 | 352/41,452 (0.8%)      | 74/11,101 (0.7%)                   |

Table 2. Kaplan-Meier-Estimated 10-year Cumulative Incidence of Re-operation on a Participant-Level for Participants in Re-operation Phase Safety Set

| Re-operation                                      | Primary Augmentation (n = 6745) | Revision Augmentation (n = 2071) | Primary Reconstruction (n = 1763) | Revision Reconstruction (n = 557) |
|--------------------------------------------------|---------------------------------|----------------------------------|----------------------------------|----------------------------------|
| All re-operations                                 | 10.5% (9.6%, 11.5%)             | 14.1% (12.3%, 16.2%)             | 20.8% (18.7%, 23.1%)             | 25.0% (21.0%, 29.6%)             |
| Excluding elective re-operation for patient-requested size change | 8.9% (8.1%, 9.8%) | 11.9% (10.2%, 13.8%) | 18.8% (16.8%, 21.0%) | 22.3% (18.5%, 26.9%) |

Table 3. Kaplan-Meier-Estimated 10-year Cumulative Incidence of Explantation on a Participant-Level for Participants in Re-operation Phase Safety Set

| Explantation                                      | Primary Augmentation (n = 6745) | Revision Augmentation (n = 2071) | Primary Reconstruction (n = 1763) | Revision Reconstruction (n = 557) |
|--------------------------------------------------|---------------------------------|----------------------------------|----------------------------------|----------------------------------|
| All explantations                                 | 4.2% (3.6%, 4.8%)               | 7.7% (6.3%, 9.4%)                | 12.8% (11.1%, 14.7%)             | 16.6% (13.3%, 20.8%)             |
| Excluding elective explantation for patient-requested size change | 2.5% (2.0%, 3.1%) | 5.3% (4.1%, 6.8%) | 10.7% (9.1%, 12.5%) | 13.7% (10.6%, 17.6%) |
demonstrated, is important to address the low accuracy of self-reported data for these endpoints). It is for this reason that the present analysis is focused on results only from the Re-operation Phase Safety Set.

### Potential Factors Impacting Low Follow-up in MemoryGel PAS Original Phase

Initially, in an attempt to ensure that the study enrollment was completed in a timely manner, participation in the study was mandatory for any women who wished to receive the newly approved MemoryGel Breast Implants (participation of the control group receiving saline-filled implants in the MemoryGel PAS Original Phase was voluntary). However, in 2007, as a result of pushback from institutional review boards questioning the appropriateness of requiring participants to enroll in the study to receive MemoryGel Breast Implants (an FDA-approved medical device), there was an amendment to change from mandatory to voluntary enrollment, asking physicians to actively encourage their patients to participate. In hindsight, it is thought that some portion of participants may have enrolled in the study to obtain the devices they desired, while recognizing that they also had the right to discontinue study participation at any point, possibly leading to a lower than desired follow-up rate.

As discussed in the 2011 General and Plastic Surgery Devices Panel, it is also understood that significantly deviating beyond standard of care in post-approval studies can lead to lower participant compliance with follow-up. Such deviations may include requiring increased frequency of follow-up, procedures and assessments beyond standard practice, and increased length of the study. In the case of MemoryGel PAS, follow-ups were required well past the typical 1-year follow-up for patients not participating in a clinical study, participants had to complete a 27-page questionnaire that was considered "arduous" and "intrusive," and the 10-year duration of the study extended far beyond normal clinical follow-up. Although multiple efforts were implemented to increase follow-up compliance, including letters from physicians to participants, an FDA letter to investigators, FDA letters to participants through investigators, modifications to the participant study website, and FDA participation at society meetings to reinforce physician involvement to increase participant follow-up, such measures ultimately proved unsuccessful. In addition to the efforts beyond standard clinical practice that were required, and the possible effect of that additional burden on follow-up, other possible reasons for the lower-than-expected follow-up included absence of complications and change in participants’ residence (leading to a lower than desired follow-up rate).
change in the health care provider). In fact, an Online Breast Augmentation Follow-Up survey reported by Young et al suggested that the 2 primary reasons why respondents of the survey who underwent breast augmentation (n = 1350) did not schedule or keep follow-up visits recommended by their surgeon were “No problems with implants and see no reason for follow-up” (24%) and “I would schedule an appointment if I thought I had a problem” (21%). Furthermore, similar to many post-approval studies, Young et al found that compliance decreased over time.6 Regarding change in residence, in a study utilizing a survey questionnaire to understand the challenges to recruitment and retention experienced by investigators in India (n = 73) suggested over one-third of investigators (36%) reported that they believed change in residence had a moderate effect on subject retention, and an additional 15% of respondents indicated they believed it had a major effect on subject retention.7

2011 FDA Advisory Panel Hearing Deliberations and Considerations

During the 2011 General and Plastic Surgery Devices Panel, methodological issues and considerations for future breast implant post-approval studies were discussed, given the challenges experienced in the present study as described above. Specifically, regarding safety endpoints, due consideration needs to be given regarding whether it might be preferable to conduct multiple studies to address different subsets of endpoints versus 1 large study. It is also important to carefully consider whether the data sought will provide the desired insight on unanswered questions, as well as what safety endpoints should be assessed, for how long and how frequently they should be assessed in a post-market setting and should this differ depending on endpoint, what is the preferred method for collecting safety data (eg, self-report or investigator report) and should this differ depending on endpoint, what type of control is appropriate (eg, comparison group of women who considered breast implants and decided against them, comparison group of women who had other breast surgeries, comparison group of women with saline implants, national norms, disease rate estimates from registries, historical control groups, or reference study populations in the literature), and how will safety be determined. It is hoped that the learnings from the experience of the MemoryGel PAS Original Phase, as well as similar post-approval studies also discussed at the 2011 FDA Advisory Panel hearing, will help to inform other ongoing and future investigations of long-term breast implant safety endpoints.

Limitations of the MemoryGel PAS Re-operation Phase

For results from the MemoryGel Re-operation Phase Safety Set, which are the focus of this report, it is important to recognize that the findings may represent an under-estimation of re-operation and explantation rates due to the lack of mandatory safety reporting and ability for participants to be treated at non-study sites.

As a result of the numerous challenges and limitations identified in relation to the MemoryGel PAS, alternative approaches for addressing safety endpoints for which the core study was not sufficiently powered are being implemented, including use of the National Breast Implant Registry to strengthen post-market surveillance infrastructure for current and future breast implant devices, the Patient Registry and Outcomes for Breast Implants and Anaplastic Large Cell Lymphoma Etiology and Epidemiology (PROFILE) to collect data on potential cases of breast-implant associated anaplastic large cell lymphoma (BIA-ALCL), as well as additional post-approval studies.

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