SurgiMend® PRS Acellular Bovine Dermal Matrix

Sponsor Executive Summary
General and Plastic Surgery Devices Advisory Panel
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1 INTRODUCTION

Breast cancer is the second most common cancer in the world, with over 2 million new cases diagnosed each year. In the United States alone, breast cancer affects one in eight women and has been characterized by the National Institutes of Health as a "modern epidemic." Surgical therapy for breast cancer, including mastectomy, continues to be a critical component of multi-disciplinary care for patients with breast cancer and those at high risk for developing breast cancer. Increasingly, women are electing to undergo breast reconstruction following mastectomy, often with little or no delay between procedures. According to the American Society of Plastic Surgeons,[1] in approximately 75% of implant-based breast reconstruction procedures in the United States in 2018, surgeons employed acellular dermal matrices, or ADMs. Accordingly, ASPS considers ADM use as the standard of care in breast reconstruction.[1] ADMs are used to support native skin, offload pressure on the overlying soft tissues in the breast and provide a stable environment around the implant. (Govshievich et al., 2015) Yet, despite the ubiquity of ADMs in such procedures, there are no ADMs on the market in the U.S. that are FDA-approved with an indication for use specific to breast reconstruction. With its pending PMA submission, Integra LifeSciences Corporation (Integra) and its subsidiary TEI Biosciences Inc. (TEI) are seeking an approval for the use of its SurgiMend® PRS Acellular Bovine Dermal Matrix (SurgiMend PRS ABDM) in certain breast reconstruction surgeries.

This Executive Summary sets forth the data submitted in support of the SurgiMend PRS ABDM PMA application which demonstrates the safety and effectiveness of SurgiMend PRS ABDM when used in accordance with the proposed indications for use. The data was obtained from Real-World Evidence using data from the comprehensive Mastectomy Reconstruction Outcomes Consortium (MROC) Study. As described further in **Section 5.2**, in an agreement with the MROC researchers at the University of Michigan, the MROC Study data was provided to FDA in a Master File and Integra was granted a right of reference to use the results of analyses of the data in the Master File in support of its marketing application. However, Integra was not granted access to the data itself, resulting in an arrangement under which FDA conducted the statistical analyses and provided the results to Integra. FDA conducted these analyses pursuant to a Statistical Analysis Plan (SAP) prepared and submitted by Integra, and that the Agency agreed upon, following substantial collaboration between Integra and FDA.

The findings from the pivotal study presented in **Section 8** are based on a novel composite endpoint, established in consultation with FDA, capturing both patient-reported perception of

[1] American Society of Plastic Surgeons, *ADM Update: The use of acellular dermal matrices (ADMs)* August 26, 2019 https://www.plasticsurgery.org/for-medical-professionals/publications/psn-extra/news/adm-update-the-use-of-acellular-dermal-matrices

physical wellbeing of the chest and safety outcomes using data from the MROC Study. The primary endpoint analysis confirms the superiority hypothesis: a higher proportion of subjects in the SurgiMend group achieved Composite Clinical Success compared with subjects in the no-ADM control group. Further, Integra's safety analysis demonstrates that SurgiMend had an overall lower rate of major complications in breast reconstruction compared to breast reconstructions performed without an ADM.

The use of Real-World Evidence from the MROC Study to demonstrate the safety and effectiveness for SurgiMend for two-stage submuscular breast reconstruction surgeries is consistent with relevant FDA guidance, "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices."[2] As described further in **Section 8:** *The Integra SurgiMend Study: Results,* the Real-World Evidence generated from the MROC Study data meets the expectations of FDA's guidance with respect to both the relevance and reliability of the Real-World Evidence. Given the difficulty in, and ethical challenges associated with, enrolling patients in a study that could randomize patients to a non-ADM control arm in light of the widespread and common use of ADM in breast reconstruction surgeries, the Real-World Evidence from the MROC Study provides a valuable and appropriate alternative to a traditional prospective and randomized controlled trial.

2 PROPOSED INDICATIONS FOR USE

Integra LifeSciences Corporation (Integra) has submitted a premarket approval (PMA) application on behalf of TEI Biosciences Inc., a subsidiary of Integra, for SurgiMend PRS Acellular Bovine Dermal Matrix with the following indications for use:

> *SurgiMend PRS Acellular Bovine Dermal Matrix is intended for use as soft tissue support in post-mastectomy breast reconstruction. SurgiMend PRS Acellular Bovine Dermal Matrix is specifically indicated for: Immediate, two-stage, submuscular, alloplastic breast reconstruction.*

3 CLINICAL BACKGROUND

Breast reconstruction following mastectomy for breast cancer or prophylaxis is a major focus of women's health today. Breast cancer is the most common cancer diagnosed in women in the U.S,

[2] Food and Drug Administration. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices *Guidance for Industry and Food and Drug Administration Staff***.** August 2017. Available from: https://www.fda.gov/media/99447/download

and the American Cancer Society estimates that over 280,000 new cases will be diagnosed in women in the U.S. in 2021.[3] Breast reconstruction following mastectomy for breast cancer or prophylaxis is a major focus of women's health today, because it improves a woman's quality of life, including perception of body image, self-esteem, and sexuality. For these reasons, the Women's Health and Cancer Rights Act of 1998 requires health plans that pay for mastectomy to also pay for breast reconstruction of a breast removed with mastectomy, as well as surgery and breast reconstruction of the opposite breast to achieve a symmetrical appearance.

Contemporary breast reconstruction is performed to restore a breast to near-normal shape and appearance following mastectomy. One approach to breast reconstruction is to use flaps of the patient's own tissue, such as abdominal skin and fat, to create the anatomical shape of the breast – "*autologous reconstruction*." Breast reconstruction based on a breast implant – "*implant-based reconstruction"* – is another option for selection by the plastic surgeon and patient if the mastectomy, with or without radiation therapy, has resulted in sufficient chest wall tissue to cover, support, and maintain the position of a breast implant.

The 2018 Plastic Surgery Statistics Report of the American Society of Plastic Surgeons, the last complete data report pre-COVID that listed ADM usage, estimates that over 100,000 U.S. women underwent breast reconstruction. Among the breast reconstructions in 2018, approximately 75% of all implant-based reconstruction procedures utilized an acellular dermal matrix (ADM)[4].

The procedure that is the focus of this Executive Summary and the SurgiMend clinical investigation is immediate, two-stage, implant-based, submuscular, alloplastic breast reconstruction.

- The *first stage* of the procedure is done in the operating room immediately after the mastectomy. An expander device is placed below the pectoral muscle of the chest (see **Figure 3-1**). During office visits over several weeks to months, the expander device is gradually filled in volume with saline to stretch the pectoral muscle and its overlying skin for later insertion of the properly sized breast implant.
- In the *second stage* operation, the expander is removed, and the permanent breast implant is positioned in the proper anatomic location under the pectoral muscle.

In the *first stage* of this operation, if the surgeon elects to use an acellular dermal matrix (ADM), the ADM is placed to create a hammock under the expander to allow gradual increases in volume

[3] American Cancer Society. Cancer Facts and Figures 2021. Available at https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf

[4] American Society of Plastic Surgeons, *ADM Update: The use of acellular dermal matrices (ADMs)* August 26, 2019 https://www.plasticsurgery.org/for-medical-professionals/publications/psn-extra/news/adm-update-the-use-of-acellular-dermal-matrices

of the expander and support the soft tissues of the lower pole of the breast pocket (see **Figure 3-1**). Over time, the ADM is revascularized and integrates with the surrounding soft tissue.

In the *second stage* operation, when the expander is removed and the breast implant is inserted, the ADM in combination with the overlying chest muscle helps to support and maintain the position of the breast implant during the healing process. Breast reconstruction surgeons elect to use ADM in breast reconstruction surgery based on many factors including patient characteristics, quality of the soft tissues in the breast pocket, planned size of the implant, surgical training, the practice and standards of the institution, and personal experience in the practice-of-surgery.

The purpose of the clinical investigation described in this Executive Summary is to compare the efficacy and safety of the use of SurgiMend PRS ABDM versus no ADM in women undergoing immediate, two-stage, implant-based, submuscular breast reconstruction.

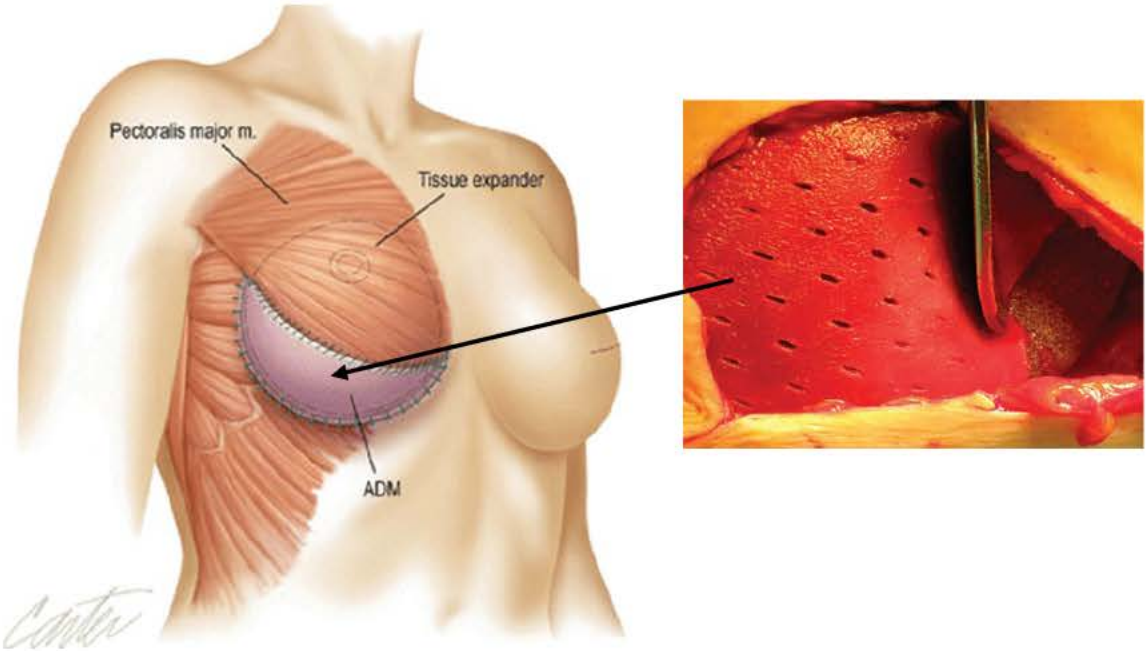


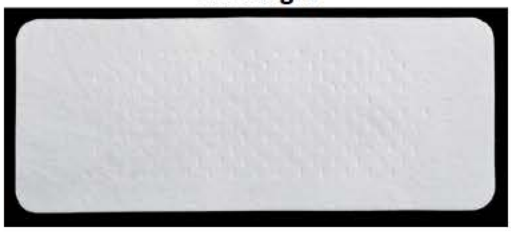
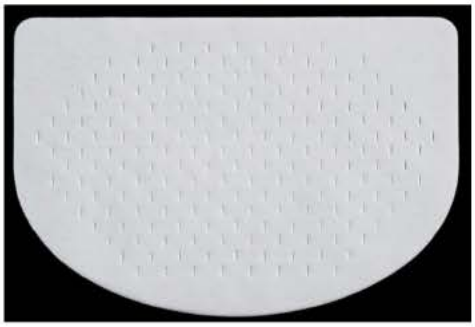
Figure 3-1: SurgiMend at First Stage Procedure

4 PRODUCT DESCRIPTION

4.1 Physical Characteristics

SurgiMend PRS Acellular Bovine Dermal Matrix (ABDM) is a pliable, porous biomaterial made from fetal bovine dermis, a tissue rich in Type I and Type III collagen. It is provided as an approximately 1mm thick sheet in the shapes and sizes as shown in **Table 4-1**,.with a pattern of small, perforating slits ("fenestrations") throughout. As shipped, it is stiff and wafer-like, and must be hydrated with normal saline at room temperature before use. Once hydrated, surgeons may further trim the SurgiMend PRS ABDM to the desired dimension and suture it in place to provide the intended support (see **Figure 3-1**).

Table 4-1: SurgiMend PRS ABDM Configurations

Shape	Size (cm)
Rectangle 	7x17 8x20 10x20
Semi-Oval 	6x16 7x17 8x16 10x15 15x15
Slant Semi-Oval 	10x15

The manufacturing of the SurgiMend PRS ABDM involves: (1) mechanically stripping fetal bovine hides of hair and epidermis on one side and residual fat and muscle on the other side to obtain the dermis; (2) decellularization to reduce lipids, carbohydrates, globular and non-collagenous proteins, and antigenic components inherent to xenogeneic tissue, and to inactivate any potential viruses; (3) freeze-drying; (4) thickness selection per intended use; (5) die-cut for shape, size, and fenestration; (6) packaging; and (7) sterilization with ethylene oxide gas. No preservatives or chemical cross-linking agents are added in the manufacturing process. The SurgiMend PRS ABDM is provided sterile with a shelf-life of 5 years.

SurgiMend PRS ADBM, following hydration, is designed to have the following characteristics: strength to support soft tissue surrounding the tissue expander or breast implant; can be held in place with suture; pliable and drapable to conform to surfaces. It is also designed to be biocompatible and to support cellular migration and vascular ingrowth associated with tissue integration. Standard performance testing was conducted on the SurgiMend PRS ABDM device and found to be within the acceptance criteria previously used for clearance under K071807. Routine in-process and finished goods testing will be performed on each lot of material before release.

4.2 Biocompatibility and Mechanical Stability Assessments for SurgiMend PRS

4.2.1 Biocompatibility Assessment

Biocompatibility testing was conducted on the previously cleared SurgiMend devices, which included cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, genotoxicity, intramuscular toxicity, hemolysis, and pyrogenicity. Since the standards for biocompatibility testing have been updated since the clearance of SurgiMend under K071807, Integra has opted to execute confirmatory biocompatibility tests to comply with the most current ISO 10993 revisions. This testing is expected to be completed by February 2022.

4.2.2 Biological and Mechanical Compatibility with Silicone Implant

Integra has also initiated a testing protocol for testing tissue expanders and breast implants in contact with SurgiMend PRS ABDM using quasi-static monotonic compression or cyclic fatigue conditions. The test method used to design the study was developed using the FDA Guidance, Saline, Silicone Gel, and Alternative Breast Implants issued September 29, 2020, ASTM F703-18 Standard Specification for Implantable Breast Prostheses, and ASTM F1441-03 Standard Specification for Soft-Tissue Expander Devices as guides. As noted previously, SurgiMend is implanted during the first surgery to provide support to the implanted expander. After 2 or more

weeks, the surgeon may determine the mastectomy incision has healed sufficiently to begin filling the expander. The expander is injected with approximately 50mL of saline on a roughly biweekly basis, with volume and frequency dependent on the surgeon's assessment of tissue adaptation and the patient's pain tolerance. Studies show that the majority of expansion results from pectoralis muscle stretching rather than ADM stretching.

4.2.3 Mechanical Stability in the Clinical Setting

The existing biocompatibility and totality of clinical evidence for SurgiMend (i.e., the SurgiMend Study described in **Section 7 through Section 9** and the published literature summarized in **Section 10**) supports the biocompatibility and long-term mechanical stability of SurgiMend after implantation as it is integrated and remodeled with host tissue to provide continuous support for implant-based reconstruction. In particular, two clinical studies prospectively studied the remodeling of SurgiMend by obtaining biopsies at the time of exchange of the tissue expander for the implant. Scheflan et al. (2018) observed evidence of SurgiMend persistence with integration in all cases at 1-year post -implantation, noting:

> *"During exchange or revision procedures, SurgiMend was inspected visually and found to be integrated in all cases. Tissue biopsy specimens were taken from areas with and without acellular dermal matrix for histologic analysis. All biopsy specimens showed less cellularity and less vascularity in the integrated acellular dermal matrix area than those taken from the bare capsule. At no time either during exchange or during revision surgery were there any instances of SurgiMend disappearance."*

Gaster, et al. (2013) prospectively studied the persistence and integration of SurgiMend in the setting of two-staged, subpectoral breast reconstruction to examine long-term breast pocket formation for implant-based reconstruction. Biopsies were obtained from 12 patients (17 reconstructions) at the time of exchange of tissue expander to permanent silicone implant. The average time between SurgiMend implantation and biopsies was 7.8 months (range, 2-23 months). Macroscopically, breasts reconstructed with SurgiMend showed no evidence of contraction, edema, or infection, with the exception of one subject who experienced an infection requiring removal of the tissue expander 2 months after the initial procedure. The SurgiMend implant was clearly distinguishable grossly and histologically at the time of each implant exchange out to 23 months. The degree of integration and neovascularization corresponded to the quality of the skin flap rather than implantation duration, with "thick" flaps associated with better vascularization, greater cellular incorporation, neovascularization, and replacement of ADM with organized (human) collagen. This study showed successful neovascularization and incorporation of SurgiMend with only limited and localized degradation associated with new, organized collagenous tissue deposited by the patient. The minimal host inflammation and absence of foreign body response to SurgiMend when placed between a tissue expander and native tissue indicate that

SurgiMend may be safely used in alloplastic breast reconstruction. The SurgiMend device was structurally and morphologically stable after nearly two years of implantation. There was no evidence of contracture that would have suggested denaturation or degradation of the native collagenous structure. The durability of SurgiMend in breast reconstruction allows for cell infiltration and tissue integration that combine to create a strong breast pocket.

5 REGULATORY HISTORY

5.1 SurgiMend 510(k) Clearance

TEI Biosciences Inc. ("TEI"), which was acquired by Integra in July 2015, first received 510(k) clearance for the SurgiMend product family on August 6, 2007 under 510(k) K071807. Subsequently, FDA has cleared an additional three 510(k)s for products in the broader SurgiMend family: K083898 (February 4, 2009); K162965 (February 16, 2017); and K171357 (June 7, 2017).

The SurgiMend products are marketed today as Class II devices with the following cleared Indications for Use:

> SurgiMend Collagen Matrix for Soft Tissue Reconstruction is intended for implantation to reinforce soft tissue where weakness exists and for the surgical repair of damaged or ruptured soft tissue membranes. SurgiMend is specifically indicated for:
> - Plastic and reconstructive surgery
> - Muscle flap reinforcement
> - Hernia repair including abdominal, inguinal, femoral, diaphragmatic, scrotal, umbilical, and incisional hernias

The subject SurgiMend PRS ABDM product under consideration in PMA (b)(4) remains the same as the product manufactured and cleared under the initial 510(k) clearance, K071807. Although the MROC Study did not record which configuration of SurgiMend was used in a given procedure, Integra believes that the SurgiMend implants used in the MROC Study are the same as those cleared under 510(k) K071807 and that are the subject of the pending PMA. Integra's belief is based upon the following information:

1. Integra determined that only two investigational sites from the MROC Study had purchased meaningful numbers of SurgiMend. A review of SurgiMend sales data was conducted for those two sites during study enrollment years of 2012-2015. For one of the sites, 99.5% of the devices purchased were those cleared under 510(k) K071807. For the second site, 47% of the devices purchased were those cleared under 510(k) K071807. The additional devices

purchased at both sites were those that were designed and marketed for hernia repair indications cleared under 510(k) K083898 which is not the subject of this PMA application. Both sites are known to have had active programs that focus on abdominal wall reconstruction at the time of the study (as well as currently).

2. The product cleared under 510(k) K071807 was the only SurgiMend device that was designed for use in breast reconstruction surgery.
3. The product cleared under 510(k) K071807 was the only SurgiMend device that TEI marketed for use in breast reconstruction surgery during the time period of the MROC Study.
4. In a review of the clinical literature regarding any and all references to the use of SurgiMend in breast reconstruction (**Section 10**), only SurgiMend PRS configurations cleared under 510(k) K071807 are described.

Integra believes that the points above provide reasonable assurance that the devices used in the MROC Study were the same as the products cleared under 510(k) K071807 and the subject of this PMA application.

5.2 Development of Regulatory and Statistical Plan for Breast Reconstruction Indication for SurgiMend

For nearly six years, Integra has engaged in series of discussions, meetings, submissions, and other interactions with FDA to identify the appropriate investigational approach to demonstrate the safety and effectiveness of SurgiMend in breast reconstruction surgeries (and TEI had been involved in the effort for nearly four years before being acquired by Integra). After initially considering a prospective, randomized controlled clinical trial, Integra quickly realized that there would be significant challenges associated with conducting a randomized controlled trial to demonstrate the safety and effectiveness of SurgiMend for breast reconstructions. Importantly, because use of ADMs in breast reconstructive surgeries was (and remains) widespread and was (and still is) considered in several major institutions to be standard of care in submuscular breast reconstruction procedures, Integra was unable to identify a control arm that could be feasibly and ethically executed. Integra learned that surgeons were hesitant to randomize patients to a non-ADM control arm.

Understanding these enrollment challenges, Integra and FDA agreed that Real-World Evidence could provide the best path forward to demonstrate the safety and effectiveness of SurgiMend PRS ABDM in breast reconstruction surgeries. Integra entered into discussions with FDA to consider the use of Real-World Evidence generated from the Real-World Data in the Mastectomy Reconstruction Outcomes Consortium (MROC) Study sponsored by the University of Michigan.

The MROC Study presented a Real-World Dataset rich in surgical and patient outcomes that provided clarity on approaches to breast reconstruction, with a unique focus on the patient perspective. In a 2019 communication to Integra, following FDA's discussion with the principal investigator of the MROC Study but prior to the Agency's receipt or analysis of the MROC data, FDA identified analysis of the MROC dataset as a "recommended, potential alternative approach" to provide clinical evidence consistent with "least burdensome" data requirements for PMA approval. FDA further stated its belief that "the [MROC] data set, endpoints, and number of SurgiMend [sic] patients would be sufficient to assess the safety and effectiveness of the subject device for [the] proposed intended use."

Accordingly, in 2019, Integra and FDA both approached the study sponsors with a goal of gaining access to the MROC Study dataset. Ultimately, the University of Michigan submitted the de-identified MROC Study dataset to FDA under a Master File, and Integra secured a right of reference to the dataset in February 2020, subject to certain conditions. Importantly, although the University of Michigan granted Integra the ability to reference the results of data analyses conducted using the Master File data, Integra was not granted access to the data itself. Rather, the terms of the right of reference required that Integra work with FDA to obtain statistical analyses of the MROC Study data. Accordingly, Integra collaborated with a statistical team at FDA to develop an agreed upon Statistical Analysis Plan (SAP) that was then executed by FDA statisticians. The results of that SAP were provided to Integra and form the basis of the statistical results reported in the subject PMA and in this Executive Summary.

5.3 Agreement on Primary Endpoint and Development of Statistical Analysis Plan

As described further in **Section 8** : *The Integra SurgiMend Study: Results,* the pivotal clinical investigation supporting the SurgiMend PRS ABDM PMA application under review uses a novel primary endpoint that combined Patient-Reported Outcome (PRO) (i.e., BREAST-Q (Pusic et al. 2009)) and assessment of the occurrence of major complications observed in all approaches to breast reconstructions.

As a result of a series of meetings and communications, Integra and FDA agreed that the use of validated PROs should comprehensively assess the patients' experience and therefore all BREAST-Q modules should be included in the study design. FDA had indicated use of BREAST-Q was an option for proof of benefit at the March 26, 2019, public advisory committee meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee.[5]

[5] Materials from this meeting are available on FDA's website at https://www.fda.gov/advisory-committees/advisory-committee-calendar/march-25-26-2019-general-and-plastic-surgery-devices-panel-medical-devices-advisory-committee .

During a March 3, 2020, teleconference with Integra, FDA proposed for Integra's consideration the use of a dichotomized primary endpoint to address both efficacy and safety for comparison of the SurgiMend PRS ABDM and control (i.e., no ADM) groups. A responder would achieve a prespecified level of improvement in the BREAST-Q Physical Well-Being score plus the absence of major safety events.

The primary endpoint used in the analysis was Composite Clinical Success (CCS), defined as a patient returning to her preoperative baseline score on the Physical Well-Being module of the BREAST-Q at Year 1, in the absence of one or more major complications (i.e., hematoma, explantation, re-operation, capsular contracture, infection, dehiscence, tissue necrosis, implant rupture, and seroma) through Year 2, or through Year 1 when Year 2 data were not available.

After agreeing on the primary endpoint, Integra and FDA continued to meet and collaborate on the design of the SAP. In May 2020, the SAP was finalized after agreement from both parties.

5.4 Role of FDA in data analysis

As described in **Section 5.2** above, to protect the proprietary information in the MROC Study dataset, the University of Michigan submitted the MROC Study dataset to FDA as a Master File and granted Integra a right of reference for any analyses performed using the data in the Master File. Because Integra was not granted direct access to the data, a team of FDA statisticians performed pre-specified data analyses in accordance with the Statistical Analysis Plan developed by Integra in consultation with FDA and submitted by Integra to the FDA statistics team. It is Integra's understanding that the FDA statisticians that performed the SAP analyses are independent from any statisticians that may be part of the PMA review team. On October 2, 2020, FDA presented Integra with the results from the executed SAP. The results of the analyses specified in the SAP are described in **Section 8** of this Executive Summary and were submitted for FDA review in the pending PMA.

6 BRIEF OVERVIEW OF THE MROC STUDY

The Mastectomy Reconstruction Outcomes Consortium (MROC Study) was funded by the National Cancer Institute (NIH/NCI #1R01CA152192-01A1) under an award (2011 - 2016) to the University of Michigan at Ann Arbor.[6] A consortium of breast reconstruction surgeons recognized the need for a well-designed prospective clinical investigation to provide "objective,

[6] Accessed at https://fundedresearch.cancer.gov/nciportfolio/search/details;jsessionid=EE0E9AB37AE24C3AB190261DB2612A4E?action=abstract&grantNum=1R01CA152192-01A1&grantID=8106705&grtSCDC=FY%202011&absID=8106705&absSCDC=CURRENT

up-to-date information on breast reconstruction outcomes from the patient's perspective" and reliable information including efficacy and complication rates of surgical options for breast reconstruction for providers and policy-makers. The NIH descriptor observes that the participating institutions performed over 2700 breast reconstructions annually.

6.1 Design and Conduct of the MROC Study

The MROC Study was a prospective observational cohort study of women undergoing first-time breast reconstruction at one of the 11 sites following mastectomy for either treatment of breast cancer or cancer prophylaxis.[7] The study recruited patients 18 years or older undergoing one of eight types of breast reconstruction.[8] It excluded patients undergoing breast reconstruction following complications of breast augmentation, lift or reduction, as well as procedures performed following previous failed breast reconstruction. Patient characteristics and patient-physician shared decision making determined which breast reconstruction procedure was used. Patients were enrolled in the MROC Study following IRB review and approval and Informed Consent. The 5-year study evaluated subjects preoperatively and at one week, three months, one year, and two years following breast reconstruction. Data collection relied on protocol-specified Patient-Reported Outcome (PRO) measures, including the BREAST-Q – a validated PRO instrument designed specifically for patients who undergo breast reconstruction surgery (Pusic et al. 2009, Cano et al. 2012, Pusic et al. 2017) – and other PRO questionnaires, as well as data in the Electronic Medical Records (EMR) and billing records. Patients completed questionnaires, including PRO instruments, before surgery and at 1 week, 3 months, 1 year, and 2 years after initial surgery. Postoperative complications, which were prespecified in the protocol, were retrospectively identified in the EMR at one year and two years after the subject's breast reconstruction. As of September 1, 2021, multiple peer-reviewed publications have been published based on the MROC Study. MROC Study publications can be found in **Section 15.**

6.2 MROC Study Data Provide Reliable and Relevant Real-World Data to Support the SurgiMend PMA

The Advisory Committee will be asked to advise FDA on key regulatory decisions for this PMA submission based on the Real-World Clinical Evidence developed from the Real-World Data in

[7] *See* https://clinicaltrials.gov/ NCT01723423.
[8] The following types of breast reconstruction were evaluated: (1) expander/implant breast reconstructions; (2) latissimus dorsi breast reconstructions with or without implant; (3) pedicle transverse rectus abdominis musculocutaneous (PTRAM)breast reconstruction; (4) free transverse rectus abdominis musculocutaneous (FTRAM); (5) deep inferior epigastric perforator (DIEP) breast reconstructions; (6) superficial inferior epigastric artery (SIEA)breast reconstruction; (7) superior gluteal artery perforator breast reconstruction; and (8) inferior gluteal artery perforator breast reconstruction

the MROC Study. CDRH has been proactive in leveraging Real-World Evidence in FDA medical device regulatory decisions.[9] The CDRH document "Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions"[10] provides many examples of its use to provide primary clinical support for original premarket approval (PMA) applications. It states:

> "*If RWD [real world data] are reliable and relevant to the regulatory question at hand, they may be considered valid scientific evidence supporting both premarket and postmarket regulatory decisions made by FDA*."

CDRH guidance clarifies that "*relevance*" of Real-World Data and evidence it generates includes whether (1) the data capture the use of the device, exposures, and the outcomes of interest in the appropriate population (i.e., the data apply to the question at hand); (2) the data are amenable to sound clinical and statistical analysis; and (3) the data and Real-World Evidence it provides are interpretable using informed clinical/scientific judgment. The "*reliability*" of Real-World Data and resultant analyses rest on how the data were collected (*data accrual*) and whether the people and processes in place during data collection and analysis provide adequate assurance that data quality and integrity are sufficient (*data assurance - quality control*). CDRH emphasizes that the "Real-World Data analysis protocol should be prospectively defined."

The MROC Study data and the analyses conducted for this PMA are relevant and reliable for the Panel's assessment of reasonable assurance of the effectiveness and safety of SurgiMend for its proposed intended use in implant-based two-stage subpectoral breast reconstruction.

- The MROC Study prospectively captured the outcomes of implant-based two-stage subpectoral breast reconstruction following mastectomy, including patient and surgeon shared decision-making regarding the type of reconstruction;
- The MROC Study reflects contemporary breast reconstruction surgical practice and techniques in 11 high volume breast surgery centers (academic and private practices) across the United States and in Canada and a diverse patient population;
- The MROC Study, which involved 58 surgeons, reflects the diversity of surgeon training, experience, and preference in the practice-of-surgery regarding the decision to use ADM or no ADM in individual patients for implant-based two-stage subpectoral breast reconstruction;

[9] Food and Drug Administration. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices *Guidance for Industry and Food and Drug Administration Staff.* August 2017. Available from: https://www.fda.gov/media/99447/download

[10] "Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions" Center for Devices and Radiological Health. Center for Devices and Regulatory Health. Available at https://www.fda.gov/media/146258/download

or no ADM in individual patients for implant-based two-stage subpectoral breast reconstruction;

- The MROC study was conducted prospectively at all sites under the identical formal protocol and procedures for data collection and aggregation in the data base;
- Patient responses to the BREAST-Q – a validated Patient-Reported Outcomes instrument specific to breast reconstruction surgery – were prospectively collected at prespecified intervals;
- Complications were explicitly defined in the MROC Study for the purpose of data collection at specified intervals after surgery from the medical records;
- The full MROC Study anonymized patient dataset was provided to FDA as a Master File, including a detailed data dictionary;
- A detailed Statistical Analysis Plan was jointly developed by Integra and FDA for this PMA submission before the FDA statisticians locked the database and conducted the analysis of the primary endpoint and other prespecified effectiveness and safety endpoints.
- The management of the database and conduct of the analyses for this PMA submission were performed under FDA's stringent internal requirements and standards for quality control and data integrity;
- CDRH has already demonstrated that it deems the MROC Study database to be *relevant* and *reliable* for regulatory analyses pertinent to the use of acellular dermal matrix (ADM) in implant-based two-stage subpectoral breast reconstruction. As noted above, prior to receiving and analyzing the MROC data, CDRH communicated to Integra its belief that the MROC data set "would be sufficient to assess the safety and effectiveness of [SurgiMend PRS ABDM] for [its] proposed intended use"; as well, CDRH has relied on the MROC Study database for public issuance of a Safety Notification with the finding that a higher complication rate for a period up to two years following surgery was observed in patients receiving certain ADM products compared with those who received SurgiMend or Alloderm[11].

[11] Food and Drug Administration. *Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates: FDA Safety Communication. March 31, 2021*. Available from: https://www.fda.gov/medical-devices/safety-communications/acellular-dermal-matrix-adm-products-used-implant-based-breast-reconstruction-differ-complication

7 DESIGN OF THE INTEGRA SURGIMEND STUDY

Integra and FDA jointly agreed with the use of the MROC Study dataset as the basis for the analysis of a population of subjects undergoing immediate, two-stage, implant-based, submuscular, alloplastic breast reconstruction. Based on the SAP developed in collaboration with FDA, two cohorts of this MROC Study population were extracted and analyzed by the FDA statistical group:

- Subjects who received SurgiMend: the SurgiMend group
- Subjects who received no acellular dermal matrix (ADM): the Control group

The overall objective of the SurgiMend Study, as described in the Statistical Analysis Plan, was to "evaluate the efficacy and safety of SurgiMend Collagen Matrix used for immediate, two-stage, submuscular [subpectoral] breast reconstruction" in comparison with the Control group.

The Statistical Analysis Plan was finalized prior to database lock and conduct of the analyses by the FDA statistical group.

7.1 Study Population for the Integra SurgiMend Study

The study population for this analysis were participants in the MROC Study who:

- met the MROC Study inclusion and exclusion criteria;
- underwent an immediate, two-stage, implant-based, subpectoral breast reconstruction procedure; and
- received either SurgiMend or no ADM during the first stage of breast reconstruction.

The inclusion and exclusion criteria of the MROC Study are publicly disclosed by its sponsor on ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT01723423NCT). The MROC Study inclusion criteria are:

- Women who present themselves for first-time breast reconstruction at one of the 11 MROC sites
- 18 years and older
- Women undergoing one of the following types of breast reconstruction after mastectomy: tissue expander/implant, LD flap (with, or without implant), PTRAM flap, FTRAM flap, DIEP flap, S-GAP flap, I-GAP flap or SIEA flap
- Immediate or delayed reconstruction
- Unilateral or bilateral reconstructions
- Women receiving mastectomy for cancer prophylaxis, without history of breast cancer, will be eligible to participate

The MROC Study exclusion criteria are:

- Patients electing reconstruction following complications of breast augmentation, mastopexy (breast lift), or breast reduction
- Procedures performed following previously failed attempts at breast reconstruction will be excluded from the study, due to potential confounding by these previous surgeries.

7.2 Analysis Populations

7.2.1 Full Analysis Set (FAS) Population

The full analysis set (FAS) to support this PMA submission consists of all subjects enrolled in the MROC Study who met the criteria specified in **Section 8.1**.

7.2.2 Per Protocol Population

The Statistical Analysis Plan specifies that the Per Protocol (PP) analysis set consists of all FAS subjects who complete required treatments and have no major protocol violations [in the MROC Study]. However, the FDA statistical group did not identify a per protocol population or present any data analyses to Integra using a per protocol population.

7.3 Primary Endpoint of the SurgiMend Study

The prespecified primary endpoint in the SurgiMend Study is Composite Clinical Success (CCS). This primary endpoint was developed in conjunction with FDA based on its proposal to Integra to consider a dichotomous responder analysis that addressed patient-reported effectiveness based on the Breast-Q PRO instrument and safety events specified in the MROC Study.

The primary endpoint in the study is analyzed on a per subject responder basis. A responder is a subject who meets both of the following criteria:

- A score of the BREAST-Q Physical Well-Being (chest) module that is not more than 4 points lower one year after surgery compared to the preoperative baseline score

  and

- The absence of any of the following nine complications captured in the MROC Study at two years after surgery or at one year after surgery if not available at two years: hematoma, explantation of the breast implant, re-operation, capsular contracture, infection (treated with either oral or IV antibiotics), dehiscence, tissue necrosis, implant rupture, and seroma.

7.3.1 Components of Primary Endpoint: Composite Clinical Success

The BREAST-Q Physical Well-Being (chest) module:

Use of the BREAST-Q Physical Well-Being (chest) module was selected because it is well-established that the patient's perception of physical well-being regarding her chest markedly declines after mastectomy with breast reconstruction and is usually not fully restored to baseline by one year after surgery (Pusic et al. 2017). As described in the Statistical Analysis Plan, the minimally important difference (MID) for the BREAST-Q Physical Well-Being (chest) module is 4 points (Voineskos et al. 2020). Therefore, a reduction in the score of 4 points or less at one-year after surgery compared with preoperative baseline score is consistent with a patient's perception of return to the state of physical well-being she experienced prior to surgery. Conversely, a reduction in the score of more than 4 points at one-year after surgery compared with baseline reports a patient's perception of the failure to return to her state of physical well-being prior to surgery.

Major complications: The safety component of the prespecified primary endpoint relies on the nine postoperative complications that were systematically captured in the MROC Study dataset. In the MROC Study publications, complications are defined as "an adverse postoperative, surgery-related event requiring additional treatment" whereas major complications are limited to complications "requiring rehospitalization or reoperation." (Wilkins et al. 2018)

Before FDA conducted the statistical analysis of the primary endpoint and before FDA delivered the analysis to Integra, FDA proposed a definition of major complications that would include wound infections requiring oral antibiotics and elective revisions. Integra agreed to this definition and to sensitivity analyses for major complications when 1) wound infections requiring oral antibiotics were not considered as major complications; 2) elective revisions were not considered as major complications; and 3) both wound infections requiring oral antibiotics and elective revisions were not considered as major complications.

7.3.2 Primary Endpoint Hypothesis

The primary endpoint hypothesis for the SurgiMend Study tests whether the proportion of subjects with Composite Clinical Success [proportion of responders] in the SurgiMend group is superior to that of the Control group. Because the SurgiMend Study is a non-randomized study, the primary endpoint analysis is also based on a propensity score adjustment prespecified in the Statistical Analysis Plan.

The statistical null and alternative hypotheses for the primary endpoint are:

H_o: $P_t - P_c \leq 0$ (null hypothesis)

H_1: $P_t - P_c > 0$ (superiority hypothesis)

where **P_t** = the proportion of subjects with Composite Clinical Success in the group treated with SurgiMend and **P_c** = the proportion of subjects with Composite Clinical Success in the Control group that was not treated with an ADM.

The statistical analysis plan specifies that the superiority hypothesis would be evaluated using a comparison of two proportions via a Z-test stratifying by the propensity score strata on the FAS population at two-sided significance level of 0.05. Sensitivity analyses would be conducted on the odds ratio scale using the Cochran-Mantel-Haenzel (CMH) test) and logistic regression analysis.

7.4 Secondary Endpoints

No confirmatory testing of additional hypotheses was performed. Per the Statistical Analysis Plan,

> "All secondary endpoints are descriptive only. For each of the Breast-Q modules and other function scores, change from baseline will be calculated between the two groups, along with corresponding two-sided 95% confidence intervals."

The secondary descriptive endpoints for the SurgiMend group and Control group (no ADM group) are:

- The change from preoperative baseline score to each MROC Study visit timepoint (postoperative 1 week, 3 months, 1 year, and 2 years) for the following:
    - Satisfaction with Breasts (BREAST-Q)
    - Psychosocial Well-Being (BREAST-Q)
    - Sexual Well-Being (BREAST-Q)
    - Satisfaction with Outcome (BREAST-Q)
    - Satisfaction with Care module (BREAST-Q)
    - Satisfaction with Nipple Reconstruction (BREAST-Q)
    - Sum of subject response to Physical Well-Being and Satisfaction with Breasts at 1-year timepoint (BREAST-Q)
    - Numerical Pain Rating Scale (NPRS)
    - McGill Pain Questionnaire (MPQ)
    - Quality of life (European Organization for Research and Treatment of Cancer [EORTC])
    - Fatigue (Brief Fatigue Inventory [BFI])
    - General health (Patient-Reported Outcomes Measurement Information System [PROMIS])
    - Patient Health Questionnaire (PHQ-9)
    - Generalized Anxiety Disorder (GAD-7)

- The proportion of subjects in the SurgiMend and Control group with a postoperative change ≥ -4 points from the preoperative baseline for the following BREAST-Q Modules i.e., the proportion of subjects with a reduction in the score of 4 points or less at one-year after surgery compared with preoperative baseline score:
    - Satisfaction with Breasts (BREAST-Q)
    - Psychosocial Well-Being (BREAST-Q)
    - Your Sexual Well-Being (BREAST-Q)
- The difference between the two treatment groups at each visit timepoint for the following BREAST-Q modules:
    - Satisfaction with Outcome (BREAST-Q)
    - Satisfaction with Care (BREAST-Q)
    - Satisfaction with Nipple Reconstruction (Breast-Q)

7.5 Safety Data

MROC Study Complications. The SurgiMend Study statistical analysis plan specifies that all safety data summaries will be presented for the FAS population. The safety data analysis is based on the complications captured in the MROC Study dataset, which also comprise a criterion for the primary endpoint: hematoma, explantation, re-operation (including elective revisions), capsular contracture, infection, dehiscence, tissue necrosis, implant rupture, and seroma. The safety evaluation in the SurgiMend Study SAP specifies identification of the numbers and proportions of subjects with complications according to device (SurgiMend or no ADM), by type of complication, and according to the time interval in the MROC Study in which they occurred.

Treatment Emergent Adverse Events. Separately, the SurgiMend Study statistical analysis plan specifies a summary of Treatment Emergent Adverse Events (TEAEs), coded using the MedDRA Medical Dictionary, that occur on or after the first surgical procedure. This analysis was not provided to Integra by the FDA statistical group. Because none of the MROC Study publications to date disclose any adverse events coded using the MedDRA Medical Dictionary or classified as TEAEs, Integra surmises that these data elements were not collected during the MROC Study and therefore are not provided in the MROC Study dataset.

7.6 Propensity Score

Due to the observational nature of the MROC Study data, a propensity score model is specified in the statistical analysis plan to reduce potential biases. The propensity score e(X) for a subject is the conditional probability of receiving treatment (Z=1) given a vector X of observed covariates, e(X) = P (Z =1|X), which was estimated by multiple logistic regression analysis. The model was

fitted based on the data for subjects in both treatment groups. The outcome is the treatment actually received, and predictor variables include the following baseline covariates that might potentially confound the relationship between treatment and outcome:

- Age
- Body mass index
- Work status
- Marital status
- Charlson Comorbidity Index (for medical comorbidities)
- Smoking
- Indication
- Reason for mastectomy (prophylactic vs. therapeutic)
- Laterality (unilaterality vs bilaterality)
- Type of mastectomy
- Implant Type: silicone vs. saline
- Implant Size
- Lymph node management
- Neoadjuvant radiation
- Adjuvant radiation
- Neoadjuvant chemotherapy
- Adjuvant chemotherapy

Data Handling Rules

For the propensity score modeling, the following rules were applied in excluding covariates:

- Percentage of missing values was >30%
- For a binary variable, number of subjects in one category was <10
- For a categorical variable, a subcategory was merged with its near category if its frequency was <10

7.6.1 Missing Covariate Data in the Propensity Score Modeling

Due to the possibility of missing data, complete case analysis was not sufficient because a few missing values in a number of baseline variables would result in omitting a large number of observations. Multiple imputations were therefore employed, with the following conventions:

- Imputations were conducted within the study, before modeling the treatment groups
- The initial variable list for the imputation was the same as specified in the Statistical Analysis Plan Protocol

- No outcome variables were used in the imputation
- The following simple imputation method was employed:
    - For a continuous variable, missing values were imputed from random values from a normal distribution, with mean and standard deviation (SD) calculated from the sample, with a seed set as 12632
    - For a categorical variable, missing values were imputed from random values from a multinomial distribution with probabilities P1, P2,…, and Pk from the sample. Seed was set as 83256

7.6.2 Stratification Algorithm

Step 1: All subjects were divided into 5 subclass quintiles based on the probability of receiving SurgiMend compared with Control. The success of the propensity score estimation was assessed by comparing covariate distributions between the Treatment and Control groups within each stratum and by examining the distribution of propensity scores between the two groups. The propensity score modeling was refined further in the case of (1) covariate imbalance within the individual stratum, or (2) dramatic differences in distributions among strata between the groups, (e.g., the choice of covariates was reconsidered, and further interactions added, etc.). Where neither condition existed, Step 2 was performed.

For each covariate in the propensity score model, the average standardized difference over the strata was used to assess covariate balance. Furthermore, visualization plots (e.g., distribution, histogram, or box plot) for each covariate by treatment group and strata were applied to identify differences in distributions.

Step 2: An overall estimate of treatment difference and its 95% CI were obtained by stratifying according to the propensity score quintiles.

7.6.3 ATT Analysis

The prospectively developed Statistical Analysis plan states that the ATT should be used for the primary analysis. ATT is the *average treatment effect in the treated population* and ATE is the *average treatment effect in the entire population*. In a general sense, the choice of ATT or ATE for the primary analysis depends on the target research question. As described in Austin, 2011, the ATT is of greater interest when it may be unrealistic to assess the effect of the treatment on the entire population. In the case of the SurgiMend Study, the source data is from the MROC Study, which is a prospective, observational study. Due to the nature of the study, the primary research question for the SurgiMend Study was to evaluate the treatment effect in the patients that received SurgiMend as opposed to the treatment effect on entire population of patients. It is not possible to assess the effect of SurgiMend treatment on patients that did not receive the product. Therefore,

the primary statistical analysis utilizing ATT weights as described in the prospective Statistical Analysis Plan that was developed in consultation with the FDA Statistical Team is the appropriate statistical approach. ATE weights remain appropriate for supporting analyses.

8 THE INTEGRA SURGIMEND STUDY: RESULTS

8.1 Subject Characteristics

A total of 987 subjects were included in the SurgiMend Study:

- 119 in the SurgiMend group
- 868 in the Control group

Subjects' demographic and clinical preoperative characteristics based on the MROC Study dataset are summarized in **Table 8-1** (per patient) and **Table 8-2** (per breast). Overall, the mean (standard deviation, SD) subject age was 48.1 (10.4) years, and the mean (SD) BMI was 25.8 (5.3) kg/m^2. In the SurgiMend group, 49.6% of subjects had unilateral and 50.4% had bilateral reconstructions; in the Control group, 38.6% had unilateral and 61.4% had bilateral reconstructions. The majority of subjects in both groups underwent mastectomy for breast cancer treatment (SurgiMend, 87.5%; Control, 92.9%), and approximately half underwent mastectomy for breast cancer prophylaxis (SurgiMend, 47.9%; Control, 52.9%). It is assumed that the apparent mismatch in percentage of subjects with breast reconstruction due to breast cancer treatment versus prophylactic treatment represents subjects for whom one breast was removed by mastectomy for breast cancer treatment and the other breast prophylactically.

As shown, demographic, clinical, and operative characteristics were generally comparable between the SurgiMend group and the Control group.

Table 8-1: Baseline Demographic, Clinical, and Operative Characteristics of the FAS Population by Treatment Group Per Patient

Characteristic	SurgiMend N = 119	Control N = 868	Total N = 987
Age:			
mean (SD)	49.7 (11.1)	47.9 (10.3)	48.1 (10.4)
(min, max)	(28, 78)	(20, 77)	(20, 78)
BMI:			
mean (SD)	25.7 (5.3)	25.8 (5.3)	25.8 (5.3)
(min, max)	(16.8, 43.8)	(16.5, 49.8)	(16.5, 49.8)
Smoking			
Never smoked	86 (72.3%)	540 (62.2%)	626 (63.4%)
Current/previous smoker	32 (26.9%)	308 (35.5%)	340 (34.4%)
Race			
White	99 (83.2%)	738 (85.0%)	837 (84.8%)
Other	17 (14.3%)	109 (12.6%)	126 (12.8%)
Work status			
Employed full-time	59 (49.6%)	455 (52.4%)	514 (52.1%)
Employed part-time	16 (13.4%)	118 (13.6%)	134 (13.6%)
Homemaker	23 (19.3%)	126 (14.5%)	149 (15.1%)
Retire	11 (9.2%)	58 (6.7%)	69 (7.0%)
Other	9 (7.6%)	86 (9.9%)	95 (9.6%)
Marital status			
Married	96 (80.7%)	639 (73.6%)	735 (74.5%)
Other (widowed, separated, divorced, single/never married)	22 (18.5%)	209 (24.1%)	231 (23.4%)
Education			
Some high school; high school diploma; or some college, trade; or university	24 (20.2%)	180 (20.7%)	204 (20.7%)
College, trade or university	51 (42.9%)	333 (38.4%)	384 (38.9%)
Some graduate study with/without Master/doctoral degree	43 (36.1%)	338 (38.9%)	381 (38.6%)
Laterality of breast reconstruction			
Unilateral	59 (49.6%)	335 (38.6%)	394 (39.9%)
Bilateral	60 (50.4%)	533 (61.4%)	593 (60.1%)
Breast cancer treatment			
Yes	102 (85.7%)	806 (92.9%)	908 (92.0%)
No	17 (14.3%)	62 (7.1%)	79 (8.0%)
Breast cancer prophylaxis			
Yes	57 (47.9%)	459 (52.9%)	516 (52.3%)
No	62 (52.1%)	409 (47.1%)	471 (47.7%)
Sentinel lymph node biopsy (SLNB)			
Yes	67 (56.3%)	493 (56.8%)	560 (56.7%)
No	52 (43.7%)	375 (43.2%)	427 (43.3%)
Axillary lymph node dissection with or without SLNB			
Yes	29 (24.4%)	290 (33.4%)	319 (32.3%)
No	90 (75.6%)	578 (66.6%)	668 (67.7%)

Characteristic	SurgiMend N = 119	Control N = 868	Total N = 987
Type of mastectomy:			
Nipple sparing	13 (10.9%)	105 (12.1%)	118 (12.0%)
Simple/ modified radical mastectomy	106 (89.1%)	763 (87.9%)	869 (88.0%)
Neo-adjuvant chemotherapy			
Yes	27 (22.7%)	131 (15.1%)	158 (16.0%)
No	92 (77.3%)	737 (84.9%)	829 (84.0%)
Adjuvant chemotherapy			
Yes	24 (20.2%)	305 (35.1%)	329 (33.3%)
No	95 (79.8%)	563 (64.9%)	658 (66.7%)
Radiation			
Yes	29 (24.4%)	227 (26.2%)	256 (25.9%)
No	89 (74.8%)	621 (71.5%)	710 (71.9%)
Charlson-Index			
<= 1	93 (78.2%)	684 (78.8%)	777 (78.7%)
> 1	26 (21.8%)	172 (19.8%)	198 (20.1%)

ALND, axillary lymph node dissection; BMI, body mass index; FAS, full analysis set; SLNB, sentinel lymph node biopsy.
* Subjects with missing values were not included. For categorical variables, all percentages were calculated using the following denominators: SurgiMend = 119, Control = 868, and Total = 987.

Table 8-2: Baseline demographic, clinical, and operative characteristics of the FAS (Per Breast)

Characteristic	SurgiMend N = 179	Control N = 1,401	Total N = 1,580
Breast cancer treatment			
Yes	111 (62.0%)	891 (63.6%)	1,002 (63.4%)
No	68 (38.0%)	510 (36.4%)	578 (36.6%)
Breast cancer prophylaxis			
Yes	68 (38.0%)	510 (36.4%)	578 (36.6%)
No	111 (62.0%)	891 (63.6%)	1,002 (63.4%)
SLNB			
Yes	104 (58.1%)	816 (58.2%)	660 (47.1%)
No	75 (41.9%)	585 (41.8%)	920 (65.6%)
ALND with or without SLNB			
Yes	41 (22.9%)	453 (32.3%)	494 (35.3%)
No	138 (77.1%)	948 (67.6%)	1086 (77.5%)
Type of mastectomy:			
Nipple sparing	21 (11.7%)	185 (13.2%)	206 (13.0%)
Simple/ modified radical mastectomy	158 (88.3%)	1216 (86.8%)	1374 (87.0%)
Radiation			
Yes	40 (22.3%)	369 (26.3%)	409 (25.9%)
No	137 (76.5%)	1002 (71.5%)	1139 (72.1%)
Missing	2 (1.1%)	30 (2.1%)	32 (2.0%)
Breast Implant Manufacturer			
Unknown	170 (95.0%)	1215 (86.7%)	1385 (87.7%)

Characteristic	SurgiMend N = 179	Control N = 1,401	Total N = 1,580
Breast Implant Fill			
Silicone	136 (76%)	992 (63.4%)	1128 (71.4%)
Saline/Missing	43 (24%)	409 (29.2%)	452 (28.6%)
Breast Implant size (ccs):			
Mean (SD)	462.6 (158.1)	496.4 (155.9)	492.5 (156.4)
(min, max)	(120, 1000)	(25, 1000)	(25, 1000)
Breast Implant (Saline) Surface Texture			
Missing/Not applicable	170 (95.0%)	1212 (86.5%)	1382 (87.5%)
Breast Implant (Silicone) Surface Texture			
Textured	16 (8.9%)	307 (21.9%)	323 (20.4%)
Smooth	119 (66.5%)	689 (49.2%)	808 (51.1%)
Missing/Not applicable	44 (24.6%)	405 (28.9%)	449 (28.4%)

ALND, axillary lymph node dissection; BMI, body mass index; FAS, full analysis set; SLNB, sentinel lymph node biopsy.
* Subjects with missing values were not included. For categorical variables, all percentages were calculated using the following denominators: SurgiMend = 179, Control = 1401, and Total = 1580.

8.2 Disposition and Accountability of Subjects

This request was specified in the agreed upon Statistical Analysis Plan. The FDA has indicated that this information will not be provided to Integra.

8.3 Propensity Analysis

Propensity score stratification was performed to adjust covariates in order to obtain an unbiased estimation of causal treatment effects. **Figure 8-1** and **Figure 8-2** below demonstrate the strong balance in the distributions of baseline covariates between the group treated with SurgiMend and the Control group after propensity score adjustment.

Figure 8-1 below shows that the standardized between-group mean differences are significantly reduced in the propensity score (PS) matched observations for the baseline covariates. All differences for the matched observations (green plus markers represent after propensity score (PS) adjustment, and red dots represent before PS adjustment) are close to zero (within the recommended range of -0.25 to 0.25) (Rosenbaum, Rubin 1985).

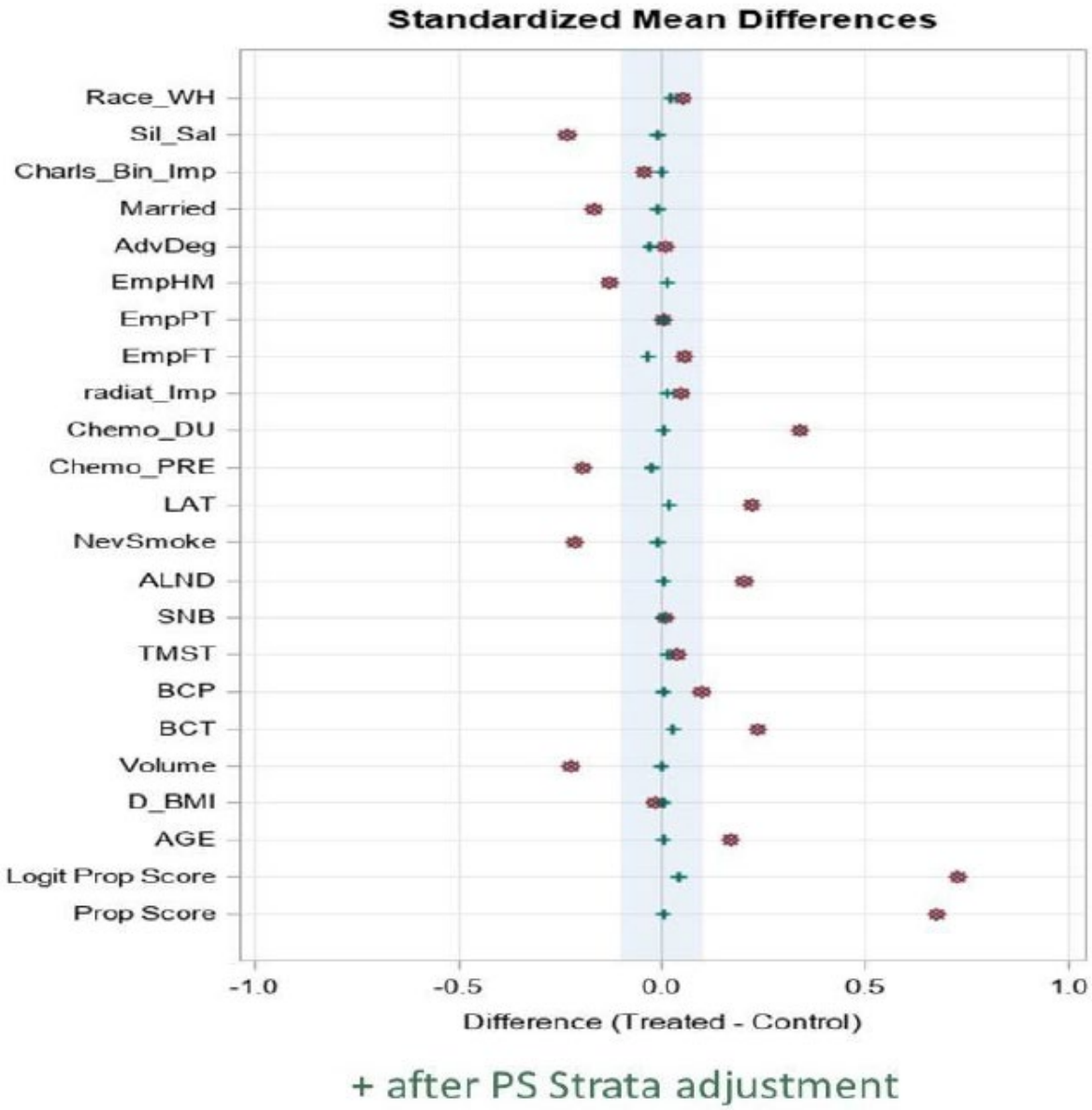


Figure 8-1: Standardized Mean Differences for Baseline Covariates

Race_WH, Race (White vs Non-white); Sil_Sal, Implant Type (Silicone vs. Saline); Charls_Bin_Imp, Charlson Co-morbidity Index (≤ 1 vs >1); Married, Marital status (Married vs Not married) AdvDeg, Advanced Degree (Yes vs No); EmpHM, Homemaker; EmpPT, Employed part-time; EmpFT, Employed full-time; radiant_Imp, Radiation (Yes vs No); Chemo_DU, Adjuvant chemotherapy (Yes vs No); Chemo_PRE, Neo-adjuvant chemotherapy; LAT, Laterality (Unilateral vs. Bilateral); NevSmoke, Smoking status (Never smoked vs. Ever smoking); ALND, Axillary Lymph Node Dissection with or without Sentinel Lymph Node Biopsy (Yes vs No); SNB, Sentinel Lymph Node Biopsy (Yes vs No); TMST, Type of Mastectomy (Nipple sparing vs Simple or modified radical mastectomy); BCP, Breast Cancer Prophylaxis (Yes vs No); BCT, Breast Cancer Treatment (Yes vs. No); Volume, Implant size; D_BMI, D_Body Mass Index; AGE, Age; Logit Prop Score, Logit Propensity Score; Prop Score, Propensity Score.

Figure 8-2 shows side-by-side box-and-whiskers plots of propensity scores by stratum for SurgiMend ("Treated") group and Control group. This figure illustrates the distribution of the numerical values of the propensity scores within each stratum for each group. For each rectangle, the left boundary is the 25th percentile and the right boundary is the 75th percentile of the propensity scores. Within each rectangle, the position of the vertical bar reports the median value and the ○ symbol reports the mean value of the propensity score. Within each stratum, there is good agreement regarding the distribution of the propensity scores between the groups.

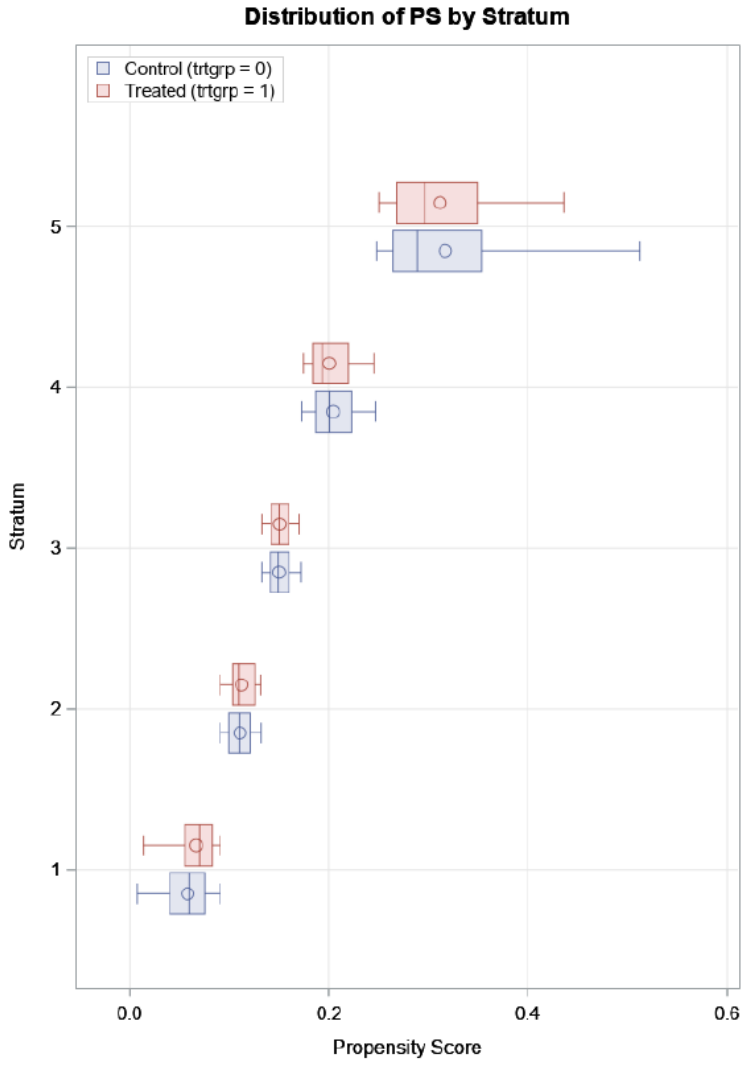


Figure 8-2: Propensity Score Distribution by Stratum for SurgiMend ("Treated") Group and Control Group

8.3.1 Propensity Score Stratification

Propensity score (PS) stratification subclassifies the study participants based on quintiles of the PS of the SurgiMend subjects. The outcomes of the participants are then compared within each of the strata, and a common estimator of the treatment effect is derived by combining the results over the strata. A common practice is to divide the PS into 5 strata; this has been shown to reduce the majority of the bias from measured confounders. Stratification approximates matching without the risk of losing unmatched participants. The stratum-specific estimates of effect are weighted by the proportion of subjects who lie within each stratum.

The stratification technique also allows the calculation of both the "*average treatment effect*" (ATE) and the "*average effect of the treatment on the treated"* (ATT) (Benedetto et al. 2018). In propensity score methodology,

- the "*average treatment effect"* (ATE) is the estimate of the effect of confounding baseline variables on outcome measures for all subjects (i.e., subjects treated with SurgiMend or use of no ADM);
- the "*average effect of the treatment on the treated*" (ATT) is the estimate of the effect of confounding baseline variables on outcome measures for subjects in the treatment group (i.e., subjects treated with SurgiMend) on an outcome measure.

Table 8-3 shows the number of subjects and the weight for each stratum in this study population based on propensity score quintile of the SurgiMend subjects.

Table 8-3: Propensity Score Strata Based on Main-Effect Only Propensity Score Model

Stratum Index	Propensity Score range		Frequencies			Stratum Weight (ATT)
	Min	Max	SurgiMend	Control	Total	
1	0.0080	0.0910	23	404	427	0.193
2	0.0910	0.1321	24	198	222	0.202
3	0.1329	0.1718	24	122	146	0.202
4	0.1724	0.2475	24	93	117	0.202
5	0.2485	0.5122	24	51	75	0.202

ATT, average treatment effect on the treated.

The primary evaluation, per the prespecified Statistical Analysis Plan, was based on the ATT analysis and supported by the ATE analysis. The analysis weights were based on the proportion of subjects who lie within that stratum. For the ATT analysis, the weights were based on all the SurgiMend treated subjects, while for the ATE analysis, the weights were based on the SurgiMend group, and the Control group subjects combined.

8.4 Primary Endpoint Result

The primary endpoint analysis confirms the superiority hypothesis: a higher proportion of subjects in the SurgiMend group achieved Composite Clinical Success compared with subjects in the Control group (no ADM).

The proportions of subjects who achieved Composite Clinical Success (CCS) in both the unadjusted and PS-adjusted populations are reported in **Table 8-4.** The prespecified primary endpoint analysis was conducted on the Full Analysis Population (FAS). As described in the statistical analysis plan, it included both elective revisions and wound infection requiring oral antibiotics as major complications in determining CCS.

The Statistical Analysis Plan specified:

> "The primary analysis on the primary endpoint will be conducted on the FAS population excluding patients with bilateral reconstruction with only unilateral SurgiMend placement." It also specified that the propensity score stratification method would be used "to obtain the average treatment effect on the treated (ATT), i.e. the five stratum-specific treatment difference will be combined to obtain ATT using weights based on the number of SurgiMend treated patients within each propensity score stratum (Yue et al. 2016)."

In the prespecified PS-adjusted analysis (ATT analysis), a statistically significantly higher proportion of subjects achieved CCS in the SurgiMend group than in the Control group (32.4% vs 21.1%; difference 11.2% [95% CI 1.7%, 20.8%]; p = 0.02).

Table 8-4: Proportion of Subjects with CCS in which Elective Revisions and Wound Infection Requiring Oral Antibiotics Were Considered as Major Complications.

Unadjusted Estimates			PS-Adjusted Estimates (ATT)		
SurgiMend (n=119)	Control (n=868)	Difference (95% CI) *	SurgiMend (n=119)	Control (n=868)	Difference (95% CI) *
32.3%	22.4%	9.9% (0.5%, 19.3%)	32.4%	21.1%	11.2% (1.7%, 20.8%) $p = 0.02$

ATT, average treatment effect on the treated; CCS, composite clinical success; PS, propensity score.
*Difference = SurgiMend – Control.

An exploratory analysis of the primary endpoint was performed using a PS-stratified ATE analysis.

Table 8-5 presents PS-stratified proportions of subjects who achieved CCS in both the unadjusted and PS-adjusted populations using an ATE analysis. Similar results were observed between unadjusted and adjusted estimates. A higher proportion of patients achieved CCS in the SurgiMend

group versus the Control. The PS-adjusted treatment difference (ATE) was 10.2% (95% CI, −1.1%, 21.4%).

Thus, consistent with the prespecified primary endpoint analysis, the proportion of subjects who achieved CCS was higher in the SurgiMend group compared with the Control group.

Table 8-5: PS-Stratified (Average Treatment Effect (ATE)) Proportion of Subjects with CCS in which Elective Revisions and Wound Infection Requiring Oral Antibiotics Were Considered as Major Complications.

Strata Index	Frequencies			Stratum Weight (ATE)	Estimates			Unadjusted Estimates			PS-Adjusted Estimates (ATE)		
	SMD	CTL	Total		SMD	CTL	Diff*	SMD (n=119)	CTL (n=868)	Diff* 95% CI	SMD (n=119)	CTL (n=868)	Diff* 95% CI
1	23	404	427	0.433	34.4%	24.5%	9.9%	32.3%	22.4%	9.9% (0.5%, 19.3%)	32.4%	22.3%	10.2% (−1.1%, 21.4%)
2	24	198	222	0.225	28.7%	20.2%	8.5%						
3	24	122	146	0.148	35.8%	21.1%	14.7%						
4	24	93	117	0.119	22.8%	22.6%	0.3%						
5	24	51	75	0.076	40.0%	17.3%	22.7%						

ATE, average treatment effect; CTL, Control; diff, difference; PS, propensity score; SMD, SurgiMend.
* Difference =SurgiMend – Control.

8.4.1 Primary Endpoint: Sensitivity Analyses

Multiple sensitivity analyses were conducted. For these sensitivity analyses (and other exploratory analyses in the Executive Summary), the 95% CIs are not based on a pre-specified hypothesis test and there was no adjustment for multiplicity.

The statistical analysis plan specifies:

> "Sensitivity analysis will be conducted for estimating average treatment effect (ATE) using weights based on the number of all patients within each propensity score stratum (Yue et al. 2016)."

Tables 8-6 through 8-9 below report the results of sensitivity analyses of the primary endpoint in which modified definitions of certain major complications were explored.

- The sensitivity analyses explore the potential directional change of the primary endpoint result if the definition of "infection" is modified to remove infections treated with oral antibiotics and include only infections requiring IV antibiotics, reoperation, and/or hospitalization.
- The sensitivity analyses also explore the directional change of the primary endpoint analysis if elective revisions are excluded from the definition of "re-operation".

Consistent with prespecified primary endpoint analysis, the proportion of subjects in each of the exploratory sensitivity analyses who achieved CCS was higher in the SurgiMend group compared with the Control group.

Table 8-6 shows that the exclusion of wound infection requiring oral antibiotics as a major complication yielded CCS estimates directionally similar to those in the primary endpoint analysis. The proportion of subjects who achieved CCS was higher in the SurgiMend group compared with the Control group. In the propensity score-adjusted analysis, 32.4% of subjects in the SurgiMend group and 21.6% in the Control group achieved CSS (difference 10.7% [95% CI 1.1%, 20.3%]).

Table 8-6: Sensitivity Analysis of the CCS in which Wound Infection Requiring Oral Antibiotics Was NOT Considered as a Major Complication.

Unadjusted Estimates			PS-Adjusted Estimates (ATT)		
SurgiMend (n=119)	Control (n=868)	Difference (95% CI) *	SurgiMend (n=119)	Control (n=868)	Difference (95% CI) *
32.3%	22.8%	9.6% (0.2%, 19.0%)	32.4%	21.6%	10.7% (1.1%, 20.3%)

ATT, average treatment effect on the treated; CCS, composite clinical success; PS, propensity score.
*Difference = SurgiMend – Control.

Table 8-7 shows that the exclusion of elective revisions as a major complication yielded CCS estimates directionally similar to those in the primary endpoint analysis. The proportion of subjects who achieved CCS was higher in the SurgiMend group compared with the Control group. In the propensity score-adjusted analysis, 38.3% of subjects in the SurgiMend group and 29.7% in the Control group achieved CCS (difference 8.6% [95% CI−1.6%, 18.8%]).

Table 8-7: Sensitivity Analysis of the CCS in which Elective Revisions Were NOT Considered as Major Complications.

Unadjusted Estimates			PS-Adjusted Estimates (ATT)		
SurgiMend (n=119)	Control (n=868)	Difference (95% CI) *	SurgiMend (n=119)	Control (n=868)	Difference (95% CI) *
38.3%	30.7%	7.6% (−2.3%, 17.5%)	38.3%	29.7%	8.6% (−1.6%, 18.8%)

ATT, average treatment effect on the treated; CCS, composite clinical success; PS, propensity score.
* Difference = SurgiMend – Control

Table 8-8 shows that the exclusion of both elective revisions and wound infection requiring oral antibiotics as a major complication yielded CCS estimates directionally similar to those in the primary endpoint analysis. The proportion of subjects who achieved CCS was higher in the

SurgiMend group compared with the Control group. In the propensity score-adjusted analysis, 40.0% of subjects in the SurgiMend group and 31.5% in the Control group achieved CCS (difference 8.4% [95% CI −1.8%, 18.7%]).

Table 8-8: Sensitivity Analysis of the CCS in which Elective Revisions and Wound Infection Requiring Oral Antibiotics were NOT Considered as Major Complications.

Unadjusted Estimates			PS-Adjusted Estimates (ATT)		
SurgiMend (n=119)	Control (n=868)	Difference (95% CI) *	SurgiMend (n=119)	Control (n=868)	Difference (95% CI) *
40.0%	32.3%	7.6% (−2.3%, 17.6%)	40.0%	31.5%	8.4% (−1.8%, 18.7%)

ATT, average treatment effect on the treated; CCS, composite clinical success; PS, propensity score.
* Difference = SurgiMend – Control

Table 8-9 reports the proportions of subjects who achieved CCS when neither elective revisions nor wound infection requiring antibiotics were considered as major complications presented using a stratum based (ATE) analysis. The proportion of subjects who achieved CCS was higher in the SurgiMend group compared with the Control group. In this propensity score-adjusted analysis, 40.1% of subjects in the SurgiMend group and 32.2% in the Control group achieved CCS (difference 7.8% [95% CI −14.2%, 19.8%]).

Table 8-9: Proportion of Subjects with CCS (ATE) in Which Elective Revisions and Wound Infection Requiring Oral Antibiotics Were NOT Considered as Major Complications.

Strata Index	Frequencies			Stratum Weight (ATE)	Estimates			Unadjusted Estimates			PS-Adjusted Estimates (ATE)		
	SMD	CTL	Total		SMD	CTL	Diff*	SMD (n=119)	CTL (n=868)	Diff* 95% CI	SMD (n=119)	CTL (n=868)	Diff* 95% CI
1	23	404	427	0.433	44.5%	34.5%	10.0%	40.0%	32.3%	7.6 (−2.3%, 17.6%)	40.1%	32.2%	7.8% (−4.2%, 19.8%)
2	24	198	222	0.225	32.8%	29.7%	3.1%						
3	24	122	146	0.148	36.5%	30.3%	6.2%						
4	24	93	117	0.119	34.0%	30.2%	3.8%						
5	24	51	75	0.076	52.0%	33.0%	19.0%						

ATE, average treatment effect; CTL, Control; PS, propensity score; SMD, SurgiMend.
* Difference = SurgiMend – Control

8.4.2 Primary Endpoint Component: BREAST-Q Physical Well-Being at 1 Year

Table 8-10 shows the proportion of subjects who achieved success in the BREAST-Q Physical Well-Being (chest) score, defined as a score that is not more than 4 points lower one year after surgery compared to the preoperative baseline score following breast reconstruction. For the BREAST-Q modules, a 4-point change has been established as the minimally important difference (MID) (Voineskos et al. 2020). In the propensity-score adjusted ATT estimates, the success rate was 44.5% in the SurgiMend group and 39.1% in the Control group (difference 5.4% [95% CI −5.2%, 16.0%]). Directionally consistent with the composite primary endpoint analysis, a higher proportion of subjects in the SurgiMend group achieved success in the BREAST-Q Physical Well-Being (Chest) Score than subjects in the Control group.

Table 8-10: Subjects' Success Rate in BREAST-Q Physical Well-Being (chest) at 1 Year Post-Reconstruction†

Unadjusted Estimates			PS-Adjusted Estimates (ATT)		
SurgiMend (n=119)	Control (n=868)	Difference (95% CI) *	SurgiMend (n=119)	Control (n=868)	Difference (95% CI) *
44.5%	40.3%	4.2% (−6.2%, 14.6%)	44.5%	39.1%	5.4% (−5.2%, 16.0%)

ATT, average treatment effect on the treated; PS, propensity score.
† Success was defined as reduction from baseline score of no more than 4 points. The percentage of missing data was approximately 35% in the SurgiMend group and 44% in the Control group.
* Difference = SurgiMend – Control

Table 8-11 summarizes the PS-stratified results of the proportion of subjects who achieved success in the BREAST-Q Physical Well-Being (chest) score at 1 year following breast reconstruction. In the propensity-score adjusted ATE estimates, the success rate was 43.9% in the SurgiMend group and 40.2% in the Control group (difference 3.8% [95% CI −8.9%, 16.4%]). Directionally consistent with the composite primary endpoint analysis, a higher proportion of subjects in the SurgiMend group achieved success in the BREAST-Q Physical Well-Being (Chest) Score than subjects in the Control group.

Table 8-11: PS-Stratified Subjects' Success Rate (ATE) in BREAST-Q Physical Well-Being at 1 Year Post-Reconstruction†

Strata Index	Frequencies			Stratum Weight (ATE)	Estimates			Unadjusted Estimates			PS-adjusted Estimates (ATE)		
	SMD	CTL	Total		SMD	CTL	Diff*	SMD (n=119)	CTL (n=868)	Diff* 95% CI	SMD (n=119)	CTL (n=868)	Diff* 95% CI
1	23	404	427	0.433	45.6%	43.6%	2.0%	44.5%	40.3%	4.2% (−6.2%, 14.6%)	43.9%	40.2%	3.8% (−8.9%, 16.4%)
2	24	198	222	0.225	41.2%	35.8%	5.3%						
3	24	122	146	0.148	41.3%	38.8%	2.6%						
4	24	93	117	0.119	38.2%	37.5%	0.7%						
5	24	51	75	0.076	56.2%	40.0%	16.2%						

ATE, average treatment effect; PS, propensity score CTL, Control; SMD, SurgiMend.
† Success was defined as a reduction of no more than 4 points from baseline score. The percentage of missing data was approximately 35% in the SurgiMend group and 44% in the Control group.
* Difference = SurgiMend – Control.

8.5 Secondary Endpoint Analyses

8.5.1 BREAST-Q Module Domain Scores

Table 8-12 reports the mean BREAST-Q scores for several domains at baseline, Year 1, and Year 2 following breast reconstruction. For each domain, a decrease in the numerical value of the score reports lower patient-reported well-being after breast reconstruction surgery compared with preoperative baseline. Subjects in both the SurgiMend and Control groups reported lower scores in the Physical Well-Being, Satisfaction with Breast, Psychosocial Well-Being, and Sexual Well-Being domains at Year 1 and Year 2 compared with baseline. Scores at Year 1 were generally maintained at Year 2.

Table 8-12: Summary of BREAST-Q Domain Scores at Baseline, Year 1, and Year 2 Following Breast Reconstruction.

BREAST-Q Domain**	Cohorts	Mean (SD) Score			Difference (95% CI) *	
	SMD, n=119 CTL, n=868	Baseline	Year 1	Year 2	Year 1	Year 2
BREAST-Q Physical Well-Being, Chest+	SMD	81.2 (15.6)	75.1 (17.2)	73.8 (20.1)	2.4 (−0.9, 5.6)	1.5 (−2.4, 5.3)
	CTL	80.5 (15.6)	72.7 (18.6)	72.3(20.9)		
BREAST-Q Satisfaction with Breast +	SMD	62.2 (21.8)	59.8 (23.2)	62.8 (24.2)	−0.4 (−4.9, 4.2)	1.6 (−2.9, 6.1)
	CTL	62.7 (21.2)	60.2 (20.3)	61.2 (26.8)		
BREAST-Q Psychosocial Well-Being +	SMD	71.6 (19.6)	71.1 (24.8)	70.4 (26.3)	3.8 (−0.8, 8.5)	1.0 (−3.8, 5.9)
	CTL	71.4 (17.7)	67.3 (22.8)	69.4 (22.8)		
BREAST-Q Sexual Well-Being +	SMD	52.8 (20.7)	45.3 (31.3)	48.0 (27.1)	−2.7 (−8.6, 3.2)	−5.2 (−11.8, 1.4)
	CTL	56.8 (20.6)	48.0 (27.1)	49.5 (36.2)		
BREAST-Q Satisfaction with Outcome +	SMD		72.3 (n=75)	72.5 (n=50)		3.4 (−1.6, 8.3)
	CTL		69.8 (n=504)	69.3 (n=333)		3.2 (−2.9, 9.3)

CTL, Control; SMD, SurgiMend.

* Difference =SurgiMend – Control.

** For each domain, a decrease in the numerical value of the score reports lower patient-reported well-being after breast reconstruction surgery compared with operative baseline.

+Note:

- missing data are imputed by the multiple imputation (MI) procedure where missing baseline covariates, missing physical well-being at pre-operative, post-operative 1 Week, 3 Month, 1 Year, 2 Year and missing satisfaction with breast at pre-operative, post-operative 1 Year, 2 Year are imputed simultaneously.
- missing data are imputed by the MI procedure where missing baseline covariates, missing physical well-being at pre-operative, post-operative 1 Week, 3 Month, 1 Year, 2 Year and missing satisfaction with breast at pre-operative, post-operative 1 Year, 2 Year are imputed simultaneously.
- missing data are imputed by the MI procedure where missing baseline covariates, missing psychosocial and sexual well-being at pre-operative, post-operative 3 Month, 1 Year, 2 Year are imputed simultaneously.

Table 8-13 reports the differences between the SurgiMend group and CTL group in the BREAST-Q Satisfaction with Nipple Reconstruction. Scores in all domains were generally comparable between the SurgiMend and Control groups at both Year 1 and Year 2.

Table 8-13: BREAST-Q Satisfaction with Nipple Reconstruction

BREAST-Q Domain	Unadjusted Estimates Difference SMD-CTL (95% CI)
How nipple looks*	
Year 1	-0.1 (-0.7, 0.6)
Year 2	0 (-0.5, 0.5)
How natural nipple looks*	
Year 1	-0.1 (-0.7, 0.5)
Year 2	0 (-0.6, 0.5)

SMD, SurgiMend; CTL, Control
*Note: The score ranged from 1 to 4. All Subjects with missing values were excluded (i.e., this is complete case analysis).

Table 8-14 shows the changes from baseline in four BREAST-Q domain scores at Month 3, Year 1, and Year 2 after breast reconstruction. For each domain, a decrease in the score reports lower patient-reported well-being after breast reconstruction surgery compared with preoperative baseline. The decrease in the score from baseline in Physical Well-Being, Psychosocial Well-Being, and Sexual Well-Being was greater at Month 3 than at Year 1 or Year 2 in both the SurgiMend and Control groups. Changes were generally consistent between Year 1 and Year 2 and were generally comparable between the SurgiMend and Control groups. (Note that week 1 data are available for the Physical Well-Being (chest), module indicating that there is marked deterioration in the perception of Physical Well-Being (chest) at week 1 after reconstructive surgery, improvement by Month 3, and further improvement in Years 1 and 2. However, there is not a return to preoperative baseline perception of Physical Well-Being for both the SurgiMend and Control groups.)

Table 8-14: Summary of Continuous Change from Baseline in BREAST-Q Domain Scores

BREAST-Q Domain	Mean (SD) Change from Baseline		Difference (95% CI) *
	SurgiMend (n=119)	Control (n=868)	
BREAST-Q Physical Well-Being, Chest†			
Week 1	−24.9 (16.1)	−24.2 (17.1)	−0.7 (−3.8, 2.4)
Month 3	−11.7 (17.5)	−13.6 (19.1)	1.9 (−1.5, 5.3)
Year 1	−6.1 (17.4)	−7.7 (20.0)	1.7 (−1.7, 5.0)
Year 2	−7.4 (21.3)	−8.2 (22.7)	0.7 (−3.3, 4.8)
BREAST-Q Satisfaction with Breast†			
Year 1	−2.3 (25.4)	−2.5 (27.4)	0.2 (−4.9, 5.2)
Year 2	0.7 (29.3)	−1.4 (33.0)	2.1 (−3.4, 7.7)
BREAST-Q Psychosocial Well-Being†			
Month 3	−7.5 (18.3)	−8.7 (20.3)	1.3 (−2.3, 4.8)
Year 1	−0.5 (23.0)	−4.1 (24.2)	3.6 (−0.8, 7.9)
Year 2	−1.2 (25.3)	−2.0 (24.4)	0.8 (−4.0, 5.5)
BREAST-Q Sexual Well-Being†			
Month 3	−14.4 (24.7)	−13.7 (24.7)	−0.8 (−5.5, 3.9)
Year 1	−7.5 (27.8)	−8.8 (26.8)	1.4 (−3.9, 6.6)
Year 2	−8.5 (33.2)	−7.3 (37.1)	−1.2 (−7.5, 5.2)

* Difference =SurgiMend – Control.
† Missing data are imputed by the multiple imputation (MI) procedure, where missing baseline covariates; missing Physical Well-Being pre-reconstruction and at Week 1, Month 3, Year 1, and Year 2 after reconstruction; and missing Satisfaction with Breast pre-reconstruction and at Year 1 and Year 2 after reconstruction are imputed simultaneously.

Table 8-15 shows the proportion of subjects in the SurgiMend and Control groups whose BREAST-Q domain scores were not more than 4 points lower one year after surgery compared to the preoperative baseline scores, indicating a return to preoperative status.

- Propensity score-adjusted analyses were available for two domains. The proportion of subjects with reduction in score that was not more than 4 points lower one year after surgery

compared to the preoperative baseline score in the Physical Well-Being domain at Year 1 in both groups (SurgiMend, 44.5%; Control, 39.1%; difference, 5.4% [95% CI −5.2%, 16.0%]) was maintained at Year 2 (SurgiMend, 42.7%; Control, 40.3%; difference 2.4% [95% CI −9.0%, 13.9%]). Similar results were observed for the Satisfaction with Breast domain. The proportion of subjects with a reduction in score that was not 4 points or lower than Baseline in the Satisfaction with Breast domain at year 1 in both groups (SurgiMend, 47.2%; Control 46.7%; difference 0.6% [95% CI −10.7%, 11.9%]) was maintained at Year 2 (SurgiMend, 52.1%; Control, 49.2%, difference 3.0% [95% CI -9.0%, 13.9%].

- Estimates that were not propensity score adjusted were available for two domains – Psychosocial Well-Being and Sexual Well-Being – at Month 3, Year 1, and Year 3. As shown in this table, the proportion of subjects in both the SurgiMend and Control groups reporting changes that were not more than 4 points lower one year after surgery compared to the preoperative baseline score in Psychosocial Well-Being and Sexual Well-Being increased from Month 3 to Year 1, indicating an improvement in Psychosocial and Sexual well-being. This improvement observed in both groups in Year 1 was maintained in Year 2.
- In addition, estimates that were not propensity score adjusted were available for the BREAST-Q Sum of Subject Response to Physical Well-Being and Satisfaction with Breast. † The proportion of subjects in both the SurgiMend and Control groups reporting changes that were not more than 4 points lower one year after surgery compared to the preoperative baseline score was maintained in Year 1 and Year 2.

Table 8-15: Proportion of Subjects with Change from Baseline ≥ −4 in BREAST-Q Domain Scores

BREAST-Q Domain	SurgiMend (n=119)	Control (n=868)	Mean Difference (95% CI) *
BREAST-Q Physical Well-Being, Chest†	**Propensity Score-adjusted Estimates**		
Year 1	44.5%	39.1%	5.4% (−5.2%, 16.0%)
Year 2	42.7%	40.3%	2.4% (−9.0%, 13.9%)
BREAST-Q Satisfaction with Breast†			
Year 1	47.2%	46.7%	0.6% (−10.7%, 11.9%)
Year 2	52.1%	49.1%	3.0% (−8.5%, 14.5%)
BREAST-Q Psychosocial Well-Being**	**Unadjusted Estimates**		
Month 3	45.5%	41.9%	3.6% (−6.7%, 14.0%)
Year 1	61.3%	51.2%	10.1% (−0.5%, 20.7%)
Year 2	57.9%	55.5%	2.5% (−8.5%, 13.5%)
BREAST-Q Sexual Well-Being**			
Month 3	30.2%	33.6%	−3.4% (−13.0%, 6.2%)
Year 1	44.8%	42.4%	2.4% (−9.7%, 14.4%)
Year 2	40.5%	44.3%	−3.7% (−15.7%, 8.2%)
BREAST-Q Sum of Subject Response to Physical Well-Being and Satisfaction with Breast†			
Year 1	67.2%	67.9%	−0.7% (−10.5%, 9.2%)
Year 2	67.3%	68.1%	−0.8% (−11.4%, 9.9%)

* Difference = SurgiMend – Control.

† Missing data (SurgiMend, 58%; Control, 63%) are imputed by the multiple imputation (MI) procedure where missing baseline covariates; missing Physical Well-Being pre-reconstruction and at Week 1, Month 3, Year 1, and Year 2 after reconstruction; and missing Satisfaction with Breast pre-reconstruction and at Year 1 after reconstruction are imputed simultaneously.

** Missing data are imputed by the MI procedure, where missing baseline covariates and missing Psychosocial and Sexual Well-Being pre-reconstruction and at Month 3, Year 1, and Year 2 are imputed simultaneously.

8.5.2 Pain: Numerical Pain Rating Scale (NPRS) and McGill Pain Questionnaire (MPQ) Scores

Table 8-16 reports mean changes from baseline in Numerical Pain Rating Scale (NPRS) and McGill Pain Questionnaire (MPQ) scores at Week 1, Month 3, Year 1, and Year 2.

- Changes from baseline in the NPRS score were highest (indicating worse pain) at Week 1 (SurgiMend, 3.0; Control, 2.9; difference 0.1 [95% CI −0.5, 0.5]) and decreased by Month 3 (SurgiMend, 0.6; Control, 1.1; difference -0.6 [95% CI −1.0, −0.1]) indicating an improvement in pain in both groups compared with baseline. Changes from baseline remained low at Year 1 and Year 2.

Changes from baseline in the MPQ score were highest (indicating worse pain) at Week 1 (SurgiMend, 9.3; Control, 8.9; difference 0.4 [95% CI −1.4, 2.3]) and decreased at Month 3 (SurgiMend, 1.9; Control, 3.0; difference -1.1 [95% CI −2.8, 0.5]), with further reduction at Year 1. Changes from baseline at Year 2 were generally consistent with those at Year 1.

Table 8-16: Summary of Continuous Change from Baseline in NPRS and MPQ Scores.

Pain Measure	Mean Change from Baseline		Difference (95% CI) *
	SurgiMend (n=119)	Control (n=868)	
NPRS†			
Week 1	3.0	2.9	0.1 (−0.5, 0.5)
Month 3	0.6	1.1	−0.6 (−1.0, −0.1)
Year 1	0.3	0.4	−0.1 (−0.5, 0.3)
Year 2	0.6	0.5	0.1 (−0.4, 0.6)
MPQ**			
Week 1	9.3 (n=77)	8.9 (n=622)	0.4 (−1.4, 2.3)
Month 3	1.9 (n=76)	3.0 (n=499	−1.1 (−2.8, 0.5)
Year 1	−0.6 (n=58)	0.3 (n=403)	−0.8 (−2.2, 0.6)
Year 2	−0.9 (n=37)	−0.6 (n=272)	−0.2 (−2.0, 1.5)

MPQ, McGill Pain Questionnaire; NPRS, Numeric Pain Rating Scale

* Difference =SurgiMend – Control.

† The NPRS score ranges from 0 to 10; higher scores indicate worse pain. Missing data are imputed by the multiple imputation procedure, where missing baseline covariates and missing Physical Well-Being and missing NPRS pre-reconstruction and at Week 1, Month 3, Year 1, and Year 2 are imputed simultaneously.

** The MPQ consists of 15 Items, with its total score ranging from 0 to 45; higher scores indicate worse pain. If the number of missing Items of MPQ is less than 8, then the missing item was imputed by the mean of the observed items; otherwise, the subject is considered as missing and excluded from the analyses.

8.5.3 General Health: Patient-Reported Outcomes Measurement Information System (PROMIS)

Table 8-17 reports changes from baseline in Patient-Reported Outcomes Measurement Information System (PROMIS) domains at Month 3, Year 1, and Year 2. For comparison of baseline minus postoperative score values, a positive number indicates worsening, and a negative value indicates improvement compared with baseline scores. The changes in the PROMIS score in the postoperative periods compared with baseline were generally consistent between the SurgiMend and Control groups. Subjects in both groups experienced improvements in the PROMIS anxiety domain at Month 3 compared with baseline (SurgiMend, −8.6; Control, −7.4; difference -1.2 [95% CI −3.1, 0.8]), which were maintained at Year 1 and Year 2. Consistent with the BREAST-Q Physical Well-Being score, the PROMIS-Physical Function score was worse at Month 3 after surgery compared with baseline in both groups and improved at Year 1 and 2 but did not return to baseline.

Table 8-17: Summary of Change from Baseline in PROMIS Domain Scores

PROMIS Domain	Subjects, n		Mean Change from Baseline		Difference (95% CI) *
	SurgiMend	Control	SurgiMend	Control	
PROMIS-Physical Function					
Month 3	96	590	2.6	3.3	−0.7 (−1.9, 0.4)
Year 1	75	511	1.0	1.6	−0.5 (−1.7, 0.6)
Year 2	49	324	1.4	0.7	0.7 (−0.2, 1.6)
PROMIS-Anxiety					
Month 3	96	589	-8.6	−7.4	−1.2 (−3.1, 0.8)
Year 1	75	497	-9.2	−8.7	−0.5 (−3.0, 2.0)
Year 2	49	324	-8.9	−9.1	0.2 (−2.9, 3.4)
PROMIS-Depression					
Month 3	96	587	-0.2	−1.3	1.1 (−0.6, 2.7)
Year 1	75	497	-1.6	−2.3	0.7 (−1.4, 2.8)
Year 2	49	324	-1.8	−3.4	1.6 (−1.2, 4.4)

PROMIS Domain	Subjects, n		Mean Change from Baseline		Difference (95% CI) *
	SurgiMend	Control	SurgiMend	Control	
PROMIS-Fatigue					
Month 3	96	511	1.1	2.7	−1.6 (−3.5, 0.3)
Year 1	73	476	-1.7	−0.2	−1.5 (−3.5, 0.5)
Year 2	48	314	-0.7	−1.2	0.5 (−2.0, 3.0)
PROMIS-Sleep					
Month 3	96	586	0.5	−0.1	0.6 (−0.4, 1.6)
Year 1	75	495	0.9	−0.1	1.0 (−0.2, 2.2)
Year 2	49	325	0.9	0	0.9 (−0.5, 2.3)
PROMIS-Social Functioning					
Month 3	96	585	-1.7	−3.6	1.9 (−0.4, 4.2)
Year 1	75	492	1.1	0.3	0.8 (−1.9, 3.5)
Year 2	49	325	0.9	1.2	−0.3 (−3.6, 3.0)
PROMIS-Pain					
Month 3	96	584	2.9	4.7	−1.8 (−3.8, 0.2)
Year 1	75	492	0.8	2.1	−1.3 (−2.9, 0.4)
Year 2	49	324	1.6	0.2	1.5 (−0.9, 3.8)

* Difference =SurgiMend – Control.

8.5.4 Quality of Life: EORTC Functional Scales

Table 8-18 reports changes from baseline in European Organization for Research and Treatment of Cancer (EORTC) functional scales at Month 3, Year 1, and Year 2. For comparison of baseline minus postoperative score values, a positive number indicates worsening, and a negative value indicates improvement compared with baseline scores. Changes in the SurgiMend and Control groups were generally comparable. Subjects in both groups reported improvement in Body Image at all timepoints compared with baseline. Changes from baseline in breast symptoms were highest (indicating worse symptoms) at Month 3 (SurgiMend, 7.2; Control, 5.8; difference 1.4 [95% CI

−2.8, 5.6]); changes from baseline in Breast Symptoms at Year 1 and Year 2 were low, indicating scores comparable with those prior to breast reconstruction. For most other domains, the score was worse at Month 3 in comparison with baseline and was improved at Year 1 and Year 2. The exception is the domain of Future Prospective where the scores continued to worsen compared with baseline in both groups.

Table 8-18: Summary of Continuous Change from Baseline in EORTC Functional Scale Scores*

EORTC Functional Scales	Subjects, n		Mean Change from Baseline		Difference (95% CI) †
	SurgiMend	Control	SurgiMend	Control	
Body Image					
Month 3	92	582	−12.3	−15.5	3.2 (−2.9, 9.4)
Year 1	72	485	−7.4	−8.6	1.4 (−5.9, 8.8)
Year 2	46	320	−5.7	−5.8	0.1 (−8.7, 8.9)
Sexual Functioning					
Month 3	94	576	3.5	4.8	−1.3 (−5.6, 3.1)
Year 1	73	488	−0.7	1.4	-2.1 (−7.9, 3.7)
Year 2	48	319	−2.4	1.9	-4.3 (−11.9, 3.3)
Sexual Enjoyment					
Month 3	59	322	9.6	10.5	−0.9 (−8.7, 7.0)
Year 1	38	273	3.5	4.9	−1.4 (−11.4, 8.6)
Year 2	30	184	7.8	3.8	4.0 (−7.3, 15.3)
Future Perspective					
Month 3	91	574	13.9	11.1	2.8 (−3.7, 9.2)
Year 1	68	478	15.2	14.3	0.9 (−8.1, 9.9)
Year 2	44	316	16.7	15.2	1.5 (−9.6, 12.5)
Systemic therapy side effects					
Month 3	95	590	5.8	12.9	−7.1 (−11.6, 2.7)
Year 1	75	496	0.7	1.8	-1.1 (−5.1, 3.0)

EORTC Functional Scales	Subjects, n		Mean Change from Baseline		Difference (95% CI) †
	SurgiMend	Control	SurgiMend	Control	
Year 2	48	324	4.9	1.3	3.5 (−0.4, 7.4)
Breast Symptoms					
Month 3	95	589	7.2	5.8	1.4 (−2.8, 5.6)
Year 1	74	495	0.5	−0.2	0.7 (−2.6, 4.0)
Year 2	49	324	0.1	−3.2	3.4 (−0.7, 7.4)
Arm Symptoms					
Month 3	95	587	8.2	9.2	−1.0 (−5.5, 3.5)
Year 1	74	494	5.2	7.4	−2.3 (−6.7, 2.2)
Year 2	49	321	5.4	3.4	2.1 (−3.2, 7.3)
Upset by hair loss					
Month 3	24	103	−5.6	8.7	−14.3 (−35.7, 7.1)
Year 1	16	80	−14.6	−5.0	−9.6 (−35.6, 16.5)
Year 2	0	0.8	0	0.8	−0.8 (−36.2, 34.7)

EORTC, European Organization for Research and Treatment of Cancer.

* The scale ranged from 0 to 100. Values are unadjusted estimates. All subjects with missing values were excluded (i.e., this is completer case analysis). If the number of missing items of the scale is greater than the half of the total number of items, then the subject is excluded from the analysis.

† Difference =SurgiMend – Control.

8.5.5 Fatigue, Anxiety, and Depression: PRO Instrument Results

Changes from baseline in the Brief Fatigue Inventory (BFI) (a tool to assess the severity and impact of cancer-related fatigue), the Anxiety and Depression (PHQ-9) (a tool to measure anxiety and depression), and the GAD scale for Anxiety and Depression (GAD-7) (a tool to identify general anxiety) are reported at Month 3, Year 1, and Year 2 in **Table 8-19**, **Table 8-20** **and** **Table 8-21**, respectively. The responses were generally comparable between the SurgiMend and Control groups in all three health-related Patient-Reported Outcome measures.

Table 8-19 shows that subjects reported very little change from baseline in fatigue scores at Month 3, Year 1, and Year 2, indicating similar scores compared with those reported prior to breast reconstruction. The responses were generally comparable between the SurgiMend and Control groups.

Table 8-19: Brief Fatigue Inventory (BFI) – Change from Baseline

	Unadjusted Estimates		
	SurgiMend	Control	Difference (SurgiMend - Control) 95%CI
Month 3	(n=97) 0.4	(n=596) 0.8	-0.3 (-0.8,0.2)
Year 1	(n=76) -0.2	(n=502) 0.1	-0.4 (-0.9,0.2)
Year 2	(n=50) 0.4	(n=327) -0.1	0.4 (-0.2, 1.1)

Note: BPI has 9 items with its total score ranged from 0 to 10. If the number of missing items is less than 5, then the missing item was imputed by the mean of the observed items. Otherwise, the subject is considered as missing and excluded from the analyses.

Table 8-20 shows that subjects in both the SurgiMend and Control groups reported feeling less bothered by symptoms of anxiety and depression at Years 1 and 2 than at baseline before surgery. For comparison of baseline minus postoperative score values, a positive number indicates worsening, and a negative value indicates improvement compared with baseline scores. The responses were generally comparable between the SurgiMend and Control groups.

Table 8-20: Anxiety and Depression (PHQ-9) – Change from Baseline

	Unadjusted Estimates		
	SurgiMend	Control	Difference (SurgiMend - Control) 95%CI
Month 3	(n=97) 0.6	(n=590) 0.2	0.4 (-0.6, 1.4)
Year 1	(n=77) -1.4	(n=508) -1.3	-0.1 (-1.0, 0.8)
Year 2	(n=50) -1.2	(n=325) -1.5	0.4 (-1.2, 1.9)

Note: PHQ-9 has 9 Items, ranged from 0 to 27. If the number of missing items is less than 5, then the missing item was imputed by the mean of the observed items. Otherwise, the subject is considered as missing and excluded from the analyses.

Table 8-21 shows that subjects reported feeling less anxiety at Month 3, Years 1 and 2 than baseline in both the SurgiMend and Control groups. For comparison of baseline minus postoperative score values, a positive number indicates worsening, and a negative value indicates improvement compared with baseline scores. The responses were generally comparable between the SurgiMend and Control groups.

Table 8-21: GAD-7 Scale for Anxiety and Depression – Change from Baseline

	Unadjusted Estimates		
	SurgiMend	Control	Difference (SurgiMend - Control) 95%CI
Month 3	(n=97) -1.4	(n=588) -1.8	0.5 (-0.4, 1.3)
Year 1	(n=77) -1.6	(n=509) -2.3	0.7 (-0.3, 1.6)
Year 2	(n=50) -1.9	(n=324) -2.3	0.4 (-1.1, 1.9)

Note: GAD-7 has 7 items, ranged from 0 to 21. If the number of missing items is less than 4, then the missing item was imputed by the mean of the observed items. Otherwise, the subject is considered as missing and excluded from the analyses.

8.6 Safety Endpoints

8.6.1 Major Complications

Note that this analysis is related to the major complications component of the Composite Clinical Success (CCS) primary endpoint, but the data presented in this section describe subjects who did experience one or more major complications. The analyses of the proportion of subjects who experienced one or more major complications in the SurgiMend group and the Control group with no use of ADM are reported in **Table 8-22** through **Table 8-24**.

Table 8-22 reports that the absolute proportion of subjects with one or more major complications for the adjusted populations was 33.7% for the SurgiMend group and 46.7% for the Control group with no ADM, resulting in a 13.1% lower incidence of complications for the SurgiMend group compared with the Control group (95% CI: −22.5%, -3.7%). This analysis provides support that subjects in the SurgiMend group experienced a lower incidence of major complications compared with subjects in the Control group without the use of ADM. Further, this analysis relies on the most inclusive and stringent definition of major complications, which was recommended by FDA,

that captures elective revisions and wound infections requiring oral antibiotics as major complications.

Table 8-22: Proportion of Subjects with Major Complications Including Elective Revisions and Wound Infection Requiring Oral Antibiotics†

Unadjusted Estimates			PS-Adjusted Estimates (ATT)		
SurgiMend (n=119)	Control (n=868)	Difference (95% CI) *	SurgiMend (n=119)	Control (n=868)	Difference (95% CI) *
33.6%	46.7%	−13.0% (−22.0%, −4.0%)	33.7%	46.7%	−13.1% (−22.5%, −3.7%)

ATT, average treatment effect on the treated; PS, propensity score.

† Note: 21 subjects (1 SurgiMend and 20 Control) without complication data during the post-operative 2 years are counted as "no" for any major complications.

* Difference =SurgiMend – Control.

Table 8-23 reports the PS-stratified proportions of subjects with one or more major complications. The estimates of the proportions of subjects with one or more complications are consistent across the 5 strata. The overall adjusted estimate of treatment difference (ATE) was -14.8% (95% CI: −25.2%, −4.4%) in favor of SurgiMend. This analysis, which also relies on the most inclusive and stringent definition of major complications, provides additional support that subjects in the SurgiMend group experienced a lower incidence of major complications than subjects in the Control group without the use of ADM.

Table 8-23: PS-Stratified (ATE) Proportion of Subjects with Major Complications Including Elective Revisions and Wound Infection Requiring Oral Antibiotics†

Strata Index	Frequencies			Stratum Weight (ATE)	Estimates			Unadjusted Estimates			PS-adjusted Estimates (ATE)		
	SMD	CTL	Total		SMD	CTL	Diff*	SMD (n=119)	CTL (n=868)	Diff* 95% CI	SMD (n=119)	CTL (n=868)	Diff* 95% CI
1	23	404	427	0.433	30.4%	47.5%	−17.1%	33.6%	46.7%	−13.0% (-22.0%, −4.0%)	31.9%	46.7%	−14.8% (−25.2%, −4.4%)
2	24	198	222	0.225	29.2%	46.0%	−16.8%						
3	24	122	146	0.148	25.0%	45.9%	−20.9%						
4	24	93	117	0.119	50.0%	43.0%	7.0%						
5	24	51	75	0.076	33.3%	51.0%	−17.6%						

ATE, average treatment effect; PS, propensity score, SMD, SurgiMend; CTL, Control.

† Note: 21 subjects (1 SurgiMend and 20 Control) without complication data during the post-operative 2 years are counted as "no" for any major complications.

* Difference =SurgiMend – Control.

Table 8-24 reports the proportion of subjects in each group who experienced one or more major complications when elective revisions and wound infections requiring oral antibiotics were excluded from the analysis of major complications. The proportion of subjects with one or more major complications was 17.7% in the SurgiMend group and 22.5% in the Control group with no use of ADM, with a 4.9% lower incidence for the SurgiMend group (95% CI: −12.5%, 2.7%). This analysis is directionally consistent with primary analysis presented in **Table 8-23** and provides additional support that subjects in the SurgiMend group experienced a lower incidence of major complications than subjects in the Control group.

Table 8-24: Proportion of Subjects with Major Complications Excluding Elective Revisions and Wound Infection Requiring Oral Antibiotics†

Unadjusted Estimates			PS-Adjusted Estimates (ATT)		
SurgiMend (n=119)	Control (n=868)	Difference (95% CI) *	SurgiMend (n=119)	Control (n=868)	Difference (95% CI) *
17.6%	23.2%	−5.5% (−12.9%, 1.9%)	17.7%	22.5%	−4.9% (−12.5%, 2.7%)

ATT, average treatment effect on the treated; PS, propensity score.

† Note: 21 subjects (1 SurgiMend and 20 Control) without complication data during the post-operative 2 years are counted as "no" for any major complications.

* Difference =SurgiMend – Control.

Table 8-25 shows the PS-stratified proportions of subjects in each group with one or more major complications when elective revisions and wound infection requiring antibiotics were excluded. In this PS-stratified analysis (ATE), the proportion of subjects with one or more major complications was 14.1% in the SurgiMend group and 23.1% in the Control group with no use of ADM, with an estimate of the treatment difference of -9.0% (95% CI: −15.9%, −2.1%). This analysis is also directionally consistent with primary safety analysis presented in Table 7-22 and provides further support that subjects in the SurgiMend group experienced a lower incidence of major complications than subjects in the Control group.

Table 8-25: PS-Stratified (ATE) Proportion of Subjects with Major Complications Excluding Elective Revisions and Wound Infection Requiring Oral Antibiotics†

Strata Index	Frequencies			Stratum Weight (ATE)	Estimates			Unadjusted Estimates			PS-Adjusted Estimates (ATE)		
	SMD	CTL	Total		SMD	CTL	Diff*	SMD (n=119)	CTL (n=868)	Diff* 95% CI	SMD (n=119)	CTL (n=868)	Diff* 95% CI
1	23	404	427	0.433	4.3%	24.8%	−20.4%	17.6%	23.2%	−5.5% (−12.9%, 1.9%)	14.1%	23.1%	−9.0% (−15.9%, −2.1%)
2	24	198	222	0.225	20.8%	21.2%	−0.4%						
3	24	122	146	0.148	20.8%	23.8%	−2.9%						
4	24	93	117	0.119	29.2%	19.4%	9.8%						
5	24	51	75	0.076	12.5%	23.5%	−11.0%						

ATE, average treatment effect; PS, propensity score; SMD, SurgiMend, CTL, Control

† Note: 21 subjects (1 SurgiMend and 20 Control) without complication data during the post-operative 2 years are counted as "no" for any major complications.

* Difference =SurgiMend – Control.

8.6.2 Major Complications: Listing by Category

Table 8-26 summarizes the number and proportion of subjects that experienced a major complication by category in postoperative Year 1, postoperative Year 2, and up to postoperative Year 2.

- Through 2 years of follow-up, the most frequent major complications in both groups were elective revision (SurgiMend, 22.7%; Control, 30.8%), revision due to complications (SurgiMend, 11.8%; Control, 10.6%), and explantation due to complications (SurgiMend, 9.2%; Control, 8.1%). The largest numerical difference between the SurgiMend and Control groups was for elective revisions, which occurred in 27 (22.7%) of SurgiMend subjects and 67 (30.8%) of Control subjects; 8.1% lower in the SurgiMend group.
- The numerical differences in the proportions of subjects with complications for wound infection requiring oral antibiotics (3.0% lower for SurgiMend), capsular contracture (1.8% lower for SurgiMend), and wound infection requiring IV antibiotics (1.7% lower for SurgiMend) were lower for SurgiMend; however, all of these complications were infrequent and occurred in ≤10 subjects in the SurgiMend arm. The remaining major complication categories had a rate difference ≤1.5% between the SurgiMend group and Control group.

The table below was provided by the FDA statistical group with numbers and percentages absent from the 2-year complication rates. FDA stated they did not provide the numbers (percentages) of SurgiMend or Control data where a complication occurred in 10 or fewer patients. The FDA has indicated that this information will not be provided to Integra.

Table 8-26: Major Complication Rate by Category in the FAS Population

Complication*	Post-Op Year 1			Post-Op Year 2			Major Complications up to Post-Op 2 Years†		
	SMD	Control	Diff	SMD	Control	Diff	SMD	Control	Diff
Any major complication	38 (31.9%)	342 (39.4%)	-7.5%	N ≤ 10		-7.5%	40 (33.6%)	405 (46.7%)	-13.1%
Any major complication excluding elective revisions and wound infection requiring oral antibiotics	21 (17.7%)	172 (19.8%)	-2.1%	N ≤ 10			21 (17.7%)	201 (23.2%)	-5.5%
Hematoma	N ≤ 10		-1.5%	N ≤ 10	N ≤ 10	-0.3%	N ≤ 10		-1.8%
Explantation (including elective revisions)	14 (11.8%)	82 (9.5%)	2.3%	N ≤ 10		-2.1%	16 (13.5%)	106 (12.2%)	1.3%
Removal due to Complications [a]	11 (9.2%)	59 (6.8%)	2.4%	N ≤ 10		-1.9%	11 (9.2%)	70 (8.1%)	1.1%
Elective removal [b]	N ≤ 10		-0.3%	N ≤ 10		-0.5%			-0.6%
Capsular contracture	N ≤ 10	N ≤ 10	-0.5%	N ≤ 10		-1.6%	N ≤ 10		-1.8%
Local moderate to severe capsular contracture	N ≤ 10	N ≤ 10	-0.5%	N ≤ 10		-1.6%	N ≤ 10		-1.8%
Revision procedure due to capsular contracture [c]	N ≤ 10	N ≤ 10	-0.1%	N ≤ 10		-0.1%	N ≤ 10	N ≤ 10	-0.2%

Complication*	Post-Op Year 1			Post-Op Year 2			Major Complications up to Post-Op 2 Years†		
	SMD	Control	Diff	SMD	Control	Diff	SMD	Control	Diff
Infection	N ≤ 10		-4.2%	N ≤ 10	N ≤ 10	-1.1%	N ≤ 10		-4.8%
Wound infection requiring oral antibiotics	N ≤ 10		-2.7%	N ≤ 10	N ≤ 10	-0.4%	N ≤ 10		-3.0%
Wound infection requiring IV antibiotics	N ≤ 10		-1.3%	N ≤ 10	N ≤ 10	-0.5%	N ≤ 10		-1.7%
Wound infection requiring surgical or percutaneous drainage of abscess	N ≤ 10		0.4%	N ≤ 10	N ≤ 10	-0.1%	N ≤ 10		0.3%
Dehiscence	N ≤ 10		-1.4%	N ≤ 10	N ≤ 10	-0.1%	N ≤ 10		-1.5%
Implant leakage, rupture and/or deflation	N ≤ 10	N ≤ 10	0.2%	N ≤ 10	N ≤ 10	-0.1%	N ≤ 10	N ≤ 10	0.1%
Seroma	N ≤ 10		0.6%	N ≤ 10	N ≤ 10	-0.4%	N ≤ 10		0.4%
Tissue necrosis	N ≤ 10		-1.5%	N ≤ 10	N ≤ 10	0%	N ≤ 10		-1.5%
Local tissue necrosis [d]	N ≤ 10		-1.0%	N ≤ 10	N ≤ 10	0%	N ≤ 10		-1.0%
Revision procedure due to Necrosis [e]	N ≤ 10		1.1%	N ≤ 10	N ≤ 10	0%	N ≤ 10		1.1%

Complication*	Post-Op Year 1			Post-Op Year 2			Major Complications up to Post-Op 2 Years†		
	SMD	Control	Diff	SMD	Control	Diff	SMD	Control	Diff
Reoperation [f] (including elective revisions)	33 (27.7%)	256 (29.5%)	-1.8%	N ≤ 10		-6.5%	35 (29.4%)	322 (37.1%)	-7.7%
Reoperation [g] (excluding elective revisions	14 (11.8%)	74 (8.5%)	3.3%	N ≤ 10		3.1%	14 (11.8%)	94 (10.8%)	1.0%
Implant malposition requiring surgical correction	N ≤ 10		-0.1%	N ≤ 10	N ≤ 10	-0.4%	N ≤ 10	N ≤ 10	-0.5%
Secondary attempt at reconstruction	N ≤ 10		1.8%	N ≤ 10		-0.4%	N ≤ 10		1.3%
Revisions due to complications	14 (11.8%)	74 (8.5%)	3.3%	N ≤ 10		3.4%	14 (11.8%)	92 (10.6%)	1.2%
Elective revisions	22 (18.5%)	202 (23.3%)	-4.8%	N ≤ 10		-4.8%	27 (22.7%)	267 (30.8%)	-8.1%
Death	N ≤ 10	N ≤ 10	0.2%	N ≤ 10	N ≤ 10	0.7%	N ≤ 10	N ≤ 10	0.2%

Diff, difference; IV, intravenous; SMD, SurgiMend.

* Note: cells with number of subjects ≤ 10 are not shown

† Any major complications during the post-operative Year 2 are counted. In the absence of post-operative year 2 data, post-operative Year 1 is used. Twenty-one subjects (20 Control and 1 SMD) without complication data during the post-operative 2 years are counted as "no" for any major complications.

[a] Removal of implant/tissue expander with/without replacement.

[b] Elective removal of implant with/without replacement.

[c] Open capsulotomy/capsulectomy for capsular contracture.

[d] Mastectomy skin flap necrosis, acute partial reconstructive flap necrosis within 30 days of surgery, or chronic fat necrosis of the reconstructed flap requiring surgical excision.

[e] Debridement/excision of partial necrosis or complete removal of flap for necrosis.

[f] Reoperation also includes elective implant removal and implant removal due to complication.

[g] Reoperation also includes implant removal due to complication.

8.7 Discussion

This study revealed a statistically significant benefit of SurgiMend in immediate, two-stage, submuscular, alloplastic, breast reconstruction compared to no ADM, as measured by a composite endpoint of the Patient-Reported Outcome (PRO) assessment indicating a return to baseline by

Year 1 on the Physical Well-Being (chest) module of the BREAST-Q and no major complications through Year 2. The objective of the current analysis was to focus on the subjects' experience, capturing both subject-reported perception of physical well-being and safety outcomes following breast reconstruction with SurgiMend. To make this assessment, we used the primary endpoint of Composite Clinical Success (CCS), i.e., a score on the Physical Well-Being (chest) module of the BREAST-Q that was not more than 4 points lower one year after surgery compared to the preoperative baseline score and the absence of any major complications over 2 years. Despite undergoing two separate operations (mastectomy with expander and SurgiMend placement followed by permanent implant placement), approximately 32% of the subjects undergoing breast reconstruction with SurgiMend met the primary endpoint definition for clinical success, compared to 21% of the propensity score-matched Control arm (no ADM) in the propensity-score matched analysis. This 11% difference was statistically significant (95% CI: 1.7%, 20.8%; p=0.02). With as many as 60,000 annual reconstructions accomplished with ADMs in recent years[12], this 11% difference also represents the potential benefit of SurgiMend use in breast reconstruction to many patients. Further, this analysis provides support that subjects in the SurgiMend group experienced a lower incidence of major complications compared with subjects in the Control group without the use of ADM.

Although at 1 year the percentage of subjects experiencing a score that was not more than 4 points lower one year after surgery compared to the preoperative baseline score in BREAST-Q Physical Well-Being, indicating a return to the subject's perception of well-being before surgery, was numerically higher in the SurgiMend group than in the Control group (44.5% vs. 39.1%), the difference was not nominally statistically significant. For all other BREAST-Q domains there was a decrease in the score from baseline to Year 1, and scores were maintained at Year 2. For each of these domains, the changes in scores compared with baseline were comparable for the SurgiMend and Control groups. This is in line with a previous analysis from the MROC Study sponsor, in which no statistically significant differences in BREAST-Q scores or other PROs were reported between the Control and the ADM groups (all ADM types were included in the dataset) (Sorkin et al. 2017). A recent systematic review of the MROC data also showed comparable satisfaction in subjects who received ADMs compared to those who did not (DeLong et al. 2019).

As expected, pain scores, as measured by the NPRS and MPQ were highest in both the SurgiMend and Control groups at Week 1 after surgery, decreased (improved) by Month 3, and remained low through Years 1 and 2. The findings in the SurgiMend and Control groups were comparable. This finding is consistent with the results of a previous randomized controlled trial in which the use of

[12] American Society of Plastic Surgeons. 2020 Plastic Surgery Statistics. Available at: https://www.plasticsurgery.org/news/plastic-surgery-statistics

an ADM was not associated with any increases in post-operative pain, post-operative narcotic use, or rate of post-operative expansion compared with no ADM[13].

Across the PROMIS domains there were small decreases from baseline in both groups for anxiety and depression (indicating improvement), and slight improvements for physical function. As anticipated, scores for Fatigue, Social Functioning, and Pain were worse at Month 3 than Year 1 or Year 2 in both groups and were comparable between the two groups. PROMIS-Sleep scores remained stable from Month 3 through Year 2. The EORTC Functional Scale score for body image, sexual function, sexual enjoyment, systemic therapy side effects, breast symptoms and upset due to hair loss were all negatively impacted following surgery in both the SurgiMend and Control groups. However, these scores improved by 1 year and were maintained through 2 years. According to the BFI, PHQ-9, and GAD-7 scores, fatigue remained stable from Month 3 through Year 2; anxiety and depression improved over time.

It has been suggested that the potential trade-off for the benefits of using ADMs for breast reconstruction may be an increased rate of complications compared to no ADM. One MROC Study publication pointed to a trend toward higher risks for major complication and failure with ADM compared with no ADM (Sorkin et al. 2017). In another, more recent publication of the MROC Study, the risk of major complications was significantly higher with ADM use compared with no ADM (22.9% vs. 16.4%; p=0.04), although brands were not distinguished and there remained no differences in terms of infection, reconstructive failure, flap necrosis, capsular contracture, seroma, hematoma, or implant malposition or rupture (Kumar et al. 2021). A recent further, brand-specific analysis of the MROC Study dataset published by the FDA revealed a higher risk of complications for FlexHD (MTF Biologics) and AlloMax (Bard Davol) compared with no ADM, SurgiMend, and AlloDerm (Allergan/Abbvie)[14].

In our analysis of the Integra SurgiMend Study presented here, the absolute rate of complications for the propensity-adjusted populations is 33.7% for reconstructions with SurgiMend and 46.7% without the use of ADM, resulting in a 13.1% lower incidence of complications for the SurgiMend group (95% CI: -22.5%, -3.7%). When elective revisions and wound infections treated with oral antibiotics are excluded, these rates are 17.7% (SurgiMend) and 22.5% (no-ADM) with a 4.9% lower incidence for the SurgiMend group (95% CI: -12.5%, 2.7%). These results strongly suggest that complications were not more frequent with SurgiMend than with no ADM.

[13] Food and Drug Administration. *Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates: FDA Safety Communication 2021.* Available from: https://www.fda.gov/medical-devices/safety-communications/acellular-dermal-matrix-adm-products-used-implant-based-breast-reconstruction-differ-complication

[14] Food and Drug Administration. *Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates: FDA Safety Communication 2021.* Available from: https://www.fda.gov/medical-devices/safety-communications/acellular-dermal-matrix-adm-products-used-implant-based-breast-reconstruction-differ-complication

One factor potentially contributing to the lower incidence of major complications in the SurgiMend group relative to Control is the decreased number of elective revisions (22.7% vs. 30.8% over the 2 years of follow-up). The remaining categories, including explantation, capsular contracture, and implant leak/rupture/deflation, had a difference ≤1.5% between the groups with no pattern of directionality (no trend of higher vs lower for SurgiMend vs Control). By absolute rates of complications, the most frequent for both groups were: elective revision, explantation, reoperation (not elective or due to complication), and explantation due to a complication (**Table 8-25**).

There are limitations to this analysis, which is based on Real-World Data from a prospective observational cohort study rather than data collected from a prospective randomized, controlled trial comparison of SurgiMend and no use of ADM. Characteristics of each subject may drive a surgeon to decide to use an ADM at the moment of the index surgery and thus unknown factors contributing to patient selection bias are possible. At the same time, these dynamics make a randomized controlled trial problematic for surgeons and subjects. CDRH has been proactive in employing the use of Real-World Evidence for regulatory decision-making, including approval of original PMA applications[15,16]. As described in detail in **Section 6.2**, the dataset used and the processes for conducting the analyses of the SurgiMend Study, in collaboration with FDA, provide reliable and relevant Real-World Evidence to support this PMA application.

Based on the analysis in the SurgiMend Study that compared the use of SurgiMend to no ADM based on the MROC dataset, SurgiMend showed a lower absolute rate of complications for breast reconstruction compared with no ADM. Furthermore, a statistically significantly greater percent of subjects who used SurgiMend met the prespecified primary endpoint definition of clinical success than subjects with no ADM. Taken together, these results demonstrate the safety and effectiveness of the use of SurgiMend in breast reconstruction procedures for patients undergoing immediate, two-stage, implant-based, unilateral or bilateral breast reconstructions after a first mastectomy for breast cancer treatment or prophylaxis.

9 POST HOC DATA ANALYSES

Following submission of the PMA and public announcement of the Advisory Committee meeting, the FDA proposed the conduct of post hoc statistical analyses that were not specified in the Statistical Analysis Plan and asked if Integra agreed to the conduct of these analyses. Integra

[15] Food and Drug Administration. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices *Guidance for Industry and Food and Drug Administration Staff*. August 2017. Available from: https://www.fda.gov/media/99447/download

[16] "Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions" Center for Devices and Radiological Health. Center for Devices and Regulatory Health. Available at https://www.fda.gov/media/146258/download

agreed that the FDA statistical group could conduct these analyses. For these analyses (and other exploratory analyses in this Executive Summary), the 95% CIs are not based on a pre-specified hypothesis test and there was no adjustment for multiplicity.

9.1 Post Hoc Analysis of Primary Endpoint Limited to only the Sites Where Both SurgiMend and No ADM were Used in the MROC Study

The FDA statistical group also conducted an exploratory post hoc analysis of the primary Composite Clinical Success endpoint that was limited to the two sites in the MROC Study where both SurgiMend and no ADM were used (Sites #1 and #9). The total number of Control group subjects (no ADM) at Site 1 and Site 9 combined is 150 and these subjects were compared to 119 SurgiMend subjects.

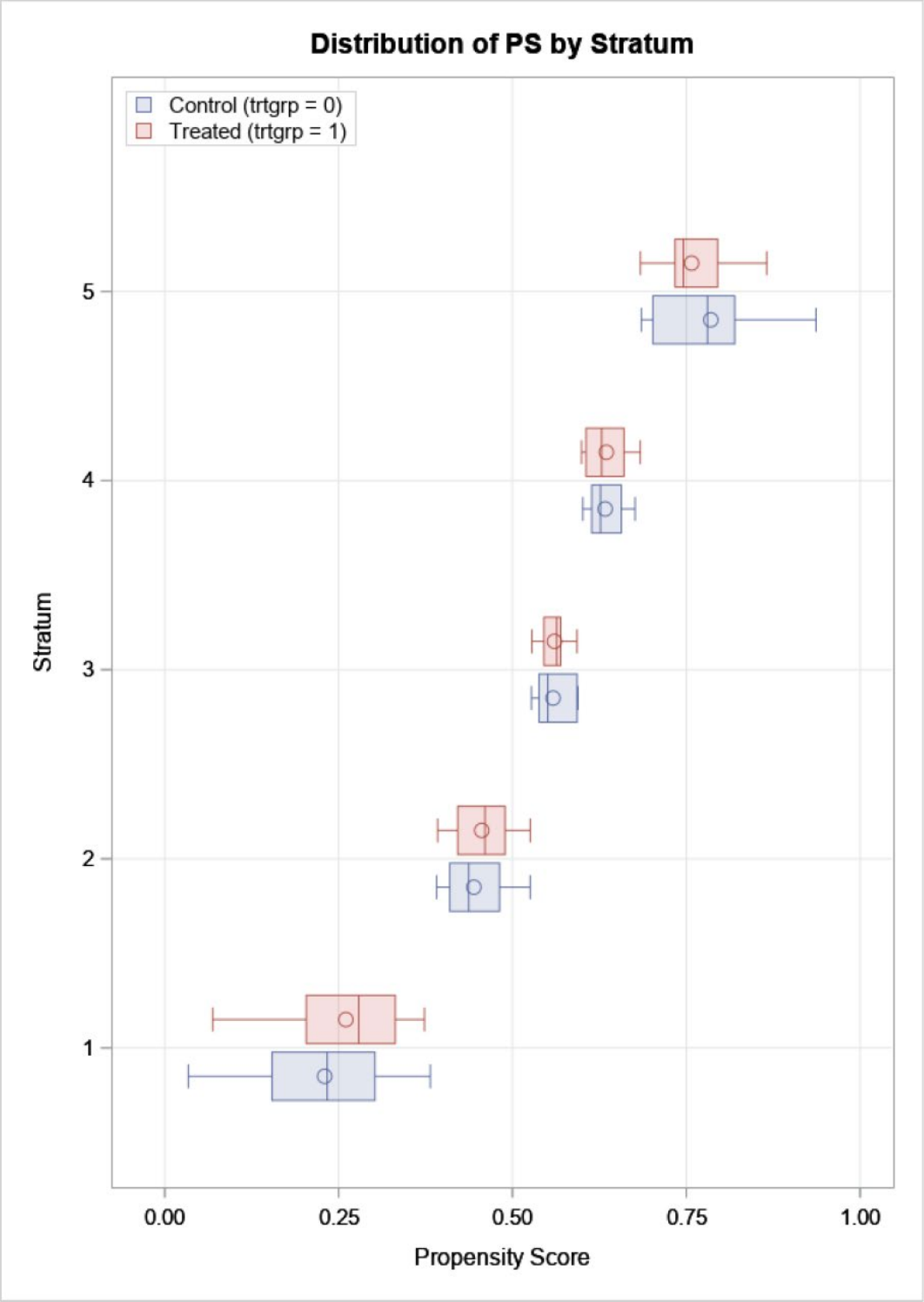


Figure 9-1: Post Hoc Propensity Score Distribution by Stratum for SurgiMend ("Treated") Group and Control Group

The following tables, **Table 9-1 through Table 9-4,** report the post hoc exploratory sensitivity analyses of the Primary Endpoint that was limited to the two sites in the MROC study where both SurgiMend and no ADM were used (Sites #1 and #9).

Table 9-1 below reports the analysis that relies on the definition of Composite Clinical Success that was prespecified in the Statistical Analysis Plan. In this analysis, 31.8% of the SurgiMend subjects and 6.1% of the Control subjects achieved Composite Clinical Success (nominal p-value = 0.001.) This analysis strongly supports the prespecified primary endpoint analysis that demonstrated superiority of the SurgiMend group compared with the Control Group regarding the proportion of subjects that achieved Composite Clinical Success.

Table 9-1: Primary Analysis – Sites 1 and 9 ATT strata and ATT weights; Statistical Comparison of the CCS in which Elective Revisions/Reoperations and Wound Infection requiring Oral Antibiotics were considered as Major Complications

Unadjusted Estimates			PS-adjusted Estimates		
SMD (n=119)	Control (n=150)	Diff (SE) 95% CI	SMD (n=119)	Control (n=150)	Diff (SE) 95% CI
32.3%	19.3%	13.0% (5.7%) (1.8%, 24.3%)	32.4%	12.9%	19.4% (5.7%) (8.3%, 30.5%)

SMD, SurgiMend; PS, propensity score

The additional three tables below, **Table 9-2** through **Table 9-4,** report further post hoc exploratory sensitivity analyses in which the definitions of major complications were varied. Each of these exploratory analyses reports PS-adjusted estimates that are directionally similar to the primary endpoint analysis specified in the Statistical Analysis Plan. In each post hoc exploratory analysis, the proportion of subjects that achieved success for the Composite Clinical Score is numerically higher in the SurgiMend group compared with the Control group.

Table 9-2: Sensitivity Analysis – Sites 1 and 9 ATT strata and ATT weights; Statistical Comparison of the CCS in which Elective Revisions/Reoperations and Wound Infection requiring Oral Antibiotics were NOT considered as Major Complications

Unadjusted Estimates			PS-adjusted Estimates		
SMD (n=119)	Control (n=150)	Diff (SE) 95% CI	SMD (n=119)	Control (n=150)	Diff (SE) 95% CI
40.0%	31.5%	8.4% (6.3%) (-4.0%, 20.8%)	40.0%	27.8%	12.2% (7.3%) (-2.2%, 26.5%)

SMD, SurgiMend; PS, propensity score

Table 9-3: Primary Analysis – Sites 1 and 9 ATT strata and ATE weights; Statistical Comparison of the CCS using ATE weights in which Elective Revisions/Reoperations and Wound Infection requiring Oral Antibiotics were considered as Major Complications

Unadjusted Estimates			PS-adjusted Estimates		
SMD (n=119)	Control (n=150)	Diff (SE) 95% CI	SMD (n=119)	Control (n=150)	Diff (SE) 95% CI
32.3%	19.3%	13.0% (5.7%) (1.8%, 24.3%)	32.9%	16.5%	16.4% (6.0%) (4.6%, 28.2%)

SMD, SurgiMend; PS, propensity score.

Table 9-4: Sensitivity Analysis – Sites 1 and 9 ATT strata and ATE weights; Statistical Comparison of the CCS using ATE weights in which Elective Revisions/Reoperations and Wound Infection requiring Oral Antibiotics were NOT considered as Major Complications

Unadjusted Estimates			PS-adjusted Estimates		
SMD (n=119)	Control (n=150)	Diff (SE) 95% CI	SMD (n=119)	Control (n=150)	Diff (SE) 95% CI
40.0%	31.5%	8.4% (6.3%) (-4.0%, 20.8%)	38.8%	29.9%	8.9% (6.8%) (-4.5%, 22.3%)

SMD, SurgiMend; PS, propensity score.

At the request of Integra, FDA statistical group attempted to perform sensitivity analyses for Site #1 and Site #9 separately. However, the number of subjects at each separate site was too small to permit PS-adjusted analyses.

10 LITERATURE SOURCES

In addition to the results of our primary clinical study presented in the PMA application, there is a substantial body of published clinical evidence that supports the safety and effectiveness of SurgiMend in breast reconstruction.

10.1 Method of selection

A thorough and objective search strategy was performed utilizing PubMed, Cochrane, Embase, Elsevier's Scopus, and Web of Science databases from inception to March 2021 to identify clinical studies with SurgiMend in breast reconstruction. The combination of databases ensured complete coverage of published literature, including European Journals, relevant clinical trials and publications of user experience published in low impact journals. This search resulted in 27 articles that address the safety and effectiveness of SurgiMend.

Titles, keywords, and abstracts were searched for Breast AND Reconstruction OR implant OR surgery OR mastectomy AND Repair OR reinforcement OR acellular matrix OR ADM OR mesh AND Review OR guideline. To further identify data regarding SurgiMend specifically, search terms also included SurgiMend OR Bovine dermis OR acellular dermal collagen OR extracellular matrix scaffold AND breast reconstruction OR breast surgery OR mastectomy.

Inclusion criteria:

- Review or systematic review or meta-analysis
- Publication in peer-reviewed journals
- Written in English or with English translation available
- Study was performed on or refers to use in human subjects
- Study refers to current therapies to reinforce soft tissue where weakness exists in subjects requiring breast reconstruction

Exclusion criteria:

- Single case reports, single study outcomes
- Conference abstracts, presentations, or posters
- Studies in which SurgiMend is one of the ADMs included but results are not differentiated by brand
- Duplication of data

10.2 Summary

As described in the PMA application, the long-term safety and effectiveness of SurgiMend in both one- and two-stage subpectoral breast reconstruction have been demonstrated in these clinical studies. Most publications describing breast reconstruction with SurgiMend have focused on the subpectoral approach. For the executive summary, we have highlighted a sub-set of those publications focusing on 1) Patient-Reported Outcomes, 2) Complication rates, and 3) Mechanical function of SurgiMend in supporting the breast pocket to better elucidate the benefits, risks, and function of SurgiMend PRS ABDM.

10.2.1 Patient Report Outcomes and Effectiveness Outcomes in SurgiMend-assisted Breast Reconstruction

Patient-reported outcomes have been captured in a number of published studies in which SurgiMend was utilized during breast reconstruction (Chehade et al. 2017, Headon et al. 2016, Sheflan et al. 2019). These studies employed BREAST-Q, in which self-reported satisfaction with aesthetic outcomes is scored on a 0-100 score range where scores ≥ 75% are considered 'very satisfied,' scores 50-75% are considered 'satisfied,' and scores < 50% are dissatisfied. In the studies utilizing BREAST-Q, SurgiMend patients reported favorable outcomes. In Chehade et al. (2017), the mean BREAST-Q score on satisfaction with aesthetic outcome in patients whose breasts were reconstructed with SurgiMend was 88. When results were reported according to whether patients were dissatisfied, satisfied, or very satisfied, 85.9-100% of patients were satisfied or very satisfied. Similarly, in Headon et al. (2016), the SurgiMend patients reported a high level of satisfaction with their reconstructions, with an average score of 85 on the BREAST-Q survey. In addition, a study by Scheflan et al. (2019), with an average follow-up time of 4.9 years, reported an average patient satisfaction BREAST-Q score of 85.9.

These investigators also used non-standardized or non-validated methods for assessing patient satisfaction among SurgiMend breast reconstruction patients, with numerical and categorical scales indicating a high level of patient satisfaction (Chehade et al. 2017, Headon et al. 2016). In the Chehade study, women whose reconstruction included SurgiMend rated satisfaction with the aesthetic outcome of their breast surgery on a visual analog scale of 0 – 10, where 10 indicated a good aesthetic outcome and 0 indicated a poor outcome. Patient satisfaction scores reported in the study exceeded 9 out of 10. When those patients rated breast hardening on a scale of 1-10, where 10 indicated severe hardening (and hence capsular contracture formation), the average response in patients reconstructed with SurgiMend was 2.6 (Chehade et al. 2017). In another study, where patients were asked to rate their overall satisfaction as "Excellent", "Good", "Fair", or "Poor", the level of satisfaction reported by patients in the SurgiMend group was "Excellent" in 32.1% of patients, "Good" in 53.6%, "Fair" in 7.1%, and "Poor" in 7.1% (Lee, Youngtae. 2015, De Vita et

al. 2015), employed the Michigan Breast Reconstruction Outcome Scale in which 43% of patients responded they were "highly satisfied" with the outcome of their reconstruction with SurgiMend, while 45.9% were "moderately satisfied," and only 10.8% were "not satisfied".

10.2.2 Complication Rates in Breast Reconstruction with SurgiMend

There are common and specific risks associated with all breast reconstruction surgeries regardless of surgical approach. The complications with the use of SurgiMend in breast reconstruction reported in the literature are similar to those reported for autologous and implant-based reconstructions in which ADMs are not used.

Multiple studies compared the use of SurgiMend with no ADM, a comparator device, or an alternative surgical method. Endress, et al, found no significant differences between the SurgiMend and no-ADM cohorts in the overall incidence of complications (SurgiMend group n=11, 20.8%, no-ADM group n=16, 13.0%, p=0.241) or for specific complications. Complications reported for the SurgiMend cohort were hematoma (n=3, 5.7%), flap necrosis (n=3, 5.7%), infection requiring explantation (n=1, 1.9%), infection requiring antibiotics (n=1, 1.9%), deflation (n=2, 3.8%), and wounds requiring explantation (n=1, 1.9%) (Endress et al. 2012). Similarly, when SurgiMend was compared to a latissimus dorsi flap overlay in immediate, two-stage stage subpectoral breast reconstructions, there were no differences in complication rates (Lee, Youngtae 2015).

Additional studies directly compared outcomes in breast reconstruction procedures using SurgiMend with those using AlloDerm (human ADM, Allergan/Abbvie). In a study by Butterfield, et al., significantly higher rates of seroma were seen in AlloDerm patients, while minor necrosis was observed more frequently in SurgiMend patients (Butterfield 2013). In contrast, the study by Ricci et al. found no statistical difference in the incidence of skin necrosis between patients reconstructed with SurgiMend and those with AlloDerm when controlling for cofactors (Ricci et al. 2016). In a third study, the type of ADM did not correlate with overall or specific complications, and the incidence of complications was not significantly different between the two groups (SurgiMend vs AlloDerm) with complications for the SurgiMend group including seroma (n=15, 11.4%), necrosis (n=29, 21.2%), infection (n=18, 13.5%), and explantation (n=14, 10.2%) (Selber et al. 2015). None of the three studies showed a statistically significant difference in overall complication rates.

In a long-term study (2010-2018) comparing subpectoral reconstructions with SurgiMend to prepectoral reconstructions using multiple other ADMs, there were no differences in rates of explantation, infection, or wound dehiscence between the groups (Ribuffo et al. 2021). The subpectoral approach with SurgiMend was associated with higher rates of seroma and hematoma ($p < 0.004$ and $p < 0.045$, respectively) and an increased rate of animation deformity. The authors

attributed the latter findings to the difference in surgical approach, as animation deformity is associated with the placement of the breast implant below the pectoralis major muscle and does not occur in prepectoral reconstructions. Studies comparing SurgiMend with a comparator device suggest that the complication rates of SurgiMend are similar, and in some studies, significantly lower, than that of other ADMs.

Taken together, the complications reported for SurgiMend suggest that breast reconstruction surgery using SurgiMend is no less safe than that employing no ADM, comparator ADM devices, or alternative surgical methods. The complications reported are typically those that can occur in breast reconstruction procedures in general, including skin necrosis, seroma, hematoma, and capsular contracture. These are inherent risks in breast reconstruction following mastectomy that plastic surgeons anticipate as part of the overall care plan for each patient, regardless of surgical approach.

10.2.3 Function:

10.2.3.1 Fill Volume

One of the purported benefits of an ADM in breast reconstruction is improved expansion dynamics and accelerated rates of volume fill (Manahan et al. 2019, Weichman et al. 2012). The retrospective study by Endress et al, discussed above in the complication section, also evaluated performance outcomes in immediate, two-stage, subpectoral breast reconstruction with SurgiMend versus reconstructions without ADM, and found that initial expander fill volume was significantly higher in the SurgiMend group versus the no-ADM group (182.1±143.3 vs 117.7±66.3, $p<0.001$) and drain duration in days was shorter (8.5±3.4 vs 11.07±5.1, $p=0.015$), without a significant increase in complications (Endress et al. 2012).

10.2.3.2 Status of SurgiMend Breast Pocket at Expander-Implant Exchange Time

As noted previously, SurgiMend is implanted during the first surgery to provide support to the implanted expander. After 2 or more weeks, the surgeon may determine the mastectomy incision has healed sufficiently to begin filling the expander. The expander is injected with approximately 50mL of saline on a roughly biweekly basis, with volume and frequency dependent on the surgeon's assessment of tissue adaptation and the patient's pain tolerance. Studies show that the majority of expansion results from pectoralis muscle stretching rather than ADM stretching.

A study by Gaster, et al. (2013) prospectively studied the persistence and integration of SurgiMend in the setting of two-staged, subpectoral breast reconstruction to examine long-term breast pocket formation for implant-based reconstruction. Biopsies were obtained from 12 patients (17 reconstructions) at the time of exchange of tissue expander to permanent silicone implant. The average time between SurgiMend implantation and biopsies was 7.8 months (range, 2-23 months). Macroscopically, breasts reconstructed with SurgiMend showed no evidence of contraction,

edema, or infection, with the exception of one subject who experienced an infection requiring removal of the tissue expander 2 months after the initial procedure. The SurgiMend implant was clearly distinguishable grossly and histologically at the time of each implant exchange out to 23 months. The degree of integration and neovascularization corresponded to the quality of the skin flap rather than implantation duration, with "thick" flaps associated with better vascularization, greater cellular incorporation, neovascularization, and replacement of ADM with organized (human) collagen. This study showed successful neovascularization and incorporation of SurgiMend with only limited and localized degradation associated with new, organized collagenous tissue deposited by the patient. The minimal host inflammation and absence of foreign body response to SurgiMend when placed between a tissue expander and native tissue indicate that SurgiMend may be safely used in alloplastic breast reconstruction. The SurgiMend device was structurally and morphologically stable after nearly two years of implantation. There was no evidence of contracture that would have suggested denaturation or degradation of the native collagenous structure.

Similarly, Scheflan et al. (2018) observed evidence of SurgiMend persistence 1-year post - implantation, noting:

> *During exchange or revision procedures, SurgiMend was inspected visually and found to be integrated in all cases. Tissue biopsy specimens were taken from areas with and without acellular dermal matrix for histologic analysis. All biopsy specimens showed less cellularity and less vascularity in the integrated acellular dermal matrix area than those taken from the bare capsule. At no time either during exchange or during revision surgery were there any instances of SurgiMend disappearance.*

Taken together with the collective body of clinical evidence showing favorable clinical outcomes, this evidence strongly supports the long-term mechanical stability of SurgiMend after implantation as it is slowly integrated and remodeled with host tissue to provide continuous support for implant-based reconstruction. The long-term mechanical stability of SurgiMend could account for the difference in elective revisions observed for SurgiMend in the analysis of MROC results. The durability of SurgiMend in breast reconstruction allows for cell infiltration and tissue integration that combine to create a strong breast pocket that may eliminate the need for fat grafting or other procedures to improve outcomes.

10.3 Conclusion of SurgiMend Literature Review

Our systematic review of the body of clinical literature on SurgiMend supports the findings of the MROC Study and further underscores its safe and effective use as an adjunct in contemporary breast reconstruction procedures. The use of SurgiMend was investigated in a substantial number

of clinical studies, providing extensive evidence to support the safety and effectiveness of SurgiMend in breast reconstruction procedures. Aesthetic outcomes, patient satisfaction, initial and final tissue expander fill volumes, and number of revision surgeries were analyzed based on identified articles in the scientific literature. The literature reports that those patients were very satisfied with overall aesthetic outcomes with the use of SurgiMend and that results similar to the use of the latissimus dorsi muscle flap can be obtained with SurgiMend without the associated morbidity associated with mobilization of a flap. In addition, SurgiMend showed similar, or in some cases better, performance when compared to competitor products such as Alloderm. Complications reported for two-stage subpectoral breast reconstruction with SurgiMend included infection, capsular contracture, dehiscence, seroma, hematoma, tissue necrosis, loss of implant and revision procedures, and red breast syndrome at rates consistent with alternative approaches to subpectoral breast reconstruction. Taken together, the data suggest that safety events and complications reported with the use of SurgiMend in the broader published literature are directionally consistent with the results of the Integra SurgiMend Study, and are those expected by surgeons with breast reconstruction procedures in general, with or without an ADM. Lastly, histological evidence supports that the long-term mechanical stability of SurgiMend after implantation provides continuous support for the mastectomy skin flaps as they heal. If a surgeon chooses to use SurgiMend with the expectation of clinical benefit, published evidence suggests the device can be used without increased risk relative to no-ADM repair.

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11 PLANNED TRAINING

There has been long clinical use of ADM in immediate, two-stage, submuscular, alloplastic breast reconstruction, including SurgiMend, in subpectoral breast reconstruction. SurgiMend has been employed in this and other breast reconstruction procedures in the U.S. for over ten years in the practice of surgery. As such, there is nothing new or unique about this product that requires specialized training prior to use.

Board-certified plastic and reconstructive surgeons are fully trained in sub-pectoral surgical breast reconstruction procedures, and while most will have experience with the use of an ADM, not all will have specific experience with SurgiMend PRS ABDM in these procedures. The surgeon education and training programs for SurgiMend PRS ABDM will therefore focus on three types of plastic and reconstructive surgeons that are seeking supplementary knowledge:

- Those desiring experience in the implantation of SurgiMend in sub-pectoral procedures.
- Those that may have used SurgiMend in the past but need refresher training post-PMA approval.
- Those experienced with allograft ADMs but not with an animal-derived ADM like SurgiMend.

Integra's Professional Education program employs a wide array of learning platforms and adult learning models to ensure participants are competent in the knowledge and skills needed to use Integra products safely and effectively. These include, but not limited to:

- Cadaver-based bio-skills laboratory programs;
- Didactic education delivered by top surgeons in the field;
- Case study presentations;
- Educational webinars, videos and other distance learning programs;
- Peer-to-peer programs;
- Fellowship grants; and/or
- Preceptorship programs.

Upon approval of the PMA, Integra will offer training in a variety of different formats including e-learning modules, live and on-demand webinars, and in-person training. The training curriculum will be developed in partnership with surgical experts residing on Integra's sub-pectoral advisory board panel. A didactic and hands-on training curriculum will be established. Training courses will be designed for plastic and reconstructive surgeons performing sub-pectoral breast reconstruction with an acellular dermal matrix. In-person training courses offering hands-on instruction will be led by recognized experts in the field. These courses will be designed to instill competence in the use of SurgiMend in sub-pectoral breast reconstruction for each stage of the patient—preoperative, intra-operative, and postoperative. Regional in-person training courses will be offered at a variety

of US-based bio-skills venues. In addition, in-person training courses will be offered at Integra's headquarters'-based cadaver lab in Princeton, New Jersey. For surgeons who prefer e-learning, Integra will create a dedicated online surgeon training portal containing surgical videos and archived webinar content that can be accessed on-demand.

Integra will work in partnership with the American Society of Plastic Surgeons (ASPS) to support educational workshops that offer training for sub-pectoral breast reconstruction for both attending and resident surgeons. Integra will also develop regional centers of excellence at recognized reconstructive breast surgery institutions throughout the country. Access to designated centers of excellence will be offered through Integra's reconstructive surgery preceptorship program. Surgeons participating in this program who desire to learn sub-pectoral technique may visit a designated center of excellence to observe surgical cases.

12 POTENTIAL POST APPROVAL STUDY (PAS) CLINICAL DATA COLLECTION

Integra has supplied data and information in the PMA, including evidence from the MROC dataset, that provide a reasonable assurance of SurgiMend PRS ABDM's safety and effectiveness for the indication under review. To supplement this existing data and information and provide continued assurance of the device's safety and effectiveness after approval, Integra intends to conduct a Post Approval Study (PAS) that meets parameters to be agreed upon with FDA. As recognized by FDA, post-market data collection is a factor to be "consider[ed] as a part of making benefit-risk determinations" and can support positive determinations enabling device approval.[17]

Integra has provided an initial Post-Approval Study proposal to FDA to conduct a prospective, multi-center, observational study to assess Patient-Reported Outcomes and complications in mastectomy reconstruction utilizing SurgiMend PRS ABDM in women undergoing primary breast reconstructions in an immediate, two-stage, implant-based subpectoral procedure. One hundred and fifty (150) subjects in the United States would be recruited for this trial at ten (10) to twenty (20) centers with follow-up at defined time periods through five years. The primary objective of this study would be to evaluate safety signals for SurgiMend PRS ABDM over a five- year period after the index procedure. The secondary objective of this study would be to assess the following Patient-Reported Outcomes (PROs):

- BREAST-Q Reconstruction module

[17] Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval; Guidance for Industry and Food and Drug Administration Staff (April 13, 2015). Available at https://www fda.gov/regulatory-information/search-fda-guidance-documents/balancing-premarket-and-postmarket-data-collection-devices-subject-premarket-approval .

- Numerical Pain Rating Scale
- McGill Pain Questionnaire

The clinical data associated with the Post-Approval Study would be assessed during follow-up visits following a prescribed study timeline. Each follow-up visit would assess outcome measurements addressing both safety endpoints and patient-reported outcomes.

The intent of this observational Post-Approval Study would be to collect data on the outcome measures outlined by the visit structure throughout the follow-up period for each patient. Safety data would be collected per standard of care. Specifically, this study would aim to collect data on the incidence and nature of adverse device effects with causal adjudication, including but not limited to:

- Major complications
  - Hematoma
  - Explantation
  - Reoperation
  - Capsular contracture
  - Infection
  - Dehiscence
  - Tissue necrosis
  - Implant rupture
  - Seroma
- Any adverse events related to the breast reconstruction device/procedure, including red breast syndrome

An interim study analysis report for the Post-Approval Study would be made available at 50% subject completion.

13 BENEFIT-RISK SUMMARY

This Advisory Committee is asked to discuss and then advise FDA on the specific questions of whether there is reasonable assurance that SurgiMend PRS Acellular Bovine Dermal Matrix is safe and effective, and whether the benefits outweigh the risks for the following indication for use:

> *SurgiMend PRS Acellular Bovine Dermal Matrix is intended for use as soft tissue support in post-mastectomy breast reconstruction. SurgiMend PRS Acellular Bovine Dermal Matrix is specifically indicated for: Immediate, two-stage, submuscular, alloplastic breast reconstruction.*

The totality of data presented in this Executive Summary provide extensive support that SurgiMend PRS Acellular Bovine Dermal Matrix is safe, effective, and that the benefits outweigh

the risks for its use in this specific type of breast reconstruction. First, this product is not a novel medical device that would be introduced for the first time for use in the practice-of-surgery by expert breast reconstruction surgeons. Under its current and longstanding availability in the US marketplace under 510(k) clearance granted by FDA, it has been extensively used by expert breast reconstruction surgeons at multiple institutions in the United States since its introduction in 2007. SurgiMend has been authorized for use in the European Union (EU), Canada, and South Korea. In the EU, SurgiMend PRS is specifically indicated for use in breast reconstruction.

Second, the pivotal clinical study (the SurgiMend Study) in support of this pending PMA, whose Statistical Analysis Plan was developed in collaboration with FDA, relies on contemporary surgical experience collected in the prospective observational MROC Study that was conducted at 11 institutions to systematically provide objective, up-to-date information on breast reconstruction outcomes from the patient's perspective and reliable information including efficacy and complication rates of surgical options for breast reconstruction for providers and policy-makers. As described in **Section 6.2** CDRH has been proactive in relying on the use of Real-World Data (RWD) for the development of Real-World Evidence (RWE) to support major regulatory decisions, including approval of new PMA submissions. Importantly, as discussed in this section, the RWD developed in the MROC Study and the subsequent rigorous process of data analysis and hypothesis testing for the SurgiMend Study meet the stringent criteria for *relevance* and *reliability* laid out in the current CDRH policy regarding the application of RWE for regulatory decision-making[18] and FDA has specifically explained that "the [MROC] data set, endpoints, and the number of SurgiMend patients would be sufficient to assess the safety and effectiveness of the subject device for the proposed intended use."[19]

Third, the SurgiMend Study relied on a formal Statistical Analysis Plan, with a prespecified hypothesis, that was developed in close collaboration with FDA before the FDA statistical group conducted the analyses. Furthermore, the primary endpoint hypothesis is based on the novel endpoint of Composite Clinical Success that addresses efficacy using the validated BREAST-Q module explicitly developed for breast reconstruction and safety based on the absence of one or more major post-operative complications identified in the MROC Study and a more rigorous and inclusive definition of major complications proposed by the FDA. The results, which are presented in detail in this Executive Summary, demonstrate that the use of SurgiMend is safe, effective and that the benefits outweigh the risk of the use of this product in the treatment of women with immediate, two-stage, submuscular, alloplastic breast reconstruction in the United States. These findings are supported by the analysis of published literature presented in this Executive Summary.

[18] Food and Drug Administration. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices *Guidance for Industry and Food and Drug Administration Staff.* August 2017 [Available from: https://www.fda.gov/media/99447/download

[19] Letter from William H. Maisel, MD – Director, CDRH/OPEQ to Integra (c/o Mark Brown. King & Spalding), dated January 17, 2019.

13.1 Reasonable Assurance of Safety for the Proposed Indication

From the pivotal clinical study presented in this Executive Summary, the proportion of subjects who experience one or more major complications for the propensity-adjusted populations is 33.7% for reconstructions with SurgiMend and 46.7% without the use of ADM, resulting in a 13.1% lower incidence of complications for the SurgiMend group. When elective revisions and wound infections treated with oral antibiotics are excluded, these rates are 17.7% (SurgiMend) and 22.5% (no ADM) with a 4.9% lower incidence for the SurgiMend group. The directional changes in the exploratory sensitivity analyses are consistent with the primary analysis for safety, which is based on the analysis of major complications that comprises a component of the primary composite endpoint. These results strongly suggest that complications were less frequent with SurgiMend than with no ADM in women undergoing implant-based two-stage subpectoral breast reconstruction

13.2 Reasonable Assurance of Effectiveness for the Proposed Indication

The pivotal study describes the benefit of SurgiMend in breast reconstruction compared to no ADM, as measured by the efficacy component of the composite primary endpoint. This pre-specified analysis of efficacy agreed upon with FDA is based on the comparison of each subject's score at year 1 after surgery compared with her preoperative baseline score on the Physical Well-Being domain of the BREAST-Q, a validated Patient-Reported Outcome (PRO) instrument specific to breast reconstruction. Following breast reconstruction surgery, it is well established that a woman's perception of physical well-being is less favorable compared with her preoperative baseline. Because the minimally important difference (MID) is greater than 4 points from preoperative baseline, in this responder analysis "success" was defined as a score that was not more than 4 points lower one year after surgery compared to the preoperative baseline score. In the propensity-adjusted analysis, 44.5% of SurgiMend subjects and 39.1% of Control subjects achieved success at 1 year compared with baseline regarding the Physical Well-Being domain, indicative of the subject's perception of physical well-being at 1 year being restored to her perception of physical well-being prior to breast reconstruction. The scores at 1 and 2 years after breast reconstruction on other domains of the BREAST-Q instrument were prespecified as secondary endpoints and are presented in this Executive Summary. These domains include: Physical Well-Being (chest); Satisfaction with Breast; Psychosocial Well-Being, Sexual Well-Being, and Satisfaction with Outcome. The results of the SurgiMend and Control subjects at 1 and 2 years after breast reconstruction were highly similar with none of the analyses showing a nominal difference between the groups or a difference between the groups that met the Minimal Important Difference (MID) for any of these domains.

Taken together, these data suggest that patient perception of post-operative effectiveness is comparable between patients treated with SurgiMend or no ADM for the proposed specific indication for use.

13.3 Benefits and Risks for the Proposed Indication

The prespecified primary endpoint of the SurgiMend Study developed in collaboration with FDA is a responder analysis of the composite endpoint: Composite Clinical Success. In this prespecified novel endpoint that is highly clinically relevant to contemporary breast reconstruction surgery, *the efficacy and safety components are equally weighted*. Specifically, a subject is counted as a success only if she (1) meets the efficacy criterion for success at 1 year compared with preoperative baseline regarding the BREAST-Q Physical Well-Being (chest) domain AND (2) meets the safety criterion of absence of one or more postoperative major complications at 2 years, or at 1 year if 2 year data are not available.

- The primary endpoint analysis confirms the superiority hypothesis: a higher proportion of subjects in the SurgiMend group achieved Composite Clinical Success compared with subjects in the Control group (no ADM).
- The results of this analysis are supported by the directional changes that favor the SurgiMend Group compared with the Control group in the multiple sensitivity analyses that were prespecified in the Statistical Analysis Plan. In addition, a post hoc analysis was requested by FDA and agreed to by Integra that tested the primary endpoint superiority hypothesis in the two institutions in the MROC Study that used both SurgiMend and no ADM in for the proposed indication in this PMA. This post hoc analysis also provides support for the primary endpoint superiority hypothesis: a higher proportion of subjects in the SurgiMend group achieved Composite Clinical Success compared with subjects in the Control group (no ADM).

The probable benefits in comparison to the risks of the device are also based on data collected in the several published clinical studies to support PMA approval as described above. This body of published scientific literature supports high-levels of patient satisfaction, higher initial and final tissue expander fill volumes, shorter drain duration, and long-term mechanical stability associated with immediate, two-stage, submuscular, alloplastic breast reconstruction utilizing SurgiMend. Additionally, published literature consistently describes that patients were very satisfied with overall aesthetic outcomes with breast reconstruction that included the use of SurgiMend.

Additional factors to be considered in determining probable risks and benefits for the SurgiMend device include:

- Currently, there is not an FDA-approved biologically-derived material indicated for use as an adjunct in post-mastectomy alloplastic breast reconstruction although a matrix

is employed in an estimated 75% of breast reconstruction procedures in the United States.[20] SurgiMend has been employed in breast reconstruction procedures in the U.S. for over ten years in the practice of surgery.

- Implant-based breast reconstruction avoids mobilization of muscle flaps associated with autologous reconstruction that potentially exacerbates patient morbidity on top of traumatic mastectomy surgery. Implant-based sub pectoral reconstruction without an ADM is possible based on the clinical judgment of the surgeon. The use of SurgiMend PRS ABDM results in an increased number of patients with clinical success and may expand the populations of patient where implant-based subpectoral procedures can be performed.
- Patient perspectives considered during the design and conduct of the SurgiMend Study included patient-reported outcomes (PROs) pre- and post-operatively related to both the primary and secondary endpoints, demonstrating clinical benefit for the primary endpoint, relative to no ADM.

14 CONCLUSION

In conclusion, the totality of the available data – including relevant and reliable Real-World Evidence from the MROC Study measuring patient-reported outcomes, supplemented by substantial published clinical studies –support that there is reasonable assurance of safety and effectiveness for SurgiMend PRS Acellular Bovine Dermal Matrix (ABDM), and that the probable benefits outweigh the probable risks when this device is used for soft tissue support in immediate, two-stage, submuscular, alloplastic post-mastectomy breast reconstruction. The criteria for FDA approval of this use are thus satisfied.

SurgiMend PRS ABDM has been available in the U.S. for more than ten years for FDA-cleared indications and, during that time, has been, and continues to be, used by surgeons in the practice of medicine for the indication under review. Approval of Integra's PMA for SurgiMend PRS ABDM will ensure that the device's labeling addresses this clinically important indication, for which no ADM is currently labeled or approved. Approval should improve access and availability to this technology with important benefits for women's health. Approval will also ensure the continued generation of clinical evidence regarding this indication through the conduct of a required Post-Approval Study.

[20] American Society of Plastic Surgeons, *ADM Update: The use of acellular dermal matrices (ADMs)* August 26, 2019 https://www.plasticsurgery.org/for-medical-professionals/publications/psn-extra/news/adm-update-the-use-of-acellular-dermal-matrices

15 REFERENCES

Copies of all references cited in this document and listed below are provided in **Appendix 1**.

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