FDA Executive Summary

General and Plastic Surgery Devices Panel

October 20, 2021

Premarket Approval

P21XXXX

Integra LifeSciences Corporation

SurgiMend PRS Acellular Bovine Dermal Matrix

(SurgiMend PRS ABDM)

Food and Drug Administration

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List of Relevant Terms and Abbreviations

Abbreviation	Term/Meaning
510k	Premarket Notification
ADM	Acellular Dermal Matrix
ATE	Average Treatment Effect
ATT	Average Treatment Effect on the Treated
BREAST-Q	Patient-Reported Outcome (PRO) Instrument Used to Assess the Outcomes of Breast Surgeries Among Women
CCS	Composite Clinical Success
CI	Confidence Interval
IBBR	Implant Based Breast Reconstruction
IDE	Investigational Device Exemption
MDR	Medical Device Reporting
MROC	Mastectomy Reconstruction Outcomes Consortium
PMA	Premarket Application
PS	Propensity Score
SAP	Statistical Analysis Plan

List of Tables and Figures

1. Introduction

This is the Executive Summary for the Premarket Approval (PMA) application submitted by Integra LifeSciences Corporation for the SurgiMend PRS Acellular Bovine Dermal Matrix (SurgiMend PRS ABDM). SurgiMend PRS ABDM is primarily composed of intact, extracellular collagen fiber matrix of fetal bovine dermis and is being proposed to be indicated for use as soft tissue support in post-mastectomy breast reconstruction and specifically for: immediate, two-stage, submuscular, alloplastic breast reconstruction.

SurgiMend PRS ABDM has been reviewed by the Plastic Surgery Implant Devices Team of the Division of Infection Control and Plastic and Reconstructive Surgery Devices within the Center for Devices and Radiological Health of the Food and Drug Administration. This Executive Summary provides an overview of the information submitted by Integra in their PMA submission, as well as the rationale for bringing the subject device to the General and Plastic Surgery Devices Panel.

This document represents the summary by the FDA review team of the description, proposed indications for use, pre-clinical testing information, and clinical investigations of the subject device.

2. General Background

2.1 Implant-Based Breast reconstruction

Immediate, two-stage, submuscular, implant-based breast reconstruction is the creation of a breast mound using either a saline-filled or silicone gel-filled breast implant in patients who have undergone a mastectomy. There are two stages to this procedure. The first stage involves the placement of a temporary tissue expander beneath the pectoralis muscle. A surgical mesh can be used to support the tissue expander and is illustrated in Figure 1. Over the subsequent weeks to months, saline is injected into the port of the temporary tissue expander until the desired expansion is achieved and a second surgery is performed. In the second surgery, the surgeon removes the tissue expander (leaving the surgical mesh in place) and inserts a saline- or silicone gel-filled breast implant. The final stages of the reconstruction may involve additional procedures to reconstruct the nipple and areola. Note that there are other surgeries which may include use of a breast implant, such as breast augmentation or gender affirmation surgery. However, the proposed indications of this PMA include breast reconstruction following mastectomy, which is not performed in breast augmentation or gender affirmation surgeries.

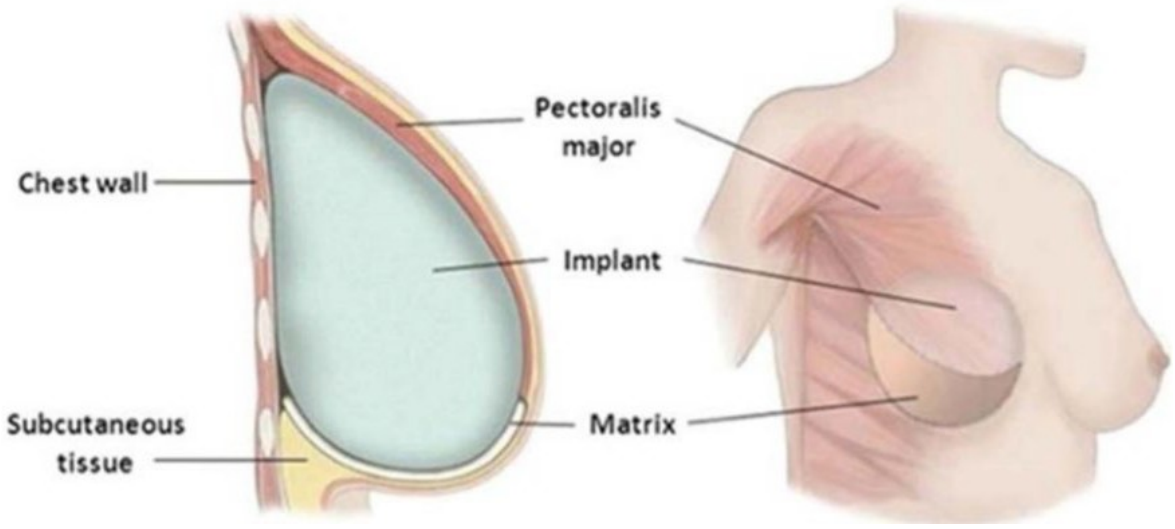

Figure 1: Breast Reconstruction using mesh and partial muscle coverage

2.1.1 Regulatory History of Surgical Mesh and Breast Reconstruction

Surgical mesh can be synthetic or biological. Synthetic surgical mesh is typically a woven or knitted implanted device composed of nonbiodegradable plastics such as polypropylene or polyester, or from biodegradable plastics such as Dexon or Vicryl. Biological meshes are biodegradable and are formed by processing and sterilizing human, cow, or pig tissue to remove cells, resulting in a collagen, acellular dermal matrix (ADM). In the past decade, surgeons have begun utilizing surgical mesh products to assist with these reconstructive procedures, and ADM mesh products are now used in the majority of implant-based breast reconstruction procedures in the United States (Sorkin et al., 2017).

However, the FDA has not cleared or approved any surgical mesh device – whether synthetic, animal collagen derived, or human collagen derived – specifically indicated for breast reconstruction.

2.2 Breast Implant Special Topics Panel Meeting

In March 2019, the FDA's General and Plastic Surgery Advisory Committee discussed the evidentiary requirements needed to assess surgical mesh benefit versus risk in breast reconstruction. Trial design considerations identified by FDA at the March 2019 Advisory Committee meeting as critical for assessing surgical mesh of device safety and effectiveness for breast reconstruction included:

- A comparison of patients treated with the subject device to a breast reconstruction control group that does not receive mesh.
- Assessment of the effectiveness of mesh for breast reconstruction compared to the no-mesh control in at least one effectiveness outcome assessing patient benefit.
- Inclusion and evaluation of relevant adverse events for both the treatment and control arms. These adverse events would be those that are reasonably likely to

occur with the combined use of a mesh implant immediately adjacent to a tissue expander or permanent breast prosthesis including but not limited to: hematoma, explantation, reoperation, capsular contracture, infection, dehiscence, tissue necrosis, implant rupture, seroma.

- An analysis comparing treatment and control on both a per-breast and per-patient basis, where feasible and appropriate.
- Pre-specified statistical analysis accounting for reasonably obtainable relevant confounding variables including but not limited to radiation, chemotherapy, patient demographics and medical history, type of reconstruction, type of mastectomy, type of breast implant.
- Premarket clinical follow-up to a minimum of 12 months post-implantation. If time to mesh resorption or time to quiescence of the inflammatory response of the tissue surrounding the mesh exceeds 12 months, then longer duration follow-up may be necessary. Post-market follow-up for longer term outcomes may be necessary.
- Evidence of a favorable benefit-risk profile for breast reconstruction with the subject device compared to breast reconstruction without the use of mesh.

2.3 Real-World Evidence

Real-world evidence[1] is clinical evidence regarding the use and potential benefits or risks of a medical product derived from analysis of real-world data. Real-world evidence can be generated by different study designs or analyses, including but not limited to, randomized trials, including large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective).

2.3.1 MROC Study Data Generated Real-World Evidence

The Mastectomy Reconstruction Outcomes Consortium (MROC) Study was a prospective, observational cohort study collecting data acquired during routine patient care and involved 11 centers, including nine academic hospitals, in the United States and Canada with high volumes of breast reconstruction. The MROC Study data contains the elements necessary to assess the benefit risk profile of ADM for breast reconstruction as discussed at 2019 Breast Implant Special Topics Panel Meeting (see section 2.2). Therefore, to understand the safety and performance of ADMs when used for implant-based breast reconstruction, FDA worked with the study sponsor to obtain access to deidentified, subject-level MROC study data.

FDA's analysis of the MROC dataset suggested that some ADMs have higher risk profiles than others, a trend also noted in multiple peer-reviewed publications. Concerns about the varying risk profiles among ADM products used without PMA

[1] In some cases, real-world evidence data gathering must be performed under an investigational device exemption (IDE). Additional guidance on real-world evidence and when an IDE may be needed for data collection on medical devices used in medical practice can be found at https://www.fda.gov/media/99447/download.

approval for breast reconstruction prompted release of a March 2021 Safety Communication by the FDA.

FDA Safety Communication: Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates

https://www.fda.gov/medical-devices/safety-communications/acellular-dermal-matrix-adm-products-used-implant-based-breast-reconstruction-differ-complication

2.3.2 Real-World Evidence to Support SurgiMend PRS ABDM PMA

The FDA supports the use of relevant and reliable real-world data for regulatory decisions. FDA conducted a preliminary assessment of the MROC study data regarding its potential relevance and reliability. This analysis concluded that the dataset was of sufficient quality to proceed with analyses of the prespecified outcomes and specific manufacturers' device performance. Because FDA has access to de-identified patient-level MROC study data, but the sponsor does not, FDA conducted an analysis of the data using a prospectively defined statistical analysis plan. Integra's PMA relies on this prospective analysis of existing observational study data to support a reasonable assurance of safety and effectiveness of the subject device (SurgiMend PRS ABDM).

A critical step in the ability to use the MROC study dataset was the prospective development of a statistical analysis plan (SAP) to compare SurgiMend vs No-Acellular Dermal Matrix (No-ADM) use in immediate, two-stage, submuscular implant-based breast reconstruction (IBBR) based on a subset of MROC study data. FDA worked with the sponsor to define and finalize an SAP while blinded to MROC study outcomes. FDA conducted the analysis as defined in the prospectively-defined SAP and wrote a Statistical Analysis Report summarizing the results, which was shared with Integra. Integra in turn included the study report in their PMA to support the safety and effectiveness of their subject device for the proposed indications for use as soft tissue support in post-mastectomy breast reconstruction and specifically indicated for: immediate, two-stage, submuscular, alloplastic breast reconstruction. This is the subject of this General and Plastic Surgery Advisory Committee meeting.

The study report is subject to limitations required to maintain patient confidentiality. Consistent with NIH and CMS practice, FDA applied a cell suppression whereby no values less than 11 were shared or otherwise reported. In addition, patient-level narratives and listings were not included in the report. Thus, use of the MROC dataset has inherent limitations that limit what can be shared with the sponsor and in this executive summary.

3. SurgiMend Background

3.1 Device Description

SurgiMend PRS ABDM is primarily composed of intact, extracellular collagen fiber matrix of fetal bovine dermis. Fetal bovine skins are mechanically stripped of

hair/epidermis and subcutaneous tissues, thereby isolating the dermis. The isolated dermis is decellularized through a series of chemical and physical processes that reduce the content of lipids, carbohydrates, and non-collagenous proteins; inactivate viruses; and reduce the antigenic components inherent to xenogeneic tissue. The decellularized dermis is then freeze-dried (lyophilized), selected for thickness (0.75 – 1.54mm), die-cut to shape (rectangles, semi-oval, slant-topped semi-oval), size (~96cm^2 to 225cm^2), and fenestrated. The 3mm slit fenestrations increase permeability of the product to facilitate body fluid egress and limit compartmentalization. The subject device does not have "sidedness" that requires orientation prior to use.

The device is supplied sterile with a shelf-life of 5 years, in uniform thickness, and in a variety of configurations and sizes to be trimmed by the surgeon to meet the individual patient's needs.

Table 1: SurgiMend PRS ABDM Configurations

Dimensions and Shape – All Fenestrated
SurgiMend PRS 7 x 17 cm Rectangle
SurgiMend PRS 10 x 20 cm Rectangle
SurgiMend PRS 8 x 20 cm Rectangle
SurgiMend PRS 10 x 15 cm Semi-Oval
SurgiMend PRS 8 x 16 cm Semi-Oval
SurgiMend PRS 15 x 15 cm Semi-Oval
SurgiMend PRS 6 x 16 cm Semi-Oval
SurgiMend PRS 7 x 17 cm Semi-Oval
SurgiMend PRS 10 x 15 cm Slant Semi-Oval

Figure 2: SurgiMend PRS ABDM 10 x 20 cm

3.2 Regulatory History

SurgiMend PRS Acellular Bovine Dermal Matrix, indicated for use in post-mastectomy breast reconstruction, has not been marketed in the United States or any foreign country. The sponsor (Integra LifeSciences Corporation) states that the device is the same as the SurgiMend device that was cleared under K071807 for plastic and reconstructive surgery on August 6, 2007 with different device configurations, sizes, and thickness and is legally marketed in the US as well as the EU, Canada, Colombia, Israel, Korea, Mexico, New Zealand, Panama, Peru and Thailand. To date, the sponsor states this SurgiMend device has not been withdrawn from marketing in any country for any reason related to the safety or effectiveness of the device.

3.2.1 SurgiMend Devices Available during MROC Study

While the sponsor believes that only devices cleared under K071807 were used in the MROC study based on marketing, there is no way to confirm this as fact based on the MROC dataset. Thus, FDA included a description of all SurgiMend devices that were available during the MROC study. There were two 510k cleared devices that were available between 2012 and 2015, which would align with the enrollment of patients into the MROC Study.

K071807: SurgiMend Collagen Matrix for Soft Tissue Reconstruction

Decision Date: 08/06/2007
Device Description: The device is an acellular dermal matrix derived from fetal bovine tissue.
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
- Reinforcement of soft tissues repaired by sutures or suture anchors, during tendon repair surgery, including reinforcement of the rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. SurgiMend is not intended to replace normal body structure or provide the full mechanical strength to support tendon repair of the rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. Sutures used to repair the tear and sutures or bone anchors used to attach the tissue to the bone provide biomechanical strength for tendon repair.

Table 2: SurgiMend (K071807) Fetal Product Line

Product Name	Thickness
Fetal	
SurgiMend PRS Fenestrated *	0.75-1.54mm
SurgiMend PRS Semi-Oval Fenestrated *	0.75-1.54mm
SurgiMend PRS Slant Semi-Oval Fenestrated *	0.75-1.54mm
SurgiMend 1.0 non-fenestrated	0.75-1.54mm
Thin Fetal	
SurgiMend Thin non-fenestrated	0.40-0.75mm
SurgiMend PRS Oval Fenestrated	0.40-1.00mm
SurgiMend PRS Thin Semi-Oval Fenestrated	0.40-0.75mm
SurgiMend PRS Thin Fenestrated	0.40-0.75mm

* indicates the device configurations of this PMA submission

K083898: SurgiMend Collagen Matrix for Soft Tissue Reconstruction

Decision Date: 02/04/2009
Device Description: The device is an acellular dermal matrix derived from neonatal bovine tissue.
Indications for Use: SurgiMend 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

Table 3: SurgiMend (K083898) Neonatal Product Line

Product Name	Thickness
Non-fenestrated Neonatal	
SurgiMend 2.0	1.30-2.50mm
SurgiMend 3.0	2.50-3.80mm
SurgiMend 3.0 Ellipse	2.50-3.80mm
SurgiMend 4.0	3.30-4.40mm
SurgiMend 4.0 Ellipse	3.30-4.40mm
Fenestrated Neonatal	
SurgiMend 2.0 Semioval Fenestrated	1.30-2.50mm
SurgiMend 3.0 Fenestrated	2.50-3.80mm
SurgiMend 3.0 Ellipse Fenestrated	2.50-3.80mm
SurgiMend 4.0 Ellipse Fenestrated	3.30-4.40mm

3.3 Proposed Indications for Use

SurgiMend PRS Acellular Bovine Dermal Matrix is indicated 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.

4. Preclinical Testing

4.1 Biocompatibility Testing

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. Because the standards for biocompatibility testing have evolved since the clearance of SurgiMend under K071807, the sponsor of this PMA submission has opted to execute confirmatory biocompatibility tests to comply with the most current ISO 10993 revisions. The table below summarizes the biocompatibility testing for the final, finished, sterilized device. This testing is expected to be completed by February 2022.

Table 4: SurgiMend Biocompatibility Testing

Biological Effect per ISO 10993-1	Test Method
Cytotoxicity	ISO MEM elution with L-929 mouse fibroblast cells
Maximization Sensitization	ISO guinea pig maximization sensitization
Irritation/Intracutaneous Reactivity	ISO intracutaneous irritation – extract
Acute Systemic Toxicity	ISO acute systemic toxicity study in mice
Pyrogenicity	USP material-mediated rabbit pyrogen
Subacute Toxicity*	13 weeks – ISO systemic toxicity following subcutaneous implantation in rats
Subchronic Toxicity*	26 weeks – ISO systemic toxicity following subcutaneous implantation in rats
Genotoxicity*	Bacterial Reverse Mutation Study
	Mouse Lymphoma Assay (in vitro)*
	Mouse Peripheral Blood Micronucleus Study (in vivo)*
Implantation*	4 weeks – ISO subcutaneous implantation in rats*
Chronic Testing*	26 weeks – ISO systemic toxicity following subcutaneous implantation in rats
Carcinogenicity*	ISO 10993-18 chemical characterization - solvent and extraction condition verification

*Indicates these tests are not yet completed

4.2 Bench Testing

4.2.1 Performance Testing

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.

Table 5: Performance Testing of SurgiMend PRS ABDM Device

Test	Method
Peak Denaturation Temperature	ASTM E1356 Standard Test Method for Assignment of the Glass Transition Temperatures by Differential Scanning Calorimetry or Differential Thermal Analysis
Suture Pullout Strength	ASTM D638 Standard Test Method for Tensile Properties of Plastics
Tensile Strength	
Tensile Strain at Max Load	
Elastic Modulus (Tensile Stiffness)	
Hydration Rate	TEI method
Color and Appearance	Visual inspection
Thickness	Conventional thickness gauge or better
Continuity	Visual inspection
Bacterial Endotoxin	USP <85> Bacterial Endotoxins Test

4.2.2 Mechanical Compatibility Testing with Tissue Expanders and Breast Implants

Biocompatibility and performance testing are normally performed on the subject device alone. However, the subject device of this PMA is intended to be used in combination with two other devices – tissue expanders and breast implants. Biocompatibility and performance tests do not offer information on how the two devices (SurgiMend + Tissue Expander and SurgiMend + Breast Implant) can affect one another.

Thus, Integra has 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.

The devices to be used for testing include:

- Mentor Siltex Textured Tissue Expanders
  - Small and large tissue expanders will be tested
  - Small = 180 - 230cc
  - Large = 650 - 850cc
- Mentor MemoryGel Xtra Smooth Silicone-Filled Breast Implants

- Small and large breast implants will be tested
- Small = 180 - 235cc
- Large = 535 - 790cc

The soluble and insoluble fractions of the wear fluid will be chemically evaluated. Additionally, the surface properties and the tensile strength of the cycled devices will be evaluated. This testing is expected to be completed by March 2022.

1. Quasistatic testing will be used to assess the mechanical performance of the device (tissue expanders and breast implants) and coupled devices (tissue expander-ADM and breast implant-ADM) under compressive conditions to failure. This will include an assessment of the loads required to induce rupture and the resulting interactions between the device and the ADM. The forces will then be used to establish the condition under which to conduct fatigue testing.
2. Fatigue testing will be used to assess repeated compressive loading cycles on the mechanical performance of the device and device-ADM. This will include an assessment of the loads and cycles required to induce rupture and the resulting interactions between the device and the ADM. The devices will be inspected for abrasive damage and changes in failure mode as a result of ADM interactions.
3. The wear fluid (saline with bovine serum and antimicrobials) from fatigue testing will be separated into soluble and insoluble (particulate) fractions and subjected to particle analysis and chemical analysis to assess particles and chemicals developed as a result of fatigue testing. This will include comparing the results from the different study groups described in the test matrix for the fatigue test procedure.
4. The silicone devices and ADM used during fatigue testing will be subjected to microscopy and mechanical evaluation. This will include comparing the damage modes and mechanisms and mechanical performance of the devices and ADM from the different study groups described in the test matrix for the fatigue test procedure.

FDA Comment:

The sponsor performed, or plans to perform, non-clinical evaluations including biocompatibility and mechanical testing. In addition, clinical data were provided. The Advisory Committee will be asked to comment on whether additional animal studies are necessary to address the time course of product absorption and tissue response to the implanted device when used next to a tissue expander or breast implant.

The sponsor plans to perform mechanical compatibility testing with a textured tissue expander and a smooth breast implant device. The Advisory Committee will be asked to comment on whether additional non-clinical studies are necessary to evaluate mechanical compatibility of SurgiMend PRS ABDM with the existing range of tissue expander and breast implant devices.

5. Clinical Data

5.1 Background

The clinical study to support this PMA, referred to as the SurgiMend study in this summary, was an analysis of a subset of data from the existing MROC study data using a prospectively developed statistical analysis plan (SAP) to compare SurgiMend vs No-Acellular Dermal Matrix (No-ADM) in immediate, two-stage, submuscular, implant-based breast reconstruction (IBBR). Please refer to Section 2.3.2 for additional information related to how the MROC study data was used for the purposes of the SurgiMend study.

5.2 SurgiMend Study Statistical Analysis Plan

The SurgiMend study was an analysis of a subset of MROC study data using a prospectively developed analysis plan to compare SurgiMend vs No-Acellular Dermal Matrix (No-ADM) in immediate, two-stage, submuscular implant-based breast reconstruction (IBBR). The inclusion/exclusion criteria listed below were incorporated for subject selection from the raw MROC datasets, so that the treatment group would include only subjects who underwent immediate, two-stage submuscular IBBR with the use of SurgiMend, and the control group would include subjects who underwent immediate, two-stage submuscular IBBR with total submuscular coverage, i.e., no ADM.

Among 4306 MROC study subjects enrolled from January 2012 to February 2016, per the pre-specified inclusion/exclusion criteria, 1792 subjects were identified to have undergone immediate, two-stage submuscular IBBR, among which 987 subjects were treated with either SurgiMend or control No-ADM and were selected into the SurgiMend study. There were 119 subjects from 2 investigational sites in the treatment group (SurgiMend) and 868 subjects from 9 investigational sites in the control group (no-ADM).

5.2.1 Surgical Procedure

The surgical procedure was an immediate, two-stage, submuscular, implant-based breast reconstruction with SurgiMend ADM device or No ADM.

5.2.2 Inclusion/Exclusion Criteria

Inclusion criteria:

- Age ≥ 18 years
- Females
- First-time breast reconstruction at one of 11 consortium sites
- Immediate, two-stage, implant-based, submuscular, breast reconstructions after mastectomy
- Unilateral or bilateral reconstructions; includes women with mastectomy for cancer prophylaxis without history of breast cancer

Exclusion criteria:

- Elective reconstruction following complications of breast augmentation, mastopexy (breast lift), or breast reduction

- Procedures performed following previously failed attempts at breast reconstruction
- Flaps (autologous tissues)
- Combination of different ADMs
- Bilateral reconstruction with unilateral SurgiMend

5.2.3 Follow Up

Subjects with outcome data collected up to 2 years were included. The key timepoints are shown below in the tables summarizing safety and effectiveness.

5.2.4 Endpoints

Primary Endpoint

The pre-specified primary endpoint in this study was the composite clinical success (CCS). A subject achieves the composite clinical success if both of the following two criteria are satisfied:

1. An assessment of BREAST-Q Physical Well-Being, Chest score ≥ (-4) point change from baseline at 1-year post implant* AND
2. Absence of major complications through year 2 or through year 1 (if year 2 data are not available). Major complications include:
    - Hematoma
    - Explantation
    - Reoperation**
    - Capsular contracture
    - Infection
    - Dehiscence
    - Tissue necrosis
    - Implant rupture
    - Seroma

The CCS rate is the proportion of subjects with CCS.

*Given that the minimally important difference (MID) for the Physical Well-Being module is 4 points, therefore being within 4 points would be below the MID and consistent with return to baseline. (Voineskos et al. 2020) The selection of BREAST-Q Physical Well-Being, Chest score greater or equal to (-4) point of pre-operative score is based upon the idea that returning to pre-operative baseline would represent a successful reconstruction.

**After the finalization of the SAP and unblinding of the clinical outcome data, discussion regarding whether wound infections requiring oral antibiotics and elective revisions not due to complications should be considered major complications occurred. Consequently, additional analyses were performed such that wound infection requiring oral antibiotics and/or elective revisions were not considered

major complications. The corresponding results are presented in the Additional Analysis in Section 5.6.

Secondary Endpoints

The secondary endpoints included in the SAP included:

Change from baseline to each visit timepoint between the two treatment groups for the following endpoints:

- Satisfaction with Breasts (BREAST-Q)
- Psychosocial Well-Being (BREAST-Q)
- Sexual Well-Being (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)]
- Anxiety and depression [Patient Health Questionnaire (PHQ-9)]
- Anxiety and depression [Generalized Anxiety Disorder (GAD-7)]
- Sum of subject response to Physical Well-Being and Satisfaction with Breasts at 1-year timepoint

The number of subjects with change of ≥ (- 4) points from baseline for the following BREAST-Q modules (pre-op and post-op):

- Satisfaction with Breasts (BREAST-Q)
- Psychosocial Well-Being (BREAST-Q)
- Your Sexual Well-Being (BREAST-Q)

Difference between the two treatment groups at each visit timepoint for the following post-op BREAST-Q modules:

- Satisfaction with Outcome (BREAST-Q)
- Satisfaction with Care (BREAST-Q)
- Satisfaction with Nipple Reconstruction (BREAST-Q)

Safety Endpoints

The secondary safety endpoints included:

- Any adverse events (AEs) related to the breast reconstruction device/procedure, including red breast syndrome
- Major complications

5.3 Hypotheses and Statistical Analysis Methods

5.3.1 Hypotheses

The null and alternative hypotheses for the primary endpoint are

$$HH_0: PP_{tt} \leq PP_{cc} \quad vvvv. \quad HH_{aa}: PP_{tt} > PP_{cc}$$

where PP_{tt} and PP_{α} are the underlying CCS rates, which are the proportions of subjects with CCS, for SurgiMend and control groups respectively.

The hypothesis test for the primary endpoint was conducted using a Z test based on propensity score stratification based average treatment effect on the treated (ATT) at a two-sided significance level of 5%. Detailed information regarding ATT approach is provided later in Section 5.3.4.

No formal hypothesis tests were pre-specified for the safety endpoints or the secondary endpoints.

5.3.2 Analysis Population

The pre-specified primary analysis population was the Full Analysis Set (FAS), which included all subjects who enrolled into the study, provided informed consent, and received the study intervention. Therefore, 119 SurgiMend subjects and 868 control subjects were selected for inclusion into the SurgiMend study from the MROC dataset per the inclusion/exclusion criteria and were all included in the FAS. All the analyses in the PMA submission were performed on the FAS.

In addition, supportive analysis was planned per the SAP to be conducted based on the per-protocol (PP) analysis population, which would consist of all FAS subjects who complete required treatments and have no major protocol violations. However, this portion of the SAP could not be completed because this information was not available in the MROC dataset or it could not be shared in order to maintain patient confidentiality (please see Section 2.3.2 for additional information). Consequently, no PP analysis is reported.

5.3.3 Study Design with Propensity Score Stratification

The SurgiMend study was an analysis of a subset of data extracted from the existing MROC dataset using a prospectively developed analysis plan. Thus, there could be potential confounding due to unbalanced distributions of baseline covariates between the SurgiMend group and the control group. To reduce potential confounding, a propensity score-based stratification approach was used.

In conducting propensity score stratification, the propensity score, defined as the probability that a subject receives investigational device instead of the control given the subject's observed baseline confounders, is first estimated for every study subject. Then, all study subjects are ranked according to their estimated propensity scores and stratified into multiple strata accordingly. As subjects in each stratum have similar propensity scores, each stratum can be conceptualized as a quasi-RCT, and the observed covariates will be better balanced between the two study groups under the assumption that there are no unobserved confounders and the propensity score model has been correctly specified. For treatment effect estimation, at first, within each stratum, the treatment effect can be estimated through direct comparison between the two study groups. Then the stratum-specific estimates of treatment effect can be pooled across stratum to estimate the overall treatment effect.

For the SurgiMend study, a logistic main-effect only model was fitted to derive the estimated propensity scores (SurgiMend group vs. control group) without access to clinical outcome data. The following covariates were included in the propensity score model:

- Age
- Race (White vs. Non-white)*
- Body mass index (BMI)
- Smoking status (Never smoking vs. Ever smoking)
- Laterality (Unilateral vs. Bilateral)
- Breast cancer treatment (Yes vs. No)
- Breast cancer prophylaxis (Yes vs. No)
- Sentinel lymph node biopsy (SLNB) (Yes vs. No)
- Axillary lymph node dissection (ALND) with or without SLNB (Yes vs. No)
- Type of mastectomy (Nipple sparing vs. Simple or modified radical mastectomy)
- Neo-adjuvant chemotherapy (Yes vs. No)
- Adjuvant chemotherapy (Yes vs. No)
- Radiation (Yes vs. No)
- Charlson-Index (<= 1 vs. > 1)
- Implant Type (Silicone vs. Saline)
- Implant Size
- Employed full-time (Yes vs. No)
- Employed part-time (Yes vs. No)
- Homemaker (Yes vs. No)
- Marital status (Married vs. Not married)
- Advanced degree (Yes vs. No)

**Although Race was not pre-specified in the SAP for PS modeling, it may be an important covariate.*

The subjects were subsequently stratified into 5 strata according to the propensity score quintiles of the SurgiMend subjects. This allows each stratum to contain roughly an equal number of SurgiMend subjects (Table 6). In addition, the analyses presented in Appendix I show that there was acceptable overlap of propensity score distributions between the two study groups within each of the 5 strata and the covariate balance between the two study groups were acceptable after the propensity score stratification.

Table 6: Number of Subjects from the SurgiMend and Control Groups Within Each Propensity Score Stratum

Group	Propensity score stratum					
	1	**2**	**3**	**4**	**5**	**Total**
SurgiMend	23	24	24	24	24	119

Control	404	198	122	93	51	868

The PS study design was agreed to by the sponsor and FDA prior to the execution of the SAP. Subsequently, the clinical outcomes were unblinded and analyzed. The results of the analysis are presented in the subsequent sections based on this PS study design.

5.3.4 Analysis Methods

The primary effectiveness endpoint was reported based on the FAS. For the pre-specified primary analysis, the propensity score stratification method as described above was used to estimate the average treatment effect on the treated (ATT) using weights based on the number of SurgiMend treated subjects within each propensity score stratum (Yue et al. 2016), and the superiority hypothesis was tested through a comparison of two proportions via a Z-test based on the ATT approach at a two-sided significance level of 0.05. The pre-specified sensitivity analysis was conducted regarding CCS using the average treatment effect (ATE) approach in which the treatment effect (ATE) was estimated using weights based on the number of all subjects within each propensity score stratum (Yue et al. 2016).

To help understand the results in this PMA submission, the terms "ATT" and "ATE" are explained here; under the potential outcomes framework, every subject in the study population has two potential outcomes: one potential outcome under the treatment and one potential outcome under the control.

- **Average treatment effect on the treated (ATT):** the population average of treatment effect on those subjects who ultimately received the treatment, defined as the average of the difference between the potential outcome under the treatment and the potential outcome under the control across all subjects who ultimately received the treatment in the study population. For the SurgiMend study, the ATT was estimated as the weighted average of the five stratum-specific treatment effects between SurgiMend and control using weights based on the number of SurgiMend subjects within each propensity score stratum (Yue et al. 2016).
- **Average treatment effect (ATE):** the population average of treatment effect of moving an entire population from control to the treatment (Austin, 2011), defined as the average of the difference between the potential outcome under the treatment and the potential outcome under the control across all subjects in the study population. For the SurgiMend study, the ATE was estimated as the weighted average of the five stratum-specific treatment effects between the SurgiMend and control groups using weights based on the number of all subjects within each propensity score stratum (Yue et al. 2016).

The secondary endpoints and the safety endpoints were reported descriptively by treatment group based on the FAS. In the PMA submission, 95% confidence intervals (CIs) were reported for some secondary and safety endpoints. Please note that there

was no multiplicity adjustment for any of the confidence intervals for the safety endpoints and the secondary endpoints reported in Appendix II of this summary.

5.3.5 Handling of Missing Outcome Data

The SAP specified that multiple imputations would be used to handle missing data issues in the analyses of the primary and secondary endpoints with the propensity score stratification method.

5.4 Clinical Study Results

5.4.1 Patient Accounting

A total of 987 eligible subjects were identified from the raw MROC dataset and included in the clinical study, including 119 subjects from 2 investigational sites in the treatment group (SurgiMend) and 868 subjects from 9 investigational sites in the control group (No-ADM). The total number of treated breasts was 179 in SurgiMend Group and 1401 in Control group.

For the pre-specified primary analysis population, the Full Analysis Set (FAS) consisted of the 119 SurgiMend subjects and 868 control subjects selected into the SurgiMend study from the MROC dataset per the inclusion/exclusion criteria. All the analyses in the PMA submission were performed on the FAS.

5.4.2 Data Missing Rates

In the MROC dataset, there are missing data for the primary endpoint CCS and secondary endpoints. Different missing data handling methods were used for different endpoints. The data missing rates and missing data handling methods for the primary and secondary endpoints are summarized in Table 7 below.

Table 7. Data Missing Rates and Missing Data Handling Methods for the Primary and Secondary Endpoints

Endpoints	Data Missing Rate						Missing Data Handling Method
	Month 3		Year 1		Year 2		
	SurgiMend %	Control %	SurgiMend %	Control %	SurgiMend %	Control %	
Primary Endpoint and Its Components:							
CCS	SurgiMend: 23.5% vs. Control: 25.7%						Multiple Imputation
BREAST-Q Physical Well-Being, Chest	21.8	31.7	34.5	44.1	58.0	62.9	Multiple Imputation
Freedom from Major Complications			0.8	2.3	23.5	16.5	Imputed as No Major complications
Secondary Effectiveness Endpoints							
BREAST-Q**							
Satisfaction with Breast	+	+	37.0	45.5	58.8	63.9	Multiple Imputation
Psychosocial Well-Being	20.2	31.1	37.0	43.5	59.7	62.6	Multiple Imputation
Sexual Well-Being	19.3	30.6	37.0	43.9	58.0	62.8	Multiple Imputation
Satisfaction with Outcome	+	+	37.0	41.9	58.0	61.6	Complete Case Analysis*
Satisfaction with Nipple Reconstruction							
How nipple looks	+	+	93.3	91.7	89.1	88.5	Complete Case Analysis*
How nature nipple loos	+	+	93.3	91.5	89.9	88.1	Complete Case Analysis*
Numerical Pain Rating Scale NPRS	26.9	36.1	37.0	42.3	62.2	63.7	Multiple Imputation
McGill Pain Questionnaire MPQ	36.1	42.5	51.3	53.6	68.9	68.7	Complete Case Analysis*
Quality of life (EORTC)							
Body Image	22.7	32.9	39.5	44.1	61.3	63.1	Complete Case Analysis*
Sexual Functioning	21.0	33.6	38.7	43.8	59.7	63.2	Complete Case Analysis*
Sexual Enjoyment	50.4	62.9	68.1	68.5	74.8	78.8	Complete Case Analysis*
Future Perspective	23.5	33.9	42.9	44.9	63.0	63.6	Complete Case Analysis*
Systemic therapy side effect	20.2	32.0	37.0	42.9	59.7	62.7	Complete Case Analysis*
Breast Symptoms	20.2	32.1	37.8	43.0	58.8	62.7	Complete Case Analysis*
Arm Symptoms	20.2	32.4	37.8	43.1	58.8	63.0	Complete Case Analysis*
Upset by hair loss	79.8	88.1	86.6	90.8	100.0	100.0	Complete Case Analysis*
Fatigue [Brief Fatigue Inventory (BFI)]	18.5	31.3	36.1	42.2	58.0	62.3	Complete Case Analysis*
General health [Patient-Reported Outcomes Measurement Information System (PROMIS)]							
Physical Function	19.3	32.0	37.0	41.1	58.8	62.7	Complete Case Analysis
Anxiety	19.3	32.1	37.0	42.7	58.8	62.7	Complete Case Analysis
Depression	19.3	32.4	37.0	42.7	58.8	62.7	Complete Case Analysis
Fatigue	19.3	41.1	38.7	45.2	59.7	63.8	Complete Case Analysis
Sleep	19.3	32.5	37.0	43.0	58.8	62.6	Complete Case Analysis
Social Functioning	19.3	32.6	37.0	43.3	58.8	62.6	Complete Case Analysis
Pain	19.3	32.7	37.0	43.3	58.8	62.7	Complete Case Analysis
Anxiety and depression [Patient Health Questionnaire (PHQ-9)]	18.5	32.0	35.3	41.5	58.0	62.6	Complete Case Analysis*
Anxiety and depression [Generalized Anxiety Disorder (GAD-7)]	18.5	32.3	35.3	41.4	58.0	62.7	Complete Case Analysis*
Safety Endpoints:							
Major Complication			0.8	2.3	23.5	16.5	Imputed as No Major complications

+: Data were not collected

*For scales with multiple items, if more than half of the items are missing, the subject is considered missing and is excluded from the analysis; otherwise, each missing item was imputed by the mean of the observed data.

**Secondary endpoint of BREAST-Q Satisfaction with Care was not reported in the PMA.

5.4.3 Demographics

Subjects' demographics and clinical characteristics prior to their first surgery (baseline) are summarized in Table 8 (per patient) and Table 9 (per breast) below. As shown, demographic, clinical, and operative characteristics were generally comparable between treatment groups. Over 80% of the information regarding breast implant manufacturer is missing. Reported brands include Allergan and Mentor. Please note that based on NIH and CMS standards (outlined in Section 2.3.2), any cells containing values <11 are not shown in the table below.

Table 8: Baseline demographic, clinical, and operative characteristics of the FAS (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 Other	99 (83.2%)	738 (85.0%)	837 (84.8%)
	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%)
Retired/Other	20 (16.8%)	144 (16.6%)	164 (16.6%)
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:			
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%)

Characteristic	SurgiMend N = 119	Control N = 868	Total N = 987
SLNB			
Yes	67 (56.3%)	493 (56.8%)	560 (56.7%)
No	52 (43.7%)	375 (43.2%)	427 (43.3%)
ALND with or without SLNB			
Yes	29 (24.4%)	290 (33.4%)	319 (32.3%)
No	90 (75.6%)	578 (66.6%)	668 (67.7%)
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 9: 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			
No	104 (58.1%)	816 (58.2%)	660 (47.1%)
	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%)
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.

5.4.4 Primary Endpoint Results

As outlined in Section 5.2.4, the pre-specified primary endpoint in this study was the composite clinical success (CCS). A subject achieves the composite clinical success if both of the following two criteria are satisfied:

1. An assessment of BREAST-Q Physical Well-Being, Chest score ≥ (-4) point change from baseline at 1-year post implant

2. An absence of major complications through year 2 or through year 1 (if year 2 data are not available).

Clinical Composite Success (CCS) – Data Accountability

The data accountability of the primary endpoint, CCS, is summarized in Table 10 below. The data missing rate for the primary CCS was 25%. Regarding 1-year change from baseline in Breast Q Physical Well-Being, Chest score, 37% of SurgiMend subjects and 47% of control subjects had missing data. In addition, 1 SurgiMend subject and 20 control subjects were missing major complication data.

Table 10. Primary Endpoint CCS – Data Accountability

	Accountability	SurgiMend (N=119) n (%)	Control (N=868) n (%)	Total (N=987) n (%)
CCS	Evaluable	91 (76.5%)	645 (74.3%)	736 (74.6%)
	Missing	28 (23.5%)	223 (25.7%)	251 (25.4%)
Change of BREAST-Q Physical Well-Being, Chest Score from Baseline at Year 1	Evaluable	75 (63.0%)	460 (53.0%)	535 (54.2%)
	Missing	44 (37.0%)	408 (47.0%)	452 (45.8%)
Major Complication at Year 2, or Year 1 if Year 2 data not available	Evaluable	118 (99.2%)	848 (97.7%)	966 (97.9%)
	Missing	1 (0.8%)	20 (2.3%)	21 (2.1%)

Clinical Composite Success (CCS) – Descriptive Results based on Observed Data

The observed results of the primary endpoint, CCS, are summarized below in Table 11. Please note that the results reported in this section are based on completers and no missing CCS data were imputed. Among 119 SurgiMend subjects and 868 control subjects included in the FAS, 91 (76.5%) SurgiMend subjects and 645 (74.3%) control subjects had evaluable primary endpoint data**. The observed CCS rate, which is the proportion of subjects achieving composite clinical success, was 29.7% for the SurgiMend group and 17.7% for the control group. Within each of the five strata, the observed CCS rate was higher in the SurgiMend group compared to the control group.**

Table 11: Descriptive Results of Primary Endpoint CCS – Observed Data

Stratum Index	Number of Subjects (Completers)			Estimate (Observed Data)		
	SurgiMend	Control	Total	SurgiMend	Control	Difference
1	16	302	318	31.3%	18.9%	12.4%
2	17	146	163	23.5%	16.4%	7.1%
3	17	91	108	35.3%	18.7%	16.6%
4	19	69	88	21.1%	18.8%	2.2%
5	22	37	59	36.4%	8.1%	28.3%
Total	**91**	**645**	**736**	**29.7%**	**17.7%**	

Clinical Composite Success (CCS) – With Multiple Imputation and Propensity Score Stratification

Because the SurgiMend Analysis is based on real-world data from the MROC study, the dataset has some inherent limitations, and some information is missing. To address the existence of missing data, the SAP outlined a multiple imputation (MI) approach to impute missing data for the primary endpoint analysis. MI was used to handle the missing data under the assumption that data were missing at random. For the primary analysis of CCS, missing BREAST-Q Physical Well-Being, Chest score data were handled through multiple imputation, and the 21 subjects (SurgiMend=1 vs. No-ADM=20) with missing major complication data were imputed as having no major complications. The CCS results with implementation of propensity score stratification and multiple imputations are reported in Table 12 below.

Using the pre-specified primary ATT approach, the primary estimated CCS rate was 32.4% for the SurgiMend group and 21.1% for the control group. The estimated difference for CCS rate between the SurgiMend and control groups was 11.2% with a 95% confidence interval of (1.7%, 20.8%), excluding 0. **The CCS rate for SurgiMend group was statistically significantly higher than that for the control group with a two-sided p-value of 0.02.**

As a pre-specified sensitivity analysis of the primary endpoint CCS, the hypothesis test was conducted based on the ATE approach. As shown below, the estimated (ATE) CCS rate for the SurgiMend group was 32.4% and it was 22.3% for the control group. The estimated difference for CCS rate between SurgiMend and the control groups was 10.2% with a 95% confidence interval of (-1.1%, 21.4%) covering 0. **No statistically significant difference in the primary CCS rate was detected between the two study groups (two-sided p value = 0.08).**

Table 12: Primary Endpoint Results: CCS – Multiple Imputation

Stratum Index	Number of Subjects			Stratum Weight (ATT)	Stratum Weight (ATE)	Estimate (Multiple Imputation)			
	Surgi Mend	Control	Total			Surgi Mend	Control	Difference	
1	23	404	427	0.193	0.433	34.4 %	24.5%	9.9%	
2	24	198	222	0.202	0.225	28.7 %	20.2%	8.5%	
3	24	122	146	0.202	0.148	35.8 %	21.1%	14.7%	

4	24	93	117	0.202	0.119	22.8 %	22.6%	0.3%	
5	24	51	75	0.202	0.076	40.0 %	17.3%	22.7%	
PS-Adjusted Estimate						Surgi Mend	Control	Difference (95% CI)	P value
ATT (Primary Analysis)						32.4 %	21.1%	11.2% (1.7%, 20.8%)	0.02
ATE (Sensitivity Analysis)						32.4 %	22.3%	10.2% (-1.1%, 21.4%)	0.08

Primary Endpoint Conclusions: The overall data missing rate for the primary endpoint CCS was approximately 25%. With the pre-specified primary ATT analysis based on the imputed data, primary endpoint CCS rate was 32.4% for the SurgiMend group and 21.1% for the control group with a difference of 11.2%, which was statistically significantly higher in SurgiMend compared to the control with a two-sided p-value of 0.02. At the same time, the pre-specified sensitivity ATE analysis based on the imputed data was 32.4% for the SurgiMend group and 22.3% for the control group with a difference of 10.2%, which resulted in no statistically significant difference in the primary CCS rate between the two study groups (two-sided p value = 0.08).

Individual Components of CCS:

Table 13: Patient Success in Breast Q Physical Well-being, Chest as the effectiveness component of the CCS (Multiple Imputation)

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%)**

[1]Note the reported 95% CI are not based on pre-specified hypothesis test and without multiplicity adjustment.

[2]Please note the presented results are based on multiple imputation method to handle missing data. The data missing rate was 37% for the SurgiMend group and 47% for the control group.

Table 14: Proportion of Patients with Major Complications (All Elective Revisions and All Wound Infections considered as 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
33.6%	46.7%	-13.0% (-22.0%, -4.0%)	33.7%	46.7%	-13.1% (-22.5%, -3.7%)

[1]Note the reported 95% CI are not based on pre-specified hypothesis test and without multiplicity adjustment.
[2]Missing major complication data were imputed as no major complications.

5.4.5 Secondary Endpoints Results

As outlined in Section 5.2.4, analysis of secondary endpoints was pre-specified in the SAP. However, there were no pre-specified hypotheses, and interpretation of the data was difficult due to missing data, which was not uniform across all secondary endpoints. Thus, no conclusions can be drawn for this section. All of the relevant tables for secondary endpoints can be found in Appendix II.

5.4.6 Safety Results

To adequately understand the safety profile of SurgiMend compared to the no ADM control, descriptive statistics in each major complication category were compared for the Full Analysis Population shown below.

Table 15: Complications with SurgiMend or No ADM control 1- and 2-years Post-Operation

Complication*	Post-Op Year 1			Post-Op Year 2			Major Complications up to Post-Op 2 Years†		
	Surgi Mend	Control	Diff	Surgi Mend	Control	Diff	Surgi Mend	Control	Diff
Any major complication	38 (31.9%)	342 (39.4%)	-7.5%	N<11		-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<11			21 (17.7%)	201 (23.2%)	-5.5%
Hematoma	N<11		-1.5%	N<11	N<11	-0.3%	N<11		-1.8%
Explantation (including elective revisions)	14 (11.8%)	82 (9.5%)	2.3%	N<11		-2.1%	16 (13.5%)	106 (12.2%)	1.3%

Complication*	Post-Op Year 1			Post-Op Year 2			Major Complications up to Post-Op 2 Years†		
	Surgi Mend	Control	Diff	Surgi Mend	Control	Diff	Surgi Mend	Control	Diff
Removal due to Complications [a]	11 (9.2%)	59 (6.8%)	2.4%	N<11		-1.9%	11 (9.2%)	70 (8.1%)	1.1%
Elective removal [b]	N<11		-0.3%	N<11		-0.5%	N<11		-0.6%
Capsular contracture	N<11	N<11	-0.5%	N<11		-1.6%	N<11		-1.8%
Local moderate to severe capsular contracture	N<11	N<11	-0.5%	N<11		-1.6%	N<11		-1.8%
Revision procedure due to capsular contracture [c]	N<11	N<11	-0.1%	N<11	N<11	-0.1%	N<11	N<11	-0.2%
Infection	N<11		-4.2%	N<11	N<11	-1.1%	N<11		-4.8%
Wound infection requiring oral antibiotics	N<11		-2.7%	N<11	N<11	-0.4%	N<11		-3.0%
Wound infection requiring IV antibiotics	N<11		-1.3%	N<11	N<11	-0.5%	N<11		-1.7%
Wound infection requiring surgical or percutaneous drainage of abscess	N<11		0.4%	N<11	N<11	-0.1%	N<11		0.3%
Dehiscence	N<11		-1.4%	N<11	N<11	-0.1%	N<11		-1.5%
Implant leakage, rupture and/or deflation	N<11	N<11	0.2%	N<11	N<11	-0.1%	N<11	N<11	0.1%
Seroma	N<11		0.6%	N<11	N<11	-0.4%	N<11		0.4%
Tissue necrosis	N<11		-1.5%	N<11	N<11	0%	N<11		-1.5%
Local tissue necrosis [d]	N<11		-1.0%	N<11	N<11	0%	N<11		-1.0%
Revision procedure due to Necrosis [e]	N<11		1.1%	N<11	N<11	0%	N<11		1.1%

Complication*	Post-Op Year 1			Post-Op Year 2			Major Complications up to Post-Op 2 Years†		
	Surgi Mend	Control	Diff	Surgi Mend	Control	Diff	Surgi Mend	Control	Diff
Reoperation [f] (including elective revisions)	33 (27.7%)	256 (29.5%)	-1.8%	N<11		-6.5%	35 (29.4%)	322 (37.1%)	-7.7%
Reoperation [g] (excluding elective revisions	14 (11.8%)	74 (8.5%)	3.3%	N<11		3.1%	14 (11.8%)	94 (10.8%)	1.0%
Implant malposition requiring surgical correction	N<11		-0.1%	N<11	N<11	-0.4%	N<11	N<11	-0.5%
Secondary attempt at reconstruction	N<11		1.8%	N<11		-0.4%	N<11		1.3%
Revisions due to complications	14 (11.8%)	74 (8.5%)	3.3%	N<11		3.4%	14 (11.8%)	92 (10.6%)	1.2%
Elective revisions	22 (18.5%)	202 (23.3%)	-4.8%	N<11		-4.8%	27 (22.7%)	267 (30.8%)	-8.1%
Death	N<11	N<11	0.2%	N<11	N<11	0.7%	N<11	N<11	0.2%

Diff, difference; IV, intravenous; 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, postoperative Year 1 is used. Twenty-one subjects (20 Control and 1 SurgiMend) without complication data during the postoperative 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.

5.6 Additional Analysis

In addition to the analysis pre-specified in the SAP, additional analysis was conducted for the purposes of better understanding the benefits and risks of the SurgiMend device for the chosen proposed indications for use.

5.6.1 Additional Analysis with Modified Definition of Major Complications

The SAP specified that the primary endpoint CCS would include the absence of major complications. However, after finalization of the SAP and unblinding of the clinical outcome data (but prior to disclosure of any results to the sponsor), it was

determined that the FDA and the sponsor had not agreed whether elective revisions or wound infection requiring oral antibiotics would be considered major complications. Prior to the disclosure of results to the sponsor, it was agreed that major complications would include elective revisions and wound infection requiring oral antibiotics, which is a more conservative approach to assessing safety of a device. However, Integra requested additional analysis whereby wound infection requiring oral antibiotics and elective revisions would not be considered major complications. Consequently, a set of analyses were performed to compare the two study groups regarding the following 3 modified definitions of the primary CCS 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. Each modified definition is referred to as a modified CCS, which includes the absence of major complications. For each of these analyses, the same propensity score stratification approach and missing data handling strategy used in the primary CCS analysis were implemented. Please note all the 95% confidence intervals (CIs) reported in this section were without a multiplicity adjustment.

Analysis of Modified CCS #1: Wound Infections Requiring Oral Antibiotics Not Considered as Major Complications

With multiple imputation (MI), the ATT analysis results of modified CCS #1 when wound infections requiring oral antibiotics were not considered as major complications are summarized in Table 16. The estimated rate of modified CCS #1 was 32.4% for the SurgiMend group and 21.6% for the control group. The estimated difference for modified CCS #1 rate between the SurgiMend and control groups was 10.7% with corresponding 95% CI (1.1%, 20.3%). **When wound infections requiring oral antibiotics were not considered as major complications, with ATT approach and implementation of multiple imputation, the estimated rate for modified CCS #1 was higher in the SurgiMend group compared to the control group.**

Table 16. ATT Analysis of Modified CCS #1: Wound Infections Requiring Oral Antibiotics Were NOT Considered as Major Complications (MI)

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%)

*The reported 95% CI of Difference (SurgiMend-Control) is without multiplicity adjustment.

Analysis of Modified CCS #2: Elective Revisions Were Not Considered as Major Complications

With MI, the ATT analysis results of modified CCS #2 when elective revisions were not considered as major complications are summarized in Table 17. The estimated rate of modified CCS #2 was 38.3% for the SurgiMend group and 29.7% for the

control group. The estimated difference for modified CCS #2 rate between the SurgiMend and control groups was 8.6% with corresponding 95%CI (-1.6%, 18.8%). **When elective revisions were not considered as major complications, with ATT approach and implementation of multiple imputation, the estimated rate for modified CCS #2 was higher in the SurgiMend group compared to the control group.**

Table 17. ATT Analysis of Modified CCS #2: Elective Revisions Were NOT Considered as Major Complications (MI)

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%)

*The reported 95% CI of Difference (SurgiMend-Control) is without multiplicity adjustment.

Analysis of Modified CCS #3: Both Wound Infections Requiring Oral Antibiotics and Elective Revisions Were Not Considered as Major Complications

With MI, the ATT and ATE analysis results of modified CCS #3 when both wound infections requiring oral antibiotics and elective revisions were not considered as major complications are summarized in Table 18. With ATT approach, the estimated rate of modified CCS #3 was 40.0% for the SurgiMend group and 31.5% for the control group, and the estimated difference between the two study groups was 8.4% with 95% CI (-1.8%, 18.7%). With ATE approach, the estimated rate of modified CCS #3 was 40.1% for the SurgiMend group and 32.2% for the control group, and the estimated difference between the two study groups was 7.8% with 95% CI (-4.2%, 19.8%). **When both wound infections requiring oral antibiotics and elective revisions were not considered as major complications, with both ATT and ATE approaches and implementation of multiple imputation, the estimated rate for modified CCS #3 was higher in the SurgiMend group compared to the control group.**

Table 18. Analyses of Modified CCS #3: Both Wound Infections Requiring Oral Antibiotics and Elective Revisions Were NOT Considered as Major Complications (MI)

	SurgiMend (n=119)	Control (n=868)	Difference (95% CI)*
Unadjusted Estimates	40.0%	32.3%	7.6% (-2.3%, 17.6%)
PS-Adjusted Estimates (ATT)	40.0%	31.5%	8.4% (-1.8%, 18.7%)
PS-Adjusted Estimates (ATE)	40.1%	32.2%	7.8% (-4.2%, 19.8%)

*The reported 95% CI of Difference (SurgiMend-Control) is without multiplicity adjustment.

5.6.2 Analysis of SurgiMend and Control at Sites 1 and 9

The MROC study had 11 investigational sites. As a part of the agreement with the study sponsor, the sites and surgeons were deidentified. Thus, the sites have been numbered 1 through 11.

While MROC contained 11 sites, not all 11 sites treated subjects with SurgiMend or No ADM. Of the 11 sites, 9 treated subjects with No ADM and 2 sites treated subjects with SurgiMend. Thus, the pre-specified analysis in the SAP does not address site or surgeon variability. At the 2 sites that used SurgiMend (Sites #1 and #9), subjects with No ADM were also treated. Thus, FDA investigated the proportion of subjects with CCS at Sites #1 and #9 only in a post-hoc fashion.

Table 19: Primary Endpoint CCS Results for Sites #1 and #9 Only (MI)

	SurgiMend (N=119)	Control (N=150)	Difference (SE) (95% CI)
Observed*	29.7% (27/91)	14.5% (17/117)	15.1%
PS-Adjusted Estimates (ATT)	32.4%	12.9%	19.4% (5.7%) (8.3%, 30.5%)
PS-Adjusted Estimates (ATE)	32.9%	16.5%	16.4% (6.0%) (4.6%, 28.2%)

[1]Note the reported 95% CIs are not based on pre-specified hypothesis test and without multiplicity adjustment.
[2]Please note the presented results are based on multiple imputation method to handle missing data. The data missing rate was 23.5% for the SurgiMend group and 22% for the control group.
*Based on completers only. No missing data imputation.

Additional Analysis (Site #1 and #9) Conclusion: The overall data missing rate for the primary endpoint was approximately 22.7% for subjects at Sites 1 and 9. With multiple imputation, the estimated treatment effect regarding CCS rate was positive, favoring the SurgiMend group, with both ATT and ATE approaches for Sites 1 and 9 subjects only.

5.7 Limitations of Using MROC Dataset for SurgiMend Study

Unlike many PMA submissions, the sponsor of this PMA did not conduct the clinical trial used to support a reasonable assurance of safety and effectiveness of their subject device. Thus, there are inherent drawbacks of using data from the MROC Study, which was not designed to evaluate the safety and effectiveness of the SurgiMend PRS ABDM device. For example, one drawback to this method is that the MROC study did not collect data on the version of the products used (such as lot numbers, sizes, fenestration) which may be important when considering manufacturing or pre-clinical testing as part of the PMA review. Other considerations regarding the MROC study are as follows:

1. The MROC study was an observational, non-randomized study. The study results are prone to confounding bias. The SurgiMend study data were a subset of the MROC study data.
2. The propensity score study design is applied in the SurgiMend study to mitigate the biases caused by observed confounders; however, potential biases may remain due to unmeasured confounders.
3. Clinical site information is deidentified and surgeon level data were not provided. Therefore, the SurgiMend study could not take into account differences in region (i.e., United States and Canada sites), site to site variability, and surgeon performance.
4. There are missing data for the primary and secondary endpoints.
    - For the primary endpoint CCS, approximately 25% of data are missing. The Breast Q – Physical well-being, chest at year 1 had 44.1% missing data for No ADM control and 34.5% for SurgiMend group. The Breast Q – Physical well-being, chest at year 2 had 62.9% missing data for No ADM control and 58% for SurgiMend group.
    - For the secondary effectiveness endpoints, the data missing rates are above 35% at year 1, above 58% at year 2.
5. MROC followed patients for 2 years after tissue expander and SurgiMend placement. Thus, there is a lack of information on long-term AEs including cancer recurrence.
6. Limited information on adverse events, serious adverse events, and other adverse events (for example causes of death)
7. Limited information on patient accounting/disposition
8. Other information not provided in MROC dataset
    - Iteration of SurgiMend used in the MROC: type, number, size, thickness
    - Reasons for elective revision (the reoperation surgery is known but not the reason for reoperation)
    - Relationship of adverse events to device
    - Severity and seriousness of adverse events
    - Systemic symptoms such as rheumatological and neurological symptoms, etc.

6. Totality of Evidence

The MROC Study provided real-world evidence that could be used to demonstrate a reasonable assurance of safety and effectiveness of SurgiMend PRS ABDM for use in immediate, two-stage, submuscular, implant-based breast reconstruction. However, a clinical study is never perfect, regardless of its design, and the determination of whether SurgiMend PRS ABDM provides a reasonable assurance of safety and effectiveness should be based on the totality of evidence including post-market adverse events and literature. The use of real-world data does not alter the regulatory standard that a device must demonstrate a reasonable assurance of safety and effectiveness.

6.1 Post-Market Adverse Events for SurgiMend in Breast Surgeries

The MDR system provides FDA with timely information on medical device performance from patients, providers, and manufacturers. The FDA uses MDRs to monitor post-market device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of devices. While the MDR system is a valuable source of information, this passive surveillance system has limitations, including incomplete, inaccurate, untimely, unverified, or biased data in the reports.

An MDR search was performed for analysis of SurgiMend use in surgical procedures. The search produced 123 MDRs, which were individually reviewed. Of the 123 MDRs, 48 reports specifically mentioned use in breast surgeries, which are summarized below.

Table 20: Summary MDR of SurgiMend in Breast Surgeries

MDR Date Range	1/1/2007 – 8/16/2021
Total MDRs (Breast)	48
Total Reports: 48 Malfunction: 1 Serious Injury: 40 Other: 7 Death: 0 Reconstruction Surgery: 39 SurgiMend PRS:11 SurgiMend: 37	• 18 MDRs report immediate reconstruction with tissue expanders resulting in flu like symptoms and poor wound healing. The reports also included mention of pain, edema, redness, and dehiscence • 10 report infections including pseudomonas and gram negative. Of these 10 reports of infection 5 do not mention that a culture was performed and 5 report that a culture was obtained. • 7 report hypersensitivity and/or erythema and/or irritation • 5 are publications • 4 report seromas • 1 MDR reports multiple cases of Capsular Contracture over last 6 months and the physician has opted to stop using SurgiMend • 1 report of red breast • 1 report of a split breast with pus, no cultures obtained • 1 report of the SurgiMend tearing during implantation

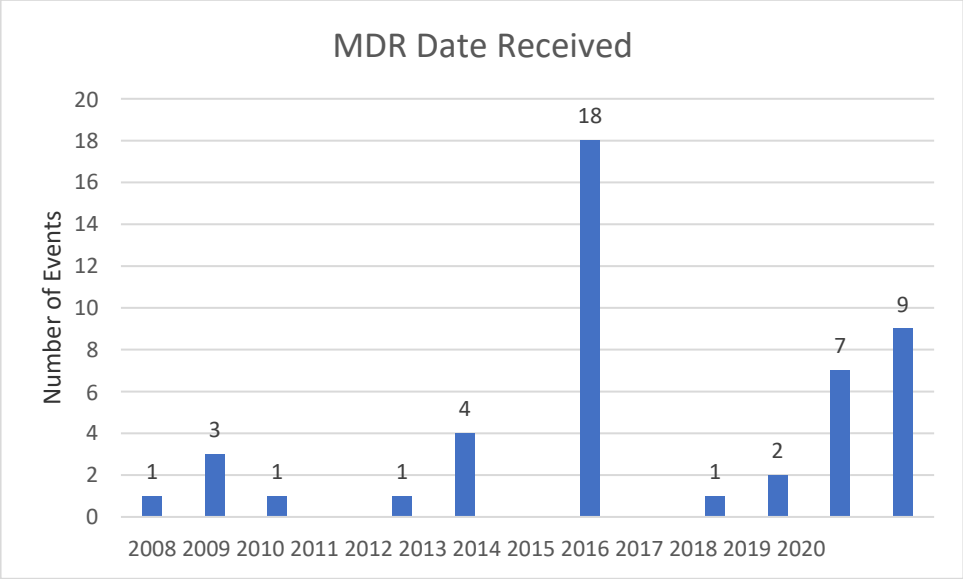

Table 21: Top 10 Patient and Device Problem Code in Breast Surgery MDRs

Patient Problem Code	Count	Device Problem Code	Count
Edema	19	Adverse Event Without Identified Device or Use Problem	19
Fever	19	Device Operates Differently Than Expected	19
Erythema	19	Insufficient Information	14
Pain	18	Melted	3
Impaired Healing	14	Appropriate Term/Code Not Available	3
Wound Dehiscence	11	Material Split, Cut or Torn	2
Unspecified Infection	10	Material Disintegration	2
Hypersensitivity/Allergic reaction	8	Unknown (for use when the device problem is not known)	1
Malaise	8	Therapeutic or Diagnostic Output Failure	1
Complaint, Ill-Defined	7	Device Appears to Trigger Rejection	1

6.2 Post-Market Adverse Events for SurgiMend in Other Surgeries

An MDR search was performed for analysis of SurgiMend use in surgical procedures. The search produced 123 MDRs, which were individually reviewed. Of the 123 MDRs, 48 reports mentioned use in breast surgery (Section 6.1), 41 reports mentioned use in hernia surgery and 34 reports mentioned bowel obstruction repair, abdominal repair, penile augmentations, or did not report a surgery type.

Table 22: Summary MDR of SurgiMend in Other Surgeries

MDR Date Range	1/1/2007 – 8/16/2021
Total MDRs	123
Hernia Surgery	

(41 reports)	
Total Reports: 41 Malfunction: 1 Serious Injury: 16 No Event Type: 2 Other: 22 Death: 0 SurgiMend MP: 1 SurgiMend: 40	• 10 report infections including MRSA • 3 report dehiscence • 3 report inflammatory syndrome • 1 reports pain • 3 report delayed wound healing • 12 report re-herniation, nine of the 12 describe failure of the SurgiMend through tearing or disintegrating • The remaining MDRs describe, "Pulling away from the suture, bowel injuries during the procedure, and pre-infected surgical sites where the SurgiMend disintegrated"
Bowel Obstruction Repair, Abdominal Repair, Penile Augmentations, or Surgery Not Reported (34 reports)	
Total Reports: 34 Malfunction: 10 Serious Injury: 5 Other: 19 Death: 1	• There is one death reported, a pediatric patient. SurgiMend was used to treat a complicated Gastroschisis with enterocutaneous fistula. It was noticed that 30 days post-op the product was attached to the wound bed. Treating physician believes the death was not related to the product. • 1 publication • 1 report of improper application of the device • 1 report of pulmonary edema • 1 report of implanting an expired device • 3 reports of re-hydration issues • 3 reports of device failure including tearing and foreign objects imbedded • 2 reports of dehiscence • Multiple reports of the device being used in procedures where the wounds were left open (infected) and the SurgiMend disintegrated.

6.3 Literature Review

AHRQ—(Agency for Healthcare Research and Quality)

In July 2021, AHRQ published results of a systematic review (SR) about surgical breast reconstruction options after mastectomy for breast cancer (or breast cancer prophylaxis). The SR addressed six Key Questions, one which was the use versus nonuse of human ADMs during IBR. The results showed that ADM use probably increases the risk of implant failure/loss or need for explant surgery and may increase the risk of infections not explicitly related to the implants or ADM. However, it was also noted that ADM use and nonuse groups probably experience comparable risks of seroma, unplanned repeat surgeries for revision, and risks of necrosis. The results were inconsistent regarding whether ADM use impacts physical well-being, psychosocial well-being, satisfaction with breasts, pain, or risks of wound dehiscence or capsular contracture. (https://effectivehealthcare.ahrq.gov/sites/default/files/cer-245-breast-reconstruction-after-mastectomy-evidence-summary_0.pdf)

6.3.1 Summary of Literature from Systematic Literature Review Performed by FDA

FDA performed a systematic literature review of ADM in breast reconstruction which showed scarce brand-specific safety information and the lack of evidence for improved safety in breast reconstructions with versus without ADM. As raised in the FDA communication (March 2021) there are varying complication rates in implant-based breast reconstructions using different ADM products per evidence from published literature and other sources.

Limitations affecting the literature analyses included small ADM brand specific subgroups and few Randomized Controlled Trials with the majority of published safety reports being based on retrospective chart reviews. Comparative safety analysis was limited by unaccounted differences in the ADM use (brand, matrix size and other processing/preparation factors such fenestration and meshing), as well as ADM-associated reconstructive techniques, outcome reporting, pre/postoperative care, and other patient/procedure-related factors.

As an example of limitations due to possible confounding effects, the predominant use of submuscular approach in SurgiMend-assisted breast reconstructions limits their safety analysis in comparison to other ADM-assisted reconstructions with different surgical approaches. Notwithstanding the limitations of the overall available evidence on ADM safety, the FDA's literature review of ADM safety revealed no major inconsistencies with the complication rates observed in the MROC Study.

7. Benefit/Risk Assessment

The evidence of clinical benefit of the SurgiMend device based on the SurgiMend analysis include:

- Favorable change in at least 1 clinical assessment that is equal to or greater than seen in the control group
- Meets a predetermined performance goal

The extent of uncertainty of benefits include:

- Subject lost-to-follow-up at critical assessment points(s)
- Missing data at critical assessment times +/- imputation
- Impact of confounding interventions or physiological factors
- Study design or results lead to lack of generalizability for the intended use population or specific clinical subpopulations

The extent of uncertainty of risks include:

- Low numbers of patients to detect serious events or false positives/false negatives
- Duration of follow-up to detect delayed/late events (1-2 years of follow up)
- Study assessed single use of the device (repeated use was not assessed)
- Missing data at critical assessment time(s) +/- imputation

- Limited details on Serious Adverse Events (SAEs) and severity and seriousness of Adverse Events (AEs)

It is unclear whether the data are sufficient to support conclusions regarding a reasonable assurance of safety and effectiveness for the proposed Indications for Use due to the following elements of uncertainty:

- The iteration of the SurgiMend device used in MROC is unknown and therefore cannot be extrapolated to a particular device.
- The SurgiMend Study was developed without prior knowledge of the MROC dataset. All of the desired outcome measures could not be completed. The MROC dataset did not contain information on other complications such as red breast syndrome, details of Serious Adverse Events (SAEs) such as death, severity of reported Adverse Events (AEs), relationship to device or procedure, the treatments or interventions for complications, the number of patients withdrawn or were discontinued, protocol deviations, and disposition of patients.
- Other data points missing include complete medical history, prior treatment, operative details, drain output/removal details, and concomitant therapies.

FDA Comment:

The Advisory Committee will be asked to comment on whether there is reasonable assurance that the SurgiMend PRS ABDM is safe for the proposed Indications for Use. If not, the Advisory Committee will be asked to explain the concerns and provide suggestions as to the best way to obtain additional safety data.

The Advisory Committee will be asked to comment on whether there is reasonable assurance that the SurgiMend PRS ABDM is effective for the proposed Indications for Use. If not, the Advisory Committee will be asked to explain the concerns and provide suggestions as to the best way to obtain additional effectiveness data. Additionally, they will be asked if an alternative indication could be justified based on the data provided.

The Advisory Committee will be asked whether the benefits of the SurgiMend PRS ABDM outweigh the risks for the proposed Indications for Use.

Proposed Indications for Use: SurgiMend PRS Acellular Bovine Dermal Matrix is indicated 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.

8. Post-Approval Study

Note: The inclusion of a Post-Approval Study (PAS) in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or

commitment does not alter the requirements for premarket approval and a recommendation from the Panel on whether the benefits of the device outweigh the risks. The pre-market data must reach the threshold for providing a reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered.

Integra has proposed the following outline for a potential PAS.

CLINICAL STUDY PLAN	
Title	Safety and Patient-Reported Outcomes of SurgiMend in immediate, two-stage, implant-based subpectoral breast reconstruction.
Short Title	Long-term follow-up of SurgiMend in subpectoral breast reconstruction
Reference	T-RESTOR-003
SPONSOR	
Name	Integra LifeSciences Corporation
Contact details	1100 Campus Road Princeton, NJ 08540 United States of America
PURPOSE/OBJECTIVE	
Primary Objective	The primary objective of this study is to evaluate safety signals arising from the use of SurgiMend in immediate, two-stage, implant-based subpectoral breast reconstruction procedures with the use of SurgiMend PRS.
Secondary Objective	The secondary objectives of this study are to record and assess specific outcomes measures (PROs) from the patient's point-of-view with the use of SurgiMend acellular dermal matrix in women undergoing first time breast reconstructions in an immediate, two-stage, implant-based subpectoral procedure.
STUDY DEVICE	
Name	SurgiMend PRS Acellular Bovine Dermal Matrix

<table>
<tr><td></td><td>
<table>
<tr><th>Dimensions and Shape – All Fenestrated</th><th>New SKU for Breast Recon (SurgiMend PRS ABDM)</th><th>Existing SKU (SurgiMend)</th></tr>
<tr><td>SurgiMend PRS 7 x 17 cm Rectangle</td><td>606-804-101</td><td>606-004-101</td></tr>
<tr><td>SurgiMend PRS 10 x 20 cm Rectangle</td><td>606-804-102</td><td>606-004-102</td></tr>
<tr><td>SurgiMend PRS 8 x 20 cm Rectangle</td><td>606-804-105</td><td>606-004-105</td></tr>
<tr><td>SurgiMend PRS 10 x 15 cm Semi-Oval</td><td>606-804-100</td><td>606-004-100</td></tr>
<tr><td>SurgiMend PRS 8 x 16 cm Semi-Oval</td><td>606-804-103</td><td>606-004-103</td></tr>
<tr><td>SurgiMend PRS 15 x 15 cm Semi-Oval</td><td>606-804-104</td><td>606-004-104</td></tr>
<tr><td>SurgiMend PRS 6 x 16 cm Semi-Oval</td><td>606-804-110</td><td>606-004-110</td></tr>
<tr><td>SurgiMend PRS 7 x 17 cm Semi-Oval</td><td>606-804-107</td><td>606-004-107</td></tr>
<tr><td>SurgiMend PRS 10 x 15 cm Slant Semi-Oval</td><td>606-804-106</td><td>606-004-106</td></tr>
</table>
</td></tr>
<tr><td colspan="2">CLINICAL STUDY POPULATION</td></tr>
<tr><td>Study Population</td><td>One-Hundred and Fifty (150) subjects in the United States will be recruited for this trial. All subjects will be undergoing primary breast reconstruction with SurgiMend acellular dermal matrix in immediate, two-stage, implant-based subpectoral breast reconstruction</td></tr>
<tr><td>Eligibility Criteria</td><td>Inclusion:
Age >=18 years
Females
Primary breast reconstruction
Immediate, two-stage, implant-based reconstructions after mastectomy.
Unilateral or bilateral reconstructions; includes women with mastectomy for cancer prophylaxis, without history of breast cancer.
Exclusion:
Elective reconstruction following complications of breast augmentation, mastopexy (breast lift), or breast reduction
Procedures performed following previously failed attempts at breast reconstruction.</td></tr>
<tr><td colspan="2">STUDY CENTERS</td></tr>
<tr><td>Number of Centers</td><td>Ten (10) to Twenty (20)</td></tr>
<tr><td>Location of Centers</td><td>United States (US); exact locations are to be determined.</td></tr>
<tr><td>Site Selection</td><td>Centers chosen for participation will be current users of SurgiMend in breast reconstruction procedures. Sites will be familiar with implanting acellular dermal matrices for immediate, two-stage</td></tr>
</table>

	implant-based post-mastectomy breast reconstruction in the subpectoral plane.
CLINICAL STUDY DESIGN	
Design	A prospective, multi-center, observational study to assess patient-reported outcomes and complications in mastectomy reconstruction utilizing SurgiMend acellular dermal matrix in women undergoing primary breast reconstructions in an immediate, two-stage, implant-based subpectoral procedure.
Primary Objective	The primary objective of this study is to evaluate safety signals arising from the use of SurgiMend in immediate, two-stage, implant-based subpectoral breast reconstruction procedures with the use of SurgiMend PRS.
Secondary Objective	The secondary objectives of this study are to record and assess specific outcomes measures from the patient's point-of-view with the use of SurgiMend acellular dermal matrix in women undergoing first time breast reconstructions in an immediate, two-stage, implant-based subpectoral procedure. PROs: • BREAST-Q Reconstruction module • Numerical Pain Rating Scale • McGill Pain Questionnaire
Follow-up visits	Complications, Adverse Events (AEs), and PROs will be assessed at Visit 0 (pre-op/index surgery), 1 week, 3 months, 1 year, 2 years, 3 years, 4 years, and 5 years. Timing is relative to the implantation of the SurgiMend. Due to the long-term nature of the study and the importance of obtaining long term follow-up data, the Sponsor will work with study centers to coordinate patient engagement and retention efforts. Centralized retention and engagement efforts will facilitate appropriate capture of product and procedure related complications and Patient Reported Outcomes.
Study Timeline	• Expected date of study initiation (i.e., subject enrollment): four (4) months after formal acceptance of final study design by FDA via PMA approval. • Post formal acceptance of final study design, it is expected that approximately three (3) sites will receive approval every two (2) months until the total number of investigative sites is reached • Expected duration of enrollment is 24 months after the first enrollment with 20% of patients (n=30) enrolled within the first 12 months of enrollment and 50% of patients (n=75) enrolled within the first 18 months of enrollment • Expected date of study follow-up completion is 60 months after the enrollment of the final patient. Total expected duration of enrollment and follow-up is 72 months

	• Expected date for Final Report submission is five (5) months from the study completion defined per the last subject's last follow-up date.
Outcome Measures	The intent of this observation study is to collect data on the outcome measures outlined by the visit structure specified above and throughout the follow-up period for each patient. Data will be collected per standard of care.

Safety Endpoints	Safety data will be collected per standard of care. However, this study specifically aims to collect data on the incidence and nature of adverse device effects with causal adjudication, including but not limited to:
	• Major complications
	  o Hematoma
	  o Explantation
	  o Reoperation
	  o Capsular contracture
	  o Infection
	  o Dehiscence
	  o Tissue necrosis
	  o Implant rupture
	• Any AEs related to the breast reconstruction device/procedure, including red breast syndrome

Patient-Reported Outcomes	PROs will be collected at post-operative visits described above: BREAST-Q Reconstruction Module: 1. Psychosocial Well-Being 2. Physical Well-Being 3. Sexual Well-Being 4. Satisfaction with Breasts 5. Satisfaction with Outcome Numerical Pain Rating Scale (NPRS) or McGill Pain Questionnaire (MPQ)
STATISTICAL PLAN	
Statistical Design	Statistical analysis of all endpoints will be descriptive
Interim Study Report	Interim Study Report at 50% subject completion

FDA Comment:

The Advisory Committee will be asked to comment on whether a post-approval study is needed for the SurgiMend PRS ABDM device.

If a post-approval study is needed the Advisory Committee will be asked to discuss whether the proposed post-approval study is acceptable. Alternatively, they will be asked for recommended changes to the proposed post-approval study.

9. *Appendix I*

Summary of Propensity Score Stratification in the SurgiMend Study

10. *Appendix II*

Summary of Secondary Endpoints

11. *Appendix III*

Statistical Analysis Report Delivered to Sponsor Following FDA Execution of SAP