FDA Report

A. *Description of the Product*

The product is a sheet of acellular dermal matrix (ADM) augmented with a hydrogel loaded with an antifibrotic and epithelial to mesenchymal transition targeting drug. The drug is pirfenidone, the hydrogel is polyethylene glycol (PEG), and the ADM is Allergen's AlloDerm SELECT™ Regenerative Tissue Matrix product. The drug is suspended in the PEG via cross-linking throughout the ADM sheet. This combination product can be cut and stitched together around any existing breast implant prior to insertion.

B. *Indications for Use*

In 2022, nearly 1.9 million breast augmentations were performed worldwide. In the US, more than 240,000 breast augmentations were performed in 2022 (International Society of Aesthetic Plastic Surgery), while over 157,000 breast reconstructions were performed in 2023 (American Society of Plastic Surgeons). Given the increase in breast cancer diagnoses, reconstruction surgeries are likely to increase along with the associated complications (Sharma). Among breast implant procedures, capsular contracture (CC) is the most common complication of breast reconstruction and augmentation surgery (Dancey et al.). CC is defined as "a tight or constricting scar tissue capsule forming around a [breast] implant, often distorting the breast shape and resulting in chronic pain" (Guimier et al.). CC is qualitatively evaluated into four tiers of severity based on the Baker Classification System (Spear and Baker):

Class I: Breast absolutely natural; no one could tell breast was augmented
Class II: Minimal contracture; surgeon can tell surgery was performed, but patient has no complaint
Class III: Moderate contracture; patient feels some firmness
Class IV: Severe contracture; obvious just from observation

Non-surgical treatments to reduce capsular contracture include physical massages to break up the capsule or injection of leukotriene/COX-2 inhibitors to suppress inflammation, however, these methods are considered an ineffective long term solution as the underlying causes of the capsule remain untreated (Hidalgo and Sinno). Grade III and IV cases often lead to patients undergoing a capsulectomy, the partial or total surgical removal of the capsule.

Incidence rates of CC vary widely, depending on numerous risk factors, including radiation therapy. Notably, capsular contracture rates after mastectomy and breast reconstruction can reach as high as 48% (Vinsensia et al.) with recurrence rates in capsulectomy patients as high as 53% (Hester et al.). Given the lack of effective, long term treatments and high rates of capsular contracture for this patient population, our product is indicated for use in patients aged 18 to 65 years old undergoing immediate, direct-to-implant breast reconstruction, particularly amid radiation therapy.

C. *Intended Use*

The product is designed to be used in tandem with the patient's chosen breast implant and is intended for use in patients undergoing immediate breast reconstruction post-mastectomy. Before or during reconstruction, the product is to be cut to the desired geometry by the surgeon and sutured together to cover the entire surface of the breast implant prior to insertion.

D. *FDA Classification*

The product is a "single-entity" combination product of a drug, hydrogel, and ADM. While structural hydrogels fall under 878.3300 as a Class II surgical mesh and hydrogels without other components fall under 878.4022 as Class I burn or wound dressings, the hydrogel here is primarily a carrier for the drug. The ADM is human tissue governed by 21 CFR Part 1271 (Allergen). The FDA's Office of Combination Products directs combination products for review based on their "primary mode of action" (US Food and Drug Administration). This product's novel and primary mode of action is the drug, with the hydrogel and ADM serving the secondary functions of drug-carrier and cell scaffold for tissue integration. As such, it will likely be directed to the Center for Drug Evaluation and Research.

While the product is most properly considered a combination drug/biologic, it could be considered a medical device due to its application alongside breast implants. By this reasoning, it would constitute a Class III device because saline and gel-filled silicone breast prostheses are classified as Class III devices under 21 CFR 878.3530 and 3540 respectively (Code of Federal Regulations).

E. *Preclinical Tests*

Preclinical tests including mechanical/material characterization, drug loading kinetics, biocompatibility, and effectiveness in animal models will ensure our PEG/ADM composite loaded with pirfenidone is ready for safe and effective clinical trials.

a. Laboratory Functional Tests

Mechanical Tests: To confirm the effectiveness of the production of the PEG/ADM composite and ensure its stability, the extent of PEG crosslinking within the ADM structure will be evaluated using equilibrium swelling assays, per FDA guidelines (Food and Drug Administration). Additionally, SEM imaging will characterize pore size distributions of the ADM/PEG composites, aiming to obtain effective pore sizing around ~80-100 μm known to support tissue integration and drug diffusion (Chen, Y et al) (Dagalakis, N. et al). To ensure the PEG/ADM composite withstands the implant site's mechanical environment, fatigue rupture testing will be conducted under cyclic loading conditions mimicking in vivo stresses, targeting >6 million cycles without failure. Finally, shelf life testing will use both real-time and accelerated aging methods to assess changes in structural and chemical integrity of the medical device over time in accordance with ISO 10993-18 (Food and Drug Administration).

Drug Loading Performance Tests: The release kinetics of pirfenidone from the ADM/PEG composite will be assessed in vitro with high-performance liquid chromatography (HPLC), where samples will be incubated in a physiological buffer at 37°C, and pirfenidone concentrations will be measured over a 2-week to 1-month period (Meng and Xu). The goal is a controlled release profile that addresses early inflammation post-implantation, maintains therapeutic levels throughout the healing period of ~1 month, and mitigates significant systemic side effects (Fayzullin et al.).

b. Biological Safety Tests

Pharmacokinetics and Toxicology: To assess the safety of our pirfenidone-loaded PEG/ADM composite, a worst-case pharmacokinetic scenario will be modeled in which the entire pirfenidone load is assumed to be immediately absorbed (Food and Drug Administration, ISO 10993-17). Estimated blood concentrations will be compared to the FDA-approved therapeutic and toxic thresholds for pirfenidone: the standard oral therapeutic dose is 2403 mg/day in adults with idiopathic pulmonary fibrosis (Genentech, Inc.). In vivo pharmacokinetic studies on Sprague-Dawley rat models will evaluate the

actual absorption, distribution, metabolism, and excretion of pirfenidone delivered via the ADM/PEG matrix, which will help determine whether local delivery effectively minimizes systemic exposure compared to oral administration. Toxicological testing will include evaluations for cytotoxicity, sensitization, irritation, acute systemic toxicity, and genotoxicity effects, following ISO 10993-2,3,5,6,10,11,13,16 standards (FDA, 2024).

c. *Efficacy Testing in Animals*

A rodent submuscular implant model using Sprague-Dawley rats will simulate the human post-mastectomy setting. Sprague-Dawley rats will be used for pharmacokinetic and efficacy testing due to their larger body size, which allows implantation of miniaturized silicone-filled hemispherical prostheses mimicking breast implants, and because of their established use in fibrosis and capsular contracture studies (Fischer et al., di Pompeo et al.). Four groups will be tested: (1) ADM alone, (2) ADM with oral pirfenidone, (3) ADM/PEG without drug, and (4) ADM/PEG with pirfenidone. Half of each group will receive localized radiation, and after one month, peri-implant tissue will be harvested (ISO 10993-2). Regular blood tests will be performed daily during the first week and weekly thereafter to monitor systemic pirfenidone levels and ensure consistent release and metabolism across animals. Histological analysis with H&E and Masson's trichrome staining will assess capsule thickness, collagen content, and remaining ADM/PEG left after one month (ISO 10993-6,10). Additionally, TGF-β1 and α-SMA levels will be evaluated by immunohistochemistry to identify the signs of EMT and onset of capsular contracture, and immune response will be quantified via CD3+ and CD68+ staining (Gancedo, M., et al.). We expect to see the ADM/PEG+ pirfenidone group to show the least fibrosis and inflammation, motivating clinical trials in humans.

F. Clinical Tests

A core study will test the product's safety and effectiveness for immediate, direct-to-implant breast reconstructions with two treatment groups: (1) ADM alone, and (2) ADM/PEG composite with pirfenidone.

a. Patient Population

Inclusion criteria: Female, between 18 and 65, English-speaking

Exclusion criteria: To accommodate surgeon preferences and multi-site implementation, high risk cases other than radiation will be excluded: active smoker; anticoagulant use;

medical conditions including obesity, diabetes, hypertension, autoimmune disease, active infection, and other cardiac and pulmonary comorbidities (Matkin et al.; Roubaud et al.; Nahabet and Crisera)

b. Controls

Patients will be stratified based on laterality and location performing the surgery (ensuring rough balance among sites), then randomized into a treatment group. Patients and clinical evaluators assessing postoperative complications will be blinded. Surgeons will not be blinded, as surgical preparation for treatment groups may differ.

c. Outcome Variables to be Measured

Timeframe: Study outcomes will be evaluated through clinical assessments performed after 2 months, then after 1, 2, 4, 6, 8, and 10 years. The primary study outcome is the number of reoperations after 2 years. Secondary outcomes are patient satisfaction and quality of life (QOL).

Safety Assessment: The clinical assessments will track at each time frame the number of reoperations and patient complications, including but not limited to rupture, capsular contracture (grades II-IV), malposition, asymmetry, changes in nipple/breast sensation, and others listed by the FDA's guidance on breast implant-related testing (Food and Drug Administration). Odds ratio analysis with confidence intervals will be applied to check for a statistically significant difference in reoperations rates between the two study arms (Bennett et al.). The study will record cumulative incidences of each complication by assessment and cohort and report Kaplan-Meier rates on reoperation, implant rotation, rupture, capsular contraction (grade III-IV), and explantation. To identify correlations of outcomes with demographics and procedural variations, the study will assess patient variables against each complication with logistic regression.

Effectiveness Assessment: Patient satisfaction and QOL can be measured with BREAST-Q Version 2.0, a self-administered, pre/post-op questionnaire that was developed to evaluate patient reported outcomes (PROs) for breast surgery patients. In 2018, the FDA approved four scales (Satisfaction with Breasts, Physical Well-being (Chest), Psychosocial Well-being, Sexual Well-being) within the breast reconstruction module to "support the effectiveness of breast reconstruction related medical devices, such as an implant or mesh" (QPortfolio). Responses for each scale are summed and

transformed onto a range from 0-100 based on the Rasch model, which provides transformation of ordinal scores into linear, interval-level variables (Pusic et al.; Tennant and Conaghan). These scales have been used to parametrically calculate mean shifts, both pre-/post-operatively (Amy et al.; Coriddi et al.; Romanoff et al.; Zhong et al.; Howes et al.), across surgery types and methods (Kazzazi et al.), and against published normative data (Oemrawsingh et al.), where the threshold is either statistical significance or a study-defined effect size of clinical relevance. When response data are not normally distributed, log-transformation can normalize right-skew (Oemrawsingh et al.) or non-parametric tests can be applied, such as a McNemar's test on score quartiles (Shamsunder et al.) or a Kruskal-Wallis test on score medians (Tomita et al.; Kazzazi et al.). Use of BREAST-Q is subject to a license, which is free to non-profit users.

d. Sample Size

Given the novelty of locally delivering pirfenidone from an ADM/PEG composite, it is difficult to defensibly quantify the expectation of improvement in reoperation rates. Therefore, sample size was estimated to enable detection of clinically relevant change in PROs via t-test, emulating Zhong et al.'s statistical analysis plan for their clinical trial on the use of ADM in breast reconstruction. Following the clinically applied guideline from BREAST-Q developers, the minimal important difference in score is defined by half a standard deviation, where normative data from field-testing gives σ =20 points or less for the four relevant scales (Cano et al.; Zhong et al.; Mundy et al.; Howes et al.). We chose type I error = 0.05 and type II error = 0.15, which is within the general standards for clinical trials (Winter and Pugh). Based on the two-tailed t-test, the equations below yield a sample size of 72 patients per treatment group. After conservatively estimating the 10-year sample loss to be 45% based on 59% loss-to-follow-up rates in other 10-year studies (Caplin), the initial target sample size is 131 per treatment group, or 262 total.

For safety assessment, this size can determine the rate of reoperation in the first 2 years to +/-7.7% precision at 95% confidence, given a baseline 33% rate from the literature (Lohmander et al.). Based on this size, a 23% difference in rates of reoperation is the minimum for statistically significant improvement.

$$n = 2\left(\frac{\left(Z_{\alpha/2}+Z_{\beta}\right)\sigma}{\Delta}\right)^2 \qquad n = \frac{Z^2 p(1-p)}{d^2} \qquad n = \frac{\left(Z_{\alpha/2}+Z_{\beta}\right)^2 p(1-p)}{\Delta^2}$$

Figure 1: Equations for sample size based on a mean shift Δ to detect (left) (Gupta et al.), for finding precision d (middle) given an average rate p (Pourhoseingholi et al.), and for finding minimum significant difference in proportions (right) (Chow et al.)

G. Consent Form

Title of Study: Composite Acellular Dermal Matrix and Pirfenidone-Loaded Hydrogel Capsular Contracture Prevention Device

Key Information

Post-mastectomy radiotherapy patients experience capsular contracture (a painful condition caused by the hardening of the tissue around the breast implant) at a rate more than double the average. This clinical trial designed to test the efficacy of a novel anti-fibrotic device aimed at reducing rates of capsular contracture in high risk patients. In the procedure, a drug secreting sheet will be cut to size and sutured around the chosen breast implant. Over the course of several years via questionnaires, we will collect information on device safety and efficacy.

Why am I being asked to take part in this research study?

You are being asked to take part in this study because you are:

- Female
- Between the ages of 18 and 65 years old
- Will be undergoing mastectomy and immediate reconstruction
- Free of high risk conditions that may cause undue complications
- Fluent in English

What to Know About Your Participation:

- Whether or not you take part is up to you
- You can agree to take part in the study and later change your mind
- Your decision to participate or not will not be held against you
- You can ask all the questions you want before deciding
- You can request that a researcher to explain all or parts of the study to you

Why is This Study Being Performed?

This study is being performed to combat disproportionate rates of capsular contracture in high-risk patients undergoing immediate breast reconstruction after mastectomy. Capsular contracture is the

painful hardening of the tissue around a breast implant which can lead to surgical removal of the capsule or implant. Almost 1 in 2 patients who receive breast reconstruction after mastectomy develop capsular contracture (Vinsensia et al.) and over half of those patients who undergo surgery to treat the condition face recurrence (Hester et al.). This clinical trial is to test a non-FDA approved medical device; ADM, PEG, and pirfenidone FDA approved for use in non breast reconstruction procedures.

What Happens If You Decide to Participate?

Using a randomized and patient blinded format, half of the survey population will receive a drug-loaded device while the other half receives a control (non drug-loaded) device. Neither participant or study doctor will have influence over the treatment type received, however, the doctor providing care during the study will know which device type was implanted. We expect that this study will take approximately 10 years to complete with patient surveying occuring at 2 months, 1 year, 2 years, 4 years, 6 years, 8 years, and 10 years post-operation. In these follow ups we will collect information on patient demographics, physical/social/sexual wellness, device complications, adverse side effects, and any care received relating to the breast reconstruction and/or device implantation procedure.

What Happens If You Decide Not to Participate or Change Your Mind Later?

Participation is entirely voluntary. If you choose not to participate, there will be no penalty to you or loss of benefits to which you are entitled. You may choose to end your participation at any point during the study. If you choose to end your participation before the conclusion of the study, you must contact survey administrators to inform them of your decision in order to enact proper exit protocol. Previously collected data will not be removed from the study database, but leaving the study early will not impact any present or future medical care.

Potential Benefits and Risks:

While we can not promise any benefits to you or any other study participants, our expected outcome for patients in the treatment group include reductions to overall rates of capsular contracture, significant decreases in severe capsular contracture cases, as well as improved social and sexual wellness compared to the control group. Potentially serious risks include but are not limited to surgical complications, infection, autoimmune disease, capsular contracture, photosensitivity, chronic diarrhea, breast implant translation, and/or pneumonia.

Works Cited

Allergen. “AlloDerm SELECT™ Regenerative Tissue Matrix Instructions for Use.” *AlloDerm.*, 2024, https://www.rxabbvie.com/pdf/alloderm_ifu.pdf. Accessed 30 April 2025.

American Society of Plastic Surgeons. “2023 Plastic Surgery Statistics Report.” *American Society of Plastic Surgeons*, 26 September 2023, https://www.plasticsurgery.org/documents/news/statistics/2023/plastic-surgery-statistics-report-2023.pdf. Accessed 7 April 2025.

Amy, Alderman, et al. “Prospective Analysis of Primary Breast Augmentation on Body Image Using the BREAST-Q: Results from a Nationwide Study.” *Plastic and Reconstructive Surgery*, 2025, https://journals.lww.com/plasreconsurg/fulltext/2016/06000/prospective_analysis_of_primary_breast.17.aspx. Accessed 22 April 2025.

Bennett, Katelyn, et al. “Comparison of 2-Year Complication Rates Among Common Techniques for Postmastectomy Breast Reconstruction.” *JAMA Surgery*, 2018, https://pmc.ncbi.nlm.nih.gov/articles/PMC6233788/. Accessed 24 April 2025.

Cano, Stefan, et al. “Interpreting Clinical Differences in BREAST-Q Scores Minimal Important Difference.” *Plastic and Reconstructive Surgery*, 2014, https://journals.lww.com/plasreconsurg/fulltext/2014/07000/interpreting_clinical_differences_in_breast_q.54.aspx. Accessed 23 April 2025.

Caplin, David. “Indications for the Use of MemoryShape Breast Implants in Aesthetic and Reconstructive Breast Surgery.” *Plastic and Reconstructive Surgery*, Journal of the American Society of Plastic Surgeons, 2014, https://journals.lww.com/plasreconsurg/fulltext/2014/09001/indications_for_the_use_of_memory shape_breast.6.aspx. Accessed 11 April 2025.

Chen, Yining, et al. “Advances on the modification and biomedical applications of acellular dermal matrices.” *Journal of Leather Science and Engineering*, vol. 4, no. 19, 2022, https://doi.org/10.1186/s42825-022-00093-4.

Chow, Shein-Chung, et al. “Sample Size Calculations in Clinical Research.” *Chapman & Hall/CRC Biostatistics Series*, 2008, http://ndl.ethernet.edu.et/bitstream/123456789/15304/1/9103.pdf. Accessed 24 April 2025.

Code of Federal Regulations. “Code of Federal Regulations.” *Electronic Code of Federal Regulations*, 2025, https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-878. Accessed 7 April 2025.

Coriddi, Michelle, et al. “Analysis of Satisfaction and Well-Being following Breast Reduction Using a Validated Survey Instrument.” *Plastic and Reconstructive Surgery*, 2013, https://journals.lww.com/plasreconsurg/fulltext/2013/08000/analysis_of_satisfaction_and_well_being_following.9.aspx. Accessed 28 April 2025.

Dagalakis, N., Flink, J., Stasikelis, P., Burke, J. F., & Yannas, I. V. “Design of an artificial skin. Part III. Control of pore structure.” *Journal of biomedical materials research, 14(4), 511–528.*, 1980, https://doi.org/10.1002/jbm.820140417.

Dancey, Anne. “Capsular contracture – What are the risk factors? A 14 year series of 1400 consecutive augmentations.” *Journal of Plastic, Reconstructive & Aesthetic Surgery*, 2012, https://www.jprasurg.com/article/S1748-6815(11)00536-5/fulltext. Accessed 7 April 2025.

di Pompeo, Fabio et al. “tudy of the Effect of Different Breast Implant Surfaces on Capsule Formation and Host Inflammatory Response in an Animal Model.” *Aesthetic Surgery Journal*, 2023, https://doi.org/10.1093/asj/sjac301.

Fayzullin, Alexey, et al. “Local Delivery of Pirfenidone by PLA Implants Modifies Foreign Body Reaction and Prevents Fibrosis.” *Biomedicines, 9, 853.*, 2021, https://doi.org/10.3390/biomedicines9080853.

FDA, Safety Comm. “Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates: FDA Safety Communication.” *Internet Archive, FDA*, 2021, https://web.archive.org/web/20220123162747/https://www.fda.gov/medical-devices/safety-communications/acellular-dermal-matrix-adm-products-used-implant-based-breast-reconstruction-differ-complication. Accessed 16 April 2025.

Fischer S et al. “Silicone Implants with Smooth Surfaces Induce Thinner but Denser Fibrotic Capsules Compared to Those with Textured Surfaces in a Rodent Model.” *PLoS ONE*, 2015, https://doi.org/10.1371/journal.pone.0132131.

Food and Drug Administration. “Saline, Silicone Gel, and Alternative Breast Implants - Guidance for Industry and Food and Drug Administration Staff.” *FDA*, 29 September 2020, https://www.fda.gov/media/71081/download. Accessed 11 April 2025.

Gancedo, M., Ruiz-Corro, L., Salazar-Montes, A. et al. “Pirfenidone Prevents Capsular Contracture After Mammary Implantation.” *Aesth Plast Surg 32, 32–40 (2008)*, https://doi.org/10.1007/s00266-007-9051-4.

Genentech, Inc. “ESBRIET- pirfenidone capsule label.” *DailyMed*, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2e8c3537-36d7-4de5-9b5c-7a624b9a9e6e.

Guimier, Eugenie, et al. “Pharmacological Approaches for the Prevention of Breast Implant Capsular Contracture.” *Wound Healing/Plastic Surgery*, Elsevier, 2022,

https://www.sciencedirect.com/science/article/pii/S0022480422004589?via%3Dihub. Accessed 7 April 2025.

Gupta, KK, et al. “Basic concepts for sample size calculation: Critical step for any clinical trials!” *Saudi Journal of Anaesthesia*, 2016, https://pmc.ncbi.nlm.nih.gov/articles/PMC4916819/. Accessed 24 April 2025.

Hester, Roderick Jr, et al. “Use of Dermal Matrix to Prevent Capsular Contracture in Aesthetic Breast Surgery.” *Plastic and Reconstructive Surgery*, Journal of the American Society of Plastic Surgeons, 2012, https://journals.lww.com/plasreconsurg/fulltext/2012/11002/use_of_dermal_matrix_to_prevent_capsular.20.aspx. Accessed 7 April 2025.

Hidalgo, David, and Sammy Sinno. “Current Trends and Controversies in Breast Augmentation.” *Plastic and Reconstructive Surgery*, Journal of the American Society of Plastic Surgeons, 2016, https://journals.lww.com/plasreconsurg/fulltext/2016/04000/current_trends_and_controversies_in_breast.10.aspx. Accessed 7 April 2025.

Howes, Benjamin, et al. “Quality of life following total mastectomy with and without reconstruction versus breast-conserving surgery for breast cancer: A case-controlled cohort study.” *Journal of Plastic, Reconstructive, and Aesthetic Surgery*, 2016, https://sci-hub.ru/10.1016/j.bjps.2016.06.004. Accessed 29 April 2025.

International Society of Aesthetic Plastic Surgery. “ISAPS Global Survey_2023.” *ISAPS*, 2023, https://www.isaps.org/media/rxnfqibn/isaps-global-survey_2023.pdf. Accessed 7 April 2025.

Kazzazi, F., et al. “A comparison of patient satisfaction (using the BREAST-Q questionnaire) with bilateral breast reconstruction following risk-reducing or therapeutic mastectomy.” *Journal of*

Plastic, Reconstructive & Aesthetic Surgery, 2018, https://sci-hub.ru/10.1016/j.bjps.2018.06.011. Accessed 28 April 2025.

Lohmander, Fredrik, et al. "Effect of Immediate Implant-Based Breast Reconstruction After Mastectomy With and Without Acellular Dermal Matrix Among Women With Breast Cancer A Randomized Clinical Trial." *JAMA Network*, 2021, https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2784613. Accessed 12 April 2025.

Matkin, Ashlee, et al. "Exploring breast surgeons' reasons for women not undergoing immediate breast reconstruction." *The Breast*, 2022, https://pmc.ncbi.nlm.nih.gov/articles/PMC8927853/. Accessed 24 April 2025.

Meng, Hui, and Yong Xu. "Pirfenidone-loaded liposomes for lung targeting: preparation and in vitro/in vivo evaluation." *Drug Des Devel Ther. 2015 Jun 30;9:3369-76.*, doi: 10.2147/DDDT.S84046. PMID: 26185416; PMCID: PMC4500626.

Mundy, Lily, et al. "Breast Cancer and Reconstruction: Normative Data for Interpreting the BREAST-Q." *Plastic Reconstructive Surgery*, 2017, https://pmc.ncbi.nlm.nih.gov/articles/PMC5713639/. Accessed 18 April 2025.

Nahabet, Edward, and Christopher Crisera. "The challenging patient in autologous breast reconstruction: obesity, breast ptosis and beyond." *Gland Surgery*, 2023, https://pmc.ncbi.nlm.nih.gov/articles/PMC10570972/. Accessed 24 April 2025.

Oemrawsingh, Arvind, et al. "BREAST-Q Breast-Conserving Therapy Module: Normative Data from a Dutch Sample of 9059 Women." *Plastic Reconstructive Surgery*, 2022, https://pmc.ncbi.nlm.nih.gov/articles/PMC9586822/. Accessed 24 April 2025.

Pourhoseingholi, Mohamad, et al. “Sample size calculation in medical studies.” *Sample size calculation in medical studies - PMC*, 2013, https://pmc.ncbi.nlm.nih.gov/articles/PMC4017493/. Accessed 12 April 2025.

Pusic, Andrea, et al. “Development of a New Patient-Reported Outcome Measure for Breast Surgery: The BREAST-Q.” *Plastic and Reconstructive Surgery*, Journal of the American Society of Plastic Surgeons, 2009, https://journals.lww.com/plasreconsurg/fulltext/2009/08000/development_of_a_new_patient_reported_outcome.1.aspx. Accessed 11 April 2025.

QPortfolio. “BREAST-Q.” *Q-Portfolio*, 2018, https://qportfolio.org/breast-q/breast-cancer/. Accessed 7 April 2025.

Romanoff, Anya, et al. “Patient-Reported Outcomes Improve Following Mastectomy for Early-Stage Breast Cancer in Nigeria: Pilot Experience Using a Translated and Validated BREAST-Q.” *JCO Global Oncology*, 2024, https://ascopubs.org/doi/10.1200/GO-24-11400. Accessed 24 April 2025.

Roubaud, Margaret, et al. “Breast reconstruction in the high-risk population: current review of the literature and practice guidelines.” *Gland Surgery*, 2021, https://pmc.ncbi.nlm.nih.gov/articles/PMC7882327/. Accessed 24 April 2025.

Shamsunder, Meghana, et al. “Understanding Preoperative Breast Satisfaction among Patients Undergoing Mastectomy and Immediate Reconstruction: BREAST-Q Insights.” *Plastic Reconstructive Surgery*, 2022, https://pmc.ncbi.nlm.nih.gov/articles/PMC8638966/. Accessed 24 April 2025.

Sharma, Rajesh. “Breast cancer incidence, mortality and mortality-to-incidence ratio (MIR) are associated with human development, 1990–2016: evidence from Global Burden of Disease Study

2016." *Springer Nature*, Springer, 2019, https://link.springer.com/article/10.1007/s12282-018-00941-4?utm_source=getftr&utm_medium=getftr&utm_campaign=getftr_pilot&getft_integrator=sciencedirect_contenthosting. Accessed 7 April 2025.

Spear, Scott, and James Baker. "Classification of Capsular Contracture after Prosthetic Breast Reconstruction." *Plastic Reconstructive Surgery*, 1995, http://sci-hub.ru/10.1097/00006534-199510000-00018. Accessed 5 April 2025.

Tennant, Alan, and Philip Conaghan. "The Rasch measurement model in rheumatology: What is it and why use it? When should it be applied, and what should one look for in a Rasch paper?" *Arthritis Care & Research*, 2007, https://onlinelibrary.wiley.com/doi/10.1002/art.23108. Accessed 28 April 2025.

Tomita, Shoichi, et al. "Detailed Analysis of Three Major Breast Reconstructions Using BREAST-Q Responses From 1001 Patients." *Aesthetic Surgery Journal*, 2023, https://academic.oup.com/asj/article/43/11/NP888/7216793. Accessed 28 April 2025.

US FDA. "Summary of Safety and Effectiveness Data (SSED): Motiva SmoothSilk Round Silicone Gel-Filled Breast Implants / Motiva SmoothSilk Round Ergonomix Silicone Gel-Filled Breast Implants." *PMA P230005, 26 Sept. 2024.*, https://www.accessdata.fda.gov/cdrh_docs/pdf23/P230005B.pdf.

US Food and Drug Administration. "Frequently Asked Questions about Combination Products." *Combination Products*, 2022, https://www.fda.gov/combination-products/about-combination-products/frequently-asked-questions-about-combination-products. Accessed 7 April 2025.

Vinsensia, Maria, et al. “Incidence and Risk Assessment of Capsular Contracture in Breast Cancer Patients following Post-Mastectomy Radiotherapy and Implant-Based Reconstruction.” *Incidence and Risk Assessment of Capsular Contracture in Breast Cancer Patients following Post-Mastectomy Radiotherapy and Implant-Based Reconstruction*, 7 January 2024, https://pmc.ncbi.nlm.nih.gov/articles/PMC10813520/. Accessed 7 April 2025.

Winter, Kathryn, and Stephanie Pugh. “An Investigator's Introduction to Statistical Considerations in Clinical Trials.” *PubMed Central*, 26 March 2019, https://pmc.ncbi.nlm.nih.gov/articles/PMC6959125/. Accessed 7 April 2025.

Zhong, Toni, et al. “The Use of Acellular Dermal Matrix in One-Stage Implant Breast Reconstruction: A Multicenter, Randomized, Controlled Trial (Multi-centered Canadian Alloderm TrialMCCAT).” *ClinicalTrials.gov*, 2011, https://cdn.clinicaltrials.gov/large-docs/84/NCT00956384/Prot_SAP_000.pdf. Accessed 7 April 2025.