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ORIGINAL ARTICLE

Scaffold-based breast conserving surgery in patients with non-malignant breast lesions: long-term follow-up of a first-in-human pilot study on the REGENERA™ biomimetic breast implant

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Abstract

Background Frequently, the breast surgeon must employ complex oncoplastic techniques (OBS) to guarantee optimal cosmetic results. The success of the REGENERA™ implant in combining the benefits of OBS with the simplicity of breast conserving surgery (BCS) has been previously reported in five patients with short follow-up. The goal of this study was to build on these promising data by reporting safety and efficacy results in a larger population with a longer follow-up.

Methods Fifteen females with non-malignant breast lesions who underwent lumpectomy and implantation of REGENERA™ device, followed-up for six months, were included in this interventional FIH study. Fourteen of these, were included in a long-term observational study (LTFU) and followed-up for 24 months. Safety (incidence of adverse events [AEs]) and performance (changes in breast appearance, interference with imaging) of the device, and investigator and patient satisfaction were evaluated. Data from these two studies are reported herein. (Registered on clinicaltrials.gov: NCT05533099 and NCT04131972).

Results A total of 113 AEs were reported. Only 3 (2.6%) were considered possibly device-related. The great majority (91,2%) were mild/moderate and only in one case the device was explanted. The REGENERA™ implant demonstrated high levels of performance, with an aesthetic score of 'Excellent' in 85.7% of patients, no interference with imaging, and high levels of patients and investigator satisfaction.

Conclusions Data continue to be strongly supportive of the use of the REGENERA™ implant in BCS, further paving the way for an innovative surgical approach.

Keywords Biomimetic scaffold · Breast conservation surgery · Tissue engineering · Safety · Performance

Introduction

Breast cancer (BC) survival rates have increased due to therapeutic advancements and earlier detection [1, 2]. As such, quality of life (QoL) has become one of the key treatment outcome considerations [3]. Breast conserving surgery (BCS) is a viable treatment option with survival benefits not inferior to mastectomy and significantly improved QoL [4, 5]. However, satisfactory aesthetic outcomes depend on lesion location and lesion to breast volume ratio (L/BV) [6–12]. Oncoplastic breast surgery (OBS) can address the potentially negative aesthetic outcome of BCS in patients requiring larger excisions, but is often more complex, and in many cases bilateral for symmetrization purposes [13, 14]. Therefore, alternatives are warranted. Cell-free implantable scaffolds were developed to provide structural support for the self-regeneration of host tissue [15–18]. However, limited success in complex tissues has been reported [19]. REGENERA™ is a synthetic, biodegradable, polyurethane-based, cell-free scaffold that has previously shown successful outcomes in patients undergoing BCS [20]. The polymeric matrix internal morphology is characterized by an open-pore interconnected structure to enable rapid infiltration of cells and vascular tissue into the inner core of

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the device. The geometry is oval symmetrical to facilitate implantation and to compensate for the volume deficit which follows surgery [21, 22].

We have previously reported the promising safety and performance of a subgroup of patients from this first-in-human (FIH) pilot study, which described the surgical procedure of REGENERA™ implantation in five patients with non-malignant breast lesions [20]. Here, we report on the full cohort of the fifteen patients enrolled and include long-term safety and performance data for up to 24 months of follow-up.

Patients and methods

Study design and participants

Details of the FIH study have been reported previously [20]. Briefly, this interventional, non-comparative, open-label, pre-market, single-center study enrolled 15 patients aged between 21 and 85 years old with a proven diagnosis of non-malignant lesions up to 200 cubic centimeters in volume, eligible for BCS, and followed up for 6 months. All eligibility criteria for the FIH study can be found in the Online Resource (Online Resource 1). The Long-term follow-up (LTFU) study is a prospective, observational study of patients enrolled in the FIH study. Patients were enrolled between July 2021 and June 2022. The planned duration of follow-up is of 48 months (commencing 12 [$\pm$4] months post-surgery), with 6 follow-up visits scheduled (Table 1). This interim analysis is the first of this follow-up study and reports on the 24-month post-operative visit (V8).

Both studies are registered on ClinicalTrials.gov: NCT04131972, NCT05533099.

Device description

Details of the REGENERA™ implant and surgical procedure have been reported previously [20–24]. In brief, REGENERA™ (Tensive S.r.l., Milan, Italy) is a biodegradable oval-shaped cross-linked poly(urethane-ester-ether)-based matrix treated with a bio adhesive macromolecule (poly-L-lysine) and hydrophobized by oleic acid (18:1 n − 9). The internal morphology is characterized by an interconnected open-pore structure (pore diameter 0.3–6.5 mm) and a 3D channel network propagating through the porous structure along *X*, *Y*, and *Z* axes (see Online Resource 2).

Study outcomes

The primary objective of the FIH and LTFU studies was to assess the safety of the REGENERA™ implant following BCS of non-malignant breast lesions. Secondary objectives included assessment of the performance of the implant, with an additional secondary endpoint in the FIH study related to the safety and feasibility of the surgical procedure.

Safety reporting

The primary outcome measure for the FIH study was the cumulative number of serious adverse events (SAEs), with the cumulative number of adverse events (AEs) associated with the surgical procedure considered a secondary safety outcome. For the LTFU study, the primary outcome measure was the rate of AEs, with each patient being followed up for AEs and adverse device effects (ADE) for a total period of 5 years. AEs are defined according to the international standards on clinical investigations (ISO 14155:2011 and 2020) as any new event not present or worsening from the previous visit. ADEs are intended as an AE with a causal relationship to the study device. For both studies, the type and severity of AEs were recorded.

Performance reporting

Investigator opinion: As reported in detail previously [20] and described in the study flow-chart (Table 1) breast appearance was evaluated before (V − 1) and after surgery at different time-points employing reproducible parameters to minimize subjectivity. Since the REGENERA™ device was implanted for reconstructive purposes with the aim not to change pre-operative breast appearance, we evaluated the impact of the device on this aspect, using a combination of physical examination, standardized photographs and anthropomorphic measurements and assigning an overall aesthetic score based on the Harvard scale [25, 26]. A visual analogue scale (VAS: 0–10) was employed different time-points to assess investigator's opinion on the initial surgical procedure and final outcome.

Patient satisfaction and QoL, and pain assessment: To assess patient satisfaction and QoL (QoL), each patient completed the BREAST-Q© questionnaire at different time-points and we quantified the changes in scores between each time-point vs baseline [5]. Pain was assessed at every visit using the VAS (0–10).

Interference with Standard of care (SoC) imaging: Ultrasound (US), Mammography (MX) and Magnetic Resonance Imaging (MRI) were used. Two independent radiologists evaluated qualitative parameters of SoC imaging suggestive of implant vascularization, reabsorption and colonization with soft tissue. Imaging also looked to identify clinically significant abnormalities (defined as the presence of findings worthy of further investigation) in the surrounding tissue. The agreement between the three imaging modalities in detecting any abnormalities, and the possible interference of the implant with their detection power was assessed.

Table 1 Flowchart of the FIH and LTFU Study

	V-1 Enrollment	V0 Surgery	V1 1 wk	V2 2 wks	V3 1 mth	V4 3 mths	V5* 6 mths	V6 12 mths	V7 18 mths	V8 24 mths	V9 36 mths	V10 48 mths	V11 60 mths
Informed Consent	X							X(b)	X(b)				
Inclusion/Exclusion Criteria	X							X(b)	X(b)				
Demographic data, Medical Hystory, Weight	X							X(b)	X(b)				
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (BP,HR)	X	X						X	X	X	X	X	X
ECG	X												
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Breast Lesion Evaluation	X												
Biopsy	X												
Blood Sampling	X												
Serum Pregnancy test	X												
Patient's Diary	X	X	X	X	X	X	X	X	X	X	X	X	X
Ultrasound (US)	X		X	X	X	X	X	X	X	X	X	X	X
Photos, Chest measurements	X		X			X	X	X	X	X	X	X	X
Mammography (MX)	X(a)							X(a)		X(a)	X(a)	X(a)	X(a)
Magnetic Resonance Imaging (MRI)	X						X		X		X		X
Surgery and REGENERA Implantation		X											
Investigator's Satisfaction (VAS)		X					X		X		X		X
Patient's Pain (VAS)	X	X	X	X	X	X	X	X	X	X	X	X	X
BREAST-Q Questionnaire	X				X		X		X		X		X
Advere events (AEs) Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X

*V5 corresponds to the last follow-up of the FIH study

a-Mammography was performed only in patients aged more than 40 years old as for clinical practice guidelines

b-Patients can be enrolled in the LTFU study at V6 or V7 depending on how many months lasted from V0. Informed consent signature, exclusion/inclusion criteria evaluation, demographic data and medical history collection are done only once, at V6 or V7 accordingly to the start of enrollment

Statistical design

Data are summarized by descriptive statistics. Continuous variables are presented as mean and standard deviation (SD), and categorical variables as the number of patients and percentages.

Results of the BREAST-Q© questionnaire are analyzed using the Fridmand test for non-parametric data matched in multiple comparisons with V – 1 (* < 0.1, ** < 0.01, *** < 0.001, **** < 0.0001). We used GraphPad Prism Version 10.4.1 (532).

Both studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and the Good Clinical Practice principles and were approved by the local Ethics Committee (FIH: Protocol No. 51965, 11 October 2018; LTFU: Protocol No. 19285, 15 April 2021), and the Italian Ministry of Health (FIH: 0066926–05/12/2018-DGDMF-MDS-P; LTFU: 0024481-06/04/2021-DGDMF-MDS-P). Written informed consent was obtained for both studies.

Results

Baseline characteristics

Detailed baseline demographics and lesion characteristics can be found in Table 2. In the FIH, fifteen patients with a mean (SD) age of 40 (9) years (range 20–52 years) were enrolled. Fourteen of these entered the LTFU study ($n=8$ at 12 ± 4 months, $n=6$ at 18 ± 4 months post-surgery). One patient dropped out due to an SAE. The mean diameter of the surgical specimens removed was of 56.5 mm and 55.5 mm for the FIH and LTFU study respectively. Regarding the width of the excised margins, in case of fibroadenomas the removed tissue corresponded to the lesion in its greatest diameter (enucleation) and in the B3 lesions, in all cases, the margins were on average 8 mm. Details of the overall trial profile can be found in Fig. 1.

Safety analysis

Details of AEs and ADEs can be found in Table 3.

Overall, in the FIH and LTFU study, 113 AEs were reported, with breast pain/discomfort accounting for the majority ($n=76$, 67.3%). Seventy-seven (59.3%) were considered unrelated to both the study procedure and the device,

Table 2 Baseline demographics and lesion characteristics

	FIH Study n=15	**LTFU Study n=14**
Age,years		
Mean (SD)	40 (9)	40.5 (9.1)
Median (IQR)	42 (37-47.8)	42 (37-47.8)
Min-Max	21-52	21-52
Weight, kilograms		
Mean (SD)	61.4 (8.7)	66 (9.8)
Sex, n(%)		
Female	15 (100%)	14 (100%)
Male	0 (0)	0 (0)
Etnicity, n(%)		
Caucasian	15 (100%)	14 (100%)
Black	0 (0)	0 (0)
Asian	0 (0)	0 (0)
Other	0 (0)	0 (0)
Maximum diameter of surgical specimen (mm)		
Mean (SD)	56.5 (19.4)	55.5 (19.8)
Definitive size of lesion (mm)		
Mean (SD)	53.8 (21.5)	53.1 (22.1)
Lesion type*, n(%)		
Fibroadenoma	7 (46.7%)	6 (42.9%)
Benign phyllodes	2 (13.3%)	2 (14.3%)
Borderline phyllodes	2 (13.3%)	2 (14.3%)
Pseudoangiomatoid hyperplasia fascicular variant (PASH)	1 (6.7%)	1 (7.1%)
Fibroadenoma+Sclerosant adenosis and fibroadenomatoid hyperplasia	2 (13.3%)	2 (14.3%)
Amartoma	1 (6.7%)	1 (7.1%)

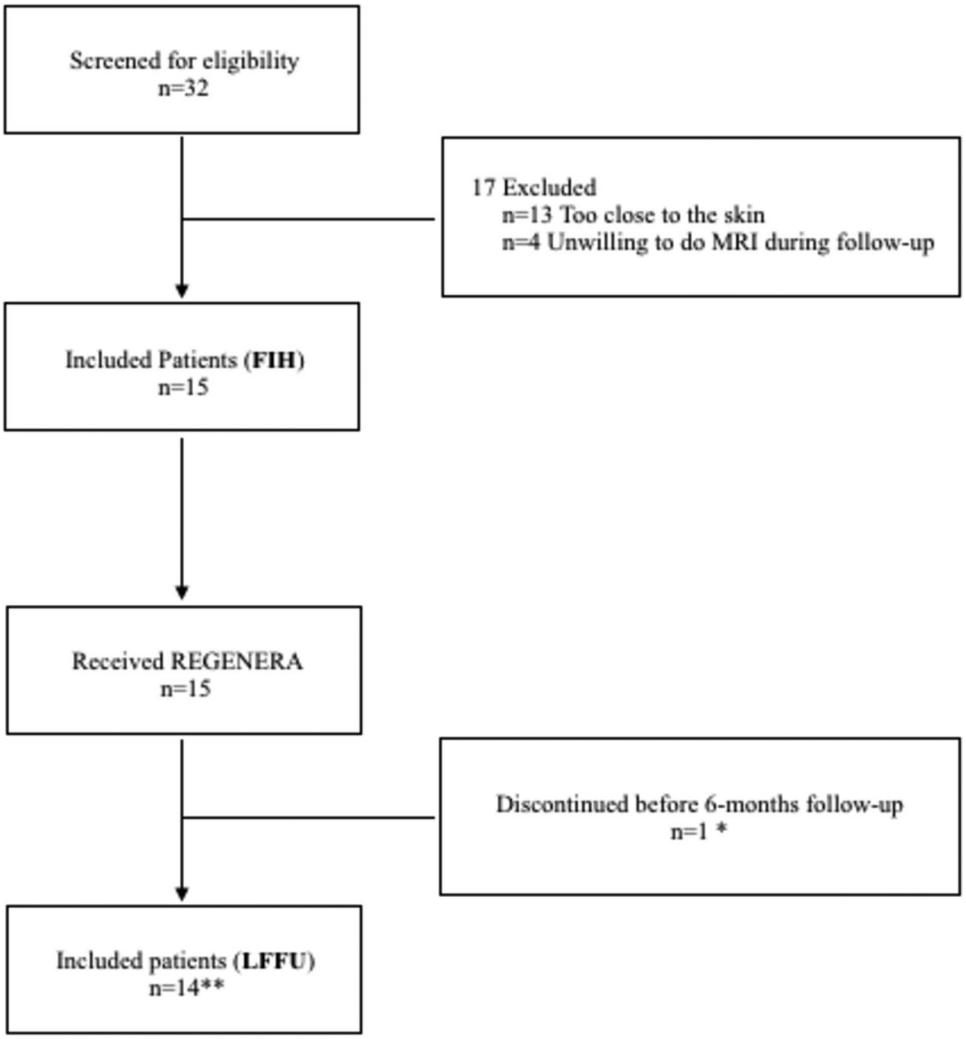

Fig. 1 Study profile of the FIH and LTFU studies. *Due to SAE of hyperemia of the right breast and secretion from the wound. The REGENERA implant was explanted because of a staphylococcus epidermidis infection found on cultural examination with antibiogram. FIH, first-in-human; LTFU, long-term follow-up; SAE, serious adverse event

with 46 (40.7%) as possibly related. Among the latter, 43 (93.5%) consisted of breast pain, which resolved without treatment; the remaining 3 (breast hyperemia, secretion from the wound and worsening of these symptoms resulting from a *Staphylococcus epidermis* infection) were associated with the SAE reported in one patient (01–09) leading to device explantation prior to V5. One hundred and three AEs (91.2%) were categorized by the patient as mild or moderate and only 10 (8.8%) as severe, of which eight (80%) consisted of breast pain resolved within a week, and 2 refer to the SAE. At the 24-month visit, only three AEs were ongoing (anxiety, hypertension and the presence of nodules), all not considered by investigators as related to the study device or procedure.

Performance analysis

Investigator Assessment: Breast asymmetry was judged to be "absent", "mild", "moderate" and "severe" in four, eight, three and no patients, respectively, at V – 1 and in five, six, two and one patient respectively at V5 and V8. In both studies, in 12 (85.7%) patients, the overall aesthetic score was "Excellent", since breast shape, size, ptosis and symmetry were unchanged and the scaffold was no longer detectable or half its size. The remaining two patients (14.3%) had an overall aesthetic score of "Fair" (patients 01–10 and 01–15), because of a keloid scar, a minus-area in the implant location, and a palpable implant with halved size in patient 01–10 and a worsening of asymmetry (from "moderate" to "severe") with a palpable implant in patient 01–15. At V8, the device was no longer palpable in eight patients (57.1%) and in the remaining six (42.9%) it was always reduced in size (with median dimension of 2,75 cm).

Representative photographs at V – 1, V0, V5, and V8, as well as the size of removed lesions, can be found in Fig. 2

Investigator satisfaction

Mean (SD) Investigator satisfaction with the surgical procedure, the device performance and clinical outcomes

Table 3 Summary of safety data for the FIH and LTFU study

	FIU Study n=15	**LTFU Study n=14**
Number of AEs, n	98	15
Number of AEs per study visit, n (%)		
V1	26 (26.5%)	
V2	14 (14.3%)	
V3	16 (16.3%)	
V4	13 (13.3%)	
V5	29 (29.6%)	
V6		2 (13.3%)
V7		7 (46.7%)
V8		6 (40%)
Description of AEs, n(%)		
-Breast pain/disconfort	66 (67.4%)	9 (60%)
-Headache	2 (2%)	0
-Dyspepsia	1 (1%)	0
-Fatigue	1 (1%)	0
-Fever	2 (2%)	0
-Pharyngodynia	1 (1%)	0
-Lipotymia	2 (2%)	0
-Limb disconfort	3 (3.1%)	0
-Paresthesia	1 (1%)	0
-Painful respiration	1 (1%)	0
-Periferal swelling	1 (1%)	0
-Periferal venous disease	1 (1%)	0
-Pruritus	3 (3.1%)	0
-Arm movement disorder	3 (3.1%)	0
-Breast ecchymotic soffusion	2 (2%)	0
-Nipple hypersensitivity	4 (4.08%)	1 (6,66%)
-Breast skin hyperemia	3 (3.1%)	0
-Secretion from the wound	1 (1%)	0
-Anxiety	0	1 (6,66%)
-Hypertension	0	1 (6,66%)
-Covid-19 infection	0	1 (6,66%)
-Evidence on US of nodules near the device which required biopsy verification	0	1 (6,66%)
	0	0
	0	0
-Gastroesophageal reflux	0	1 (6,66%)
Severity, n(%)		
Mild	63 (64.3%)	14 (93.3%)
Moderate	25 (25.5%)	1 (6.7%)
Severe	10 (10.2%)	0 (0)
Relationship with the study device/procedure, n(%)		
Not related	60 (61.2%)	7 (46.7%)
Possibly	38 (38.8%)	8 (53.3%)
Causal	0 (0)	0 (0)

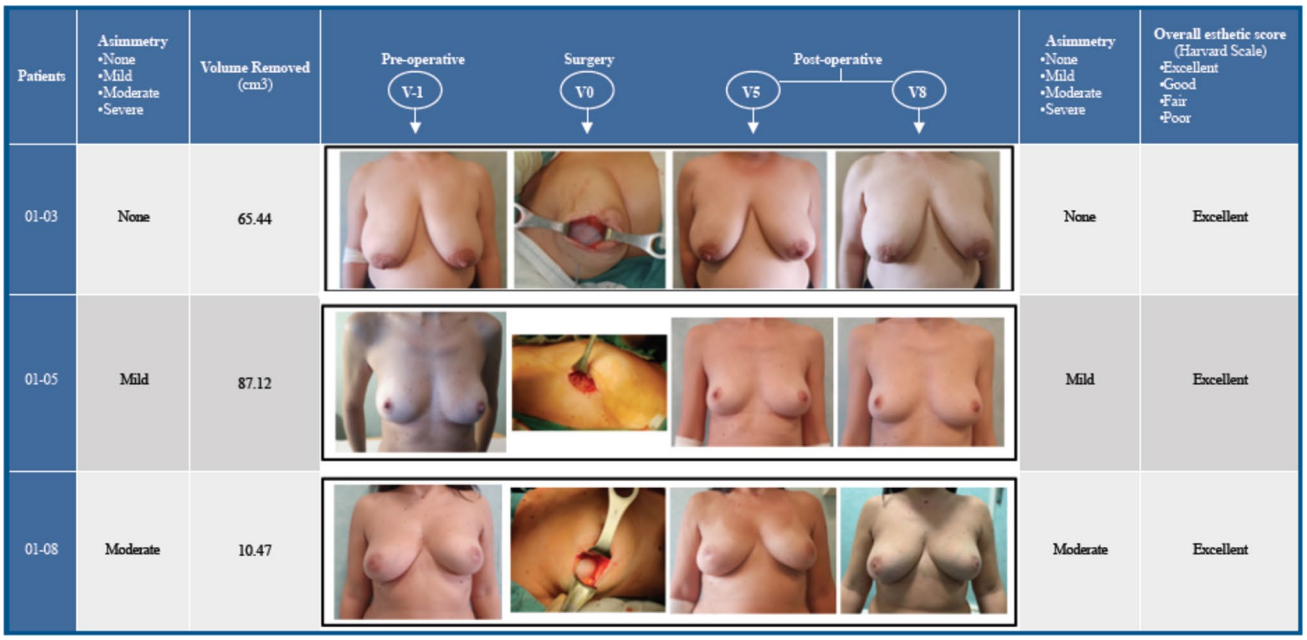

Fig. 2 Photographic assessment of breast appearance and surgical procedure in three representative cases throughout the FIH and LTFU study: Degree of breast asymmetry and volume of tissue removed (cubic centimeters) in the pre-operative evaluation (V − 1); degree of asymmetry and overall aesthetic score (Harvard Scale) in the final post-operative evaluation after 6 months (V5) and 2 years (V8)

at V0, V5 and V7 was 8.7 (0.8), 8.4 (2.0), and 8.6 (2.1), respectively.

Patient Assessment Fig. 3 details the findings of the BREAST-Q questionnaire on QoL and patient satisfaction.

Satisfaction with breast scored a mean (SD) of 54.7 (15.9) at V − 1, 71.0 (18.7) at V5 and 75.6 (19) at V7. The scores of psychosocial well-being were 61.5 (17.9) at V − 1, 74.3 (18.4) at V5 and 77.4 (17.4) at V7. For sexual well-being, the QoL scores ranged from 60.1 (17.1) at V − 1, 67.7 (21.5) at V5 and 71.4 (18.1) at V7. The scores of physical well-being were of 32.8 (16.9) at V − 1, 41.4 (17.5) at V5 and 86 (13.2) at V7. Satisfaction with the surgical team was consistently high. Mean (SD) pain intensity was 2.1 (2.0) at V0. Over time, the mean (SD) values were all reduced and all patients reported a score of 0 since V5.

Evaluation of SoC imaging Representative US, MRI and mammography images can be found in Fig. 4.

Under US, in all patients at V1, REGENERA™ implant appeared as a 6 cm scaffold with a heterogeneous pattern consisting of multiple millimetric hypo-echoic and hyper-echoic micro artifacts. It always showed peri- and intra-scaffold doppler signals. An anechoic peri-scaffold liquid collection more evident at the poles was detected in nine patients (64.3%). Eight patients (57%) had hyperechogenicity of the tissue surrounding the scaffold, and in eleven patients (78.6%) internal millimetric hypo-echoic bands, parallel to each other and placed at a constant 1 cm distance inside the scaffold, were detected. Over time, in 100% of patients we documented a progressive reduction of the size of the implant (median diameter of 4 cm at V5 and 3 cm at V8), of micro artifacts (completely disappeared in three cases at V8), and of internal hypo-echoic bands (no longer detectable at V8 in 7 patients). Surrounding hyperechogenicity and peri-scaffold collection reduced in all patients in which they were initially documented, being detectable at V8 only in one and three patients, respectively. Doppler signals persisted in all patients none ever presented with axillary lymphadenopathy.

At MRI, in 100% of patients, the scaffold showed a reduction in size (median dimension of 4.6 cm at V5 and 3.7 cm at V8) and it always appeared hypo-intense in T1 weighted sequences (T1ws) and hyper-intense in T2 weighted sequences (T2ws), with rim enhancement after contrast medium (CM) administration.

Ten patients underwent MX (age > 40 years). In all cases the area occupied by the scaffold appeared as a radiopaque area and it always showed a reduction of size and radiopacity over time (median dimension of 3.8 cm at V5 and 3.2 cm at V8). No patient ever developed calcifications nor liponecrosis.

Overall, the REGENERA™ implant did not interfere with SoC imaging and there was a complete coherence among the different imaging techniques on the assessment of clinically significant abnormalities.

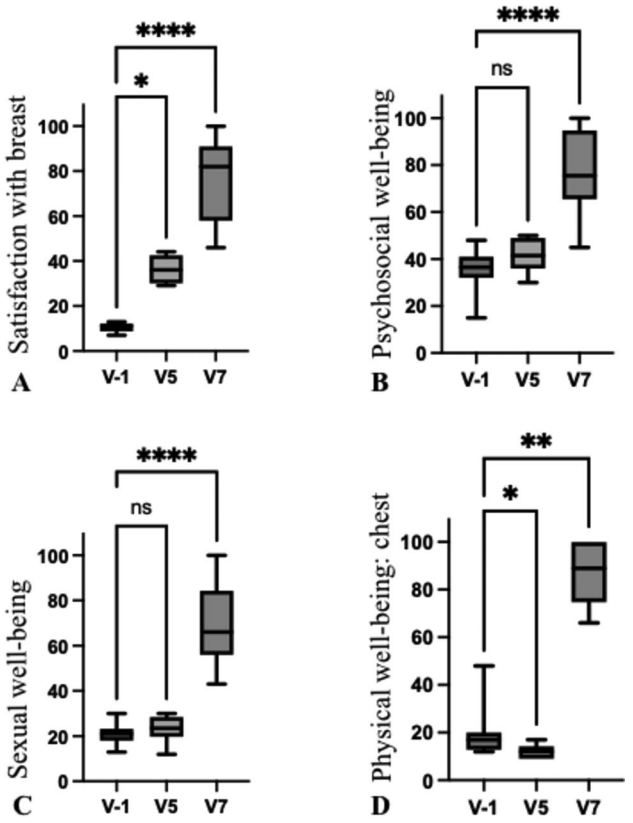

Fig. 3 BREAST-Q survey results on QoL and patient satisfaction: Results of the BREAST-Q© questionnaire are analyzed using the Fridmand test for non-parametric data matched in multiple comparison with V – 1 (* < 0.1, ** < 0.01, *** < 0.001, **** < 0.0001)

Discussion

Limitations of BCS are well recognized, with performance outcomes largely dependent on the degree of tissue removal, particularly in relation to the L/BV ratio. Indeed, in some cases, BCS requires significant tissue remodeling, and a bilateral approach to maintain pre-operative symmetry, with a potential increase of invasiveness and morbidity [12]. Identifying an approach to address aesthetic requirements whilst minimizing invasiveness is warranted. Biomimetic scaffolds are viable alternatives [27]. The REGENERA™ implant is intended for providing structural support for self-regeneration of host soft-tissue resembling fat, to restore a natural breast shape and consistency after removal of clinically relevant volumes with BCS (i.e. up to 200 cc). As such, its use might change the paradigm of BCS.

Here we show that implantation of the REGENERA™ device in BCS following removal of non-malignant breast lesions is associated with high levels of investigator and patient satisfaction, and an excellent safety profile, confirming previous results in a small cohort of patients enrolled in the FIH study [20].

In terms of safety, a very low incidence of complications over 2 years of follow-up was found. Breast pain/discomfort accounted for the majority (67.3%) and was reported predominantly in the immediate post-operative period, indicating that the device did not impact negatively on the post-operative recovery, which takes about 30 days even after traditional BCS. Moreover, most of these early AEs (59.3%) were not considered device- or procedure-related. Of those that were, almost all (93.5%) were considered by the investigator to be associated with the surgical procedure alone (i.e., breast pain/discomfort). Only three AEs (breast hyperemia, secretion from the wound and worsening of the above symptoms) were considered possibly device-related and were categorized as SAE. They all occurred in the same patient (pt 01–09) who developed an infection leading to device explantation. AEs, including seroma, hematoma, and infection are commonly reported with breast reconstruction

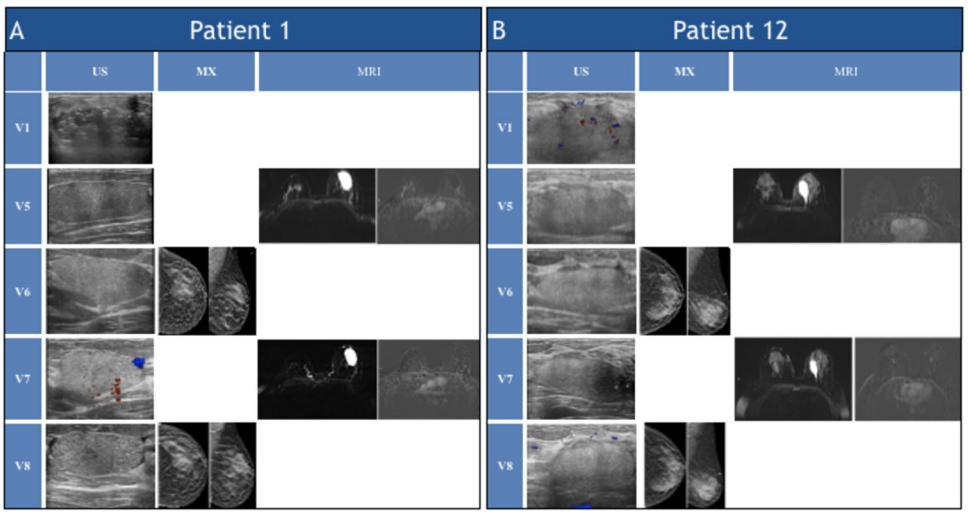

Fig. 4 Representative Ultrasound (US), Mammography (MX) and Magnetic Resonance (MRI) images from patient 01–01 (**A**) and 01.12 (**B**): US images are provided at every timepoint; MX images are provided 1 year and 2 years after surgery (MX performed annually as per standard clinical practice); MRI images are provided at 6 months (V5) and 18 months (V7) after surgery

devices, sometimes leading to implant removal and/or replacement [28, 29] and further investigation found patient 01–09 to be a heavy smoker, an independent risk factor for post-operative complications in implant-based surgery [30]. Furthermore, most AEs (91.2%) were mild or moderate in severity. Of those defined by the patient as severe, most (80%) were not considered by the investigator to be device-related (i.e., breast pain), the remaining are those clinked to the SAE. Importantly, the majority resolved spontaneously, and 14/15 devices remained implanted.

We believe that early US observations of internal micro-artifacts can be attributed to hydration liquid and gasses present at the moment of implantation. Accordingly, their reduction over time suggests reabsorption of liquids and gasses and colonization and replacement of the pores with cells and vascular tissue. Internal hypoechoic bands, detected one week after the implantation in 78.6% of patients, and reduced after 2 years in the majority of them (63.6%), may be attributed to the implant channels. Since their presence is directly related to the space of each channel still to be colonized and replaced by the patient's own tissue, the kinetics of this process may vary from one patient to the other. The ongoing presence of doppler signals indicates vascular tissue infiltration. The surrounding tissue hyperechogenicity observed in eight patients one week after the implantation, and subsequently reduced in all of them, was interpreted as parenchymal compression and/or edema. Accordingly, its evolution was attributed to implant colonization and/or edema resolution. The minimal anechoic peri-scaffold collection, detected in 64.3% of patients one week after the implantation, and reduced in the majority of cases (57%) with no need for aspiration, was attributed to reactive effusion. These last two findings and the absence of lymphadenopathy suggest an absence of inflammation.

At MRI, the hyperintensity in T2ws, hypointensity in T1ws and the rim enhancement after CM administration detected in all patients, are suggestive of the presence of cellular vascularized tissue inside the implant, and of tissue remodeling, particularly referring to replacement with newly formed adipose tissue with no evidence of inflammation.

At MX, the progressive reduction of radiopacity of the area occupied by the scaffold observed in all patients over time, was interpreted as new adipocytes-predominant tissue repopulation.

With all of these imaging modalities, a progressive reduction in the size of the scaffold was detected, reinforcing the hypothesis of its gradual reabsorption and repopulation.

Overall, long-term imaging results indicate that the implant did not cause inflammation, appeared vascularized and integrated with surrounding tissue, with a progressive reabsorption of the polymeric matrix and colonization by newly-formed tissue and did not impact the ability to study the surrounding parenchyma.

In terms of aesthetic evaluation, it is worth reinforcing that this device was not implanted for aesthetic reasons, per se, but to fill volume deficits created after breast lesion removal, maintaining the preoperative appearance. The overall favourable physical, photographic, and anthropomorphic assessments in both studies and the high levels of investigator and patient satisfaction support the excellent performance of the implant. Indeed, the surgical scar was in order in all but one patient (01–10) who developed a keloid scar, suggesting that the implant does not impact negatively on wound healing. More than half (57%) of the implants were not palpable 24 months post-surgery, suggesting a resemblance of the mechanical properties of the newly regenerated tissue to the surrounding one [30]. In all the remaining 6 cases in which it was still detectable on palpation, it was always reduced in size (median size of 2.75 cm) indicating an ongoing slower reabsorption process. Breast asymmetry remained unchanged in 12 patients (85.7%). As for the remaining two patients, in one (01.11) it changed for the better (from ‘mild’ to ‘absent’) and only in one case (0.15) it changed negatively (from ‘moderate' to ‘severe’). This data suggests that in almost all cases except for one, the device did not impact on breast appearance or even improved it. Only two patients reported clinically significant abnormalities, with an overall aesthetic result defined as ‘Fair’ and these were hypothesized to be the result of a lack of cellular repopulation either through an unfavorable L/BV ratio (patient 01–10) or capsule formation(01–15). Whilst capsule formation may not necessarily indicate an inflammatory response, it may reduce the level of biocompatibility of the device by creating a barrier to cellular colonization [31, 32]. Indeed, device biocompatibility is vital to ensure low levels of immunogenicity and the cross-linked aliphatic poly(urethane-ester-ether) material of the REGENERA™ implant has already been reported in a clinical setting for wound healing and other indications [33]. Furthermore, we have previously reported preclinical findings showing that this implant is highly biocompatible, further supported by the clinical evidence here, demonstrating low levels of immunogenicity illustrated by lack of clinically significant changes in lymph node size [20–24].

It is important to emphasize that the primary endpoint of our study was to evaluate the safety of an innovative device in humans, which is why we included only patients with benign lesions who therefore did not require adjuvant therapies, so as to obtain results more clearly device-related. Evaluation of the cosmetic outcome was included among the various secondary outcomes and, similarly to the others, yielded extremely encouraging results. However, these data on the impact of REGENERA™ on the cosmetic outcome, need to be confirmed in the study on malignant lesions, because about half of the cases of the FIH and LTFU studies were fibroadenomas, which are normally excised with a

simple enucleation with optimal cosmetic results. The fact that the cosmetic outcome would probably have been optimal even in the absence of the device, confirms only that its use is not detrimental in terms of aesthetic outcome but gives results comparable to those of the standard of care surgical technique. Compared to this, however, the device is repopulated with autologous tissue and is progressively reabsorbed, a fundamental aspect where the intervention is not a simple enucleation of a benign lesion but the removal of breast tissue in BC patients. In this cases, being able to proceed with a simple 'volume replacement' instead of more complex glandular remodeling procedures to obtain a valid cosmetic result might be fundamental.

As previously reported [20]implantation of the REGENERA™ device is a simple procedure with the potential to reduce operating time, hospitalization rates, and patient recovery. Surgeons found the implant easy to use, patients reported always very low levels of post-operative pain, with the highest score immediately after surgery and no pain at all in all cases already after 6 months. Furthermore, the device showed a positive impact on patients QoL, indeed all the scores reported in the BREAST-Q questionnaire increased both at V5 and V7 compared to V – 1, reaching statistical significance in all the domains.

With regard to the limitation of the FIH study herein presented, FIH study designs are typically single-arm with a small cohort of patients, preventing comparisons and requiring caution in the interpretation of findings. Importantly, we have already initiated a pivotal multicentric open-label study of the REGENERA™ implant in patients with malignant breast lesions treated by lumpectomy, with a planned enrollment of over 90 patients (registered on ClinicalTrials.gov:NCT05941299). The advantages of this study are twofold. Firstly, the increased patient population will add to the robustness of the study data. Secondly, as many patients undergoing BCS require adjuvant therapy, this study will be able to assess the safety and performance of the REGENERA™ implant when exposed to adjunctive therapies, particularly important given that the implant removal rate is higher following radiation therapy [34].

To conclude, we show that in BCS, patients can benefit from scaffold insertion, avoiding any bilateral surgery, extensive autologous tissue remodeling, or secondary surgical procedures. Moreover, this novel surgical approach has the potential to decrease morbidity and healthcare costs.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Maria Donatella Mariniello, Matteo Ghilli, Benedetta Favati/Claudio Bandini, Irini Gerges, Margherita Tamplenizza, Maria Ghilardi, and Manuela Roncella. The first draft of the manuscript was written by Maria Donatella Mariniello and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability All the data reported herein are available on demand

Declarations

Conflict of interest The authors declare the following financial/non-financial interests which may be considered as potential competing interests: Authors I.G., M.T., A.T. and F.M. are shareholders and members of the board of directors of Tensive S.r.l. They have received the grant H2020-EIC-SMEInst-2018–2020 (Grant agreement number: 812002) from the European Commission. The remaining authors have no relevant financial or non-financial interests to disclose.

Ethical approval These studies involving human participants, were conducted in accordance with the ethical standards of the institutional (AOUP Ethical Committee:Protocol # 51965, 11 October 2018 and Protocol #19285, 15 April 2021) and national (Italian Ministry of Health-0066926-05/12/2018-DGDMF-MDS-P and 0024481-06/04/2021-DGDMF-MDS-P) research committee and with the 1964 Helsinki declaration and its later amendments and the Good Clinical Practice principles.

Informed consent Written informed consent was obtained from all individual participants included in the study.

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