DE NOVO CLASSIFICATION REQUEST FOR INSPACE™ SUBACROMIAL TISSUE SPACER SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Resorbable shoulder spacer. A resorbable shoulder spacer is intended to act as a temporary spacer, creating a physical barrier between tissues in the shoulder, for the treatment of massive irreparable rotator cuff tears.

NEW REGULATION NUMBER: 21 CFR 888.3630

CLASSIFICATION: Class II

PRODUCT CODE: QPQ

BACKGROUND

DEVICE NAME: InSpace™ Subacromial Tissue Spacer System

SUBMISSION NUMBER: DEN200039

DATE DE NOVO RECEIVED: June 12, 2020

SPONSOR INFORMATION:

Ortho-Space Ltd.
7 Halamish Street
Caesarea, 3079579
Israel

INDICATIONS FOR USE

The InSpace™ Subacromial Tissue Spacer System is indicated for the treatment of patients with massive, irreparable full-thickness torn rotator cuff tendons due to trauma or degradation with mild to moderate gleno-humeral osteoarthritis in patients greater than or equal to 65 years of age whose clinical conditions would benefit from treatment with a shorter surgical time compared to partial rotator cuff repair.

LIMITATIONS

The sale, distribution, and use of the InSpace Subacromial Tissue Spacer System are restricted to prescription use in accordance with 21 CFR 801.109.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The InSpace™ Subacromial Tissue Spacer System (**Figure 1**) is a prescription-use device that is comprised of a biodegradable implant provided pre-loaded on a deployer. The deployer is designed for deployment, inflation, sealing, and detachment of the implant in the subacromial space between the humeral head and the acromion. The system is single-use, supplied sterile, and ready for use in the operating room upon removal from the package. Once positioned in the subacromial space, the implant is filled with sterile saline (0.9%, not provided) to the pre-defined volume, sealed, and released from the deployer. Following implantation, it is designed to biodegrade over approximately one year.

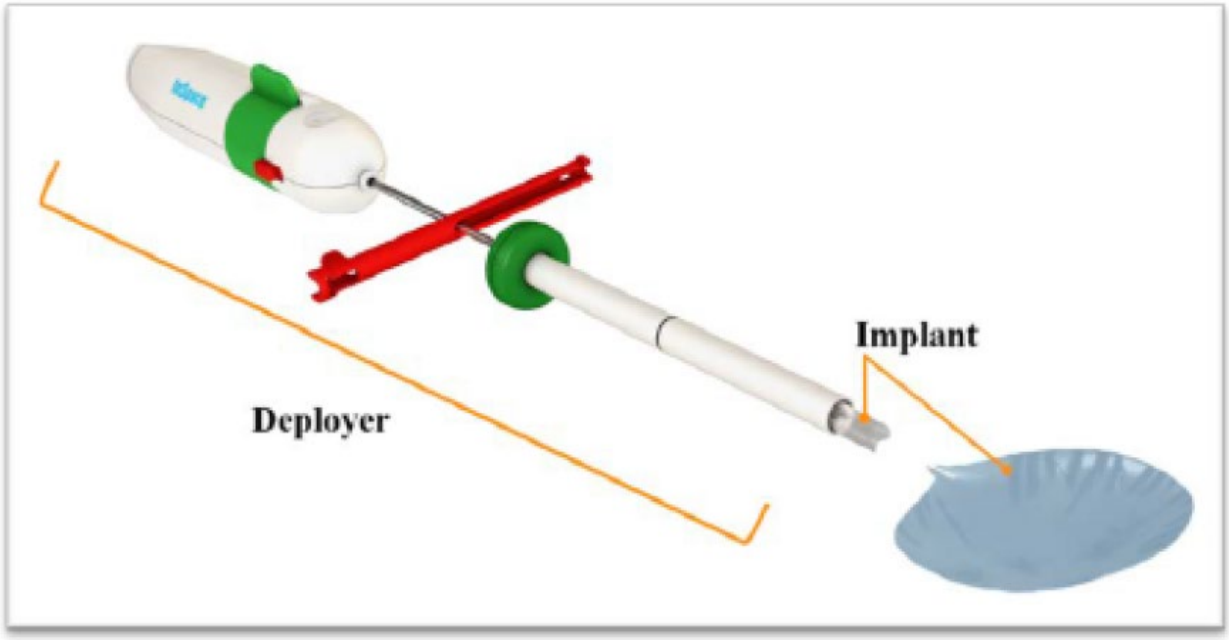

Figure 1: InSpace System Components, including the Deployer and Implant (in both folded and unfolded states)

The implant is supplied pre-folded within the cylindrical protective tube of the deployer to facilitate insertion into the subacromial space and achieves its final shape by subsequent unfolding via inflation with sterile saline, sealing, and detachment. It is supplied in three sizes to accommodate individual anatomical variations (Small, Medium, or Large). The InSpace implant is designed to reduce pain and restore function to the gleno-humeral joint by acting as a temporary spacer between the humeral head and acromion, enabling smooth gliding between the bones and reducing acromio-humeral contact pressure while depressing the humeral head to a more central anatomical position on the glenoid, similar to that of a shoulder with an intact rotator cuff.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY

The InSpace™ Subacromial Tissue Spacer System implant is manufactured from the following material shown in Table 1:

Table 2: InSpace Implant Material, Patient Contact Status, and Contact Duration

Description	Material	Direct Patient Contact	Contact Duration
Implant	Poly L-Lactide-co-Ɛ-caprolactone (Resomer® LC 703)	Yes	Permanent (>30 d)

Table 3: InSpace Implant Material, Patient Contact Status, and Contact Duration

Biocompatibility evaluation of the implant and the deployer have been completed according to FDA Guidance, *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process*. Cytotoxicity, intracutaneous irritation, systemic sub-acute and chronic toxicity, sensitization and material mediated pyrogenicity testing were conducted per ISO-10993-1. Chemical characterization and toxicological risk assessment were evaluated to address systemic toxicity, genotoxicity, and carcinogenicity endpoints for the implant. Exhaustive extraction along with characterization of the extract, did not show any extract in concentrations that would be of biocompatibility concern. Based on all the biocompatibility testing and evaluations, the InSpace Subacromial Tissue Spacer System was determined to be biocompatible.

STERILITY/PACKAGING/SHELF LIFE/PYROGENICITY

Sterility:

The subject device is provided sterile to the end user. The device is sterilized by ethylene oxide in accordance with ISO 11135:2008 "Sterilization of health care products -Ethylene oxide: Requirements for development, qualification, and routine control of a sterilization process for medical devices" to a sterility assurance level (SAL) of. 10^{-6}.

Packaging:

Packaging for the subject device is composed of three layers: the sterile barrier system (blister pack), moisture barrier system (foil pack), and final packaging system (single unit carton pack with IFUs). Packaging validation testing included visual inspection, peel strength testing, dye penetration testing, bubble emission testing, and simulated distribution testing in accordance with ISO 11607-1:2006 and ISO 11607-2:2006.

Shelf Life:

Representative sterilized samples real-time aged to 3 years were used to determine the shelf life of the device. Functionality testing was conducted to verify that the devices still functioned as expected after: 1-year real-time aged samples, 3-year accelerated aged samples, and 3-year real-time aged samples. The material and packaging properties did not degrade significantly during accelerated or real-time aging, and the devices passed the functionality testing after aging.

Pyrogenicity:

In accordance with the FDA Guidance Document, "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile" (2016) and the recommendations and limits specified in United States Pharmacopeia 38, National Formulary 33, General Chapter <161>, devices that are intended to be implantable should meet pyrogen limit specifications of <20 endotoxin units ("EU") per device. Testing was conducted on the subject device and results demonstrated an acceptable level. To address the possibility of endotoxin-mediated pyrogenicity, an endotoxin monitoring plan has been developed for the subject device. A risk assessment was performed based on the severity and probability of a pyrogenic response to the subject device, in accordance with ANSI/AAMI ST72:2019. This assessment included consideration of the intended use of the device, as well as manufacturing processes, characteristics and features of the device, and passing results of endotoxin testing using a validated test method. Per the alternative sampling plan for the InSpace system, bacterial endotoxin testing will be performed on three (3) units monthly according to the turbidimetric method used to detect the presence of bacterial endotoxins.

Reprocessing:

There are no reusable or reprocessed components in this device.

MAGNETIC RESONANCE (MR) COMPATIBILITY

The subject device is composed entirely of non-metallic components; per the FDA guidance document "Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment," the device is MR safe and poses no safety hazards in the MR environment.

PERFORMANCE TESTING - BENCH

The sponsor provided the following biochemical characterization and bench performance testing to demonstrate the integrity (mechanical and chemical stability), degradation profile and usability of the subject device.

Table 2: Physicochemical and mechanical tests conducted for the subject device.

Test	Purpose	Method	Results
In vitro degradation	To study the degradation mechanism and profile of the implant	Physiochemical test	Characterized the degradation of the implant over time via hydrolysis. At week (b) (4) (final time point), the implant was mostly degraded.
In vitro versus *in vivo* degradation	To correlate between *in vitro* and *in vivo* degradation	Physiochemical test	Demonstrated *in vitro-in vivo* correlation in terms of molecular weight and viscosity. The acceptance criteria were met in each case ((b) (4) degradation after (b) (4) weeks).
Fatigue testing of inflated implants	To demonstrate the ability of the device to withstand fatigue cycles under simulated condition	Mechanical test	Results showed average weight loss after (b) (4) days of periodical cyclic testing was (b) (4) considering standard deviation which met the acceptance criterion of less than (b) (4) weight loss. Additionally, there were no signs of degradation or failure observed during visual inspection.
Resistance to external loads	To demonstrate resistance of the device to loads simulating extreme physiological forces in the shoulder	Mechanical test	The acceptance criteria required that the implants could sustain a load greater than or equal to (b) (4) (b) (4) representing two times the maximum force expected on the implant in the subacromial space during the early post-operative period. Results showed that the average maximum load at failure was (b) (4) range: (b) (4) (b) (4) thus meeting the acceptance criteria. Furthermore, statistical analysis of the data showed that with (b) (4) reliability, the implants could withstand loads

			greater than (b) (4) (safety factor of (b) (4)

PERFORMANCE TESTING - ANIMAL

The objective of the pilot animal study was to assess biocompatibility, device degradation and safety of the subject device following implantation in the shoulder joint of (b) (4) A Good Laboratory Practices (GLP) study was performed in this model (n=30) to assess the biocompatibility of the subject device in the (b) (4) shoulder at (b) (4) and (b) (4) -weeks post-treatment, and of healing through histopathologic examination as well as determination of hematology and biochemistry parameters. The observed long-term tissue and cellular response to the implant material in the (b) (4) shoulder was within accepted parameters for a foreign body reaction to a biodegradable material, and the changes were indicative of excellent tolerance of the device. Another GLP study in (b) (4) (n=15) was performed to assess biodegradability of the subject device following subcutaneous implantation at (b) (4) (b) (4) and (b) (4) -weeks post-treatment. The results demonstrated similar degradation rates between in vitro and in vivo datasets based on molecular weight and inherent viscosity, meeting the pre-specified acceptance criteria. While these studies support biocompatibility of the device material, the animal performance testing is inadequate to assess the effectiveness of the device for its intended use. There is not a validated animal model to assess the effectiveness of this device primarily due to differences in biomechanics between quadrupeds and bipeds. As such, the utility of the animal model is limited to testing biocompatibility parameters.

SUMMARY OF CLINICAL INFORMATION

Study Design

A pivotal clinical trial was conducted with a non-inferiority, prospective, single blinded, multi-center, randomized, controlled study design at 22 sites (19 sites in the US and 3 sites in Canada). The study enrolled 184 subjects (93 investigational; 91 control) who were ≥ 40 years old with: positive diagnosis upon magnetic resonance imaging (MRI) of a full-thickness massive rotator cuff tear (MRCT) that could not be fully repaired surgically; baseline visual analog score (VAS) pain score > 30 mm; and, baseline Western Ontario Rotator Cuff index (WORC) total score ≥420. The purpose of the study was to evaluate the safety and effectiveness of the device as a primary surgical treatment for a MRCT compared to partial repair of a full-thickness MRCT performed during an arthroscopic procedure. Subjects were subsequently followed out to Month 24 post-treatment for the end of study analysis.

Subject Demographics

A total of 184 subjects were enrolled and randomized. The study included an active, standard of care control treatment group (Partial Repair) and an investigational treatment group (InSpace™). The two treatment groups were similar in terms of demographics and baseline characteristics, with an overall mean age of approximately 66 years (range: 44 to 84 years). The study population was 55% male with average body mass index ("BMI") of 30. On average, subjects

began experiencing symptoms 33.5 months prior to enrollment. The most common reported causes of the MRCT, in both treatment groups, were tendon degeneration associated with age, low energy fall, other, and fall from height. The racial composition of the study was 88% white, 8% black/African American, 1% Asian, and 3% other. Most subjects were not Hispanic or Latino (98%).

Primary Effectiveness Endpoints

The Primary Composite Endpoint for the study was defined as follows at 24 months:

- Western Ontario Rotator Cuff ("WORC") improvement of ≥275 points from pre-operative baseline;
- American Shoulder and Elbow Surgeons Standardized Shoulder Assessments ("ASES") improvement of ≥6.4 points from pre-operative baseline;
- No subsequent secondary surgical interventions ("SSSI") in the index shoulder through post-surgery; and
- Absence of Serious Adverse Device Effects ("SADEs"), through post-surgery.

The sponsor originally proposed pain and function assessments at Week 6 post-surgery and only those subjects identified as a success were considered for evaluation at Month 12 post-surgery (later revised to Month 24 post-surgery based upon FDA feedback). FDA requested that the Primary Composite Endpoint be assessed only at the Month 24 post-surgery visit due to differences in post-surgery rehabilitation and the resulting effect on outcomes at the Week 6 timepoint. The Per-Protocol (PP) analysis population is used for non-inferiority testing for the Primary Composite Endpoint. Results are presented in Table 3 for all study subjects at the Month 24 timepoint only (as requested by FDA), as well as in the subpopulations of subjects less than 65 years of age and 65 years of age and older.

The Revised Primary Composite Endpoint was assessed when all subjects reached their Month 24 post-treatment visit. Results are presented in the table below for all study subjects, as well as in the subpopulations of subjects less than 65 years of age and 65 years of age and older. As shown below, Month 24 post-treatment success rates are above 77% for all presented subpopulation analyses of both the treatment groups in both the PP and intent-to-treat (ITT) analysis populations. While non-inferiority was not statistically achieved for the population containing all subjects (p=0.06), non-inferiority was established in the subgroup of subjects 65 years of age and older (p=0.01). Additionally, it is noted that the InSpace™ group success rate was 84.8%, compared to 94.6% for the Partial Repair group in the PP population for patients < 65 years and did not meet the 10% margin for non-inferiority (p=0.93) demonstrating substantial variation in the effectiveness profile of the subject device based upon age less than or greater to or equal to 65 years of age.

Table 3: Primary Composite Endpoint Success at Month 24 post-treatment

	InSpace™			Partial Repair			P-value*
	N	N	%	N	n	%	
Per Protocol Population	82	71	86.6%	79	72	91.1%	0.06
< 65 years	33	28	84.8%	37	35	94.6%	0.93
≥ 65 years	49	43	87.8%	42	37	88.1%	0.01

*P-value for non-inferiority (10% margin)

Secondary Effectiveness Endpoints

Secondary endpoints assessed during the study included WORC, ASES, range of motion ("ROM"), Constant Murley, VAS Pain, and EQ-5D-5L. Results for mean change from baseline for each endpoint at each time point, as well as the 95% confidence intervals, are provided in Table 4 below. The results showed a mean improvement across all endpoints over time for the InSpace™ group, with very similar results for the InSpace™ group compared to Partial Repair at almost all time points. Notably, InSpace™ subjects demonstrated higher ROM (forward elevation) compared to the Partial Repair subjects, with a greater number of subjects exceeding baseline ROM levels at Month 24 post-treatment (InSpace™ – 71/82, 87%; Partial Repair – 58/77, 75%).

Table 4: Summary of Secondary Endpoints Through Month 24 post-treatment

	Visit	InSpace™ (N=93) Mean (95% CI)	Partial Repair (N=91) Mean (95% CI)	Mean Difference
WORC Scale: 0 to 2100 points (decrease indicates improvement)	Day 10	-268.60 (-348.13, -189.07)	-153.52 (-225.83, -81.22)	-115.08
	Week 6	-442.95 (-530.85, -355.04)	-357.27 (-439.95, -274.60)	-85.68
	Week 12	-576.28 (-670.82, -481.74)	-590.97 (-690.11, -491.82)	14.69
	Month 6	-875.73 (-974.81, -776.64)	-851.54 (-949.34, -753.73)	-24.19
	Month 12	-1000.34 (-1102.08, -898.60)	-943.82 (-1046.55, -841.08)	-56.52
	Month 24	-1083.37 (-1199.94, -966.81)	-1007.00 (-1108.34, -905.67)	-76.37
ASES Scale: 0 to 100 points (increase indicates improvement)	Day 10	5.84 (1.88, 9.81)	1.79 (-2.02, 5.59)	4.05
	Week 6	19.24 (14.87, 23.61)	13.81 (9.52, 18.09)	5.43
	Week 12	25.05 (20.33, 29.78)	24.57 (19.95, 29.20)	0.48
	Month 6	38.21 (33.90, 42.52)	36.34 (32.07, 40.60)	1.87

	Visit	InSpace™ (N=93) Mean (95% CI)	Partial Repair (N=91) Mean (95% CI)	Mean Difference
	Month 12	40.90 (36.58, 45.22)	41.25 (37.19, 45.32)	-0.35
	Month 24	46.22 (41.66, 50.79)	42.53 (37.96, 47.10)	3.69
ROM Scale: 0-180 degrees (increase indicates improvement)	Day 10	-57.61 (-71.93, -43.28)	-80.36 (-97.41, -63.30)	22.75
	Week 6	-12.85 (-23.69, -2.02)	-45.91 (-58.24, -33.57)	33.06
	Week 12	6.10 (-2.52, 14.72)	-3.92 (-13.26, 5.42)	10.02
	Month 6	27.38 (19.19, 35.57)	16.44 (8.11, 24.78)	10.92
	Month 12	35.39 (27.40, 43.38)	19.53 (11.95, 27.12)	15.86
	Month 24	36.89 (28.02, 45.76)	18.16 (9.33, 26.98)	18.73
Constant-Murley Shoulder Scale: 0 to 100 (increase indicates improvement)	Day 10	NA	NA	NA
	Week 6	-3.36 (-7.88, 1.16)	-10.33 (-14.19, -6.47)	6.97
	Week 12	9.27 (5.27, 13.27)	7.32 (3.90, 10.73)	1.95
	Month 6	21.35 (17.41, 25.30)	19.28 (15.55, 23.02)	1.55
	Month 12	26.27 (22.20, 30.35)	23.78 (20.05, 27.51)	2.49

	Visit	InSpace™ (N=93) Mean (95% CI)	Partial Repair (N=91) Mean (95% CI)	Mean Difference
	Month 24	28.22 (23.92, 32.51)	21.81 (16.99, 26.63)	6.41
VAS Pain Scale: 0 to 100 mm (decrease indicates improvement)	Day 10	-37.27 (-43.27, -31.27)	-35.15 (-41.34, -28.96)	-2.00
	Week 6	-40.80 (-46.91, -34.69	-41.15 (-46.65, -35.66)	0.35
	Week 12	-43.20 (-49.03, -37.36)	-43.20 (-49.03, -37.36)	0.00
	Month 6	-54.45 (-59.61, -49.29)	-48.94 (-54.78, -43.10)	-5.51
	Month 12	-54.86 (-59.93, -49.78)	-52.15 (-57.55, -46.75)	-2.71
	Month 24	-56.55 (-61.78, -51.32)	-54.55 (-59.92, -49.19)	-2.00
EQ-5D-5L (decrease indicates improvement)	Day 10	-0.49 (-1.11, 0.12)	-0.10 (-0.69, 0.49)	-0.39
	Week 6	-1.90 (-2.52, -1.28)	-1.62 (-2.15, -1.09)	-0.28
	Week 12	-2.22 (-2.88, -1.55)	-2.48 (-3.05, -1.92)	0.26
	Month 6	-3.85 (-4.46, -3.24)	-3.33 (-3.98, -2.68)	-0.52
	Month 12	-4.30 (-4.97, -3.62)	-3.99 (-4.61, -3.37)	-0.31

	Visit	InSpace™ (N=93) Mean (95% CI)	Partial Repair (N=91) Mean (95% CI)	Mean Difference
	Month 24	-4.65 (-5.36, -3.94)	-4.00 (-4.61, -3.39)	-0.65

Additionally, regarding surgical times as shown in Table 5, the InSpace™ group had a mean advantage over the Partial Repair for all times: Duration in Operating Room (InSpace™: 84 minutes; Partial Repair: 113 minutes), Duration of Anesthesia (InSpace™: 91 minutes; Partial Repair: 121 minutes) and Duration of Procedure (InSpace™: 45 minutes; Partial Repair: 71 minutes).

Table 5: Comparison of Surgical Treatment Details for the Investigational and Control Groups

Parameter (minutes)	InSpace (N=93)	Partial Repair (N=91)
	Mean	Mean
Duration in the Operating Room	84	113
Duration of Anesthesia	91	121
Duration of Procedure	45	71

Safety Data:

A summary of key findings of the 24-month safety data is provided in Table 6 below. The relative risk of the InSpace™ Group compared to Partial Repair Group for AEs of the index shoulder was 1.47 with a 95% CI of (1.02, 2.10), showing that the risk of AE for InSpace™ is higher than Partial Repair, with 95% certainty. Additionally, 31 of 93 subjects in the InSpace™ group (33%) had 45 adverse events involving the index shoulder, and 22 of 91 subjects in the Partial Repair group (24%) had 30 adverse events involving the index shoulder (RR 1.47; 95% CI 1.00, 2.15). In total, there was an excess of 15 mild-to-moderate adverse events of the index shoulder in the InSpace™ group compared to the Partial Repair group.

Table 6: Summary Adverse Event Data for the Investigational and Control Groups Through Month 24 post-treatment

Parameter	**InSpace (N=93)**	**Partial Repair (N=91)**	**Relative Risk**	**95% CI**
Adverse Events (AEs) of the index shoulder				
Subjects with AEs of the index shoulder, n (%)	31 (33%)	22 (24%)	1.38	0.87, 2.19

Total number of AEs of the index shoulder	45	30	1.47	1.02, 2.10
Non-Related Non-Serious	42	28	1.47	1.00, 2.15
Non-Related Serious	3	2	1.47	0.25, 8.58
Related Non-Serious	0	0	-	-
Related Serious	0	0	-	-
Subsequent secondary surgical interventions (SSSIs)	4 (4%)	3 (3%)	1.30	0.30, 5.67
Medications for AEs of the index shoulder				
Subjects who received any medication, n (%)	23 (25%)	17 (19%)	1.44	0.76, 2.31
Subjects who received non-narcotic medication only, n (%)	6 (6%)	3 (4%)	1.96	0.50, 7.59
Subjects who received opioids, n (%)	6 (6%)	6 (7%)	0.98	0.33, 2.92
Subjects who received injections, n (%)	11 (12%)	10 (11%)	1.08	0.48, 0.41
Subjects with open opioid prescriptions at last follow-up or study conclusion	3 (3%)	2 (2%)	1.47	0.25, 8.58
Subjects with unresolved AEs of the index shoulder, n (%)	13 (14%)	12 (13%)	1.06	0.51, 2.20

A summary of the AEs by type in both treatment groups is provided in Table 7 below. The most commonly reported event in both groups was pain (n=33, InSpace™; n=22, Partial Repair) and the majority of events in both groups (93% InSpace™, 90% Partial Repair) were classified as mild or moderate in severity.

Table 7: Adverse Event By Type Reported for the Investigational and Control Groups Through Month 24 post-treatment

Characteristic	**InSpace (45 AEs)**	**Partial Repair (30 AEs)**
Adverse Events Type		

Pain, number of AEs	33	22
Bursitis, number of AEs	1	3
Spasm, number of AEs	3	0
Swelling, number of AEs	3	0
Other, number of AEs	5	5
Adverse Events Severity		
Mild, number of AEs (%)	29	15
Moderate, number of AES	13	12
Severe, number of AEs	3	3
Average time for onset post-operatively (days)	219	251
Averaged duration for resolved events (days)	94	193
Total number of AEs of the index shoulder resolved	30	18
Total number of AEs of the index shoulder unresolved	15	12
Subjects with resolved AEs of the index shoulder, n (%)	28 (30%)	10 (11%)
Subjects with unresolved AEs of the index shoulder, n (%)	13 (14%)	12 (13%)
Subjects who could not be ruled out for a drug dependency or opioid use disorder	3 (3%)	2 (2%)

During the course of the study, 7 subjects (4 InSpace™ and 3 Partial Repair) had a subsequent secondary surgical intervention ("SSSI"), all occurring after Month 12 post-treatment. For 4 of the subjects, the cause was continuing pain, for 2 subjects, the cause of the SSSI was a serious adverse event ("SAE"), and for one subject in the InSpace™ group, the SSSI was precipitated by a proximal humerus fracture following a fall. It should also be noted that one subject in the Partial Repair group had an SSSI precipitated by a motor vehicle accident. Three subjects in the InSpace™ group compared to two patients in the Partial Repair Group had reverse total shoulder arthroplasty procedures and these patients accounted for all the non-device-related serious adverse events. No subject had a serious device-related adverse effect during the study.

Twenty-three of 93 InSpace™ subjects (25%) compared to 17 of 91 Partial Repair subjects (19%) received medication (oral medication or injections) for adverse events of the index shoulder. InSpace™ subjects compared to Partial Repair subjects had an increased relative risk that is not statistically significant for being treated with any medication for an adverse event of

the index shoulder (RR 1.44; 95% CI 0.76, 2.31). Three out of 93 InSpace™ subjects (3%) compared to 2 of 91 Partial Repair subjects (2%) with an adverse event of the index shoulder had a Clinical Events Committee (CEC) Determination of Drug Dependency/Opioid Use Disorder "Cannot be Established" based on available information (refer to Table 6). InSpace™ subjects compared to Partial Repair subjects have an increased relative risk that is not statistically significant for experiencing an adverse event that is associated with a serious risk of the index shoulder which includes both medical (e.g., a CEC Determination of Drug Dependency/Opioid Use Disorder "Cannot be Established") for surgical (reverse total shoulder arthroplasty) treatments. It should be noted that the sample size used for the study design was driven by effectiveness and not safety.

Magnetic Resonance Imaging Safety Data

Magnetic resonance imaging (MRI) endpoints were at Week 6 post-treatment to assess device inflation and location in the subacromial space (subset of patients) and at Month 12 post-treatment to assess device residuals, and condition of the shoulder joint and surrounding tissue. Of ninety-three (93) subjects randomized to InSpace™, a subgroup of thirty-four (34) subjects completed the Week 6 MRI. A Comparison of the InSpace™ MRI Reassessment Success Criteria by the Core Imaging Lab and FDA Independent Assessment is outlined in Table 8 below:

Table 8: Comparison of the InSpace MRI Reassessment Success Criteria by the Core Imaging Lab and FDA

Component	FDA Independent Assessment	MRI Reassessment by the Core Imaging Lab
Implant Inflation*	≥ 5 mm	Contains any fluid
Implant Location**	Sagittal plane: 10:00 to 2:00 AND Coronal plane: above humeral head	Subacromial space

*Note more stringent definition used by FDA in its independent assessment. 5 mm was chosen for acceptable implant inflation to reflect impact on restoration of humeral head alignment, given that studies have shown normal acromio-humeral intervals of 7-14 mm, and that proximal humeral migration is associated with larger rotator cuff tears. The sponsor stated that MRI acquisition parameters were established with "ongoing recruitment across study sites" so that the resulting image quality was not appropriate for quantitative measurements of implant inflation.

**In both definitions, only a portion of the implant needed to be visualized in the defined spaces. The sponsor's new image review charter further defined the subacromial space as being bounded by the "humeral head articular surface inferiorly, the acromion superoposteriorly, the coracoacromial ligament superiorly, and the coracoid anteriorly." This is concordant with the FDA's independent assessment definition of success criteria for implant location.

A summary of the Week 6 MRI Reassessment by the Core Imaging Lab and FDA Independent Musculoskeletal Radiologist Assessment of the 32 patients with evaluable MRIs of the 93 total patients in the InSpace™ Group is presented in Table 9 below. Migration or collapse/rupture is an issue with the subject device that has been identified with 6-week MRI data in 28% to 53% of

cases, according to the Sponsor and FDA independent musculoskeletal radiologic assessments respectively.

Table 9: Summary of 6 Week InSpace™ MRI Reassessment by the Core Imaging Lab and FDA Independent Musculoskeletal Radiologist

	Implant Inflation		Implant Location		Combined Inflation/Location	
	Success	%	Success	%	Success	%
Core Imaging Lab	28/32	88%	27/32	84%	23/32	72%
FDA Independent Musculoskeletal Radiologist	25/32	78%	20/32	63%	15/32	47%

From the Core Imaging Lab independent radiological assessment of the Week 6 MRIs, the InSpace™ implant was determined to be both inflated and located in the subacromial space in 23 of 32 (72%) of subjects with evaluable imaging. Separately, the InSpace™ implant was observed to be inflated in 28 of 32 subjects (88%) and located in the subacromial space in 27 of 32 subjects (84%).

Of the 171 MR images assessed at Month 12, 89 were in the InSpace™ group, and 82 were in the Partial Repair group. Ninety-four percent (94%) of the InSpace™ subjects assessed (83/89) did not exhibit any device residual at Month 12. Fifty subjects across both treatment groups were identified with radiological observations of synovitis and/or possible device residuals; however, the status of the radiological findings in the index shoulder in 35 of 37 (95%) of InSpace™ subjects and 11 of 13 (85%) of Partial Repair subjects was assessed to be "Minor" in nature. The condition of the shoulder joint and surrounding tissue at Month 12 was similar for both groups, except that a higher percentage of the InSpace™ group (42%) reported bone cysts compared to the Partial Repair group (26%).

In conclusion, the data demonstrates that the InSpace Group compared to the Partial Repair Group had an increased risk of total AEs, with 95% certainty, as well as a higher numerical percentage and corresponding relative risk ratios for a number of safety adverse events related to the subject device. This may be attributed to that the subject device is resorbing and that 28%-53% of implants are neither reliably located in the subacromial space nor reliably reducing acromio-humeral contact pressure to prevent patient symptomatology as well as having subsequent medical treatments and surgical treatments to disease progression. Massive, full-thickness rotator cuff tear disease progression can include a spectrum of shoulder pathology characterized by rotator cuff insufficiency, diminished acromiohumeral distance with impingement syndromes, and arthritic changes of the glenohumeral joint that are often associated with pain and was demonstrated in the safety assessment of the subject device. However, most event types identified in the index shoulder in both treatment groups (e.g., pain, stiffness, swelling) were prospectively identified as expected findings that may occur post-operatively with an arthroscopic treatment for a full thickness, irreparable MRCT. The majority of events in both groups (93% InSpace™, 90% Partial Repair) were classified as mild or moderate in severity. No subject had a serious device-related adverse effect during the study.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

The labeling consists of the following: device description, indications for use, instructions for use including surgical steps (e.g., device selection and placement), principles of device operation, identification of device materials, contraindications, warnings, precautions, MR compatibility, a list of potential adverse effects, importance of patient compliance with post-operative activity restrictions, and a summary of the clinical data. Furthermore, the sterile packaging includes a shelf life for the device.

The labeling meets the requirements of 21 CFR 801.109 for prescription devices.

RISKS TO HEALTH

Table 10 below identifies the risks to health that may be associated with use of the resorbable shoulder spacer and the measures necessary to mitigate these risks.

Table 10: Identified Risks to Health and Mitigation Measures

Identified Risk to Health	Mitigation Measures
No improvement in shoulder function and pain reduction due to device failure from: ▪ Device migration ▪ Device malposition ▪ Device collapse	Clinical performance testing Non-clinical performance testing Animal performance testing Labeling
Increased risk of adverse events (AEs) of the index shoulder (e.g., pain, spasm, and swelling, subsequent medical and surgical treatments secondary to disease progression)	Clinical performance testing Labeling
Adverse tissue reaction	Biocompatibility evaluation Animal performance testing Non-clinical performance testing Labeling
Infection	Sterilization validation Pyrogenicity testing Shelf life testing Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the resorbable shoulder spacer is subject to the following special controls:

1) Clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use and include the following:
    i. Evaluation of improvement of shoulder function and reduction of symptoms (e.g., pain and function) for the indications for use; and
    ii. Evaluation of relevant adverse events.
2) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use and include the following:
    i. Integrity testing of the device, including mechanical and chemical stability; and
    ii. Characterization of the device degradation profile.
3) Animal performance testing must include evaluation of the following:
    i. Adverse effects, including gross necropsy and histopathology; and
    ii. Device degradation to verify in vitro versus in vivo degradation correlation.
4) All patient-contacting components of the device must be demonstrated to be biocompatible.
5) Performance data must support the sterility and pyrogenicity of the device components intended to be sterile.
6) Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.
7) Labeling must include the following:
    i. Instruction for use, including specific instructions regarding device selection and placement;
    ii. A detailed summary of the clinical performance testing with the device, including procedure- and device-related complications or adverse events; and
    iii. A shelf life.

BENEFIT-RISK DETERMINATION

BENEFITS:

1) The clinical study demonstrated non-inferiority (p=0.01) compared to the standard of care, (partial repair of rotator cuff) group in improving shoulder function and reducing symptoms (e.g., pain) for patients ≥ 65 years of age at 24 months post-treatment.

2) The clinical study demonstrated positive results in secondary endpoints that support long-term, clinically meaningful, patient valued benefits — in particular Range of Motion (ROM) and VAS pain — at a magnitude similar to, or numerically greater than, those observed with the control group (partial repair).

3) The clinical study reported a shorter surgical time (25- 30 minutes) and a less invasive surgery for the subject device as compared to the control group (partial repair).

RISKS:

1) There is a 47% increased relative risk of total adverse events of the operative shoulder, with 95% certainty (Risk Ratio: 1.47; 95% CI 1.02, 2.10) when using the subject device compared to undergoing a partial rotator cuff repair in the arthroscopic treatment of full thickness, irreparable massive rotator cuff tears.

2) The InSpace™ subjects have a 44% increased relative risk for being treated with any medication (oral medications or injections) for an adverse event of the index shoulder as compared to the control (partial repair) subjects.

3) The InSpace™ subjects have an increased relative risk for experiencing an adverse event that is associated with a serious risk of the index shoulder, which includes both medical (e.g., open opioid prescriptions at last follow-up or study conclusion) and surgical (e.g., reverse total shoulder arthroplasty) treatments as compared to the control (partial repair) subjects.

4) Migration or collapse/rupture of the subject device has been identified with 6-week MRI data in 28% to 53% of cases according to the manufacturer and FDA independent musculoskeletal radiologic assessments, respectively.

Based on the totality of the evidence, the InSpace™ Subacromial Tissue Spacer System demonstrated a reasonable assurance of safety and effectiveness for the device for its intended use/indications for use and there is a low degree of uncertainty in this finding. In conclusion, the benefits of using the subject device for its intended use/indications for use outweigh the risks to health.

Patient Perspectives

Patient perspectives considered for the InSpace™ Subacromial Tissue Spacer System included:

The primary composite study endpoints included assessment of improvement in pain and function using patient reported metrics (i.e., ASES and WORC scores) at month 24. Additionally, pre-specified secondary effectiveness study endpoints included the following scales: WORC, ASES, including range of motion ("ROM"), Constant-Murley Shoulder Scale, VAS Pain Scale, and EQ-5D-5L to evaluate the treatment effect throughout the study. Of note, both the InSpace and partial repair group performed similarly on patient reported function and pain metrics (i.e., WORC, ASES, VAS pain). These patient reported outcomes are used to demonstrate a clinically meaningful improvement in pain and function.

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

> The InSpace™ Subacromial Tissue Spacer System is indicated for the treatment of patients with massive, irreparable full-thickness torn rotator cuff tendons due to trauma or degradation with mild to moderate gleno-humeral osteoarthritis in patients greater than or equal to 65 years of age whose clinical conditions would benefit from treatment with a shorter surgical time compared to partial rotator cuff repair.

The probable benefits outweigh the probable risks for the InSpace™ Subacromial Tissue Spacer Systems. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the InSpace™ Subacromial Tissue Spacer System is granted and the device is classified as follows:

Product Code: QPQ
Device Type: Resorbable shoulder spacer
Regulation Number: 21 CFR 888.3630
Class: II