DE NOVO CLASSIFICATION REQUEST FOR BEAR® (BRIDGE-ENHANCED ACL REPAIR) IMPLANT

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Resorbable implant for anterior cruciate ligament (ACL) repair**. A resorbable implant for anterior cruciate ligament (ACL) repair is a degradable material that allows for healing of a torn ACL that is biomechanically stabilized by traditional suturing procedures. The device is intended to protect the biological healing process from the surrounding intraarticular environment and not to replace biomechanical fixation via suturing. This can include devices that bridge or surround the torn ends of a ruptured ACL.
>
> **NEW REGULATION NUMBER:** 21 CFR 888.3044
>
> **CLASSIFICATION:** Class II
>
> **PRODUCT CODE:** QNI

BACKGROUND

> **DEVICE NAME:** BEAR® (Bridge-Enhanced ACL Repair) Implant
>
> **SUBMISSION NUMBER:** DEN200035
>
> **DATE DE NOVO RECEIVED:** June 4, 2020
>
> **SPONSOR INFORMATION:**
>
> Miach Orthopaedics, Inc.
> 69 Milk Street, Suite 100
> Westborough, Massachusetts 01581

INDICATIONS FOR USE

The BEAR® (Bridge-Enhanced ACL Repair) Implant is indicated as follows:

> The BEAR® (Bridge Enhanced ACL Repair) Implant is a bovine extracellular matrix collagen-based implant for treatment of anterior cruciate ligament (ACL) injuries. The BEAR® Implant is indicated for skeletally-mature patients at least 14 years of age with a complete rupture of the ACL, as confirmed by MRI. Patients must have an ACL stump attached to the tibia to construct the repair.

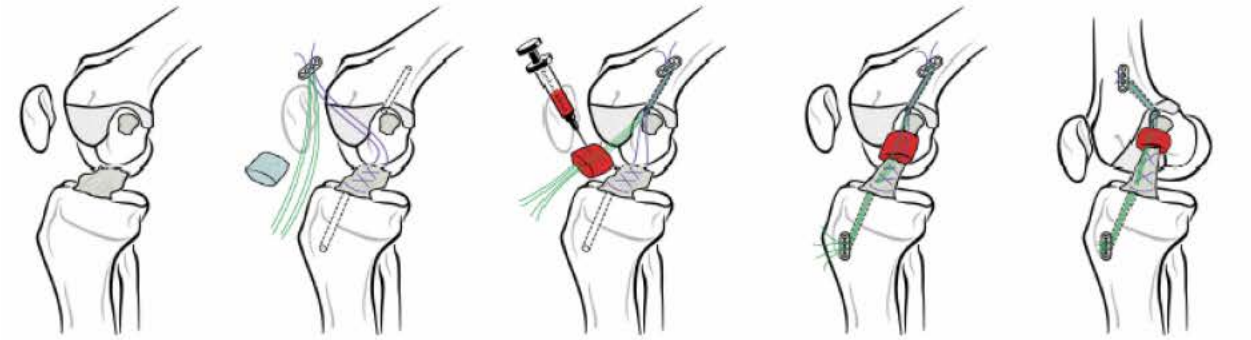
LIMITATIONS

The sale, distribution, and use of the BEAR® Implant 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 BEAR® Implant (22 mm in diameter and 45mm in length) is cylindrical in shape and comprised of collagen and extracellular matrix derived from bovine connective tissue, which has been cleaned, disinfected and processed by a proprietary manufacturing method. The implant has been terminally sterilized by electron-beam irradiation and is intended to be used with up to 10 ml of autologous blood drawn during the surgical implantation procedure. The BEAR® Implant stabilizes the blood in the gap between the torn ligament ends. The BEAR® Implant is resorbed within 8 weeks and replaced with a fibrovascular repair tissue.



SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The BEAR® Implant is manufactured from the following materials:

Description	Material	Direct Patient Contact	Contact Duration
Implant	Bovine collagen and extracellular matrix	Yes	Permanent (>30 d)

Biocompatibility evaluation has 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"*

SHELF LIFE/STERILITY

E-beam Sterilization:
The subject implant is provided sterile to the end user. The sterilization method is e-beam radiation at a dose of (b) (4) kGy. Sterilization was validated using the VDmax method as per ISO 11137-1:2006(R/2018) *Sterilization of health care products – Radiation Requirements for development, validation, and routine control of a sterilization process for medical devices* to ensure that a Sterility Assurance Level (SAL) of 10^{-6} is achieved.

Representative sterilized samples real-time aged to (b) (4) years were used to determine the shelf life of the device. Seal width, seal strength, and package integrity (bubble test) were used on accelerated aged samples to determine the sterile barrier packaging shelf life. Non-clinical performance testing of the representative devices was used to assess the performance shelf life.

Viral Inactivation and Titer Testing:
The Viral Inactivation properties of the BEAR® Implant manufacturing process have been validated to at least (b) (4) reduction for (b) (4) model viruses and at least (b) (4) reduction for the (b) (4) model virus, following the guidance in ISO 22442-3:2007 *Medical devices utilizing animal tissues and their derivatives- Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE)*, as well as the FDA guidance document *"Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices, March 2019)"*. This addresses the ability of the process to inactivate/eliminate viruses that might enter the process via the tissue used as a starting material. In addition, viral safety was confirmed via titer testing of representative product lots and incorporation of viral titer testing into the lot release criteria.

Reprocessing:
There are no reusable or reprocessed components in this device.

MAGNETIC RESONANCE (MR) COMPATIBILITY

The BEAR® Implant is a non-ferromagnetic, collagen-based material. The subject device is considered MR Safe.

PERFORMANCE TESTING - BENCH

The sponsor provided both biochemical characterization and bench performance testing to demonstrate the device's ability to absorb blood and be sutured.

Test	Purpose	Method	Acceptance Criteria	Results
Collagen content	Lot release criteria	Biochemical characterization	> (b) (4)	Mean (b) (4)
DNA content	Lot release criteria	Biochemical characterization	< (b) (4)	Mean: (b) (4)
Phospholipid content	Lot release criteria	Biochemical characterization	< (b) (4)	Mean: <LOQ

Pepsin activity	Lot release criteria	Biochemical characterization	< (b) (4)	Mean: <LOQ
GAG content	Lot release criteria	Biochemical characterization	> (b) (4)	Mean: (b) (4) µg/g
SDS-PAGE	Lot release criteria	Biochemical characterization	Presence of (b) (4) (b) (4) typical of Type I Collagen	All samples show α, β, and γ protein banding typical of Type I Collagen
DSC	Lot release criteria	Biochemical characterization	(b) (4) °C average peak temperature	Mean: (b) (4) °C
Endotoxin content	Lot release criteria	LAL test per ANSI/AAMI ST72	< (b) (4) EU/device	Mean: < (b) (4) EU/device
Density	Lot release criteria	Mass and dimensional measurement	(b) (4)	Mean: (b) (4) g/cm3
Blood absorption	Structural integrity	10mm thick disc sample placed in blood	(b) (4)	Mean absorption time: (b) (4) sec; Mean height reduction: (b) (4) %
Keith needle test	Structural integrity	Functional testing of the device's ability to retain mass while having 4 Keith needles with sutures passed through its length	(b) (4)	Mean: (b) (4) %

PERFORMANCE TESTING - ANIMAL

(b) (4) ACL transection models were utilized for pivotal animal studies on an investigational version of the subject device. These tests were utilized for design validation of the sterilization process, histologic evidence of device resorption within 8 weeks, and biomechanical evaluation of healed ligaments.

	VIV-003	VIV-004
Title	Retention Time of E-Beam Sterilized Miach [Implant] in the Porcine Knee	Aseptic vs. Ebeam Process In Vivo Trial
Date of Study	July 2013	November 2013
Objective	To determine how long residual particles of e-beam sterilized BEAR® Implant are found in synovium, ligament and popliteal lymph nodes after implantation in ACL wound site.	To determine if terminal sterilization with e-beam has any significant effect on the mechanical properties of primary ACL repairs performed with the BEAR® Implant eight weeks in vivo.
Animal Model	(b) (4)	(b) (4)
Number of Animals	(b)	(b) (4) per group)
Study Design	ACL transection created surgically in one knee of each animal; ACL repaired with BEAR Implant; treated ACL and contralateral ACL harvested and examined histopathologically; synovium and popliteal lymph nodes also harvested and examined histopathologically	ACL transection created surgically in one knee of each animal; ACL repaired with BEAR Implant; treated ACL and contralateral ACL harvested, tested for biomechanical function and examined histopathologically; synovium and popliteal lymph nodes also harvested and examined histopathologically

	VIV-003	VIV-004
Survival	(b)(animals each at 4 weeks and 6 weeks	8 weeks for all animals in both groups
Test Article	BEAR® Implant (30 mm x 22 mm) sterilized by e-beam at (b) (4) kGy	Group 1: BEAR® Implant (30 mm x 22 mm) sterilized by e-beam at (b) (4 kGy Group 2: BEAR® Implant (30 mm x 22 mm) aseptically prepared, no terminal sterilization
Results	No serious adverse effects to ACL, synovium, or popliteal lymph nodes. Implant material resorbed rapidly with near complete resorption by 6 weeks post-surgery. Implant material was associated with an expected mild mononuclear inflammatory reaction that was not considered excessive, likely contributing to its resorption and possibly helping establish a framework for local healing. BEAR® synovium mildly inflamed and hyperplastic compared to control joints. This was considered a normal reaction to surgery and expected to resolve over time. BEAR®-related popliteal lymph nodes had mild follicular and paracortical hyperplasia and sinus histiocytosis. This is consistent with inflammation associated with surgery. No implant was visualized in lymph nodes.	Biomechanical properties (linear stiffness, yield load, maximum load ratio, anteroposterior [AP] laxity) numerically lower in e-beam group than aseptic group but differences not statistically significant. Devices in both groups completely resorbed by 8 weeks post-surgery. Overall, no significant differences in the histologic appearance of the ligament, synovium or popliteal lymph nodes between the two treatment groups.
Conclusions	Near-complete resorption of the implant by 6 weeks post-surgery; no evidence of implant material in synovium or popliteal lymph nodes.	Minor alterations in the implant itself caused by irradiation most likely do not have a detrimental effect on the outcome after repair. Electron beam irradiation at (b) (4) kGy effectively sterilizes the implant without significantly harming the in vivo function of the implant as indicated by histopathological and biomechanical testing.

SUMMARY OF CLINICAL INFORMATION

Study Design

There were two completed clinical studies using the BEAR® Implant, including an early feasibility study (BEAR I; G140151) with (b) (4) patients, (b) (4) of whom received the BEAR® Implant, and a larger pivotal study (BEAR II; G150268). The sponsor relied on the pivotal BEAR II study to support the clinical performance of the BEAR® Implant.

In the BEAR II Study, the BEAR® Implant was studied in a randomized (2:1 ratio) controlled trial of (b) (4) subjects with complete ACL rupture, performed at one U.S. site by three surgeons. (b) (4) subjects were randomized to the BEAR® Implant and (b) (4) to the control treatment, ACL reconstruction (ACLR) with autograft (b) (4) subjects received a hamstring graft and (b)(received a bone-patellar-tendon-bone [BPTB] graft). Following surgery, subjects underwent a prescribed physical therapy regimen and were followed up at 1-2 and 6 weeks, and 3, 6, 12 and 24 months. Various outcomes were measured at the follow-up visits, including patient-reported outcomes, strength and functional measurements and imaging (X-ray, magnetic resonance imaging [MRI]). The primary endpoints, International Knee Documentation Committee (IKDC) Subjective Score, KT-instrumented AP knee laxity, and various safety parameters, were evaluated at 24 months (two years) post-surgery.

The primary analysis population was the modified Intent-to-Treat (mITT) population, which consisted of all ITT patients who had the BEAR procedure attempted. This included (b) (4) subjects, (b) (4) in the BEAR group and (b) (4) in the control group. (b) (4) subjects were consented and

randomized, but did not undergo surgery for various reasons. Thus, the ITT population was 109 subjects. The As-Treated (AT) population, analyzed for safety, was the same as the mITT population.

Subject Demographics

Subjects participating in the BEAR II study were young, with an overall mean age of 19.6±5.2 years and a median age of 17.5 years; overall, 64.2% of subjects were 18 years and younger, and 35.8% were 19 years and older. To be eligible for the study, all patients had to have closed femoral and tibial physes and were therefore skeletally mature. More females than males were enrolled in the study (55.0% female, 45.0% male). Time from injury to surgery averaged 35.5±7.9 days, with a range of 12.0 to 46.0 days. There were no significant differences between the treatment groups at baseline.

	BEAR N=73	Control N=36	Total N=109	p-value [1]
Age (years) [2]				
Mean ± SD (N)	19.5 ± 5.2 (73)	19.8 ± 5.3 (36)	19.6 ± 5.2 (109)	0.784
Median (Min, Max)	17.4 (13.8, 35.6)	17.7 (14.1, 35.6)	17.5 (13.8, 35.6)	
Age Group % (n/N)				0.674
18 Years Old and Under	65.8% (48/73)	61.1% (22/36)	64.2% (70/109)	
19 Years Old and Over	34.2% (25/73)	38.9% (14/36)	35.8% (39/109)	
Gender % (n/N)				0.838
Female	56.2% (41/73)	52.8% (19/36)	55.0% (60/109)	
Male	43.8% (32/73)	47.2% (17/36)	45.0% (49/109)	
BMI (kg/m^2)				
Mean ± SD (N)	24.7 ± 3.8 (72)	23.5 ± 4.6 (36)	24.3 ± 4.1 (108)	0.147
Median (Min, Max)	24.5 (18.1, 36.9)	22.2 (17.2, 38.3)	24.0 (17.2, 38.3)	
Time from Injury to Surgery (days)				
Mean ± SD (N)	34.7 ± 8.1 (65)	36.9 ± 7.6 (35)	35.5 ± 7.9 (100)	0.189
Median (Min, Max)	36.0 (12.0, 46.0)	39.0 (15.0, 46.0)	37.5 (12.0, 46.0)	

[1] p-value from two-sample t-test or Fisher's Exact test comparing BEAR arm to Control arm.
[2] Age = (Date of informed consent - date of birth)/365.25.

Safety Endpoints

There were no cases of deep joint infection or incision and drainage of deep surgical site infection and no evidence of graft/implant rejection in either group. Graft or repair failure occurred in nine BEAR subjects (13.8%) and two control subjects (5.7%), p=0.320. Additional surgical procedures (other than ACL surgery) were required on the study knee in eight BEAR subjects (12.3%) and four control subjects (11.4%), p=1.000. Neither comparison reached statistical significance. Bovine IgE antibody levels were positive at the 6-month follow-up in two BEAR subjects (3.1%) and no control subjects; both results were low positive (0.39 kU/L, just

slightly above the threshold of 0.35 kU/L) and resolved at 15 months and two years post-surgery. Neither subject had any adverse events related to the transient antibody elevation.

	BEAR N=65	Control N=35	p-value [1]
Deep Joint Infection/Incision and Drainage of Deep Surgical Site Infection	0% (0/65)	0% (0/35)	1.000
Evidence of Graft or Implant Rejection	0% (0/65)	0% (0/35)	1.000
Graft or Repair Failure	13.8% (9/65)	5.7% (2/35)	0.320
Additional Surgical Procedures Required on Study Knee [2]	12.3% (8/65)	11.4% (4/35)	1.000
Bovine IgE Ant body Levels >=0.35kU/L [3]	3.1% (2/64)	0% (0/33)	0.546
Bovine Antibody Level (kU/L)			
Mean ± SD (N)	0.39 ± 0.00 (2)		
Median (Min, Max)	0.39 (0.39, 0.39)		

[1] p-value from a two-sided Fisher's Exact Test, testing the null hypothesis that the true proportions are equal for the two treatments versus the alternative hypothesis that they are not equal.
[2] Not including subjects requiring a second ACL surgery.
[3] Subjects who tested positive resolved after 15 months and 2 years post procedure date.

Graft or repair failure was determined by positive pivot shift exam, Lachman exam with >6 mm side to side difference, absence of tissue in expected ACL location on MRI, evidence of graft or repair loss of continuity on MRI or symptomatic instability requiring revision ACL surgery. Of the nine BEAR subjects who experienced repair failure, five were non-compliant with post-operative requirements (physical therapy and/or brace use), returned to sports prior to surgeon clearance, had an accident or had a very high body mass index (BMI), and three returned to sports prior to 9 months post-surgery. All subjects who re-tore the ACL, in both groups, were age 18 years or younger. Results of the BEAR II study were compared to data from a historical control for which the manufacturer was able to access subject-level data and to data from a structured literature review. The analyses demonstrated that the rate of ACL re-tear with the BEAR® Implant was similar to the historical control and was consistent with the published literature. In conclusion, the BEAR® Implant had a similar safety profile to ACLR, and repair failure was more likely to occur in younger subjects, which is consistent with the experience of ACLR as documented in the literature.

Primary Effectiveness Endpoints

The BEAR II Study had two co-primary effectiveness endpoints, IKDC score and instrumented AP knee laxity, both at 24 months (two years) post-surgery (Table 3). In the primary analysis of the mITT population using multiple imputation for missing data, IKDC score for the BEAR group at 24 months was found to be non-inferior to control based on the null hypothesis that the true difference in the means between treatment groups was less than or equal to -11.5, which is considered a clinically significant difference and was the pre-specified non-inferiority delta.

Mean IKDC score in the BEAR group was 88.6±13.4 and in the control group 84.6±13.3. The 95% confidence interval for the difference in the means was 4.03 (-1.55, 9.61) ($p<0.001$).

Instrumented AP knee laxity using the KT device at 24 months was found to be non-inferior to control based on the null hypothesis that the true difference in the means between treatment groups was greater than or equal to 2.0 mm, which is considered a clinically significant difference and was the pre-specified non-inferiority delta. Mean instrumented AP knee laxity in the BEAR group was 1.7±3.2 mm and in the control group 1.8±2.8 mm. The 95% confidence interval for the difference in the means was -0.10 (-1.45, 1.25) ($p<0.001$).

Both primary endpoints were confirmed by multiple sensitivity analyses, including a tipping point analysis.

	BEAR N=65	Control N=35	Difference in Means BEAR - Control (95% CI) [2]	p-value
IKDC Patient Reported Score at 24 Months [3]				
Mean ± SD	88.6 ± 13.4	84.6 ± 13.3	4.03 (-1.55, 9.61)	<0.001
Median (Min, Max) [4]	91.95 (35.63, 100.00)	89.08 (47.13, 100.00)		
KT Instrumented AP Knee Laxity (mm) at 24 Months (Injured Knee - Non-Injured Knee) [5]				
Mean ± SD	1.7 ± 3.2	1.8 ± 2.8	-0.10 (-1.45, 1.25)	0.001
Median (Min, Max) [4]	1.88 (-8.50, 7.00)	1.38 (-6.00, 6.00)		

[1] Analysis done on mITT population with multiple imputation used for missing data. In the BEAR group, 3 (4.6%) patients are missing IKDC and 7 (10.8%) patients are missing AP knee laxity at 24 months. In the control group, 1 (2.9%) patient is missing IKDC and 3 (8.6%) are missing AP knee laxity at 24 months.
[2] Confidence interval based on the t-distribution.
[3] p-value from a one-sided, two-sample t-test of the null hypothesis that the true difference in means is less than or equal to -11.5 versus the alternative hypothesis that it is greater than -11.5.
[4] Median, minimum and maximum values are shown for the observed data only, and do not include imputed values.
[5] p-value from a one-sided, two-sample t-test of the null hypothesis that the true difference in means is greater than or equal to 2.0 versus the alternative hypothesis that it is less than 2.0.

Secondary Effectiveness Endpoints

Twelve secondary effectiveness endpoints were statistically tested using multiple imputation for missing data and were tested hierarchically in the order specified below to control the Type I error rate and adjust for multiple testing, whereby further testing would stop if a result was not significant. These endpoints were:

- Hamstring strength, reported as percentage of the contralateral side, and as determined by hand-held dynamometer at 6 months post-surgery (superiority)
- Hamstring strength, reported as percentage of the contralateral side, as determined by hand-held dynamometer at 12 months post-surgery (superiority)
- Hamstring to quadriceps ratio for the operated knee at 6 months post-surgery (superiority)
- Hamstring to quadriceps ratio for the operated knee at 12 months post-surgery (superiority)
- ACL Return-to-Sport Index (RSI) score at 6 months post-surgery (superiority)

- Knee Injury and Osteoarthritis Outcome Score (KOOS) at 12 months post-surgery – Pain (non-inferiority)
- KOOS at 12 months post-surgery – Symptoms (non-inferiority)
- KOOS at 12 months post-surgery – Sports and Recreation (non-inferiority)
- KOOS at 12 months post-surgery – Quality of Life (QOL; non-inferiority)
- KOOS at 12 months post-surgery – Activities of Daily Living (ADL; non-inferiority)
- KOOS at 12 months post-surgery – Pain (superiority)
- KOOS at 12 months post-surgery – Symptoms (superiority)

All 12 endpoints were statistically significant, either for non-inferiority or for superiority, as defined in the statistical analysis plan (SAP). Prone hamstring strength and hamstring to quadriceps ratio, both tested for superiority at both 6- and 12-months post-surgery, were significantly better in the BEAR group than the control group. Mean prone hamstring strength, which is measured as the proportion of the strength of the injured knee to the non-injured knee, was more than (absolute) 30% higher in the BEAR group than control at 6 months (on average, 93.3% vs. 59.1%, respectively [$p<0.001$]), and this finding was sustained at 12 months (on average, 96.6% vs. 65.2%, respectively [$p<0.001$]). Similarly, mean hamstring to quadriceps ratio at 6 months was 0.5 ± 0.2 in the BEAR group vs. 0.3 ± 0.1 in the control group ($p<0.001$); at 12 months, the difference between treatment groups was slightly smaller but still statistically significant in favor of BEAR (0.4 ± 0.1 vs. 0.3 ± 0.1, $p<0.001$).

The mean ACL RSI in the BEAR group was superior to control by 12 points at 6 months post-surgery (71.5 ± 19.5 compared to 58.9 ± 24.1, $p=0.005$), the timepoint that was tested for this analysis.

All five KOOS domains, including pain, symptoms, sports and recreation, QOL and ADL, were tested for non-inferiority at 12 months; all were statistically significant for non-inferiority, and in all cases the BEAR value was numerically higher than the control value. KOOS-pain and KOOS-symptoms were also tested for superiority at 12 months and found to be significantly better in the BEAR group than control.

The secondary endpoints were confirmed with sensitivity analysis.

	BEAR N=65	**Control N=35**	**Difference in Means BEAR - Control (95% CI) [2]**	**p-value [3]**
Prone Hamstring Strength at 6 Months (%) (100*(Injured Knee/Non-injured Knee)) (superiority) [4]				
Mean ± SD	93.3 ± 23.6	59.1 ± 21.3	34.21 (24.70, 43.72)	<0.001 [S]
Median (Min, Max) [5]	91.7 (29.6, 188.5)	56.4 (27.0, 124.0)		
Prone Hamstring Strength at 12 Months (%) (100*(Injured Knee/Non-injured Knee)) (superiority) [6]				
Mean ± SD	96.6 ± 16.7	65.2 ± 18.5	31.37 (24.08, 38.66)	<0.001 [S]

	BEAR N=65	Control N=35	Difference in Means BEAR - Control (95% CI) [2]	p-value [3]
Median (Min, Max) [5]	96.8 (40.0, 164.0)	61.9 (36.0, 114.5)		
Hamstring to Quadriceps Ratio at 6 Months (Hamstring Strength/Quadriceps Strength) (superiority) [4]				
Mean ± SD	0.5 ± 0.2	0.3 ± 0.1	0.16 (0.10, 0.22)	<0.001 [S]
Median (Min, Max) [5]	0.4 (0.2, 1.2)	0.3 (0.1, 0.7)		
Hamstring to Quadriceps Ratio at 12 Months (Hamstring Strength/Quadriceps Strength) (superiority) [6]				
Mean ± SD	0.4 ± 0.1	0.3 ± 0.1	0.13 (0.09, 0.17)	<0.001 [S]
Median (Min, Max) [5]	0.4 (0.2, 0.7)	0.3 (0.2, 0.5)		
ACL RSI Score at 6 Months (superiority) [7]				
Mean ± SD	71.5 ± 19.5	58.9 ± 24.1	12.59 (3.74, 21.44)	0.005 [S]
Median (Min, Max) [5]	75.0 (0.8, 100.0)	64.2 (11.7, 95.0)		
KOOS at 12 months (Pain) (non-inferiority) [8]				
Mean ± SD	94.4 ± 6.6	91.2 ± 7.1	3.19 (0.37, 6.02)	<0.001 [N]
Median (Min, Max) [5]	97.2 (66.7, 100.0)	91.7 (77.8, 100.0)		
KOOS at 12 months (Symptoms) (non-inferiority) [8]				
Mean ± SD	88.3 ± 9.3	82.4 ± 12.0	5.87 (1.54, 10.19)	<0.001 [N]
Median (Min, Max) [5]	89.3 (57.1, 100.0)	85.7 (57.1, 100.0)		
KOOS at 12 months (Sports and Recreation) (non-inferiority) [8]				
Mean ± SD	86.0 ± 15.7	83.0 ± 18.9	2.96 (-4.05, 9.98)	<0.001 [N]
Median (Min, Max) [5]	87.5 (15.0, 100.0)	85.0 (15.0, 100.0)		
KOOS at 12 months (Quality of Life) (non-inferiority) [8]				
Mean ± SD	69.4 ± 19.7	64.6 ± 17.5	4.76 (-3.19, 12.72)	<0.001 [N]
Median (Min, Max) [5]	68.8 (25.0, 100.0)	62.5 (37.5, 100.0)		
KOOS at 12 months (Activities of Daily Living) (non-inferiority) [8]				
Mean ± SD	98.8 ± 2.4	98.0 ± 4.2	0.74 (-0.59, 2.07)	<0.001 [N]
Median (Min, Max) [5]	100.0 (88.2, 100.0)	100.0 (77.9, 100.0)		
KOOS at 12 months (Pain) (superiority) [8]				
Mean ± SD	94.4 ± 6.6	91.2 ± 7.1	3.19 (0.37, 6.02)	0.027 [S]
Median (Min, Max) [5]	97.2 (66.7, 100.0)	91.7 (77.8, 100.0)		

	BEAR N=65	Control N=35	Difference in Means BEAR - Control (95% CI) [2]	p-value [3]
KOOS at 12 months (Symptoms) (superiority) [8]				
Mean ± SD	88.3 ± 9.3	82.4 ± 12.0	5.87 (1.54, 10.19)	0.008 [S]
Median (Min, Max) [5]	89.3 (57.1, 100.0)	85.7 (57.1, 100.0)		

N=non-inferiority test; S=superiority test

[1] Analysis done on mITT population with multiple imputation used for missing data.
[2] Confidence interval based on the t-distribution.
[3] These are to be Tested in a hierarchical manner so that if a significant result is reached the next variable will be tested. If a result is not significant (p>0.05) then testing will not continue.
For tests of superiority, the p-value is from a two-sided, two-sample t-test, testing the null hypothesis that the true means are equal versus the alternative hypothesis that they are not equal.
For tests of non-inferiority, the p-value is from a one-sided, two-sample t-test of the null hypothesis that the true difference in means is less than or equal to -10 versus the alternative hypothesis that it is greater than -10.
[4] Data for prone hamstring strength and hamstring to quadriceps ratio at 6 months was imputed for 1 (1.5%) patient in the BEAR group, and 1 (2.9%) patient in the control group.
[5] Median, minimum and maximum values are shown for the observed data only, and do not include imputed values.
[6] Data for prone hamstring strength and hamstring to quadriceps ratio at 12 months was imputed for 3 (4.6%) patients in the BEAR group, and 3 (8.6%) patients in the control group.
[7] Data for ACL RSI Score at 6 months was imputed for 1 (1.5%) patient in the BEAR group, and 1 (2.9%) patient in the control group.
[8] Data for KOOS (all parts) at 12 months was imputed for 1 (1.5%) patient in the BEAR group, and 2 (5.7%) of patients in the control group.

LABELING

The labeling consists of the following: device description, indications for use, instructions for use including surgical steps, compatibility of device with other soft tissue repair devices, 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

The table below identifies the risks to health that may be associated with use of the resorbable implant for ACL repair and the measures necessary to mitigate these risks.

Identified Risks to Health	Mitigation Measures
Repaired ACL has inadequate durability, leading to re-tear	Animal testing Clinical performance testing Labeling
Repaired ACL is loose or functionally limited, leading to joint instability	Clinical performance testing
ACL does not heal due to inadequate resorption or migration of implant	Non-clinical performance testing Animal testing
Adverse tissue reaction	Biocompatibility evaluation Labeling

Infection	Sterilization validation Shelf life testing Labeling
Febrile response due to endotoxins	Pyrogenicity testing
Implant is incompatible with other ACL repair instrumentation and sutures, leading to inability to complete surgery	Non-clinical performance testing Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the resorbable implant for ACL repair 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) Post-operative evaluation of knee pain and function; and
    (ii) Durability as assessed by re-tear or re-operation rate.
(2) Animal performance testing must demonstrate that the device performs as intended under anticipated conditions of use and include the following:
    (i) Device performance characteristics, including resorption and ligament healing at repair site; and
    (ii) Adverse effects as assessed by gross necropsy and histopathology.
(3) Non-clinical testing must demonstrate that the device performs as intended under anticipated conditions of use and include the following:
    (i) Characterization of materials, including chemical composition, resorption profile, and mechanical properties; and
    (ii) Simulated use testing, including device preparation, device handling, compatibility with other ACL repair instrumentation, and user interface.
(4) The device must be demonstrated to be biocompatible.
(5) Performance data must demonstrate the device to be sterile and non-pyrogenic.
(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) Identification of device materials and specifications;
    (ii) A summary of the clinical performance testing conducted with the device;
    (iii) Instructions for use, including compatibility with other ACL repair instrumentation or devices;
    (iv) Warnings regarding post-operative rehabilitation requirements; and
    (v) A shelf life.

BENEFIT-RISK DETERMINATION

The sponsor has collected adequate data to assess the safety profile of the subject device and has identified that there are benefits. Compared to the standard-of-care ACL reconstruction procedures, treatment with the subject device results in no donor site morbidity, which is confirmed via superiority in hamstring strength secondary endpoints at 6 and 12 months post-

operative. The KOOS pain and function subscales and RSI scores also demonstrated superiority at the 6- and 12-month post-operative time points. There is also a presumed benefit from a repair procedure preserving more native anatomy than a reconstruction, which requires wider bone tunnels. Device-related serious adverse events such as infection or rejection/immunogenic response were not observed in the clinical data and are mitigated by design controls and processing controls. Serious adverse events that necessitated reoperation (i.e., re-tear) were observed with similar frequency between ACL repairs with the subject device and ACL reconstructions. In conclusion, the benefits of using the subject device for its intended use/indications for use outweigh the risks to health.

PATIENT PERSPECTIVES

This submission did not include specific information on patient perspectives for this device.

BENEFIT/RISK CONCLUSION

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

> The BEAR® (Bridge Enhanced ACL Repair) Implant is a bovine extracellular matrix collagen-based implant for treatment of anterior cruciate ligament (ACL) injuries. The BEAR® Implant is indicated for skeletally-mature patients at least 14 years of age with a complete rupture of the ACL, as confirmed by MRI. Patients must have an ACL stump attached to the tibia to construct the repair.

The probable benefits outweigh the probable risks for the BEAR® Implant. The device provides benefits and the risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The De Novo request for the BEAR® (Bridge-Enhanced ACL Repair) Implant is granted and the device is classified as follows:

Product Code: QNI
Device Type: Resorbable implant for anterior cruciate ligament (ACL) repair
Regulation Number: 21 CFR 888.3044
Class: II