PearlMatrix™ P-15 Peptide Enhanced Bone Graft
Instructions for Use

DESCRIPTION

PearlMatrix™ P-15 Peptide Enhanced Bone Graft is a composite drug-device combination bone graft material consisting of synthetic P-15 peptide bound onto calcium phosphate particles, which are incorporated into a collagen matrix carrier.

The calcium phosphate particles, also known as anorganic bone mineral (ABM), provide a scaffolding and source of calcium for new bone growth. The calcium phosphate particles are highly porous, irregularly shaped and sized at 106-1000 microns (average size = 481 microns).

P-15 peptide is the active agent in PearlMatrix Bone Graft. P-15 peptide is a synthetically derived fifteen amino acid sequence that mimics a cell binding domain of Type 1 collagen, thus providing a favorable environment that facilitates attachment and activation of osteogenic cells to accelerate new bone formation.

The ABM/P-15 particles are incorporated into a fibrous collagen matrix as a carrier to facilitate handling and containment of the P-15 coated particles at the intended fusion site. PearlMatrix™ Bone Graft is composed of 80% (w/w) ABM/P-15 particles and 20% (w/w) collagen.

PearlMatrix Bone Graft is provided as a freeze-dried material that, when hydrated, forms a moldable putty that can be shaped as desired. PearlMatrix Bone graft is provided sterile and is intended for single use only.

INDICATIONS FOR USE

PearlMatrix Bone Graft is indicated for intervertebral body fusion of the spine in skeletally mature patients. PearlMatrix Bone Graft is intended to be used in conjunction with a PEEK TLIF Fusion Device and supplemental internal spinal fixation systems cleared by the FDA for use in the lumbosacral spine. The system is to be used in patients who have had at least six months of non-operative treatment. PearlMatrix Bone Graft is intended for use at one level in the lumbar spine (L2-S1) for the treatment of degenerative disc disease (DDD) with up to Grade I spondylolisthesis. DDD is defined as back and/or radicular pain of discogenic origin with degeneration of the disc confirmed by history, physical exam, and radiographic studies.

CONTRAINDICATIONS

PearlMatrix Bone Graft should not be used in situations where there is:

- An absence of load bearing structural support at the graft site
- Sensitivity to components of PearlMatrix Bone Graft
- Active infection at the operative site
- Operative site subject to excessive impact or stress

WARNINGS

- As with any surgical procedure, care should be exercised in treating individuals with preexisting conditions that may affect the success of the surgical procedure. This includes, but is not limited to, individuals with bleeding disorders of any etiology, long-term steroidal therapy, immunosuppressive therapy or high dosage radiation therapy.
- PearlMatrix Bone Graft is designed for single patient use only. Do not attempt to re-sterilize or re-use.
- The effect of PearlMatrix Bone Graft on pregnant or nursing patients has not been evaluated.
- PearlMatrix Bone Graft in a TLIF procedure is associated with a higher rate of secondary surgical interventions compared to TLIF with local autograft and cancellous allograft. It was not studied prospectively what pre-operative risk factors, if any, increase the risk of secondary surgical interventions with the use of PearlMatrix over TLIF with local autograft and cancellous allograft.

PRECAUTIONS

- PearlMatrix Bone Graft has been compared to TLIF with local autograft and cancellous allograft in the interbody space alone, without posterolateral fusion and without iliac crest autograft in any location. Its performance with respect to use of iliac crest autograft was not evaluated. Its performance compared with posterolateral fusion as an adjunct to interbody fusion or with anterior or lateral lumbar interbody fusion was not evaluated.
- PearlMatrix Bone Graft should only be used by physicians who are experienced with TLIF procedures. A lack of adequate experience and/or training may lead to a higher incidence of adverse events, including neurological complications.
- PearlMatrix Bone Graft is not intended to provide load-bearing structural support during the healing process. Supplemental internal fixation systems are required (see the Indications for Use statement).
- **DO NOT USE IF STERILE PACKAGING IS OPENED OR DAMAGED.** Discard or return damaged packaging and all contents.
- Do not use after the printed expiration date on the label.
- Discard unused contents.
- PearlMatrix Bone Graft should only be used in surgical procedures where it can be adequately contained at the bony void or defect. Avoid overfilling the bone void or pressurizing the treatment site.

POTENTIAL ADVERSE EVENTS

Potential adverse effects associated with any surgical procedure:

- Anesthesia complications, including an allergic reaction or anaphylaxis, or other reactions to anesthesia
- Reactions to transfused blood
- Anemia
- Blood loss/hemorrhage
- Heart or vascular complications, including:
    - Excessive bleeding or injury to blood vessels
    - Edema
    - Hematoma or seroma
    - Ischemia
    - Cardiac event
    - Myocardial infarction
    - Embolism, including pulmonary embolism
    - Thrombosis
    - Thromboembolism
    - Thrombophlebitis
    - Phlebitis
    - Stroke
    - Hemorrhage or vascular damage resulting in catastrophic or potentially fatal bleeding
- Septicemia
- Cerebral Vascular Accident (Stroke)
- Pulmonary complications, including atelectasis, pneumothorax or pneumonia, pulmonary edema and respiratory distress
- Blindness secondary to pressure on the eye during surgery
- False aneurysm
- Headache
- Infection (wound, local, and/or systemic) abscess, or cellulitis
- Soft tissue damage or fluid collections, including edema, hematoma or seroma, which may require drainage, aspiration, or debridement or other intervention
- Surgical wound dehiscence, necrosis, or scarring of tissue around the wound
- Post-surgical pain, bruising, tenderness or discomfort at the surgical site or incision and/or skin or muscle sensitivity over the incision which may result in skin breakdown, pain, and/or irritation
- Impairment of the gastrointestinal system including ileus or bowel obstruction, nausea or vomiting
- Impairment of the genitourinary system including incontinence, bladder dysfunction, urinary tract infection, or reproductive system complications
- Neurological complications including nerve damage, paralysis, seizures or convulsions, changes to mental status, or reflex sympathetic dystrophy
- Psychological illness
- Injury to muscles, or organs
- Insomnia
- Narcotic addiction
- Numbness
- Complications of pregnancy including miscarriage or congenital defects

- Inability to resume activities of daily living
- Death

Potential adverse effects associated with the single-level TLIF spinal procedures include:

- Risks to neurological structures:
    - Dural tear, dural leak and/or dural injury with or without CSF leakage
    - Arachnoiditis
    - Compressive neuropathy
    - Neurologic deterioration - injury to nerves or nerve roots associated with the spinal cord (resulting in pain, weakness, paralysis (partial or complete), paresthesia, altered reflexes, numbness, tingling, or other changes in sensation)
    - Coordination abnormalities
    - Gait disturbance
    - Headache
    - Otitis media
    - Tremors
    - Cerebrospinal fluid leakage
    - Cerebrospinal fistula
    - Reflex Sympathetic Dystrophy (RSD)
- Cauda equina syndrome
- Damage to nerves, blood vessels, and nearby tissues
- Impaired muscle or nerve function
- Epidural bleeding, hematoma, or fibrosis
- Bone necrosis
- Degenerative changes in adjacent segment
- Surgery at incorrect level
- Osteolysis
- Loss of bowel or bladder function
- Incontinence (loss of bowel or bladder control)
- Fracture of the vertebrae, spinous process, or other damage to bony structures during or after surgery
- Postoperative muscle and tissue pain
- Development of disc degeneration at adjacent levels
- Inflammatory conditions
- Loss of disc height
- Disc herniation
- Undesirable change in lordosis
- Scarring or soft tissue damage
- Spinal instability
- Spondylolisthesis acquisita (vertebral slippage)
- Retrolisthesis
- Spinal stenosis (narrowing of the spinal canal)
- Spondylosis
- Facet joint deterioration
- Infection of the bone, or surrounding soft tissue
- Musculoskeletal spasms (back or leg)

- Perineural fibrosis
- Surgery may not reduce the preoperative pain
- Pain and discomfort associated with the presence of implants
- Pain and discomfort associated with the surgical procedure (e.g., cutting of muscles, ligaments, and tissue) and healing
- The spine may undergo adverse changes or deterioration including loss of proper spinal curvature, correction, height, and/or reduction, or malalignment, and another surgery may be required
- Adverse bone/implant interface reaction
- Extrusion or migration resulting in pain, neural impingement, physical impairment, or loss of function, any of which may require revision surgery
- Abnormal bone formation in an unintended location
- Excessive or incomplete bone formation

Potential adverse effects specific to PearlMatrix Bone Graft:

- Allergic reaction to components of PearlMatrix Bone Graft

For specific adverse events that occurred in the clinical study, see **TABLES 5-8.**

SUMMARY OF CLINICAL STUDY

Overview of Clinical Study

The PearlMatrix Bone Graft in Transforaminal Lumbar Interbody Fusion with Instrumentation Study was a multi-center, single blinded, randomized, controlled clinical trial. The objective of the study was to evaluate if the PearlMatrix Bone Graft is not inferior in effectiveness and safety to local autologous bone (and allograft as extender where necessary) when applied in instrumented transforaminal lumbar interbody fusion (TLIF) in subjects with degenerative disc disease.

Subjects were enrolled according to the inclusion/exclusion criteria outlined below. Subjects were required to meet all the inclusion and none of the exclusion criteria.

Inclusion Criteria:

1. Skeletally mature adults between 22 and 80 years old (inclusive)
2. Back pain with radicular symptoms as evidenced by leg pain, confirmed by history and physical exam
3. Radiographically determined discogenic origin of the pain demonstrating at least one of the following characteristics: Degenerated/dark disc on MRI, instability (angulation ≥ 5° and/or translation ≥ 3mm on flexion/extension radiographs), osteophyte formation, ligamentous thickening, decreased disc height compared to adjacent levels on radiographic film, CT, or MRI, and disc herniation on CT or MRI
4. Oswestry Low Back Pain Disability Questionnaire score of ≥ 35
5. Involved disc(s) between L2 and S1
6. Planned lumbar fusion at a single level only
7. Failed to gain adequate relief from at least 6 months of adequate non-operative treatment
8. Able and willing to give consent to participate in study

9. Willing and able to participate in the study follow-up according to the protocol
10. Willing and able to comply with postoperative management program

Exclusion Criteria:

1. Systemic infection such as AIDS, HIV, and active hepatitis
2. Autoimmune disease that affects bone formation
3. Significant metabolic disease that in the surgeon's opinion might compromise bone growth such as osteoporosis, osteopenia, or osteomalacia
4. Taking medication for the prevention of osteoporosis or other medications that may interfere with fusion (e.g. steroids, or has received drugs that interfere with bone metabolism within 2 weeks of surgery)
5. Circulatory, cardiac, or pulmonary problems that could cause excessive surgical risk
6. Active malignancy
7. Nondiscogenic source of symptoms (e.g. tumor, etc.
8. Multiple level symptomatic degenerative disc disease where more than one level requires fusion
9. Previous spinal instrumentation or a previous interbody fusion procedure at the involved level
10. Isthmic Spondylolisthesis
11. Spondylolisthesis ≥ grade 2 if present
12. Active local or systemic infection
13. Known allergy to components within PearlMatrix Bone Graft including bovine collagen; PEEK, or materials in supplemental fixation systems
14. Pregnant or planning to become pregnant in the next 2 years
15. More than one level to be fused (note: multi-level decompression is acceptable)
16. Has a history of substance abuse (e.g. recreational drugs, alcohol) within the past 2 years
17. Is a prisoner
18. Is currently involved in a study of another investigational product for similar purpose
19. Has a disease process that would preclude accurate evaluation (e.g. neuromuscular disease, significant psychiatric disease)
20. Has active or recent (within the past 2 years) Worker's compensation litigation
21. Any condition that would interfere with the subject's ability to comply with the study-related requirements

STUDY DESIGN/METHODS

A total of 293 subjects were randomized in a 1:1 ratio to either the Investigational arm (TLIF with the PearlMatrix Bone Graft) or the active Control arm (TLIF with local autograft bone optionally mixed with allograft to supplement autograft volume if required) for the modified Intent to Treat (mITT) analysis set: 143 subjects in the PearlMatrix arm and 150 subjects in the Control Arm. For the As Treated analysis set, a total of 141 subjects were treated in the PearlMatrix arm of the study and a total of 149 subjects were treated in the Control arm. The As Treated population was the analysis set based on the product each subject actually received, i.e., PearlMatrix or the Control.

The primary study hypothesis was that the PearlMatrix Bone Graft is non-inferior to the control with respect to a composite clinical success. Composite Clinical Success (CCS) was defined as all of the following at month 24: Achievement of fusion, at least a 15-point improvement in ODI from baseline, no new or worsening, persistent neurological deficit relative to baseline, no index level secondary

surgical intervention, and no serious device-related adverse events. Fusion was assessed using thin-cut CT and required continuous bridging bone from endplate to endplate with no intervening fractures or discontinuities. Index-level secondary surgical interventions included any adjustments to the index level even in the case of surgery for adjacent-level disease.

The evaluations performed in relation to the index procedure pre-operatively, as well as assessments performed which are used to assess the endpoints post-operatively, are shown in **TABLE 1**. Adverse events (AEs) and complications were recorded at all visits, including unscheduled visits, as also outlined in **TABLE 1**.

TABLE 1 - Study visits and collection of outcome measurements

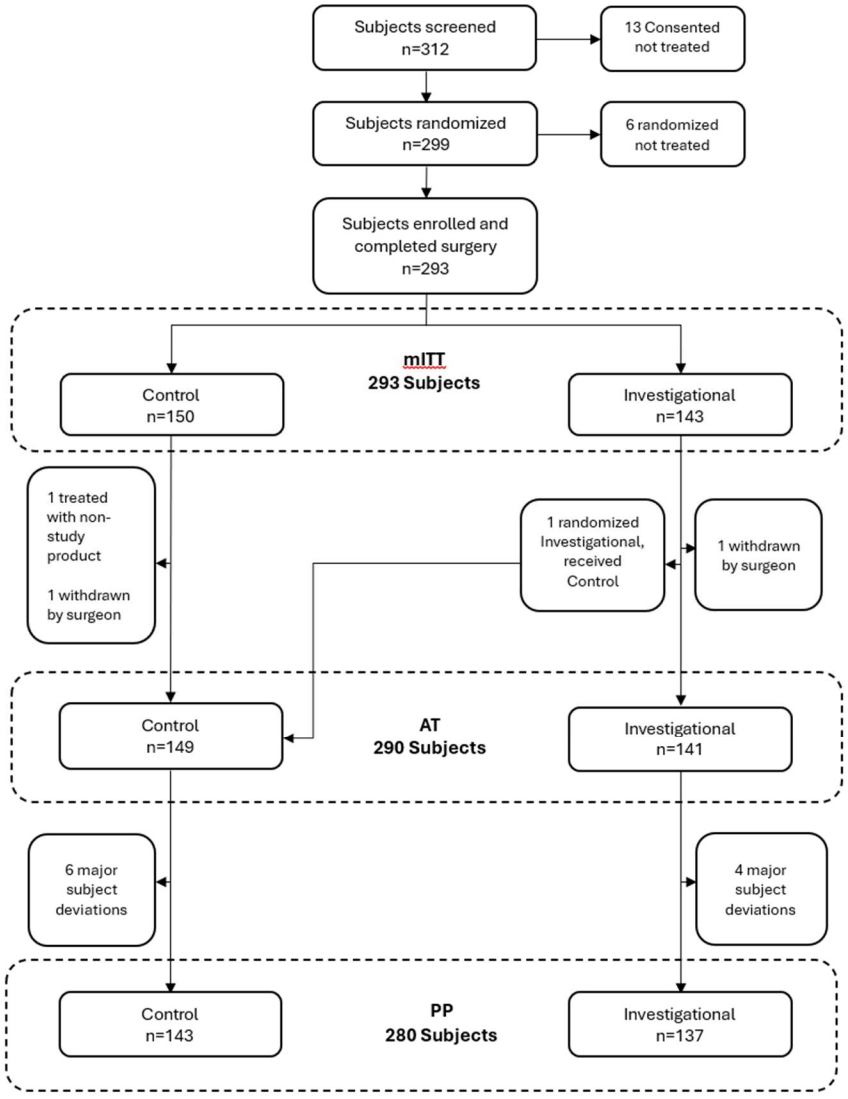
Procedure	Visit 1 (-60 to -1 d)	Visit 2 (day 0)	Visit 3 (+/- 10d)	Visit 4 (+/- 14d)	Visit 5 (+/- 30d)	Visit 6 (+/- 60d)	Visit 7 (+/- 60d)	Visit 8 (+/- 120d)	Visit 9 (+/- 120d)	Visit 10 (+/- 120d)	Visit 11 (+/- 120d)
	Baseline	Surgery	6w	3m	6m	12m	24m	36m	48m	60m	72m
Informed Consent	X										
Medical History	X										
Demographics	X										
Subject Eligibility Verification	X										
Randomization		X									
Treatment		X									
Pregnancy test	X[c]										
VAS	X		X	X	X	X	X	X	X	X	X
Clinical exam	X		X	X	X	X	X	X	X	X	X
ODI	X			X	X	X	X	X	X	X	X
SF-12	X				X	X	X	X	X	X	X
Blood Draw	X[f]		X	X	X	X	X[a]	X[a]	X[a]	X[a]	X[a]
Radiographs (Flexion/ Extension)	X[d]						X				
Radiographs (AP/Lateral)	X[d]	X[e]	X[e]	X[e]	X[e]	X[e]	X	X	X	X	X
Prior Medications	X										
CT					X	X[b]	X[b]				
Concomitant Medications		X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X

a - Blood draw is required only if baseline sera results are not achieved.
b - To reduce unnecessary radiation exposure, visits 6 (month 12) and 7 (month 24) CT will not be required if independent review is deemed fused at the 6- or 12-month assessment.
c - Pregnancy test can be collected on day of surgery based on institution's standard policies. Both urine and serum pregnancy testing are acceptable.
d - Radiographs collected prior to the 60-day window in the baseline visit that were used to diagnose the need for surgery will be accepted to reduce additional radiation exposure
e - Obtain any standard of care x-rays of the lumbar region.
f - Collection of the blood draw may be completed on the day of surgery prior to treatment.

Subject Accountability

Subjects were enrolled at 33 sites in the United States. A total of 293 subjects were enrolled (143 Investigational and 150 Control) in the modified Intent to Treat (mITT) population. Three (3) randomized subjects did not receive a study treatment (1 Investigational and 2 Controls) and one (1) subject randomized to the Investigational arm received the Control treatment. The As Treated (AT) Population excluded the three (3) randomized subjects not treated and accounted for the other subject in the Control arm. Thus, the AT population included 290 subjects: 141 Investigational and 149 Control. Subject accountability for the mITT population is shown in **FIGURE 1** for all subjects who were randomized into the study. Clinical visit follow-up among expected due subjects at 24 months was 86.7% and 86.9% for the PearlMatrix and Control arms, respectively. Based on theoretical due status and subtracting only deaths among theoretical due and those not yet overdue, 85.8% in the PearlMatrix arm and 86.6% in the Control arm were evaluable for Month 24 CCS.

FIGURE 1 – Subject Accountability



Demographics and Baseline Characteristics

There were no significant differences in baseline characteristics between groups with respect to age, gender, height, weight body mass index (BMI), race/ethnicity and nicotine use status. Subjects were stratified by higher risk (nicotine use, BMI≥30, and/or type 2 diabetes) and normal risk. There was no significant difference between groups relative to the risk classification. About 62% of the PearlMatrix subjects and 63% of the Control subjects were classified as higher risk.

Clinical Endpoints

The subjects were masked to the treatment assignment. In addition, the fusion evaluations and neurological outcomes were performed by masked evaluators. The primary effectiveness endpoint was defined as Month 24 Composite Clinical Success (CCS). All the following had to be achieved for a subject to be classified as achieving primary Month 24 CCS:

- No index level secondary surgical intervention to Study Day 730 (i.e., 24 months);
- Achievement of fusion by Month 24 visit (Fusion is defined as evidence of bridging trabecular bone between the vertebral bodies by CT scan on axial, sagittal or coronal reconstructions);
- At least 15-point improvement in ODI from baseline to Month 24 visit on a 100-point scale;
- No new or worsening, persistent neurological deficit comparing Month 24 to baseline (i.e., maintenance or improvement of the baseline motor and sensory scores on 5-point scales), and
- No serious device-related adverse event to Study Day 730 (i.e., 24 months).

Secondary endpoints evaluated during the study included the following: time to fusion; back pain and leg pain, as measured by a 10-point Visual Analog Scale ("VAS"); quality of life, assessed using the SF12® questionnaire.

Surgery and Operative Characteristics

The operative characteristics recorded included surgical approach (open versus minimally invasive), duration of surgery, level operated, blood loss, decortication of facet joints. There were no significant differences between groups. A summary of the surgery and operative characteristics is provided in **TABLE 2**.

TABLE 2 – Surgery and Operative Characteristics – mITT Population

	PearlMatrix™ N=142	Control N=148
Surgery Level	n (%)	n (%)
L1-L2	0 (0.0%)	1 (0.7%)
L2-L3	6 (4.2%)	2 (1.4%)
L3-L4	12 (8.5%)	20 (13.5%)
L4-L5	88 (62.0%)	88 (59.5%)
L5-S1	36 (25.4%)	37 (25.0%)
Facet Joint Decortication	92 (64.8%)	104 (70.3%)
Surgical Procedure		
Open	84 (59.2%)	75 (50.7%)
Minimally Invasive	58 (40.8%)	73 (49.3%)
Duration of Anesthesia (min)	238.5 ± 59.8 Range: 114.0-480.0 N=141	243.5±61.3 Range: 160.0-461.0 N=148
Duration of Surgery (min)	172.9.1±51.6 Range: 71.0-382.0 N=141	178.5±54.7 Range: 79.0-360.0 N=147
Blood Loss (mL)	145.5±143.8 Range: 10.0-1100.0 N=142	158.0±161.2 Range: 5.0-1000.0 N=148

Safety Results

A summary of the adverse event rates over the course of the study is provided in **TABLE 3**. The proportion of subjects with any adverse event was 86.5% in the PearlMatrix arm and 81.2% in the Control arm. The difference in adverse event rates was not statistically significant. The proportion of subjects with any serious adverse event was 31.9% in the PearlMatrix arm and 29.5% in the Control arm. The rate of serious adverse events was similar in both arms.

TABLE 3 – Summary of Adverse Event Rates – AT Population

Date of data transfer 14JUN2024	P15L (N=141)			Autologous Bone (N=149)			P15L vs. Autologous Bone[1]		
	Events	n	%	Events	n	%	Diff (%)	LB	UB
Any adverse event (per patient)	607	122	86.5	617	121	81.2	5.3	-3.1	13.8
Any device related AE[2]	28	22	15.6	22	20	13.4	2.2	-5.9	10.3
Any procedure related AE[2]	189	80	56.7	141	59	39.6	17.1	5.8	28.5
Any SAE	68	45	31.9	76	44	29.5	2.4	-8.2	13.0
SAE, device/procedure related	45	37	26.2	24	20	13.4	12.8	3.7	21.9
SAE, device/procedure related that resulted in SSI	17	11	7.8	4	4	2.7	5.1	0.0	10.3
SAE, device related	8	8	5.7	8	7	4.7	1.0	-4.1	6.1
SAE, device related that resulted in SSI	7	7	5.0	4	4	2.7	2.3	-2.2	6.7
SAE, procedure related	45	37	26.2	24	20	13.4	12.8	3.7	21.9
SAE, procedure related that resulted in SSI	17	11	7.8	4	4	2.7	5.1	0.0	10.3
Any AE of Special Interest	23	18	12.8	31	19	12.8	0.0	-7.7	7.7
Deaths	2	2	1.4	1	1	0.7	0.7	-1.6	3.1

Notes:

[1] Unadjusted device group differences and 95% confidence intervals (CI) for group differences.

[2] Device or Procedure relatedness includes possible, probably, and definitely related.

A summary of all adverse events is provided in **TABLE 4**. The number of these individual types of adverse events was comparable between groups throughout the study.

TABLE 4 – Summary of specific adverse events – AT Population

Adverse Event	PearlMatrix n=141			Control n=149		
	Subjects	%	Events	Subjects	%	Events
Any Adverse Event	122	86.5	607	121	81.2	617
Dural tear	6	4.3	6	4	2.7	4
Graft complication	1	0.7	1	0	0.0	0
Lumbar vertebral fracture	3	2.1	3	2	1.3	2
Pain in extremity	18	12.8	24	25	16.8	33
Pseudarthrosis	2	1.4	2	5	3.4	5
Incomplete spinal fusion	3	2.1	3	4	2.7	4
Cerebrospinal fluid leakage	1	0.7	1	2	1.3	2
Lumbar radiculopathy	5	3.5	5	3	2.0	3
Back pain	45	31.9	55	37	24.8	50
Radicular pain	3	2.1	4	2	1.3	2
Radiculopathy	11	7.8	11	12	8.1	12
Sciatica	5	3.5	5	5	3.4	5
Spinal claudication	0	0.0	0	1	0.7	1
Device dislocation	1	0.7	1	0	0.0	0
Implant subsidence	4	2.8	4	0	0.0	0
Postoperative wound infection	4	2.8	5	0	0.0	0
Wound infection	2	1.4	2	0	0.0	0
Heterotopic ossification	0	0.0	0	0	0.0	0
Osteolysis	0	0.0	0	0	0.0	0
Seroma	2	1.4	2	0	0.0	0
Others[1]	47	33.3	473	57	38.3	494

[1]Others includes blood and lymphatic system disorders; cardiac disorders; congenital, familial and genetic disorders; ear and labyrinth disorders; eye disorders; gastrointestinal disorders; general disorders; hepatobiliary disorders; immune system disorders; infections and infestations; injury, poisoning and procedural complications; investigations; metabolism and nutrition disorders; musculoskeletal and connective tissue disorders; neoplasms benign, malignant and unspecified; nervous system disorders; psychiatric disorders; renal and urinary disorders; reproductive system and breast disorders; respirator, thoracic and mediastinal disorders; skin and subcutaneous tissue disorders; surgical and medical procedures; and vascular disorders. Includes 3 unclassified events in the PearlMatrix arm.

A summary of serious adverse events is provided in **TABLE 5**. The number of these individual types of adverse events was comparable between groups throughout the study.

TABLE 5 – Serious adverse events – AT Population

Adverse Event	PearlMatrix n=141			Control n=149		
	Subjects	%	Events	Subjects	%	Events
Any Adverse Event	45	31.9	68	44	29.5	76
Dural tear	2	1.4	2	0	0.0	0
Graft complication	0	0.0	0	0	0.0	0
Lumbar vertebral fracture	1	0.7	1	1	0.7	1
Pain in extremity	2	1.4	2	1	0.7	1
Pseudarthrosis	1	0.7	1	2	1.3	2
Incomplete spinal fusion	1	0.7	1	2	1.3	2
Cerebrospinal fluid leakage	1	0.7	1	2	1.3	2
Lumbar radiculopathy	4	2.8	4	1	0.7	1
Back pain	6	4.3	6	1	0.7	1
Radicular pain	0	0.0	0	1	0.7	1
Radiculopathy	2	1.4	2	0	0.0	0
Sciatica	0	0.0	0	0	0.0	0
Spinal claudication	0	0.0	0	1	0.7	1
Device dislocation	0	0.0	0	0	0.0	0
Implant subsidence	1	0.7	1	0	0.0	0
Postoperative wound infection	1	0.7	1	0	0.0	0
Wound infection	2	1.4	2	0	0.0	0
Heterotopic ossification	0	0.0	0	0	0.0	0
Osteolysis	0	0.0	0	0	0.0	0
Seroma	0	0.0	0	0	0.0	0
Others[1]	23	16.3	44	33	22.1	64

[1]Others includes blood and lymphatic system disorders; cardiac disorders; congenital, familial and genetic disorders; ear and labyrinth disorders; eye disorders; gastrointestinal disorders; general disorders; hepatobiliary disorders; immune system disorders; infections and infestations; injury, poisoning and procedural complications; investigations; metabolism and nutrition disorders; musculoskeletal and connective tissue disorders; neoplasms benign, malignant and unspecified; nervous system disorders; psychiatric disorders; renal and urinary disorders; reproductive system and breast disorders; respirator, thoracic and mediastinal disorders; skin and subcutaneous tissue disorders; surgical and medical procedures; and vascular disorders. Includes one (1) unclassified event in the PearlMatrix arm.

A summary of procedure-related adverse events is provided in **TABLE 6.** The number of these individual types of adverse events was comparable between arms throughout the study. However, there were more total procedure-related adverse events in the PearlMatrix arm than the Control arm, even though the surgical procedure was identical in both arms.

TABLE 6 – Procedure-related adverse events – AT Population

Adverse Event	PearlMatrix n=141			Control n=149		
	Subjects	%	Events	Subjects	%	Events
Any Adverse Event	80	56.7	189	59	39.6	141
Dural tear	6	4.3	6	2	1.3	2
Graft complication	1	0.7	1	0	0.0	0
Lumbar vertebral fracture	1	0.7	1	1	0.7	1
Pain in extremity	6	4.3	6	3	2.0	4
Pseudarthrosis	2	1.4	2	5	3.4	5
Incomplete spinal fusion	2	1.4	2	4	2.7	4
Cerebrospinal fluid leakage	1	0.7	1	2	1.3	2
Lumbar radiculopathy	4	2.8	4	1	0.7	1
Back pain	25	17.7	27	14	9.4	16
Radicular pain	2	1.4	2	1	0.7	1
Radiculopathy	9	6.4	9	8	5.4	8
Sciatica	1	0.7	1	1	0.7	1
Spinal claudication	0	0.0	0	1	0.7	1
Device dislocation	1	0.7	1	0	0.0	0
Implant subsidence	4	2.8	4	0	0.0	0
Postoperative wound infection	4	2.8	5	0	0.0	0
Wound infection	2	1.4	2	0	0.0	0
Heterotopic ossification	0	0.0	0	0	0.0	0
Osteolysis	0	0.0	0	0	0.0	0
Seroma	2	1.4	2	0	0.0	0
Others[1]	30	21.3	113	28	18.8	95

[1]Others includes blood and lymphatic system disorders; cardiac disorders; ear and labyrinth disorders; endocrine disorders; gastrointestinal disorders; general disorders; infections and infestations; injury, poisoning and procedural complications; investigations; metabolism and nutrition disorders; musculoskeletal and connective tissue disorders; nervous system disorders; psychiatric disorders; renal and urinary disorders; reproductive system and breast disorders; respirator, thoracic and mediastinal disorders; skin and subcutaneous tissue disorders; surgical and medical procedures; and vascular disorders.

A summary of device-related adverse events is provided in **TABLE 7**. The number of these individual types of adverse events was comparable between arms throughout the study.

TABLE 7 – Device-Related Adverse Events – AT Population

Adverse Event	PearlMatrix n=141			Control n=149		
	Subjects	%	Events	Subjects	%	Events
Any Adverse Event	22	15.6	28	20	13.4	22
Dural tear	0	0.0	0	0	0.0	0
Graft complication	1	0.7	1	0	0.0	0
Lumbar vertebral fracture	0	0.0	0	1	0.7	1
Pain in extremity	1	0.7	1	0	0.0	0
Pseudarthrosis	2	1.4	2	4	2.7	4
Incomplete spinal fusion	1	0.7	1	4	2.7	4
Cerebrospinal fluid leakage	0	0.0	0	0	0.0	0
Lumbar radiculopathy	0	0.0	0	0	0.0	0
Back pain	5	3.5	5	3	2.0	3
Radicular pain	0	0.0	0	0	0.0	0
Radiculopathy	3	2.1	3	2	1.3	2
Sciatica	1	0.7	1	1	0.7	1
Spinal claudication	0	0.0	0	1	0.7	1
Device dislocation	1	0.7	1	0	0.0	0
Implant subsidence	1	0.7	1	0	0.0	0
Postoperative wound infection	0	0.0	0	0	0.0	0
Wound infection	1	0.7	1	0	0.0	0
Heterotopic ossification	0	0.0	0	0	0.0	0
Osteolysis	0	0.0	0	0	0.0	0
Seroma	1	0.7	1	0	0.0	0
Others[1]	6	4.3	10	4	2.7	6

[1]Others includes infections and infestations; injury, poisoning and procedural complications; musculoskeletal and connective tissue disorders; and nervous system disorders.

Effectiveness and Safety Results

The Overall Success (Composite Clinical Success or CCS) at 24 months was specified as the primary effectiveness outcome. **TABLE 8** provides the Overall Success (CCS) for the mITT Population. The CCS was 55.4% in the PearlMatrix arm and 36.4% in the Control arm. These results demonstrated that the PearlMatrix arm was both noninferior to and superior to the Control arm in overall success, a composite of five (5) measures of safety and effectiveness, at 24 months. The superiority result was primarily driven by the fusion rate in the Control arm, which was substantively lower than the event rates for the other four variables within the Control arm. By contrast, ODI improvements, neurological outcomes, and serious device-related adverse event rates were similar in both arms and the PearlMatrix arm had a higher rate of index-level secondary surgeries than the Control arm. Since CCS requires success on all variables, the minimum value among the variables sets the maximum possible value for CCS. Overall results on the composite endpoint should be evaluated together with performance on the individual elements of the composite as shown in **TABLE 8**.

The fusion rate in the PearlMatrix arm was significantly higher than the Control arm at 24 months. Thus, PearlMatrix is associated with an increase in radiographic fusion over the Control when the control

shows a fusion rate lower than the other event rates within the arm (57.3%). The clinical impact of superiority is difficult to ascertain due to the fusion rate of 57.3% in the Control arm.

There was an elevated rate of revisions (secondary surgeries) in the PearlMatrix arm versus the Control arm (9.1% versus 2.7%) at 24 months. The device-related secondary surgeries between the PearlMatrix arm and the Control arm were similar at 24 months (5.0% versus 2.7%, respectively).

The ODI outcomes, the Neurological outcomes, and the number of serious device-related adverse events at 24 months were similar in both the PearlMatrix arm and the Control arm.

TABLE 8 – Composite Clinical Success at 24 months for the modified Intent to Treat Population

Data Locked 14JUN2024	PearlMatrix (N=143)			Autologous Bone (N=150)			PearlMatrix - Autologous Bone		
	N	n	%	N	n	%	Diff (%)	LB[1]	UB
Composite Clinical Success[6]	**121**	**67**	**55.4**	**129**	**47**	**36.4**	**18.9**	**8.7**	**29.1**
(1) No index level secondary surgical intervention to Study Day 730	143	130	90.9	150	146	97.3	-6.3	-11.7	-1.0
(2) Achievement of fusion by Month 24 visit (Fusion is defined as evidence of bridging trabecular bone between the vertebral bodies by CT scan)[2]	129	108	83.7	131	75	57.3	26.5	15.8	37.1
(3) At least 15-point improvement in ODI from baseline to Month 24 visit among subjects without a secondary surgical intervention[3]	111	87	78.4	126	102	81.0	-2.5	-12.8	7.7
(4) No new or worsening, persistent neurological deficit comparing Month 24 to baseline[4]	118	111	94.1	126	116	92.1	1.9	-4.4	8.2
No motor deficit	119	115	96.6	127	123	96.9	-0.3	-4.7	4.1
No sensory deficit	120	117	97.5	126	120	95.2	2.2	-2.4	6.9
(5) No serious device-related adverse event to Study Day 730[5]	143	136	95.1	150	145	96.7	-1.5	-6.1	3.0

Notes: * The mITT analysis set was constructed by adding 3 randomized subjects that started surgery but with failure to commence their intended treatment (1 P15-L and 2 controls) to the AT analysis set. These subjects were defined as failures when conducting statistical tests for non-inferiority in CCS, superiority in time-to-fusion, and superiority in CCS (and in row 2. For consistency with AT analyses, these subjects were defined to have not experienced an SSI (row 1) and to not have experienced an SAE (row 5) since the denominators for these rows is intended to be the total analysis set sample size. These 3 subjects were not assigned values for rows 3 and 4. In addition, there was one subject randomized to P15-L but received control treatment. For the mITT analysis set, this subject was analyses as randomized (P15-L) and not As Treated. Therefore, the sample sizes for the mITT analysis set is N=143 for P15-L and N=150 for controls.

[1] Group differences and confidence intervals (CI) are adjusted for risk group using Mantel-Haenszel stratified analyses and so risk group adjusted differences are not necessarily equal to the difference in observed rates. LB is lower bound of the two-sided 90% confidence interval (CI) or equivalently, the LB of the one-sided 95% non-inferiority CI . The primary study success criterion is LB > -12.5%. Since +8.7% >> -12.5%, the results from this study strongly support non-inferiority of P15-L relative to control. All other CIs are two-sided 95% CIs.

[2] Once fusion is radiographically confirmed by CT, it is assumed that fusion has occurred at all subsequent time points without the need to reconfirm fusion status at later time points. *The number of subjects with any fusion assessment (Mo. 6, 12, or 24) were 139 and 145 in the AT P15-L and control groups, respectively, or 141 and 146 in the mITT analysis set after defining the 3 added subjects as fusion 'absent' at every time point assigning the subject randomized to P15-L but receiving control to the P15-L group. These are the sample sizes used in the mITT Kaplan-Meier comparison of time-to-fusion. In contrast, Row 2 also excludes subjects without a Month 24 fusion assessment but with an earlier assessment indicating absence of fusion. These subjects are missing definitive Month 24 fusion status.*

[3] ODI censored subsequent to SSI; [4] Motor and sensory failures adjudicated by CEC; [5] Device-related Includes 'Definitely', 'Probable', and 'Possible'.

[6] Z for non-inferiority = (observed risk group weighted difference + non-inferiority margin) / standard error = (0.1890 + 0.125)/0.0620 = 5.063. Therefore, the 1-sided p-value for testing non-inferiority is 0.0000002. Since 0.0000002 << 0.05, it can be concluded that P15-L is clinically non-inferior to control. In higher risk stratum, the group difference (90% CI) = 14.2% (0.1% to 27.4%). In the lower risk group the group difference is 25.9% (10.1% to 41.8%).

Z for superiority is 0.1890/0.0620 = 3.048. Therefore, the 1-sided p-value for testing superiority is 0.0012. There are two secondary endpoints with multiplicity controls, superiority in CCS and superiority in time-to-fusion. The two superiority endpoints were each tested at 1-sided 0.025/2=0.0125. Since 0.0012 << 0.0125, it can be concluded that P15-L is superior to control. The 95% two-sided CI is 6.8% to 31.1%.

Fusion success was also evaluated over time and is provided in **TABLE 9**. The PearlMatrix arm fusion rates were substantially higher than those of the Control arm at 6 months, 12 months, and 24 months.

TABLE 9 – Fusion success[1] by follow-up visit for the mITT Population

Visit	PearlMatrix		Control	
	N	Fused (%)	N	Fused (%)
6 mo	136	80 (58.8%)	137	39 (28.5%)
12 mo	131	95 (72.5%)	137	59 (43.1%)
24 mo	129	108 (83.7%)	131	75 (57.3%)

[1]Cumulative fusion defined as once fusion is observed, fusion is assumed at all subsequent visits

Subgroup Analysis

TABLE 10 provides the Overall Success (CCS) by group based on the preoperative characteristics and surgical approach. In all of these cases, the CCS results for the PearlMatrix arm were directionally higher than those for the Control arm.

TABLE 10 – Composite Clinical Success at 24 months based on preoperative characteristics and surgical approach for the mITT Population

Characteristic	PearlMatrix			Control			PearlMatrix-Control			
	N	n	%	N	n	%	Diff (%)	Adjusted Diff (%)[1]	LB[1]	UB
Higher Risk[2]	72	37	51.4	78	29	37.2	14.2	14.2	1.0	27.4
Nicotine Use	14	5	35.7	17	5	29.4	6.3	4.5	-23.9	32.9
Type 2 Diabetes	23	12	52.2	26	8	30.8	21.4	21.6	-1.7	44.9
BMI≥30	64	33	51.6	64	21	32.8	18.8	19.0	4.9	33.1
Open Surgery	71	38	53.5	64	25	39.1	14.4	13.9	-0.2	28.8
Minimally Invasive Surgery	49	29	59.2	63	22	34.9	24.3	24.2	8.9	39.4
Age≥65 years	47	26	55.3	51	17	33.3	22.0	22.4	6.3	38.6
Age < 65 years	74	41	55.4	78	30	38.5	16.9	16.8	3.5	30.1
Female	68	39	57.4	66	27	40.9	16.5	16.3	2.2	30.3
Male	53	28	52.8	63	20	31.7	21.1	20.0	5.2	34.8

[1] Group differences and confidence intervals (CI) are adjusted for risk group using Mantel-Haenszel stratified analyses and so risk group adjusted differences are not necessarily equal to the difference in observed rates. LB is lower bound of the two-sided 90% confidence interval (CI) or equivalently, LB is the lower bound of the one-sided 95% LB of the non-inferiority CI determined from a Mantel-Haenszel stratified estimate of the common risk difference.
[2]Higher risk was predefined as smoker, BMI>30, and/or Type 2 diabetes.

Secondary Effectiveness Results

As pre-specified in the investigational plan, analysis of secondary efficacy endpoints was performed at 24 months for the mITT analysis set. Time to fusion was tested as a secondary endpoint using a Kaplan-Meier survival rate to include missing fusion status at 24 months. Per this analysis, the PearlMatrix arm achieved fusion rates of 56.7%, 68.5% and 80.6% at 6 months, 12 months, and 24 months, respectively, and the Control arm achieved fusion rates of 26.7%, 40.5%, and 53.8% at 6 months, 12 months, and 24 months, respectively (log rank $p<0.001$). Thus, PearlMatrix provided statistically faster fusion than the Control.

The PearlMatrix arm also demonstrated substantially faster fusion than the Control arm in the higher risk population. Using the higher risk mITT analysis set and a Kaplan-Meier survival rate to include missing fusion status at Month 24, the PearlMatrix arm achieved fusion rates of 57.1%, 67.9% and 75.9% at 6 months, 12 months, and 24 months, respectively, and the Control arm achieved fusion rates of 22.2%, 38.0% and 54.9% at 6 months, 12 months, and 24 months, respectively.

Note that the statistical method used for the time to fusion analysis (Kaplan-Meier survival rate to include missing fusion status at Month 24) differed from that of the fusion success (see **TABLE 9**) and, as such, yielded slightly different fusion rates at each time point.

TABLE 11 provides the additional secondary efficacy outcomes by treatment arm in the modified Intent to Treat (mITT) population. On average, there was a significant improvement at 24 months in VAS scores and SF-12® Scores relative to baseline in both treatment groups.

TABLE 11 – Secondary Effectiveness Outcomes – Change from Baseline at 24 months – mITT Population

Secondary Endpoint	PearlMatrix		Control		PearlMatrix-Control[1]		
	N	Mean	N	Mean	Diff	LB	UB
VAS Change from Baseline (back pain)	111	-37.7±31.9	126	-47.2±28.8	9.5	1.7	17.3
VAS Change from Baseline (leg pain)	111	-43.2±39.0	126	-47.1±34.2	3.9	-5.5	13.3
SF-12 v2 PCS Change from Baseline	107	12.9±12.0	122	13.1±12.6	-0.2	-3.4	3.0
SF-12 v2 MCS Change from Baseline	107	5.4±10.8	122	5.9±13.2	-0.5	-3.7	2.6

[1]Device group difference and 95% confidence intervals (CI) for group differences.

ANTIBODY RESULTS

Blood draws were taken for subjects through at least the 12-month visit to test for antibodies to P-15 peptide, C1q protein, human collagen, and bovine collagen. No subjects tested positive for measurable P-15 peptide antibodies, or human collagen antibodies at any timepoint. A total of 7.2% of the subjects (9.2% of Control and 5.2% of Test) tested positive for C1q antibodies in their pre-Op serum samples. These subjects tested positive for C1q antibodies in their post-Op serum samples at similar titers to the pre-Op levels. No subject tested positive for C1q antibodies that did not have pre- existing, pre-Op antibodies. A total of 19.8% of the Investigational subjects and 19.0% of the Control subjects tested positive for bovine collagen antibodies prior to surgery. A total of 42.4% of the Investigational subjects and 27.1% of the Control subjects tested positive for bovine collagen at least one follow-up visit after surgery. For these subjects, 26.8% of the Investigational subjects and 76.3% of the Control subjects returned to a baseline level of bovine collagen antibodies by 12 Months. In all the remaining subjects with measurable bovine collagen antibodies, the antibody level had either decreased or plateaued.

A total of 1241 subject serum samples were tested for the presence of antibodies. Of those 70, (5.6%) of the samples were considered hemolyzed and 244 (19.6%) of the samples were considered lipemic. No subject sera samples (normal, hemolyzed or lipemic) were found to contain antibodies to P-15 peptide. No subject sera samples (normal, hemolyzed or lipemic) were found to contain antibodies to human Type I collagen. No patient sera samples (normal, hemolyzed or lipemic) were found to contain antibodies to human C1q protein post-operatively that were not already present preoperatively.

Of the 1241 subject sera samples tested for antibodies to bovine Type I collagen, 364 samples were found to be positive (29%). Of the 70 patient sera samples considered to be hemolyzed, 16 samples were found to contain antibodies to bovine Type I collagen (23%). Of the 244 patient sera samples considered to be lipemic, 61 samples were found to contain antibodies to bovine Type I collagen (25%).

It should be noted that all patient sera samples were centrifuged prior to use to remove as much lipid as possible. In addition, patient sera samples were diluted 1:4 for the anti-P-15 antibody assay and 1:50 for both anti-collagen antibody assays and the C1q assay. It was concluded that hemolyzed and lipidemic sera did not affect the ability to detect antibodies in human sera.

CONCLUSIONS DRAWN FROM THE PIVOTAL STUDY DATA

The clinical data demonstrate the safety and effectiveness of PearlMatrix P-15 Peptide Enhanced Bone Graft when used in accordance with the indications for use. The primary hypothesis of non-inferiority for Composite Clinical Success (CCS) was met. A pre-specified and multiplicity controlled secondary hypothesis of superiority for CCS was met. The non-inferiority and superiority results were primarily driven by the fusion proportion in the Control arm (57.3%), which was substantively lower than the event rates for the other four variables within the Control arm. PearlMatrix provided higher fusion rate (83.7%) relative to the Control.

PearlMatrix was associated with a higher rate of index-level secondary surgeries (9.1%) than the Control arm (2.7%). The ODI improvements, neurological outcomes, and serious device-related adverse event rates were similar in both arms. Overall results for the composite endpoint should be evaluated together with the performance on the individual elements of the composite as shown in **TABLE 9**. PearlMatrix demonstrated statistically faster time to fusion than the Control between 0 and 24 months post-surgery. Based on the clinical study results and preclinical data, the data demonstrate that the PearlMatrix Bone Graft has a reasonable assurance of safety and effectiveness when used in accordance with its indications for use including its contraindications, warnings, and precautions listed above, which specifically mitigate risks or uncertainties.

HOW SUPPLIED

The product is supplied in a double tray pack configuration. Each of the two trays is sealed with a foil laminate lid. The double tray configuration allows the circulating nurse to open the outer tray and dispense the inner sterile tray onto the operative sterile field.

PearlMatrix Bone Graft is designed for single use only and cannot be resterilized.

PearlMatrix Bone Graft is offered in the following configurations:

Catalog Number	Description	Approximate Dimensions
730-010	PearlMatrix Bone Graft, 1.0cc	25mm x 25mm x 4mm
730-025	PearlMatrix Bone Graft, 2.5cc	25mm x 50mm x 4mm
730-050	PearlMatrix Bone Graft, 5.0cc	25mm x 50mm x 8mm
730-100	PearlMatrix Bone Graft, 10.0cc	25mm x 100mm x 8mm

STORAGE

The product should be stored in its original packaging at ambient room temperature. Do not freeze or expose to extreme heat.

DIRECTIONS FOR USE

Familiarization with the device and proper bone grafting and rigid fixation techniques are extremely important. Radiographic evaluation of the defect site is essential to accurately assess the extent of a traumatic defect and to aid in the selection and placement of the PearlMatrix Bone Graft and fixation devices. To prepare the PearlMatrix Bone Graft, add sterile surgical solution (i.e., saline or Ringer's lactate) using the following approximate fluid volumes:

Product volume	Approximate Fluid volume
1.0cc	1.0cc
2.5cc	2.5cc
5.0cc	5.0cc
10.0cc	10.0cc

Knead until hydrated. Separate the product as necessary and mold into the desired shape(s). Insert the bone graft into the surgical site using standard surgical techniques. PearlMatrix can be implanted in either an open or minimally invasive surgical procedure.

The product is intended to be packed inside and around a PEEK TLIF spacer in the lumbar spine. Anatomical reduction and rigid fixation in all planes must be obtained to ensure that the graft is not supporting load.

Postoperative patient management should follow the same regimen as with other bone grafts or autogenous bone grafts. Standard postoperative practices should be followed, particularly as applicable to defect repairs involving the use of fixation devices.

FURTHER INFORMATION

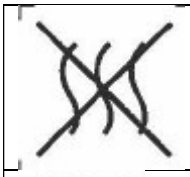
If further information is required, please contact Cerapedics at the address below.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a licensed physician.

SYMBOLS GLOSSARY

All symbols taken from BS EN ISO 15223-1:2021, Medical devices - Symbols to be used with information to be supplied by the manufacturer.

Symbol	Title	ISO/IEC Symbol Number and Registration Date
	Manufacturer	ISO 7000-3082 2011-10-02
	Sterilized using irradiation	ISO 7000-2502 2004-01-15
	Single sterile barrier system with protective packaging inside	ISO 7000-3708 2019-10-18
	Do not resterilize	ISO 7000-2608 2004-01-15
	Do not use if package is damaged	ISO 7000-2606 2004-01-15
	Temperature limit	ISO 7000-0632 2014-06-04
	Do not re-use	ISO 7000-1051 2004-01-15
	Consult IFU or electronic IFU	ISO 7000-1641 2004-01-15
	Medical device	N/A

	Non-pyrogenic	ISO 7000-2722 2005-09-08
	Use-by date	ISO 7000-2607 2004-01-15
	Batch code	ISO 7000-2492 2004-01-15
	Catalogue number	ISO 7000-2493 2004-01-15
	Unique device identifier	N/A

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