SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Peptide Enhanced Bone Graft Substitute
Device Trade Name:	PearlMatrix™ P-15 Peptide Enhanced Bone Graft, or PearlMatrix™ Bone Graft
Device Product Code:	NOX
Applicant's Name and Address:	Cerapedics, Inc. 11025 N. Dover Street, Suite 1600 Westminster, CO 80021
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P240001
Date of FDA Notice of Approval:	June 18, 2025

Breakthrough Device: Granted breakthrough device status on April 14, 2021, because the combination product represents a novel technology for intervertebral body fusion of the lumbar spine when used in conjunction with a transforaminal lumbar interbody fusion (TLIF) device and internal spinal fixation.

II. 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.

III. 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

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the PearlMatrix™ Bone Graft labeling.

V. DEVICE DESCRIPTION

PearlMatrix™ Bone Graft is a composite bone graft material consisting of a synthetic peptide (P-15) found naturally occurring in human Type I collagen, adsorbed onto calcium phosphate particles, which are incorporated into a bovine collagen matrix as an inert carrier. The calcium phosphate particles, also known as porcine anorganic bone mineral (pABM), are derived from porcine bone and provide a scaffolding and source of calcium for new bone growth. The synthetic collagen fragment (P-15) is a short chain 15 amino acid peptide that mimics a cell binding domain of human Type I collagen, thus providing a more favorable environment that facilitates cell attachment on the pABM scaffold. The pABM/P-15 particles are the functional component of the bone graft, whereas the bovine collagen simply acts as an inert carrier, aiding in the placement and containment of the particles at the graft site. After implantation, the collagen is resorbed via naturally occurring cellular enzyme digestion and the pABM/P-15 particles are concomitantly enveloped and stabilized by new tissues and are eventually remodeled into native bone via cell mediated resorption.

The composition of PearlMatrix™ Bone Graft is shown in the following table.

TABLE 1 – *PearlMatrix™ Bone Graft Composition*

Components	Quantity per 1cc	Proportion (w/w)
pABM/P-15 particles	0.61g	80%
Collagen	0.15g	20%

PearlMatrix™ Bone Graft is provided in four different volumes (1.0cc, 2.5cc, 5.0cc, and 10.0 cc) and is prepared by the surgeon by hydrating it with sterile solution (i.e., saline or Ringer's lactate) and kneading it to produce a putty form that can be molded into the desired shape.

A picture of PearlMatrix™ Bone Graft pre-hydration is provided in **FIGURE 1**. A picture of PearlMatrix™ Bone Graft after hydration and kneading is provided in **FIGURE 2**.

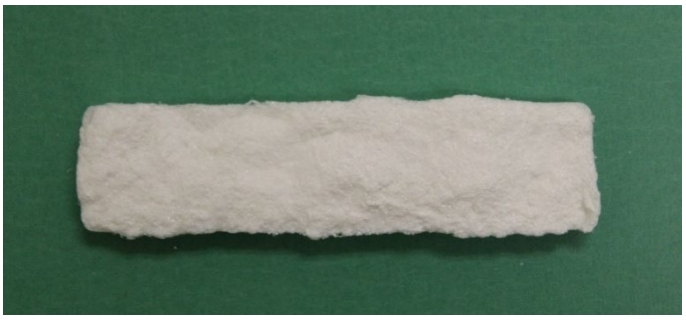


FIGURE 1 - *PearlMatrix™ Bone Graft before hydration*

FIGURE 2 – *PearlMatrix™ Bone Graft after hydration and kneading to form a putty*

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several non-surgical and surgical alternatives for the treatment of lumbar DDD. Non-surgical alternative treatments may include physical therapy and/or pain relief medications. Surgical alternatives may include lumbar fusion (with or without the use of metallic implants) with autograft or allograft bone, or artificial lumbar disc replacement surgery. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

PearlMatrix™ Bone Graft has been marketed in Canada in April 2020 under the name i-FACTOR®+ Matrix Bone Graft. The device has not been withdrawn from distribution/marketing for safety or effectiveness reasons.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the product. The adverse effects are sub-divided into three categories: (1) those commonly associated with any surgical procedure; (2) those associated with lumbar spinal surgery procedures using a transforaminal approach; and (3) those associated with the use of a bone graft, including those pertaining to PearlMatrix™ Bone Graft. In addition to the risks listed below, there is also the risk that the procedure may not be effective and may not relieve or may cause worsening of pre-operative symptoms. Additional surgery may be required to correct some of the potential adverse effects.

Potential adverse effects associated with any surgical procedure include:

- Anesthesia complications, including allergic reaction, anaphylaxis, or other reactions to anesthesia
- Reaction to transfused blood
- Anemia
- Blood loss/hemorrhage
- Heart or vascular complications, including:
  - Excessive bleeding or injury to blood vessels
  - Edema
  - Hematoma or seroma
  - Hypotension or hypertension
  - 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, 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, 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 an instrumented single-level TLIF surgery with any type of bone graft 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 of the bone graft, 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 associated with the use of PearlMatrix™ Bone Graft include:

- Allergic/immune response to components of the PearlMatrix™ Bone Graft

For the specific adverse events that occurred in the clinical study please see **Section X(D)**.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

Biocompatibility

The components of PearlMatrix™ Bone Graft (ABM, P-15 peptide, and bovine collagen) have well established safety and biocompatibility profiles when used separately or in combination with other materials. Previous PMA approvals on ABM/P-15 based products were supported by appropriate ISO 10993 biocompatibility testing.

Standard biocompatibility testing was conducted on PearlMatrix™ Bone Graft in accordance with international standard ISO 10993-1, Biological *Evaluation of Medical Devices - Part 1: Evaluation and Testing*. The following tests were performed:

- Cytotoxicity
- Sensitization
- Irritation
- Acute Systemic Toxicity
- Pyrogenicity
- Genotoxicity (*In Vitro* Chromosomal Aberration Study in Mammalian Cells)
- Implantation

The ISO 10993 testing determined PearlMatrix™ Bone Graft to be nontoxic, nonirritating, non-sensitizing, and non-mutagenic.

B. Animal Studies

TABLE 2 - Nonclinical Tests Performed on PearlMatrix™ Bone Graft

Test	Method	Results
Ovine Critical Size Defect	Drill hole model to demonstrate the kinetics of new bone formation initiated by PearlMatrix™ Bone Graft	PearlMatrix™ Bone Graft yielded more bone formation than i-FACTOR Bone Graft and ABM/Collagen
Rabbit Ectopic Bone Formation	Implantation of PearlMatrix™ Bone Graft in a Rabbit muscle pouch	PearlMatrix™ Bone Graft did not induce ectopic bone formation

Both the nonclinical laboratory tests and in-vivo tests on PearlMatrix™ Bone Graft have demonstrated that PearlMatrix™ Bone Graft is safe for use in lumbar procedures. PearlMatrix™ Bone Graft has been shown to be biocompatible. Animal models have demonstrated that PearlMatrix™ Bone Graft is equivalent to or better than previously approved i-FACTOR relative to bone formation. Both animal and

human studies have demonstrated that P-15 peptide-based bone grafts do not elicit a measurable adverse immune response.

C. Additional Studies

Sterilization, Shipping, and Shelf Life

PearlMatrix™ Bone Graft is terminally sterilized in the final package configuration using gamma radiation. Sterilization validation was performed on the product in its packaging according to AAMI/ISO 11137-Part 1: 2006 and Part 2: 2013 – Sterilization of Health Care Products – Radiation. The sterilization validation confirmed the dose range capability of providing a sterility assurance level (SAL) of 10^{-6}.

PearlMatrix™ Bone Graft was tested for the rigors of shipping and handling per ASTM D 4169-16: Performance Testing of Shipping Containers and Systems.

PearlMatrix™ Bone Graft is currently specified to have a shelf life of three (3) years from the date of sterilization. Results of stability study showed that accelerated and real-time aged product stored at ambient room temperature and humidity conditions remains stable and sterile over the shelf life of three (3) years.

X. SUMMARY OF PRIMARY CLINICAL STUDY

Cerapedics performed a clinical study to establish a reasonable assurance of safety and effectiveness of the PearlMatrix™ Bone Graft for treatment of degenerative disc disease (DDD) with up to Grade I spondylolisthesis at one level in the lumbar spine (L2-S1) when used in conjunction with a polyetheretherketone (PEEK) cage device cleared for TLIF and supplemental internal spinal fixation systems in patients who have had at least six months of non-operative treatment. The clinical study was conducted in the US under IDE G170300. Data from this clinical study were reviewed for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subjects (patients) were treated between July 26, 2018, and February 3, 2022. The database for this PMA reflected data collected through June 14, 2024, and included 293 subjects. There were 33 investigational sites.

The study titled "An Assessment of P-15L Bone Graft in Transforaminal Lumbar Interbody Fusion with Instrumentation" (ASPIRE) was a multi-center single (subject)-blinded randomized controlled trial clinical study. The objective of the study was to evaluate whether PearlMatrix™ Bone Graft was non-inferior to local autologous bone optionally mixed with allograph when applied in instrumented TLIF with use of an interbody spacer in subjects with lumbar degenerative disc disease. In addition to the general overall objective, planned sub-group analyses were performed on the higher risk subject population (nicotine use, obesity, type 2 diabetes), as previous studies have suggested negative effects of smoking, obesity and diabetes on

fusion and bone healing, increased peri/postoperative complications, and lower patient-reported outcome scores.

Subjects were randomized and treated in a 1:1 ratio to either the Investigational arm (TLIF with the PearlMatrix™ Bone Graft) or the active Control arm. The Control arm consisted of subjects undergoing a TLIF procedure with local autograft bone optionally mixed with allograft. A total of 141 subjects were treated in the PearlMatrix™ Bone Graft arm of the study and a total of 149 subjects were treated in the Control arm of the study.

In both arms, bone grafting was in the interbody space alone, without decortication nor bone grafting of the posterolateral gutters; facet decortication/resection was allowed for surgical exposure or facet arthrosis as needed, also without bone grafting.

The primary outcome measure for the non-inferiority hypothesis was composite clinical success. Composite Clinical Success (CCS) was defined as a subject level endpoint. To achieve CCS, a subject must have all 5 variables in the composite at month 24: no index level secondary surgical intervention; radiographic fusion by computed tomography (CT); at least a 15-point improvement in Oswestry Disability Index (ODI) from baseline; no new or worsening persistent neurological deficit relative to baseline; and no serious device-related adverse events.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the ASPIRE study was limited to patients who met the following inclusion criteria:

   - Skeletally mature adults between 22 and 80 years old (inclusive)
   - Back pain with radicular symptoms as evidenced by leg pain, confirmed by history and physical exam
   - 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
   - Oswestry Low Back Pain Disability Questionnaire score of ≥ 35
   - Involved disc(s) between L2 and S1
   - Planned lumbar fusion at a single level only
   - Failed to gain adequate relief from at least 6 months of adequate non-operative treatment
   - Able and willing to give consent to participate in study
   - Willing and able to participate in the study follow-up according to the protocol
   - Willing and able to comply with postoperative management program

Patients were not permitted to enroll in the ASPIRE study if they met any of the following exclusion criteria:

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

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations for up to 72 months postoperatively. This included time during initial hospitalization (baseline), and planned follow-up visits, which consisted of 6 weeks ± 10 days, 3 months ± 14 days, 6 months ± 30 days, 12 months ± 60 days, 24 months ± 60 days, 36 months ± 120 days, 48 months ± 120 days, 60 months ± 120 days, and

72 months ± 120 days. The key timepoints and assessment are shown below in **TABLE 3**.

TABLE 3 - *Study Schedule*

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.

Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

The primary endpoint was the Month 24 Composite Clinical Success (CCS). All the following had to be achieved for a patient 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 CCS superiority and time-to-fusion superiority were prespecified endpoints with a multiplicity-controlled hypothesis. Other secondary endpoints evaluated during the study included the following: back pain and leg pain, as measured by a 10-point Visual Analog Scale ("VAS"); quality of life, assessed using the SF12® questionnaire.

B. Accountability of PMA Cohort

At the time of database lock, of 293 subjects enrolled in the PMA study (mITT set), 121 subjects in the PearlMatrix™ Bone Graft arm and 129 subjects in the Control arm were evaluable for Month 24 CCS.

The definitions of the analysis populations are provided below.

- Modified Intent-to-Treat (mITT): All randomized patients with a surgical or anesthesia start time were specified to be included in the intent-to-treat (ITT) analysis set according to the device group to which they were randomized. A modified ITT (mITT) population included all subjects who were randomized and had surgical procedures initiated. There were three (3) subjects who were randomized and for whom surgery was started, but they were removed from the study at surgery because they did not receive any study treatment. In addition, there was one subject who was randomized to PearlMatrix™ Bone Graft but received the Control treatment. This subject is still accounted for in the PearlMatrix™ Bone Graft population in the mITT accountability. The mITT set is the primary analysis set for the primary endpoint.

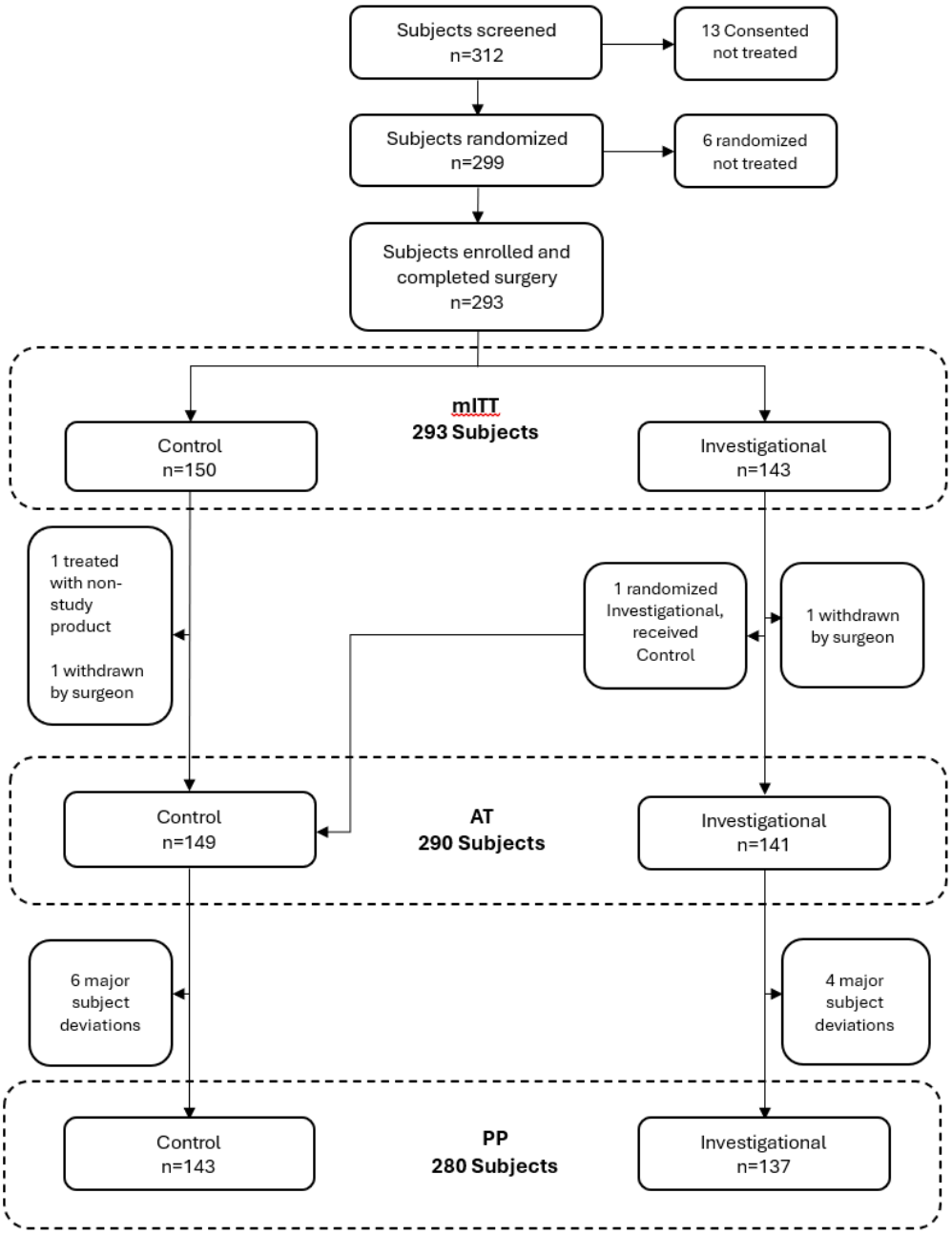
- As Treated (AT): The As Treated (AT) analysis set was defined similarly to the ITT analysis set except that patients were analyzed according to the device actually received. Primary safety analyses were conducted in the AT analysis set. All randomized subjects were treated according to the assigned treatment with the exception of one subject at Site 20 in which the subject was randomized to the investigational arm but was treated as a control subject. This subject was included in the Control arm in the AT population.

- Per-Protocol (PP): The PP analysis set excluded from the ITT analysis set patients that did not receive a device, with clinically significant violations of inclusion or exclusion criteria or post randomization protocol violations that may reasonably be predicted to impact on effectiveness endpoints. Subjects were analyzed according to the actual treatment received. The PP set is reported as a sensitivity analysis in addition to the mITT set when its reporting is useful.

Subject accountability for the mITT population is shown in **FIGURE 3** and is based on 293 subjects. Clinical visit follow-up of subjects at 24 months in the mITT population was 86.7% and 86.9% for the PearlMatrix™ Bone Graft and Control arms, respectively. Based on theoretical due status and subtracting only deaths among theoretical due, 85.8% in the PearlMatrix™ Bone Graft arm and 86.6% in the Control arm were evaluable for Month 24 CCS.

Subject accountability for the As Treated (AT) population is provided in **FIGURE 3** and is based on 290 subjects. The AT population excluded the three (3) subjects who were randomized and received a non-study treatment. In addition, the subject who was randomized to the PearlMatrix™ Bone Graft arm but received a Control treatment is accounted for in the Control arm.

FIGURE 3 – Subject (Patient) Accountability



The randomization sequence was generated using block randomization; two block sizes (2 and 4 subjects per block) were included in the algorithm and were randomly shuffled. This scheme made breaking the blind by working out the block pattern extremely difficult and reasonably protects against biased allocation of subjects. Randomization was performed in a 1:1 ratio between the Investigational and Control arms within site and risk group (higher and normal risk). The risk group stratification was introduced to promote between group balance in the numbers of subjects in the

higher and normal risk groups and to optimize sub-group analysis of the higher risk subject population (nicotine use, obesity, and Type 2 diabetes). In total, 299 patients were randomized. Among these 299 subjects, 141 subjects received the Investigational (PearlMatrix™ Bone Graft) treatment, and 149 subjects received the Control treatment (local bone mixed with allograft chip if needed). These subjects comprised the As Treated (AT) analysis set. One subject was randomized to PearlMatrix™ Bone Graft but received Control. This subject was analyzed as treated in the AT analysis set. There were 3 randomized subjects that commenced their index surgery, but there was no attempt at delivering a study treatment. These subjects were included in the mITT analysis set as CCS failures. In the mITT analysis set, the subject randomized to the PearlMatrix™ Bone Graft arm but who received control was analyzed as randomized. The six (6) randomized subjects that withdrew prior to surgery were not included in either the AT or mITT analyses sets. The mITT study population was 62.2% (N=89) high risk in the PearlMatrix™ Bone Graft arm and 63.3% (N=95) in Control arm).

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a degenerative disc disease interbody fusion study performed in the US.

TABLE 4 provides the study population demographics. The average age of all subjects treated in the PearlMatrix™ Bone Graft arm was 58.7 years (standard deviation (SD) 12.2) and the average age of the Control arm was 59.6 years (SD 10.9). Overall BMI was similar for both groups, 31.2 with a SD of 6.4 for the PearlMatrix™ Bone Graft arm and 31.3 with a SD of 5.9 for the Control arm.

For all males, the average age of subjects treated in the PearlMatrix™ Bone Graft arm was 58.6 years (SD 11.9) and the average age of the Control arm was 59.2 years (SD 10.8). Overall BMI was 31.1 (SD 5.7) for those in the PearlMatrix™ Bone Graft arm and the overall BMI for those in the Control arm was 30.9 (SD 5.7).

For all females, the average age of subjects treated in the PearlMatrix™ Bone Graft arm was 58.8 years (SD 12.5) and the average age of the Control arm was 60.0 years (SD 11.0). Overall BMI was 31.3 (SD 7.0) for those in the PearlMatrix™ Bone Graft arm and 31.6 (SD 6.0) for those in the Control arm.

Regarding functional status, the ODI was a contributor to the primary composite endpoint. The baseline ODI for the PearlMatrix™ Bone Graft arm was 54.7 (SD 13.5) while the Control arm baseline ODI was 53.7 (SD 14.5). Per the protocol, the baseline minimum ODI for inclusion in the study was 35. There were two documented protocol deviations in the Control arm for ODI scores below the minimum (28 and 32).

TABLE 4 - ***Summary of Baseline and Demographic Continuous Variables – mITT Population***

	PearlMatrix™ Bone Graft						Autologous bone						PearlMatrix™ Bone Graft - Autologous Bone[1]		
Demographics - All	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Age at surgery (yrs)	143	58.7	12.2	59.0	26.0	80.0	150	59.6	10.9	61.0	30.0	79.0	-0.9	-3.6	1.8
Height (in)	143	67.0	4.3	67.0	58.0	79.0	147	67.0	3.9	67.0	59.0	76.0	0.0	-1.0	0.9
Weight (lb)	143	200.1	48.7	195.0	95.3	360.0	147	200.1	42.1	194.0	121.0	327.0	0.0	-10.5	10.5
BMI (k/m^2)	143	31.2	6.4	31.2	16.4	49.7	147	31.3	5.9	30.4	21.6	47.8	-0.1	-1.5	1.3
Demographics - Male	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Age at surgery (yrs)	66	58.6	11.9	59.0	32.0	78.0	75	59.2	10.8	60.0	36.0	79.0	-0.7	-4.5	3.1
Height (in)	66	70.7	2.8	70.4	65.0	79.0	73	69.8	3.2	70.0	60.0	76.0	0.9	-0.1	2.0
Weight (lb)	66	221.9	47.0	215.0	150.0	360.0	73	213.9	40.2	210.0	137.0	327.0	8.0	-6.6	22.7
BMI (k/m^2)	66	31.1	5.7	30.6	20.8	49.7	73	30.9	5.7	29.4	22.1	47.8	0.2	-1.7	2.1
Demographic - Female	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Age at surgery (yrs)	77	58.8	12.5	59.0	26.0	80.0	75	60.0	11.0	62.0	30.0	79.0	-1.1	-4.9	2.6
Height (in)	77	63.8	2.6	64.0	58.0	70.0	74	64.3	2.4	65.0	59.0	69.0	-0.5	-1.3	0.3
Weight (lb)	77	181.5	42.1	187.0	95.3	278.0	74	186.5	39.7	183.2	121.0	302.0	-5.1	-18.2	8.1
BMI (k/m^2)	77	31.3	7.0	31.3	16.4	47.4	74	31.6	6.0	30.6	21.6	46.8	-0.3	-2.4	1.8
Baseline Functional Status	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Oswestry Disability Index (ODI)	143	54.7	13.5	52.0	36.0	93.0	150	53.7	14.5	52.0	28.0	100.0	1.0	-2.2	4.2
VAS Back Pain	143	67.7	23.5	75.0	0.0	100.0	150	65.6	25.3	70.0	0.0	100.0	2.1	-3.5	7.7
VAS Worse Leg Pain	143	70.3	24.9	78.0	0.0	100.0	150	70.6	23.7	74.0	0.0	100.0	-0.3	-5.8	5.3
VAS Left Leg Pain	143	54.0	33.5	62.0	0.0	100.0	150	47.3	35.4	50.0	0.0	100.0	6.7	-1.3	14.6
VAS Right Leg Pain	143	44.4	35.3	46.0	0.0	100.0	150	49.6	33.2	55.0	0.0	100.0	-5.2	-13.1	2.7
SF12 v2 Physical Component	140	27.4	6.9	27.4	8.5	47.3	148	27.3	7.4	27.6	9.5	52.3	0.1	-1.6	1.7
SF12 v2 Mental Component	140	43.4	12.2	44.1	15.6	70.0	148	45.9	13.0	47.7	7.6	74.6	-2.4	-5.3	0.5

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

Additional demographic characteristics for the treated population are shown in **TABLE 5**.

TABLE 5 - ***Summary of Baseline and Demographic - Categorical Variables – mITT Population***

	PearlMatrix™ Bone Graft		Autologous bone		PearlMatrix™ Bone Graft - Autologous Bone[1]		
	n	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Number of subjects	143		150				
Males	66	46.2	75	50.0	-3.8	-15.3	7.6
Females	77	53.8	75	50.0			
Ethnicity	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Hispanic or Latino	8	5.6	2	1.3	4.3	0.1	8.5
Not Hispanic or Latino	135	94.4	148	98.7			
Race (check all that apply)	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
American Indian/Alaskan Native	0	0.0	1	0.7	-0.7	-2.0	0.6
Asian	0	0.0	1	0.7	-0.7	-2.0	0.6
Black	7	4.9	14	9.3	-4.4	-10.3	1.4
Native Hawaiian/Pacific Islander							
White	136	95.1	134	89.3	5.8	-0.3	11.8
Other							
Is subject of child-bearing potential?	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	11	14.3	7	9.3	5.0	-5.3	15.2
No	66	85.7	68	90.7			

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

A summary of baseline risk factors is provided in **TABLE 6**. As noted previously, the subject randomizations were further stratified as either normal or higher risk. Subjects with one of the following were defined to be in the higher-risk stratum: nicotine use defined as once per day or more of cigarettes, vaping, patches, or chewing tobacco; BMI $\geq$ 30 kg/m^2; and/or diabetes defined as confirmed diagnosis of Type 2 diabetes. All other subjects were defined to be in the normal risk stratum. Overall, the percentage of both higher and normal risk subjects was similar in both arms. The most frequently observed higher risk factor for both treatment groups were obesity with 50.3% (72/143) for the PearlMatrix™ Bone Graft arm and 48.7% (73/150) for the Control arm. Among subjects with nicotine use, there were 15 subjects with use 6 or more times per day in the control arm (62.5% of subjects with any nicotine use). There were 6 such subjects in the PearlMatrix™ Bone Graft arm (37.5% of subjects with any nicotine use).

TABLE 6 - *Summary of Baseline Risk Factors – mITT Population*

	PearlMatrix™ Bone Graft		Autologous bone		PearlMatrix™ Bone Graft - Autologous Bone[1]		
High Risk?	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	89	62.2	95	63.3	-1.1	-12.2	10.0
No	54	37.8	55	36.7			
Number of Risk Factors[2]	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
0	54	37.8	55	36.7	0.678		
1	66	46.2	67	44.7			
2	21	14.7	25	16.7			
3	2	1.4	3	2.0			
Diabetes Type 2	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	26	18.2	29	19.3	-1.2	-10.1	7.8
No	117	81.8	121	80.7			
Nicotine Use: (Cigarettes, vaping, patches, chewing tobacco)							
Yes	16	11.2	24	16.0	-4.8	-12.6	3.0
No	127	88.8	126	84.0			
Nicotine Use: Times per day[2]	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
1	4	25.0	5	20.8	0.266		
2	1	6.3	2	8.3			
3	2	12.5	1	4.2			
4	1	6.3	0	0.0			
5	2	12.5	1	4.2			
6 or more	6	37.5	15	62.5			
Obesity (BMI ≥ 30 k/m^2)	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	72	50.3	73	48.7	1.7	-9.8	13.1
No	71	49.7	77	51.3			

Note:
[1] Device group differences and 95% confidence intervals (CI) for group differences.
[2] Wilcoxon rank sum test for ordinal data

1. 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. Variables are similar between groups. A summary of the surgery and operative characteristics is provided in **TABLE 7**. The most common surgical level was L4-L5 and the second most common was L5-S1 in both arms.

TABLE 7 – *Surgery and Operative Characteristics - mITT Population*

	PearlMatrix™ Bone Graft 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 ± 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

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the "As Treated" (AT) cohort of 290 patients/procedures available for the 24-month evaluation. The primary analysis set for the study is the modified intention-to-treat (mITT) analysis set; however, safety data presented alone (and outside the composite primary endpoint) are usefully presented for the AT set to reflect data associated with specific events. Adverse events are reported in **TABLES 8-13**.

Adverse events that occurred in the PMA clinical study:

Adverse events were defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device. Adverse events were summarized as counts and per patient incidence by device, overall, and by categories of adverse events including specific AE, relatedness, severity, and whether or not the AE was serious.

All adverse events were collected and recorded, regardless of whether they were believed to be related to the device or anticipated. This included the following:

- Adverse Device Effects (ADEs) – adverse event related to the use of an investigational medical device.

- Serious Adverse Events (SAEs) – an adverse event that led to death; led to serious deterioration in the health of the subject, that either resulted in: a life-threatening illness or injury; a permanent impairment of a body structure or a body function; in-patient or prolonged hospitalization; medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; led to fetal distress, fetal death or congenital abnormality/birth defect.

- Unanticipated Adverse Device Effects (UADEs) – any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

- Device deficiency – inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

The proportion of subjects with any reported adverse event, serious adverse event, adverse event of special interest, or death by 24 months in the AT population is shown in **TABLE 8**. The proportion of subjects with any adverse event was 86.5% in the PearlMatrix™ Bone Graft arm (122/141) and 81.2% in the Control arm (121/149), a difference of 5.3% (95% CI -3.1, 13.8). Regarding serious adverse events (SAEs), the proportion of subjects with any device/procedure-related SAEs was 26.2% in the PearlMatrix™ Bone Graft arm (37/141) and 13.4% in the Control arm (20/149), a difference of 12.8% (95% CI 3.7, 21.9). When considering SAEs that were adjudicated as device-related, the proportion was 5.7% in the PearlMatrix™ Bone Graft arm (8/141) and 4.7% in the Control arm (7/149), a difference of 1.0% (95% CI -4.1, 6.1). When considering SAEs that were adjudicated as procedure-related, the proportion was 26.2% in the PearlMatrix™ Bone Graft arm (37/141) and 13.4% in the Control arm (20/149), a difference of 12.8% (95% CI 3.7, 21.9).

TABLE 8 - ***Summary of Adverse Event Rates in the AT Population***

	PearlMatrix™ Bone Graft (N=141)			Autologous Bone (N=149)			PearlMatrix™ Bone Graft -Autologous[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.

The proportion of subjects with any reported adverse event, serious adverse event, adverse event of special interest, or death by 24 months in the "Per Protocol" (PP) population is shown in **TABLE 9**.

TABLE 9 - *Summary of Adverse Event Rates in the PP Population*

	PearlMatrix™ Bone Graft (N=137)			Autologous Bone (N=143)			PearlMatrix™ Bone Graft vs. Autologous Bone[1]		
	Events	**n**	**%**	**Events**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Any adverse event (per patient)	586	118	86.1	602	116	81.1	5.0	-3.6	13.7
Any device related AE[2]	28	22	16.1	22	20	14.0	2.1	-6.3	10.5
Any procedure related AE[2]	179	76	55.5	136	55	38.5	17.0	5.5	28.5
Any SAE	66	44	32.1	72	41	28.7	3.4	-7.3	14.2
SAE, device/procedure related	43	36	26.3	22	18	12.6	13.7	4.5	22.9
SAE, device/procedure related that resulted in SSI	17	11	8.0	4	4	2.8	5.2	-0.1	10.5
SAE, device related	8	8	5.8	8	7	4.9	0.9	-4.3	6.2
SAE, device related that resulted in SSI	7	7	5.1	4	4	2.8	2.3	-2.3	6.9
SAE, procedure related	43	36	26.3	22	18	12.6	13.7	4.5	22.9
SAE, procedure related that resulted in SSI	17	11	8.0	4	4	2.8	5.2	-0.1	10.5
Any AE of Special Interest	23	18	13.1	31	19	13.3	-0.1	-8.1	7.8
Deaths	2	2	1.5	1	1	0.7	0.8	-1.7	3.2

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.

TABLE 10 shows a summary of the number of adverse events by body system over time for the AT population, regardless of severity, seriousness, or relatedness to the device or procedure. For both groups, musculoskeletal and connective tissue disorders and nervous system disorders were the most common adverse events reported at each post-operative visit; the number of these adverse events was comparable between groups.

TABLE 10 - ***Adverse Events by Body System and Preferred Term Over Time***

	Day of Surgery to 30 Days		>30 to 90 Days		>90 to 180 Days		>180 to 365 Days		>365 to 730 Days		>730 Days		Totals	
Adverse Event Description	I	C	I	C	I	C	I	C	I	C	I	C	I	C
BLOOD AND LYMPHATIC SYSTEM DISORDERS	4	3	1	0	0	1	0	1	1	1	0	1	6	7
CARDIAC DISORDERS	5	3	2	1	0	2	3	0	2	3	0	7	12	16
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1	0	0	0	0	0	0	0	0	0	0	0	1	0
EAR AND LABYRINTH DISORDERS	1	0	2	0	0	1	0	0	0	0	0	2	3	3
ENDOCRINE DISORDERS	0	0	1	0	1	0	1	0	1	0	1	0	5	0
GASTROINTESTINAL DISORDERS	6	3	4	2	5	2	2	5	4	8	1	9	22	29
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3	7	2	4	5	0	1	2	2	2	1	4	14	19
HEPATOBILIARY DISORDERS	0	0	0	0	1	0	0	0	0	1	2	1	3	2
IMMUNE SYSTEM DISORDERS	0	1	0	0	0	0	0	0	0	0	1	0	1	1
INFECTIONS AND INFESTATIONS	14	2	10	3	8	10	8	12	13	6	5	12	58	45
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	26	14	5	6	3	4	9	11	19	13	7	14	69	62
INVESTIGATIONS	4	1	2	0	1	0	1	1	0	0	1	2	9	4
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	27	19	17	31	40	21	27	42	59	71	27	51	197	235
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	1	2	0	0	2	0	4	0	3	0	4	2	14
NERVOUS SYSTEM DISORDERS	20	16	13	13	14	14	20	16	12	18	20	18	99	95
PSYCHIATRIC DISORDERS	4	1	4	0	0	0	1	0	1	3	1	0	11	4
RENAL AND URINARY DISORDERS	7	4	1	0	0	2	1	0	1	2	4	3	14	11
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	2	0	0	2	1	2	2	1	0	0	1	5	6
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	7	2	2	1	3	0	0	4	6	4	3	3	21	14
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3	1	1	2	3	1	1	3	2	2	0	3	10	12
SURGICAL AND MEDICAL PROCEDURES	0	0	1	0	0	0	1	1	0	0	0	0	2	1
VASCULAR DISORDERS	8	7	1	1	2	2	1	1	1	5	2	4	15	20
PRODUCT ISSUES	1	0	2	0	2	0	4	0	0	1	0	0	9	1

TABLE 11 shows the counts and percentages of patients with device-related adverse events by body system, regardless of seriousness or severity. Device-related adverse events most frequently resulted in musculoskeletal and connective tissue disorders for both groups (PearlMatrix™ Bone Graft, 12 subjects (8.5%); Control, 11 subjects (7.4%)). Overall, back pain (PearlMatrix™ Bone Graft, 5 subjects (3.5%); Control, 3 subjects (2.0%)), radiculopathy (PearlMatrix™ Bone Graft, 3 subjects (2.1%); Control, 2 subjects (1.3%)) and pseudoarthrosis (PearlMatrix™ Bone Graft, 2 subjects (1.4%); Control, 4 subjects (2.7%)) were the most frequently occurring device-related adverse events. Device-related adverse events occurred more often in the PearlMatrix™ Bone Graft arm.

For nervous system disorders, device-related adverse events occurred in 6 subjects for both the PearlMatrix™ Bone Graft arm (7 events, 4.3% of subjects) and in the Control arm (6 events, 4.0% of subjects). For the Control arm, device-related adverse events occurred more often in the injury, poisoning, and procedural complications category versus the PearlMatrix™ Bone Graft arm.

For the PearlMatrix™ Bone Graft arm, device-related adverse events occurred more often in the infections and infestations, and musculoskeletal and connective tissue disorders categories versus the Control arm. In the infections and infestations category, there one (1) instance of device-related infection (wound infection) in one (1) patient of the PearlMatrix™ Bone Graft arm, while there were no instances of infection in the Control arm. In the musculoskeletal and connective tissue disorders category, 12 events occurred in 12 subjects of the PearlMatrix™ Bone Graft arm (arthralgia (1), back pain (5), lumbar spinal stenosis (1), pain in extremity (1), pseudoarthrosis (2), spondylolisthesis (1), vertebral foraminal stenosis (1)), while 11 events occurred in 11 subjects of the Control arm (back pain (3), disc space narrowing (1), lumbar spinal stenosis (2), musculoskeletal pain (1), and pseudoarthrosis (4)).

TABLE 11 – ***Counts and Percentages of Subjects with Device-Related Adverse Events by Body System in the AT Population***

	PearlMatrix™ Bone Graft (N=141)			Autologous Bone (N=149)			PearlMatrix™ Bone Graft vs Autologous Bone[1]		
Adverse Event Description	**No. of Events**	**No. of Pts.**	**% of Pts.**	**No. of Events**	**No. of Pts.**	**% of Pts.**	**Diff**	**LB**	**UB**
INFECTIONS AND INFESTATIONS	1	1	0.7	0	0	0.0	0.7	-1.9	3.9
wound infection	1	1	0.7	0	0	0.0	0.7	-1.9	3.9
INJURY, POISONING & PROCEDURAL COMPLICATIONS	3	3	2.1	5	5	3.4	-1.2	-5.9	3.2
graft complication	1	1	0.7	0	0	0.0	0.7	-1.9	3.9
incomplete spinal fusion	1	1	0.7	4	4	2.7	-2.0	-6.1	1.5
lumbar vertebral fracture	0	0	0.0	1	1	0.7	-0.7	-3.8	2.0
seroma	1	1	0.7	0	0	0.0	0.7	-1.9	3.9
MUSCULOSKELETAL & CONNECTIVE TISSUE DISORDERS	12	12	8.5	11	11	7.4	1.1	-5.4	8.0
arthralgia	1	1	0.7	0	0	0.0	0.7	-1.9	3.9
back pain	5	5	3.5	3	3	2.0	1.5	-2.7	6.4
intervertebral disc space narrowing	0	0	0.0	1	1	0.7	-0.7	-3.8	2.0
lumbar spinal stenosis	1	1	0.7	2	2	1.3	-0.6	-4.2	2.7
musculoskeletal pain	0	0	0.0	1	1	0.7	-0.7	-3.8	2.0
pain in extremity	1	1	0.7	0	0	0.0	0.7	-1.9	3.9
pseudarthrosis	2	2	1.4	4	4	2.7	-1.3	-5.5	2.7
spondylolisthesis	1	1	0.7	0	0	0.0	0.7	-1.9	3.9
vertebral foraminal stenosis	1	1	0.7	0	0	0.0	0.7	-1.9	3.9
NERVOUS SYSTEM DISORDERS	7	6	4.3	6	6	4.0	0.2	-4.9	5.5
hypoaesthesia	1	1	0.7	1	1	0.7	0.0	-3.2	3.3
paraesthesia	2	2	1.4	0	0	0.0	1.4	-1.2	5.1
piriformis syndrome	0	0	0.0	1	1	0.7	-0.7	-3.8	2.0
radiculopathy	3	3	2.1	2	2	1.3	0.8	-3.0	5.0
sciatica	1	1	0.7	1	1	0.7	0.0	-3.2	3.3
spinal claudication	0	0	0.0	1	1	0.7	-0.7	-3.8	2.0
RENAL AND URINARY DISORDERS	1	1	0.7	0	0	0.0	0.7	-1.9	3.9
micturition urgency	1	1	0.7	0	0	0.0	0.7	-1.9	3.9
PRODUCT ISSUES	4	3	2.1	0	0	0.0	2.1	-0.5	6.1
device dislocation	1	1	0.7	0	0	0.0	0.7	-1.9	3.9
device fastener issue	2	1	0.7	0	0	0.0	0.7	-1.9	3.9
implant subsidence	1	1	0.7	0	0	0.0	0.7	-1.9	3.9
Subjects with at least 1 adverse event		22			20				

Notes:
[1] 95% exact binomial confidence interval.

TABLE 12 shows the counts and percentages of patients with procedure-related adverse events by body system regardless of seriousness or severity. Procedure-related adverse events most frequently resulted in injury, poisoning, and procedural complications (PearlMatrix™ Bone Graft, 23 subjects (16.3%); Control, 22 subjects (14.8%)), musculoskeletal and connective tissue disorders (PearlMatrix™ Bone Graft, 40 subjects (28.4%); Control, 30 subjects (20.1%)), and nervous system disorders (PearlMatrix™ Bone Graft, 33 subjects (23.4%); Control, 21 subjects (14.1%)). Overall, dural tears (PearlMatrix™ Bone Graft, 6 subjects (4.3%); Control, 2 subjects (1.3%)), pain in extremity (PearlMatrix™

Bone Graft, 6 subjects (4.3%); Control, 3 subjects (2.0%)), radiculopathy (PearlMatrix™ Bone Graft, 9 subjects (6.4%); Control, 8 subjects (5.4%)), and back pain (PearlMatrix™ Bone Graft, 25 subjects (17.7%); Control, 14 subjects (9.4%)) were the most frequently occurring procedure-related adverse events.

Differences between the PearlMatrix™ Bone Graft and Control arms were present for procedure-related adverse events. Postoperative wound infections in the "Infections and Infestations" category had more adverse events in the PearlMatrix™ Bone Graft arm versus the Control arm; the group difference was 2.8 (95% CI 0.2, 7.2). Back pain in the musculoskeletal and connective tissue disorders category also had more adverse events in the PearlMatrix™ Bone Graft arm versus the Control arm, where back pain was greater in the PearlMatrix™ Bone Graft arm compared to the control, the group difference was 8.3 (95% CI 0.3, 16.7). The nervous system disorders category had more adverse events in the PearlMatrix™ Bone Graft arm versus the Control arm, the group difference was 9.3 (95% CI 0.2, 18.5), where patients reported headaches more often in the PearlMatrix™ Bone Graft arm compared to the control with a group difference of 2.8 (95% CI 0.2, 7.2). Lastly, the product issue category had more adverse events in the PearlMatrix™ Bone Graft arm versus the control with a group difference of 5.0 (95% CI 1.0, 10.3), where patients experienced implant subsidence more often in the PearlMatrix™ Bone Graft arm compared to the control with a group difference of 2.8 (95% CI 0.2, 7.2).

TABLE 12 - ***Patients with Procedure-Related Adverse Events by Body System in the AT Population***

Adverse Event Description	PearlMatrix N=141			Autologous Bone N=149			PearlMatrix vs Autologous		
	No. of Events	No. of Pts.	% of Pts.	No. of Events	No. of Pts.	% of Pts.	Diff	LB	UB
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3.0	3.0	2.1	4.0	3.0	2.0	0.1	-3.9	4.4
anaemia	2.0	2.0	1.4	1.0	1.0	0.7	0.7	-2.5	4.6
haemorrhagic anaemia	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
leukocytosis	1.0	1.0	0.7	2.0	2.0	1.3	-0.6	-4.2	2.7
CARDIAC DISORDERS	3.0	2.0	1.4	3.0	3.0	2.0	-0.6	-4.6	3.3
acute myocardial infarction	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
arrhythmia	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
atrial fibrillation	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
cardiac arrest	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
myocardial infarction	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
tachycardia	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
EAR AND LABYRINTH DISORDERS	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
hypoacusis	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
ENDOCRINE DISORDERS	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
hypothyroidism	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
GASTROINTESTINAL DISORDERS	7.0	6.0	4.3	5.0	3.0	2.0	2.2	-2.1	7.3
abdominal pain	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
anal incontinence	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
colitis	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
constipation	3.0	3.0	2.1	2.0	2.0	1.3	0.8	-3.0	5.0
eructation	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
nausea	2.0	2.0	1.4	0.0	0.0	0.0	1.4	-1.2	5.1
vomiting	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2.0	2.0	1.4	8.0	8.0	5.4	-4.0	-9.1	0.4
ill-defined disorder	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
impaired healing	1.0	1.0	0.7	2.0	2.0	1.3	-0.6	-4.2	2.7
medical device site pain	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
peripheral swelling	0.0	0.0	0.0	2.0	2.0	1.3	-1.3	-4.8	1.4
pyrexia	0.0	0.0	0.0	3.0	3.0	2.0	-2.0	-5.9	0.7
INFECTIONS AND INFESTATIONS	14.0	11.0	7.8	4.0	4.0	2.7	5.1	-0.1	11.2
clostridial sepsis	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
corona virus infection	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
diverticulitis	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
gastroenteritis	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
pneumonia	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
postoperative wound infection	5.0	4.0	2.8	0.0	0.0	0.0	2.8	0.2	7.2
staphylococcal infection	1.0	1.0	0.7	1.0	1.0	0.7	0.0	-3.2	3.3
urinary tract infection	3.0	3.0	2.1	0.0	0.0	0.0	2.1	-0.5	6.1
urinary tract infection bacterial	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
wound infection	2.0	2.0	1.4	0.0	0.0	0.0	1.4	-1.2	5.1

Adverse Event Description	PearlMatrix N=141			Autologous Bone N=149			PearlMatrix vs Autologous		
	No. of Events	No. of Pts.	% of Pts.	No. of Events	No. of Pts.	% of Pts.	Diff	LB	UB
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	25.0	23.0	16.3	24.0	22.0	14.8	1.5	-7.0	10.2
adjacent segment degeneration	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
contusion	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
corneal abrasion	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
device deployment issue	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
dural tear	6.0	6.0	4.3	2.0	2.0	1.3	2.9	-1.1	8.0
fall	0.0	0.0	0.0	3.0	2.0	1.3	-1.3	-4.8	1.4
graft complication	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
incision site dermatitis	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
incision site erythema	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
incision site haemorrhage	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
incision site pain	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
incision site pruritus	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
incomplete spinal fusion	2.0	2.0	1.4	4.0	4.0	2.7	-1.3	-5.5	2.7
ligament sprain	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
lumbar vertebral fracture	1.0	1.0	0.7	1.0	1.0	0.7	0.0	-3.2	3.3
overdose	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
post procedural fever	0.0	0.0	0.0	2.0	2.0	1.3	-1.3	-4.8	1.4
post procedural persistent drain fluid	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
post-traumatic pain	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
postoperative wound complication	1.0	1.0	0.7	1.0	1.0	0.7	0.0	-3.2	3.3
procedural complication	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
procedural pain	3.0	3.0	2.1	1.0	1.0	0.7	1.5	-1.8	5.5
procedural site reaction	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
seroma	2.0	2.0	1.4	0.0	0.0	0.0	1.4	-1.2	5.1
wound dehiscence	1.0	1.0	0.7	1.0	1.0	0.7	0.0	-3.2	3.3
wound secretion	2.0	2.0	1.4	0.0	0.0	0.0	1.4	-1.2	5.1
INVESTIGATIONS	2.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
blood pressure increased	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
heart rate increased	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
METABOLISM AND NUTRITION DISORDERS	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
hyponatraemia	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0

Adverse Event Description	PearlMatrix N=141			Autologous Bone N=149			PearlMatrix vs Autologous		
	No. of Events	No. of Pts.	% of Pts.	No. of Events	No. of Pts.	% of Pts.	Diff	LB	UB
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	67.0	40.0	28.4	52.0	30.0	20.1	8.2	-1.8	18.2
arthralgia	3.0	3.0	2.1	3.0	3.0	2.0	0.1	-3.9	4.4
back pain	27.0	25.0	17.7	16.0	14.0	9.4	8.3	0.3	16.7
cervical spinal stenosis	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
chondromalacia	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
facet joint syndrome	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
femoroacetabular impingement	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
groin pain	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
intervertebral disc protrusion	3.0	3.0	2.1	1.0	1.0	0.7	1.5	-1.8	5.5
intervertebral disc space narrowing	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
lumbar spinal stenosis	1.0	1.0	0.7	6.0	6.0	4.0	-3.3	-8.0	0.4
muscle spasms	6.0	5.0	3.5	3.0	2.0	1.3	2.2	-1.8	6.9
muscle swelling	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
muscle tightness	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
muscular weakness	2.0	2.0	1.4	3.0	2.0	1.3	0.1	-3.6	3.9
musculoskeletal pain	2.0	2.0	1.4	1.0	1.0	0.7	0.7	-2.5	4.6
musculoskeletal stiffness	1.0	1.0	0.7	1.0	1.0	0.7	0.0	-3.2	3.3
myalgia	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
myofascial pain syndrome	2.0	2.0	1.4	0.0	0.0	0.0	1.4	-1.2	5.1
neck pain	3.0	2.0	1.4	0.0	0.0	0.0	1.4	-1.2	5.1
pain in extremity	6.0	6.0	4.3	4.0	3.0	2.0	2.2	-2.1	7.3
pseudarthrosis	2.0	2.0	1.4	5.0	5.0	3.4	-1.9	-6.5	2.1
sacroiliitis	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
scoliosis	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
spinal column stenosis	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
spinal osteoarthritis	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
spondylolisthesis	1.0	1.0	0.7	1.0	1.0	0.7	0.0	-3.2	3.3
trigger finger	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
vertebral foraminal stenosis	1.0	1.0	0.7	1.0	1.0	0.7	0.0	-3.2	3.3

Adverse Event Description	PearlMatrix N=141			Autologous Bone N=149			PearlMatrix vs Autologous		
	No. of Events	No. of Pts.	% of Pts.	No. of Events	No. of Pts.	% of Pts.	Diff	LB	UB
NERVOUS SYSTEM DISORDERS	41.0	33.0	23.4	25.0	21.0	14.1	9.3	0.2	18.5
cerebrospinal fluid leakage	1.0	1.0	0.7	2.0	2.0	1.3	-0.6	-4.2	2.7
cerebrovascular accident	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
dizziness	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
dysarthria	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
headache	4.0	4.0	2.8	0.0	0.0	0.0	2.8	0.2	7.2
hemiparesis	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
hypoaesthesia	6.0	6.0	4.3	5.0	4.0	2.7	1.6	-3.2	6.7
lumbar radiculopathy	4.0	4.0	2.8	1.0	1.0	0.7	2.2	-1.2	6.6
migraine	2.0	2.0	1.4	0.0	0.0	0.0	1.4	-1.2	5.1
nervous system disorder	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
neuralgia	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
paraesthesia	4.0	4.0	2.8	2.0	2.0	1.3	1.5	-2.4	6.0
peroneal nerve palsy	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
piriformis syndrome	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
radicular pain	2.0	2.0	1.4	1.0	1.0	0.7	0.7	-2.5	4.6
radiculopathy	9.0	9.0	6.4	8.0	8.0	5.4	1.0	-4.8	7.1
sciatica	1.0	1.0	0.7	1.0	1.0	0.7	0.0	-3.2	3.3
sensory disturbance	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
spinal claudication	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
syncope	2.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
tremor	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
PSYCHIATRIC DISORDERS	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
delirium	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
RENAL AND URINARY DISORDERS	4.0	4.0	2.8	4.0	3.0	2.0	0.8	-3.3	5.3
micturition urgency	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
pollakiuria	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
urinary incontinence	1.0	1.0	0.7	2.0	2.0	1.3	-0.6	-4.2	2.7
urinary retention	2.0	2.0	1.4	1.0	1.0	0.7	0.7	-2.5	4.6
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1.0	1.0	0.7	2.0	2.0	1.3	-0.6	-4.2	2.7
genital paraesthesia	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
scrotal pain	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
testicular swelling	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2.0	2.0	1.4	1.0	1.0	0.7	0.7	-2.5	4.6
acute respiratory failure	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
atelectasis	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
respiratory failure	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0

Adverse Event Description	PearlMatrix N=141			Autologous Bone N=149			PearlMatrix vs Autologous		
	No. of Events	No. of Pts.	% of Pts.	No. of Events	No. of Pts.	% of Pts.	Diff	LB	UB
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2.0	2.0	1.4	0.0	0.0	0.0	1.4	-1.2	5.1
hyperhidrosis	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
rash maculo-papular	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
VASCULAR DISORDERS	5.0	5.0	3.5	6.0	6.0	4.0	-0.5	-5.5	4.6
deep vein thrombosis	1.0	1.0	0.7	2.0	2.0	1.3	-0.6	-4.2	2.7
embolism	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
haematoma	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
hypotension	2.0	2.0	1.4	3.0	3.0	2.0	-0.6	-4.6	3.3
orthostatic hypertension	0.0	0.0	0.0	1.0	1.0	0.7	-0.7	-3.8	2.0
PRODUCT ISSUES	9.0	8.0	5.7	1.0	1.0	0.7	5.0	1.0	10.3
device breakage	1.0	1.0	0.7	1.0	1.0	0.7	0.0	-3.2	3.3
device dislocation	1.0	1.0	0.7	0.0	0.0	0.0	0.7	-1.9	3.9
device fastener issue	3.0	2.0	1.4	0.0	0.0	0.0	1.4	-1.2	5.1
implant subsidence	4.0	4.0	2.8	0.0	0.0	0.0	2.8	0.2	7.2
Subjects with at least 1 adverse event	.	80.0	.	.	59.0	.	.	.	.

A summary of serious adverse events, regardless of device or procedure-relatedness, is provided in **TABLE 13**. The definition of serious is any adverse event that led to death; led to serious deterioration in the health of the subject, that either resulted in: a life-threatening illness or injury; a permanent impairment of a body structure or a body function; in-patient or prolonged hospitalization; medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; led to fetal distress, fetal death or congenital abnormality/birth defect.

TABLE 13 – Serious Adverse Events

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™ Bone Graft arm.

2. Safety and Effectiveness Results

The analysis of effectiveness was based on the 293-subject mITT data set at the 24-month time point. Key effectiveness outcomes are presented in **TABLES 14** to **23**. The mITT was the primary analysis set with the PP and AT analysis sets presented as sensitivity analysis.

Primary Endpoint – Clinical Composite Success

The primary endpoint was the Month 24 Composite Clinical Success (CCS), a composite of five (5) measures of safety and effectiveness at 24 months. CCS was defined as all the following at month 24:

- No index level secondary surgical intervention;
- Achievement of fusion;
- At least a 15-point improvement in ODI from baseline (on a 100-point scale);
- No new or worsening, persistent neurological deficit relative to baseline; and
- No serious device-related adverse events.

Note that randomization was performed within risk group for each center. To account for the randomization within risk group, the estimated difference and its standard error were determined for the higher risk and normal risk groups separately. Then, the overall group difference was estimated as a weighted average of the stratum-specific group differences using Mantel-Haenszel weights that are designed to minimize the variance of the pooled stratified estimate of the treatment group difference. Because the differences and confidence intervals are adjusted for the risk groups, the risk-adjusted differences are not necessarily equal to the differences in observed rates.

The CCS in the mITT population is shown in **TABLE 14**, where 55.4% of the PearlMatrix™ Bone Graft arm (67/121) and 36.4% of the Control arm (47/129) achieved CCS. The risk-adjusted difference between groups for CCS was 18.9% (90% CI 8.7%, 29.1%). Since the one-sided p-value for testing non-inferiority is 0.0000002, it can be concluded that PearlMatrix™ Bone Graft was clinically non-inferior to control. In higher risk stratum, the group difference was 14.2% (90% CI 0.1% to 27.4%). In the lower risk group, the group difference was 25.9% (10.1% to 41.8%). Thus, it was concluded that the PearlMatrix™ Bone Graft was non-inferior to the control with respect to the composite clinical success, a composite of five (5) measures of safety and effectiveness, at 24 months in a randomized clinical trial, in the mITT analysis set.

There are two pre-specified secondary endpoints with multiplicity controls: superiority in CCS and superiority in time-to-fusion. The one-sided p-value for testing superiority was 0.0012 (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 PearlMatrix™ Bone Graft was superior to control. A 95% two-sided confidence interval for the group difference was 6.8% to 31.1%.

Both the non-inferiority result and the superiority result were 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 had similar event rates both between arms and within the same arm relative to each other. The PearlMatrix™ Bone Graft 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 14**.

Missing data for the primary composite clinical success (CCS) endpoint was addressed using multiple imputation (MI). The fully conditional specification (FCS) approach was used to produce 20 complete multiple imputed data sets. To implement the MI, simplified CCS endpoints were determined at Months 6 and 12 as available. The FCS included these simplified CCS and the set of variables that were pre-specified for stratified analyses including risk strata, amount of bone graft material (over 8cc or not), gender, whether age over 65 years, race being non-white or white, whether investigator declared financial interest, whether facet joint involved, whether spine intervention level was above L4-L5, and whether the procedure was open vs closed. The simplified CCS at Month 6 and Month 12 were based on whether or not the subject experienced a secondary surgical intervention (SSI), fusion status, and an ODI improvement of ≥ 15. **TABLE 14** provides the multiple imputation results.

TABLE 14 - *Percentages of Subjects Achieving Month 24 Success in the mITT Population*

	PearlMatrix™ Bone Graft (N=143)			Autologous Bone (N=150)			PearlMatrix™ Bone Graft - 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[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
mITT using Multiple Imputation (MI)[7]	143	78.5	54.9	150	55.1	36.7	17.9	7.7	28.1

Notes: * The mITT analysis set was constructed by adding 3 randomized subjects that started surgery but with failure to commence their intended treatment (1 PearlMatrix™ Bone Graft 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 PearlMatrix™ Bone Graft but received control treatment. For the mITT analysis set, this subject was analyses as randomized (PearlMatrix™ Bone Graft) and not As Treated. Therefore, the sample sizes for the mITT analysis set are N=143 for PearlMatrix™ Bone Graft 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 PearlMatrix™ Bone Graft 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 PearlMatrix™ Bone Graft 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 PearlMatrix™ Bone Graft but receiving control to the PearlMatrix™ Bone Graft 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 PearlMatrix™ Bone Graft 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 PearlMatrix™ Bone Graft is superior to control. The 95% two-sided CI is 6.8% to 31.1%.

[7] A fully conditional specification (FCS) approach was used to produce 20 multiple imputations. To implement the MI, simplified CCS endpoints were determined at Months 6 and 12. The FCS included these simplified CCS as available and the following variables specified for stratified analyses including risk strata, amount of bone graft material (over 8cc or not), gender, whether age over 65y, race being non-white or white, whether investigator declared financial interest, whether facet joint involved, whether spine intervention level was above L4-L5, and whether the procedure was open vs closed. The simplified CCS at intermediate time points were based on SSI, fusion, and ODI improvement >=15. Sample sizes for successes are fractional as they are computed across 20 multiply imputed data sets.

As a sensitivity analysis, the CCS in the AT population is shown **TABLE 15,** where 55.5% of the PearlMatrix™ Bone Graft arm (66/119) and 37.5% of the Control arm (48/128) achieved CCS. The risk-adjusted difference between groups for CCS was 18.0% (90% CI 7.7%, 28.3%). The 1-sided p-value for testing non-inferiority is 0.0000006, so it can be concluded that PearlMatrix™ Bone Graft was clinically non-inferior to control in the AT analysis. In higher risk stratum, the group difference was 14.0% (90.1% CI 0.6% to 27.3%). In the lower risk stratum, the group difference was 23.9% (7.9% to 39.9%).

There are two secondary endpoints with multiplicity control, superiority in CCS and superiority in time-to-fusion. The one-sided p-value for testing superiority was 0.0020. The two superiority endpoints were each tested at 1-sided 0.025/2=0.0125. Since 0.0020 << 0.0125, it can be concluded that PearlMatrix™ Bone Graft was superior to Control with respect to composite clinical success, a composite of five (5) measures of safety and effectiveness, at 24 months in a randomized clinical trial. The 95% two-sided CI was 5.7% to 30.2%.

The other pre-specified secondary superiority endpoint with multiplicity control is time to fusion (see Time to Fusion Section). In addition to superiority being demonstrated for the time to fusion endpoint, the results in this table also reflect substantially improved achievement of fusion for PearlMatrix™ Bone Graft over the Control arm by Month 24. The risk-adjusted group difference in cumulative fusion rates was 25.8% (95% CI 15.2%, 36.4%). The month 24 fusion rate of the Control arm at 58.5% was consistent with the autograft fusion rate in studies with similar subjects and procedures.

TABLE 15 - ***Percentages of Subjects Achieving Month 24 Success in the AT Population***

	PearlMatrix™ Bone Graft (N=141)			Autologous Bone (N=149)			PearlMatrix™ Bone Graft - Autologous Bone		
	N	n	%	N	n	%	Diff (%)	LB[1]	UB
Composite Clinical Success[6]	**119**	**66**	**55.5**	**128**	**48**	**37.5**	**18.0**	**7.7**	**28.3**
(1) No index level secondary surgical intervention to Study Day 730	141	128	90.8	149	145	97.3	-6.5	-11.9	-1.1
(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]	127	107	84.3	130	76	58.5	25.8	15.2	36.4
(3) At least 15-point improvement in ODI from baseline to Month 24 visit[3]	110	86	78.2	127	103	81.1	-2.9	-13.1	7.4
(4) No new or worsening, persistent neurological deficit comparing Month 24 to baseline[4]	117	110	94.0	127	117	92.1	1.8	-4.5	8.1
No motor deficit	118	114	96.6	128	124	96.9	-0.3	-4.7	4.1
No sensory deficit	119	116	97.5	127	121	95.3	2.2	-2.4	6.8
(5) No serious device-related adverse event to Study Day 730[5]	141	134	95.0	149	144	96.6	-1.6	-6.2	3.0

Notes:

[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 +7.7% >> -12.5%, the results from this study strongly support non-inferiority of PearlMatrix™ Bone Graft 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 PearlMatrix™ Bone Graft and control groups respectively. These are the sample sizes used in the 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 = (0.1797 + 0.125)/0.0625 = 4.872. Therefore, the 1-sided p-value for testing non-inferiority is 0.0000006. Since 0.0000006 << 0.05, it can be concluded that P15-L is clinically non-inferior to control. In higher risk stratum, the group difference (90% CI) = 14.0% (0.6% to 27.3%). In the lower risk group, the group difference is 23.9% (7.9% to 39.9%). Z for superiority is 0.1797/0.0625 = 2.873. Therefore, the 1-sided p-value for testing superiority is 0.0020. There are two secondary endpoints with multiplicity control, 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 0.0020 << 0.0125, it can be concluded that PearlMatrix™ Bone Graft is superior to control. The 95% two-sided CI is 5.7% to 30.2%.

As a sensitivity analysis, the CCS in the PP population is shown **TABLE 16**, where 56.4% of the PearlMatrix™ Bone Graft arm (66/117) and 38.4% of the Control arm (48/125) achieved CCS. The risk-adjusted difference between groups for CCS was 18.0% (90% CI 7.6%, 28.4%) and (95% CI 5.6% to 30.4%), thus the PearlMatrix™ Bone Graft was non-inferior and superior to the control with respect to the composite clinical success in the PP analysis set.

TABLE 16- ***Percentages of Subjects Achieving Month 24 Success in the PP Population***

	PearlMatrix™ Bone Graft (N=137)			Autologous Bone (N=143)			PearlMatrix™ Bone Graft - Autologous Bone		
	N	n	%	N	n	%	Diff (%)	LB[1]	UB
Composite Clinical Success[6]	**117**	**66**	**56.4**	**125**	**48**	**38.4**	**18.0**	**7.6**	**28.4**
(1) No index level secondary surgical intervention to Study Day 730	137	124	90.5	143	139	97.2	-6.6	-12.2	-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]	124	105	84.7	125	73	58.4	26.3	15.5	37.0
(3) At least 15-point improvement in ODI from baseline to Month 24 visit among subjects without a secondary surgical intervention[3]	107	84	78.5	124	101	81.5	-2.9	-13.3	7.5
(4) No new or worsening, persistent neurological deficit comparing Month 24 to baseline[4]	115	108	93.9	124	114	91.9	1.9	-4.5	8.4
No motor deficit	115	111	96.5	125	121	96.8	-0.3	-4.8	4.2
No sensory deficit	117	114	97.4	124	118	95.2	2.3	-2.5	7.0
(5) No serious device-related adverse event to Study Day 730[5]	137	130	94.9	143	138	96.5	-1.6	-6.3	3.2

Notes:

[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 +7.6% >> -12.5%, the results in the Per Protocol analysis set strongly support non-inferiority of PearlMatrix™ Bone Graft 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.

[3] ODI censored subsequent to SSI.

[4] Motor and sensory failures adjudicated by CEC.

[5] Device-related Includes 'Definitely', 'Probable', and 'Possible'.

[6]The 1-sided p-value for testing non-inferiority is 0.0000007. Since 0.0000007 << 0.05, it can be concluded that PearlMatrix™ Bone Graft is clinically non-inferior to control.

The 1-sided p-value for testing superiority is 0.0022. 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 0.0022 << 0.0125, it can be concluded that PearlMatrix™ Bone Graft is superior to control.

The 95% two-sided CI for the difference is 5.6 to 30.4.

Fusion

Fusion was defined as evidence of continuous bridging trabecular bone in the intervertebral space. Fusion status was evaluated via review of CT images submitted to a centralized imaging lab (Medical Metrics, Inc, Houston, TX). CTs were read by two independent, blinded evaluators; disagreements between the two reviewers were resolved by a third independent, blinded reviewer with application of majority rule. Bridging bone was defined as mature, bony continuity from endplate to endplate with no intervening fractures or discontinuities. Continuous bridging occurs because of osseous remodeling and incorporation of the interbody graft with the vertebral endplates and/or formation of new bone adjacent to the graft that spans the interbody space. Visible bridging was evaluated on at least 2 contiguous CT images or 2 orthogonal planes at 1.0mm intervals. Bridging bone was not evaluated outside the interbody space as there was no bone grafting of the posterolateral gutters nor facets.

Cumulative fusion status at 6, 12, and 24 months is shown in **TABLE 17** in the mITT analysis set. Once fusion was observed, fusion was assumed at all subsequent visits and was not re-evaluated radiographically. At 6 months, 58.8% of the PearlMatrix™ Bone Graft arm (80/136) had interbody bridging / fusion present, whereas 28.5% of the Control arm (39/137) had fusion present. By 12 months, 72.5% of the PearlMatrix™ Bone Graft arm (95/131) had fusion present, with 43.1% the Control arm (59/137) having fusion present. By 24 months, 83.7% of the PearlMatrix™ Bone Graft arm (108/129) had fusion present while 57.3% of the Control arm (75/131) had fusion present. The PearlMatrix™ Bone Graft arm fusion rate was substantially higher than that of the Control arm in these descriptive comparisons.

The pre-planned, multiplicity-controlled, time-to-fusion analysis using the Kaplan-Meier survival rates and log-rank statistics is provided in the Time to Fusion section. This analysis confirmed the superiority of PearlMatrix™ Bone Graft relative to the Control in the time-to-fusion distributions.

TABLE 17 - ***Qualitative Assessment of Interbody Bridging/Fusion Cumulative Fusion – mITT Population***

	Month 6					Month 12					Month 24				
	PearlMatrix™ Bone Graft		Autologous Bone		Diff.	PearlMatrix™ Bone Graft		Autologous Bone		Diff.	PearlMatrix™ Bone Graft		Autologous Bone		Diff.
	n	%	n	%		n	%	n	%		n	%	n	%	
1 - Present[1]	80	58.8%	39	28.5%	**30.4%**	95	72.5%	59	43.1%	**29.5%**	108	83.7%	75	57.3%	**26.5%**
0 - Absent	56	41.2%	98	71.5%		36	27.5%	78	56.9%		21	16.3%	56	42.7%	
Difference															
Total	136		137			131		137			129		131		

Notes:
[1] 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 in the mITT analysis set with any fusion assessment (Mo. 6, 12, or 24) were 139 and 145 in the PearlMatrix™ Bone Graft and control groups respectively. These are the sample sizes used in the Kaplan-Meier comparison of time-to-fusion. In contrast, for this table, Month 24 cumulative fusion rates are computed excluding subjects without a definitive Month 24 fusion assessment even if Month 6 or Month 12 fusion assessments indicated absence of fusion. This is because these subjects are missing definitive Month 24 fusion status. The sample sizes in this table correspond to the fusion component of the primary composite clinical success endpoint.
[2] Three subjects added to the mITT analysis with no follow-up due to starting but not completing their randomized treatment are defined as having fusion absent at Month 6, Month 12, and Month 24 for consistency with composite endpoint analyses and time-to-fusion analyses. These include two subjects randomized to control (04-002 and 06-002) and one subject randomized to PearlMatrix™ Bone Graft (09-007). One subject randomized to PearlMatrix™ Bone Graft but who received control is included in the PearlMatrix™ Bone Graft group in the mITT analysis set.
[3] Chi-square p-value for group difference.

Cumulative fusion status at 6, 12, and 24 months in the higher risk group is shown in **TABLE 18**. Once fusion was observed, fusion was assumed at all subsequent visits. At 6 months, 60.0% of the PearlMatrix™ Bone Graft arm (48/80) had interbody bridging / fusion present, whereas 24.7% of the Control arm (20/81) had fusion present. By 12 months, 72.7% of the PearlMatrix™ Bone Graft arm (56/77) had fusion present, with 42.5% the Control arm (34/80) having fusion

present. By 24 months, 81.3% of the PearlMatrix™ Bone Graft arm (61/75) had fusion present while 60.5% of the Control arm (46/76) had fusion present.

TABLE 18 - *Qualitative Assessment of Interbody Bridging/Fusion Cumulative Fusion in Higher Risk Group – mITT Population*

	Month 6					Month 12					Month 24				
	PearlMatrix™ Bone Graft		Autologous Bone		Diff.	PearlMatrix™ Bone Graft		Autologous Bone		Diff.	PearlMatrix™ Bone Graft		Autologous Bone		Diff.
	n	%	n	%		n	%	n	%		n	%	n	%	
1 - Present[1]	48	60.0%	20	24.7%	**35.3%**	56	72.7%	34	42.5%	**30.2%**	61	81.3%	46	60.5%	**20.8%**
0 - Absent	32	40.0%	61	75.3%		21	27.3%	46	57.5%		14	18.7%	30	39.5%	
Difference															
Total	80		81			77		80			75		76		

Notes:
[1] 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 in the mITT analysis set with any fusion assessment (Mo. 6, 12, or 24) were 139 and 145 in the PearlMatrix™ Bone Graft and control groups respectively. These are the sample sizes used in the Kaplan-Meier comparison of time-to-fusion. In contrast, for this table, Month 24 cumulative fusion rates are computed excluding subjects without a definitive Month 24 fusion assessment even if Month 6 or Month 12 fusion assessments indicated absence of fusion. This is because these subjects are missing definitive Month 24 fusion status. The sample sizes in this table correspond to the fusion component of the primary composite clinical success endpoint.
[2] Risk group is defined as higher risk versus normal risk for non-fusion based on presence of any one of the following: diabetes, current tobacco user, obesity (BMI ≥ 30 kg/m^2).

Oswestry Disability Index (ODI)

Per the analysis plan, patient reported outcomes such as ODI were censored after secondary surgical intervention to avoid interpreting successful secondary treatment as successful primary treatment. Therefore, follow-up values are conditional on no prior secondary surgical intervention.

The percentages of subjects achieving a decrease in ODI score greater than 15 points on a 100-point scale is shown in **TABLE 19**. At least a 15-point improvement in ODI from baseline was required for the CCS. By 24 months, 78.4% of the PearlMatrix™ Bone Graft group (87/111) and 81.0% of the Control arm (102/126) had achieved at least a 15-point improvement in ODI scores. The difference in ODI scores for the PearlMatrix™ Bone Graft arm and Control arm at 24 months was -2.6% (95% CI -12.9, 7.7).

TABLE 19 - ***Percentages of Subjects Achieving a Decrease in ODI Score of at Least 15 Points in the mITT Population***

	Number and Percentage Meeting Criteria								
	PearlMatrix™ Bone Graft			Autologous Bone			PearlMatrix™ Bone Graft - Autologous Bone[1]		
	N	n	%	N	n	%	Diff (%)	LB	UB
Month 3	129	97	75.2%	137	109	79.6%	-4.4	-14.4	5.7
Month 6	130	97	74.6%	138	122	88.4%	-13.8	-23.0	-4.6
Month 12	124	97	78.2%	139	118	84.9%	-6.7	-16.1	2.7
Month 24	111	87	78.4%	126	102	81.0%	-2.6	-12.9	7.7

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

ODI values at pre-op, 3, 6, 12, and 24 months are summarized in **TABLE 20**. The average pre-op / baseline score of the PearlMatrix™ Bone Graft arm (N = 143) was 54.7 ± 13.5 with a median score of 52.0, minimum score of 36.0, and maximum score of 93.0. Likewise, the average baseline score for the Control arm (N = 150) was 53.7 ± 14.5 with a median score of 52.0, minimum score of 28.0, and maximum score of 100.0. The difference in average ODI score between the PearlMatrix™ Bone Graft arm and Control arm at baseline was 1.0 (95% CI -2.2, 4.2).

The average score of the PearlMatrix™ Bone Graft arm (N = 111) at month 24 was 24.2 ± 18.0 with a median score of 22.0, minimum score of 0.0, and maximum score of 72.0. The average score for the Control arm (N = 126) at month 24 was 22.1± 18.5 with a median score of 18.0, minimum score of 0.0, and maximum score of 80.0. The difference in average ODI score between the PearlMatrix™ Bone Graft arm and Control arm at baseline was 2.1 (95% CI -2.6, 6.7). Thus, the distribution of ODI changes to Month 24 was comparable between the two groups.

TABLE 20 - *ODI Scores in the mITT Population*

	PearlMatrix™ Bone Graft						Autologous Bone						PearlMatrix™ Bone Graft - Autologous Bone[1]		
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	Diff	LB	UB
Pre-0p	143	54.7	13.5	52.0	36.0	93.0	150	53.7	14.5	52.0	28.0	100.0	1.0	-2.2	4.2
Month 3	129	25.8	17.5	26.0	0.0	84.0	137	25.9	17.9	22.0	0.0	74.0	-0.2	-4.4	4.1
Month 6	130	25.3	17.8	24.0	0.0	64.0	138	20.8	16.8	18.0	0.0	84.0	4.5	0.3	8.7
Month 12	124	23.8	18.8	20.0	0.0	80.0	139	20.2	17.6	16.0	0.0	68.0	3.5	-0.9	7.9
Month 24	111	24.2	18.0	22.0	0.0	72.0	126	22.1	18.5	18.0	0.0	80.0	2.1	-2.6	6.7

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

Neurological Success

Neurological success status from comparing month 24 to baseline in the mITT population is shown in **TABLE 14**. The neurologic success rate was 94.1% in the PearlMatrix™ Bone Graft arm (111/118) and 92.1% in the Control arm (116/126). In the PearlMatrix™ Bone Graft arm, 4/7 subjects failed on the motor component while 3/7 subjects failed in the sensory component. In the Control arm, 4/10 subjects failed on the motor component while 6/10 subjects failed in the sensory component. The difference in neurologic success rates between the PearlMatrix™ Bone Graft and the Control arms was 1.9% (95% CI, -4.4%, 8.2%).

Subsequent Surgeries

As provided in the CCS results (**TABLE 14**), thirteen (13) Investigational subsequent surgeries and four (4) Control subsequent surgeries occurring prior to the 2-year timepoint were ruled by the DSMB to be failures of the composite endpoint. There was an elevated rate of revisions (secondary surgeries) for the PearlMatrix™ Bone Graft arm versus the Control arm (9.1% versus 2.7%) at 24 months. Seven (7) of the Investigational subsequent surgeries and four (4) of the Control subsequent surgeries were device related (5.0% versus 2.7% respectively).

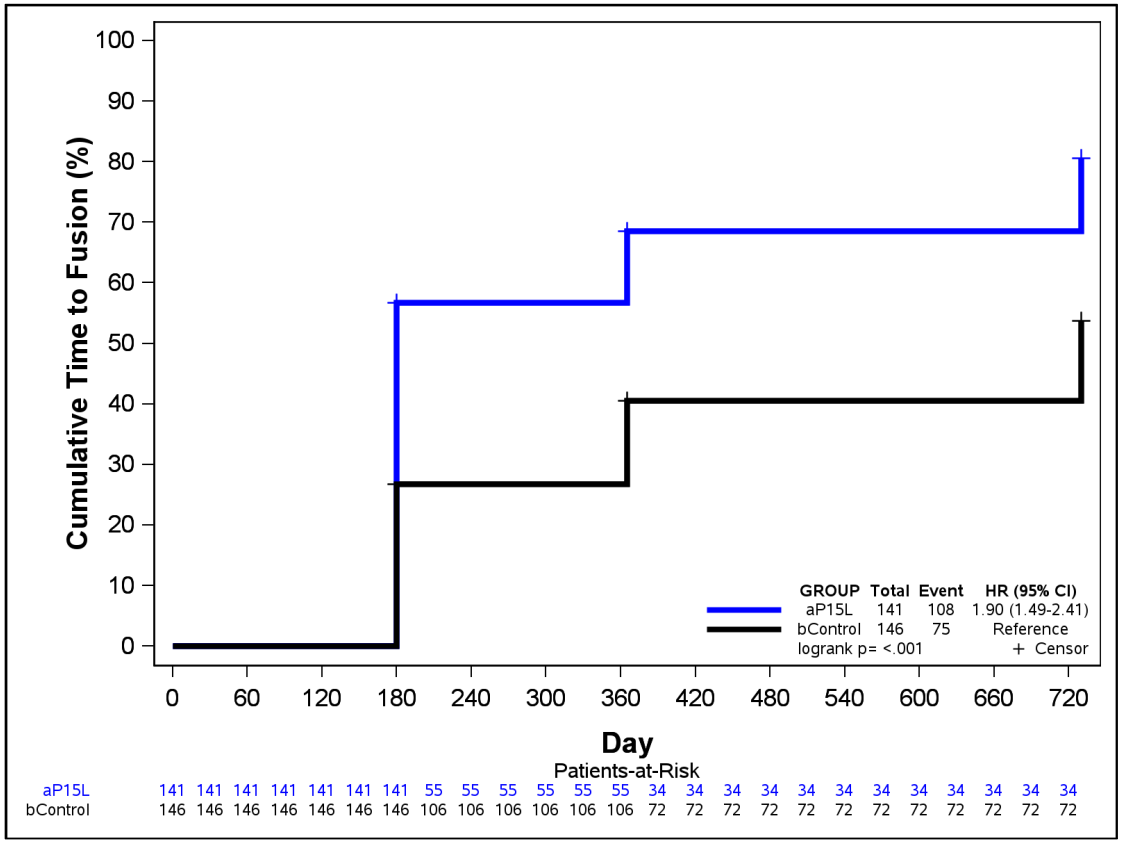
3. Multiplicity-Controlled Prespecified Secondary Endpoint – Time to Fusion

Time to fusion was pre-specified as a secondary endpoint with multiplicity control. If non-inferiority in terms of Month 24 CCS was demonstrated, then superiority in terms of visit at which fusion was observed was to be testing at one-sided type 1 error rate of α=0.0125.

Cumulative time to fusion through 24 months in the mITT population is shown **in FIGURE 4**. Note that, for the time-to-fusion analysis, a Kaplan-Meier survival rate was used to include missing fusion status at month 24. As a result, the fusion rates are different from those reported in the CCS (**TABLE 14)** and the Fusion Success in **TABLE 15**. At month 6, 56.7% of the PearlMatrix™ Bone Graft arm and 26.7% of the Control arm had achieved fusion. At month 12, 68.5% of the PearlMatrix™ Bone Graft arm and 40.5% of the Control arm had achieved fusion. At month 24, 80.6% of the PearlMatrix™ Bone Graft arm and 53.8% of the Control arm had achieved fusion. The log-rank test p-value for comparing the cumulative fusion distributions in the mITT population was $p<0.001$. This p-value was less than $0.025/2=0.0125$ and so there is robust evidence that the PearlMatrix™ Bone Graft was statistically superior to the Control for time to fusion.

The PearlMatrix™ Bone Graft arm time-to-fusion was also improved compared to the Control arm in the higher risk mITT subjects. Note that, for the time-to-fusion analysis, a Kaplan-Meier survival rate was used to include missing fusion status at month 24. As a result, the fusion rates are different from those reported in the Fusion Success in **TABLE 18**. At month 6, 57.1% of the PearlMatrix™ Bone Graft arm and 22.2% of the Control arm had achieved fusion. At month 12, 67.9% of the PearlMatrix™ Bone Graft arm and 38.0% of the Control arm had achieved fusion. At month 24, 75.9% of the PearlMatrix™ Bone Graft arm and 54.9% of the Control arm had achieved fusion.

FIGURE 4 - ***Log-Rank Graph Depicting Cumulative Time to Fusion – mITT Population***



4. Other Secondary Endpoints

VAS Pain Scores

VAS scores are summarized in **TABLE 21**. Both arms experienced a substantial improvement in both back pain and leg pain from baseline to month 24. The average back pain improvement was 37.7 in the PearlMatrix™ Bone Graft arm and 47.2 in the Control arm. Overall, 69.4% of the PearlMatrix™ Bone Graft subjects and 78.6% of the Control subjects reported at least a 20mm improvement in back pain VAS score at month 24. The average leg pain score (worst leg) improvement was 43.2 in the PearlMatrix™ Bone Graft arm and 47.1 in the Control arm. Overall, 75.5% of the PearlMatrix™ Bone Graft subjects and 79.4% of the Control subjects reported at least a 20mm improvement in leg pain VAS score at month 24.

TABLE 21 – ***Summary of Visual Analogue Scale (VAS) Scores - mITT Population***

	PearlMatrix™ Bone Graft						Autologous Bone						PearlMatrix™ Bone Graft - Autologous Bone[1]		
Back Pain	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Pre-Op	143	67.7	23.5	75.0	0	100	150	65.6	25.3	70.0	0.0	100	2.1	-3.5	7.7
Month 24	111	28.4	28.1	18.0	0	92	126	18.4	23.9	7.5	0.0	98	10.0	3.4	16.7
Back Pain Change from Baseline	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Month 24	111	-37.7	31.9	-38.0	-96	53	126	-47.2	28.8	-45.0	-100	16	9.5	1.7	17.3
Back Pain % Subjects with Decrease of at least 20mm	**N**		**n**		**%**		**N**		**n**		**%**		**Diff (%)**	**LB**	**UB**
Month 24	111		77		69.4%		126		99		78.6%		-9.2	-20.4	2.0
Leg Pain (worst side)	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Pre-Op	143	70.3	24.9	78.0	0	100	150	70.6	23.7	74.0	0.0	100	-0.3	-5.8	5.3
Month 24	111	25.8	30.3	7.0	0	94	126	23.3	29.0	7.0	0.0	98	2.5	-5.1	10.1
Leg Pain Change from Baseline	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Month 24	111	-43.2	39.0	-49.0	-100	87	126	-47.1	34.2	-48.5	-100	52	3.9	-5.5	13.3
Leg Pain % Subjects with Decrease of at least 20mm	**N**		**n**		**%**		**N**		**n**		**%**		**Diff (%)**	**LB**	**UB**
Month 24	111		84		75.5%		126		100		79.4%		-3.7	-14.3	7.0

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

Short Form Health Survey 12v2

A summary of the SF-12 results is provided in **TABLE 22**. From baseline to month 24, the PearlMatrix™ Bone Graft arm had a mean physical component score (PCS) improvement of 12.9 ± 12.0. From baseline to 24 months for the Control arm, the mean PCS improvement was 13.1 ± 12.6. Overall, 86.9% for the PearlMatrix™ Bone Graft arm and 84.4% for the Control arm reported a maintained or improved PCS at 24 months. From baseline to month 24, the PearlMatrix™ Bone Graft arm had a mean Mental Component Score (MCS) improvement of 5.4 ±10.8 and the Control arm had a mean MCS improvement of 5.9 ± 13.2. Overall, 67.3% for the PearlMatrix™ Bone Graft arm and 70.5% for the Control arm reported a maintained or improved MCS at 24 months.

TABLE 22 – ***Summary of Short Form Health Survey 12v2 Results – Physical Component Score (PCS) and Mental Component Score (MCS) – mITT Population***

	PearlMatrix™ Bone Graft						Autologous Bone						PearlMatrix™ Bone Graft - Autologous Bone[1]		
PCS	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Pre-Op	140	27.4	6.9	27.4	8.5	47.3	148	27.3	7.4	27.6	9.5	52.3	0.1	-1.6	1.7
Month 24	110	40.1	11.8	39.6	9.5	62.1	123	40.7	11.7	41.0	14.5	64.6	-0.6	-3.6	2.5
PCS Change	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Month 24	107	12.9	12.0	11.1	-12.9	42.6	122	13.1	12.6	13.6	-23.5	42.1	-0.2	-3.4	3.0
% Subjects Maintaining or Improving PCS	**N**		**n**		**%**		**N**		**n**		**%**		**Diff (%)**	**LB**	**UB**
Month 24	107		93		86.9%		122		103		84.4%		2.5	-6.6	11.6
MCS	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Pre-Op	140	43.4	12.2	44.1	15.6	70.0	148	45.9	13.0	47.7	7.6	74.6	-2.4	-5.3	0.5
Month 24	110	49.9	10.3	51.7	10.9	69.1	123	51.4	10.7	54.2	15.1	68.6	-1.5	-4.2	1.2
MCS Change	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Month 24	107	5.4	10.8	5.0	-20.6	31.0	122	5.9	13.2	4.6	-35.4	59.1	-0.5	-3.7	2.6
% Subjects Maintaining or Improving MCS	**N**		**n**		**%**		**N**		**n**		**%**		**Diff (%)**	**LB**	**UB**
Month 24	107		72		67.3%		122		86		70.5%		-3.2	-15.2	8.8

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

5. Subgroup Analyses

Baseline characteristics were evaluated for potential association with safety and effectiveness outcomes. These analyses were exploratory and were not powered nor multiplicity controlled.

Financial Interest

For subjects at sites with a financial interest, there were seven (7) and five (5) subjects, respectively, randomized to the PearlMatrix™ Bone Graft arm and the Control arm. Of those, four (4) PearlMatrix™ Bone Graft subjects and five (5) of the Control subjects were evaluable for CCS. For subjects at sites with a financial interest, 75.0% of the PearlMatrix™ Bone Graft arm (3/4) and 20.0% of the Control arm (1/5) achieved CCS. The risk-adjusted difference between groups for CCS was 53.8% (90% CI 3.7, 100.0). Although the PearlMatrix™ Bone Graft subjects achieved a higher CCS success rate than the Control subjects, there were too few subjects from sites in which investigators have a financial interest to make meaningful inferences in this subset.

For subjects at sites with no financial interest, 54.7% of the PearlMatrix™ Bone Graft arm (64/117) and 37.1% of the Control arm (46/124) achieved CCS. The risk-adjusted difference between groups for CCS was 17.6% (90% CI 7.2%, 28.0%). These results were consistent with those of the entire study population.

Additional Subgroup Analyses

TABLE 23 provides the CCS by arm for additional subgroups analyzed. The sample sizes in **TABLE 23** differ from those in **TABLE 6**, because not all subjects were evaluable for CCS. The subgroups with the response rates most different from the full mITT set are the "Nicotine Use" subgroup and the "Surgery Above L4-L5" subgroup. The number of subjects in these subgroups was low. The full mITT set shows CCS success for 55.4% of the PearlMatrix™ Bone Graft arm and 36.4% of the Control arm, a risk-adjusted difference of 18.9%. In the Nicotine Use subgroup, CCS success was 35.7% for PearlMatrix™ Bone Graft and 29.4% for Control, a decrease of 19.7% for PearlMatrix™ Bone Graft and 7.0% for Control relative to the full mITT set. This larger decrease in mITT response in the PearlMatrix™ Bone Graft group is despite a nominally higher rate of nicotine use among Controls — 15 subjects with use nicotine use "6 or more" times per day in the Control arm (62.5% of subjects with any nicotine use) versus 6 such subjects in the PearlMatrix™ Bone Graft arm (37.5% of subjects with any nicotine use) (**TABLE 6**). In the Surgery Above L4-L5 subgroup, the CCS success was 30.8% for PearlMatrix™ Bone Graft and 34.8% for Control, a difference of -4.0%.

TABLE 23 – *CCS Results for Other Subgroups – mITT Population*

Characteristic	PearlMatrix™ Bone Graft			Control			PearlMatrix™ Bone Graft - Control			
	N	n	%	N	n	%	Diff (%)	Adjusted Diff (%)[1]	LB[1]	UB
Normal Risk	49	30	61.2	51	18	35.3	25.9	25.9	10.0	41.8
Higher Risk[2]	72	37	51.4	78	29	37.2	14.2	14.2	1.0	27.4
No Nicotine Use	107	62	57.9	112	42	37.5	20.4	20.4	9.5	31.3
Nicotine Use	14	5	35.7	17	5	29.4	6.3	4.5	-23.9	32.9
No Type 2 Diabetes	98	55	56.1	103	39	37.9	18.2	18.3	6.9	29.7
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
BMI<30	57	34	59.6	65	26	40.0	19.6	19.7	4.9	34.4
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
Surgery Above L4-L5	13	4	30.8	23	8	34.8	-4.0	-3.6	-31.0	23.8
Surgery L4-L5	79	44	55.7	76	28	36.8	18.9	18.7	5.7	31.6
Surgery L5-S1	28	19	67.9	28	11	39.3	28.6	28.6	7.5	49.6
Facet Joint Decortication	78	43	55.1	91	34	37.4	17.7	17.9	5.5	30.4
No Facet Joint Decortication	42	24	57.1	36	13	36.1	21.0	21.3	3.1	39.5
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 nicotine use, BMI≥30, and/or Type 2 diabetes.

The study was not specifically powered for sex, age, or ethnicity within the subgroups.

6. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 33 investigators of which none were full-time or part-time employees of the sponsor and three (3) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 0
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 3

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. Seven (7) subjects in the investigational cohort and five (5) subjects in the control cohort were treated at these three sites.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Protocol Deviations

In the PearlMatrix™ Bone Graft arm, there were four (4) subjects with deviations categorized as major, which excluded the subjects from the PP population. These included the use in one (1) subject of a polyetherketoneketone (PEKK) cage, not a PEEK cage as stipulated in the protocol, and three (3) improper placements of the investigational product in the surgery. In the Control arm, there were six (6) subjects with deviations categorized as major, which excluded the subjects from the PP population. These included the use in two (2) subjects of cage types (PEEK/titanium and an expandable cage) not stipulated in the protocol and four (4) subjects with study criteria violations.

There were a total of 1144 minor deviations reported in the study. The largest category being missed assessment accounting for 756 deviations (66.1%) followed by 230 out of window visits (20.1%), 95 X-ray or CT out of window (8.3%), 37 other (3.2%), 7 surgical technique (<1%), 5 informed consent (<1%) respectively. The informed consent deviations are considered minor as all subjects were consented appropriately at the baseline visit and these four instances represent missed reconsent at subsequent follow-up visits, however subjects were ultimately reconsented appropriately. Of note, this study enrolled during the COVID-19 pandemic which accounted for a number of missed assessments and out of window visits.

XIII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopedic and Rehabilitation Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness and Safety Conclusions

Thirty-three investigator sites in the United States enrolled and randomized 299 subjects with Degenerative Disc Disease with a planned single level TLIF procedure into this IDE study. The investigation arm included PearlMatrix™ Bone Graft, and the control arm included local autograft (supplemented with allograft chip as an extender when necessary). In both arms, bone grafting was in the interbody space alone, without decortication nor bone grafting of the posterolateral gutters; facet decortication/resection was allowed for surgical exposure or facet arthrosis as needed without bone grafting. The primary analysis set was the mITT set, which included 293 subjects: 143 PearlMatrix™ Bone Graft and 150 Control subjects.

The primary outcome measure was composite clinical success. Composite Clinical Success (CCS) was defined as a subject level endpoint. To achieve CCS, a subject must have all 5 variables in the composite at month 24: no index level secondary surgical intervention; radiographic fusion by computed tomography (CT); at least a 15-point improvement in ODI from baseline; no new or worsening persistent neurological deficit relative to baseline; and no device-related serious adverse events.

The results were presented in **TABLE 14**. The proportion of subjects achieving CCS was 55.4% in the PearlMatrix™ Bone Graft arm (67/121) and 36.4% in the Control arm (47/129), a difference of -6.3% (95% CI -11.7, -1.0). The primary hypothesis of non-inferiority for 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 rate in the Control arm, which was substantively lower than the event rates for the other four variables within the Control arm. Since CCS requires success on all variables, the minimum value among the variables sets the maximum possible value for CCS. The PearlMatrix™ Bone Graft arm had a higher rate of secondary surgical interventions (SSIs) than the Control arm. By contrast ODI improvements, neurological outcomes, and device-related serious adverse events (SAEs) were similar in both arms. Overall results on the composite endpoint should be evaluated together with performance on the individual elements of the composite.

Fusion was defined as evidence of continuous bridging trabecular bone in the intervertebral space defined as mature, bony continuity from endplate to endplate with no intervening fractures or discontinuities. Visible bridging was evaluated on at least two (2) contiguous CT images or 2 orthogonal planes at 1.0mm intervals. At 6 months, 58.8% of the PearlMatrix™ Bone Graft arm (80/136) had interbody bridging / fusion present, whereas 28.5% of the Control arm (39/137) had fusion present. By 12 months, 72.5% of the PearlMatrix™ Bone Graft arm (95/131) had fusion present, with 43.1% the Control arm (59/137) having fusion present. By 24 months, 83.7% of the PearlMatrix™ Bone Graft arm (108/129) had fusion present while 57.3% of the Control arm (75/131) had fusion present.

Time to fusion was a pre-specified, multiplicity controlled secondary endpoint. Using the Kaplan-Meier survival rate, the PearlMatrix™ Bone Graft 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 $p<0.001$).

Other secondary endpoint and subgroup analyses were performed. These were not powered nor multiplicity controlled and are descriptive. With respect to secondary endpoints, VAS back pain, VAS leg pain, and SF-12 MCS and PCS scales were similar between groups.

With respect to subgroup analyses, three subgroups had the response rates most different from the full mITT set: the "Nicotine Use" subgroup; the "Surgery Above L4-L5" subgroup; and the "Financial Interest" subgroup. In all three subgroups, the number of subjects was low. The full mITT set shows CCS success for 55.4% of the PearlMatrix™ Bone Graft arm and 36.4% of the Control arm, a difference of 18.9% (risk-adjusted). In the Nicotine Use subgroup, CCS success was 35.7% for PearlMatrix™ Bone Graft and 29.4% for Control, a decrease of 19.7% for PearlMatrix™ Bone Graft and 7.0% for Control relative to the full mITT set. This larger decrease in mITT response in the PearlMatrix™ Bone Graft group is despite a nominally higher rate of nicotine use among Controls — 15 subjects with use nicotine use "6 or more" times per day in the Control arm (62.5% of subjects with any nicotine use) versus 6 such subjects in the PearlMatrix™ Bone Graft arm (37.5% of subjects with any nicotine use). (TABLE 5). In the Surgery Above L4-L5 subgroup, the CCS success was 30.8% for PearlMatrix™ Bone Graft and 34.8% for Control, a difference of -4.0%.

The pivotal clinical study included 33 investigators of which (3) had disclosable financial interests/arrangements as defined in 21 CFR 54.2: significant equity interest held by investigator in sponsor of covered study. For subjects at sites with a financial interest, 75.0% of the PearlMatrix™ Bone Graft arm (3/4) and 20.0% of the Control arm (1/5) achieved CCS. The risk-adjusted difference between groups for CCS was 53.8% (90% CI 3.7, 100.0). For subjects at sites with no financial interest, 54.7% of the PearlMatrix™ Bone Graft arm (64/117) and 37.1% of the Control arm (46/124)

achieved CCS. The risk-adjusted difference between groups for CCS was 17.6% (90% CI 7.2, 28.0).

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in the pivotal clinical study conducted to support PMA approval. The analysis of safety was based on the "As Treated" (AT) cohort of 290 patients/procedures available for the 24-month evaluation. The AT set is a subset of the mITT set. The mITT analysis set included an additional three (3) subjects (1 PearlMatrix™ Bone Graft and 2 Controls) that were randomized and commenced surgery, but were withdrawn inter-operatively, prior to any attempt at a study treatment. The mITT set also included a subject in the PearlMatrix™ Bone Graft arm randomized for PearlMatrix™ Bone Graft but treated with the Control.

The proportion of subjects with any adverse event (AE) was 86.5% in the PearlMatrix™ Bone Graft arm (122/141) and 81.2% in the Control arm (121/149), a difference of 5.3% (95% CI -3.1, 13.8). Regarding serious adverse events (SAEs), the proportion of subjects with any SAE was 31.9% in the PearlMatrix™ Bone Graft arm (45/68) and 29.5% in the Control arm (44/76), a difference of 2.4% (95% CI -8.2, 13.0). The rates of any AE and any SAEs were similar in both arms in the AT population at the 24-month primary timepoint.

Regarding serious adverse events (SAEs), the proportion of subjects with any device/procedure-related SAEs was 26.2% in the PearlMatrix™ Bone Graft arm (37/141) and 13.4% in the Control arm (20/149), a difference of 12.8% (95% CI 3.7, 21.9). When considering SAEs that were adjudicated as device-related, the proportion was 5.7% in the PearlMatrix™ Bone Graft arm (8/141) and 4.7% in the Control arm (7/149), a difference of 1.0% (95% CI -4.1, 6.1). When considering SAEs that were adjudicated as procedure- related, the proportion was 26.2% in the PearlMatrix™ Bone Graft arm (37/141) and 13.4% in the Control arm (20/149), a difference of 12.8% (95% CI 3.7, 21.9). Among these procedure-related SAEs, the proportion of subjects in the Infections and Infestations group was 7.8% in the PearlMatrix™ Bone Graft arm (11/141) and 2.7% in the Control arm (4/149), a difference of 5.1% (95% CI -0.1, 11.2). The SAEs were adjudicated by an independent data monitoring committee (DMC).

Thirteen (13) Investigational subsequent surgeries and four (4) Control subsequent surgeries occurring prior to the 2-year timepoint were ruled by the Data Monitoring Committee to be failures of the composite endpoint. There was an elevated rate of revisions (secondary surgeries) for the PearlMatrix™ Bone Graft arm versus the Control arm (9.1% versus 2.7%) at 24 months. Seven (7) of the Investigational subsequent surgeries and four (4) of the Control subsequent surgeries were device-related (5.0% versus 2.7% respectively).

In summary, rates of device-related SAEs were similar between the two arms. The greater proportion of subjects with device/procedure-related SAEs in the PearlMatrix™ Bone Graft arm (when device-related and procedure-related SAEs are grouped) was driven by the procedure-related SAEs; procedure-related SAEs included events such as infections for which there was a nominally higher rate in the investigation arm.

C. Benefit-Risk Determination

Summary of Benefits

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. A primary benefit of PearlMatrix™ Bone Graft is that it offers alternative bone graft to cancellous chip allograft when local autograft alone is inadequate in quantity and/or quality. The overall clinical outcomes are non-inferior between subjects as measured by the Composite Clinical Success at 24 months, a composite of five measures of safety and effectiveness. One of the five measures in the composite, spinal fusion by CT is superior in the PearlMatrix™ Bone Graft group due to the proportion of subjects achieving fusion in the Control arm being 57.3% versus 83.7% of the PearlMatrix™ Bone Graft arm. Other important measures of safety in the composite are similar between groups, including the proportion of subjects with neurologic success, the proportion with device-related SAEs, and the proportion with ODI success (a patient reported outcome). The study met its pre-specified multiplicity-controlled superiority hypothesis for CCS.

There are several sources of uncertainty in the assessment of benefits. The surgical technique in the control arm reflects one pattern of contemporary surgical practice. A radiographic fusion rate of 57.3% the control arm does not reflect the use of iliac crest graft as a gold standard, and the superiority of PearlMatrix™ Bone Graft is with respect to the reference standard technique in the control arm. The benefit due to lack of donor site morbidity, if any, cannot be assessed, as the study did not include such an arm. The superiority of the PearlMatrix™ Bone Graft group for Composite Clinical Success was driven by the rate of fusion in the control arm; in the subject-level composite, the lowest proportion of the five variables within the arm sets the maximum value of the composite. There were two findings in the descriptive subgroup analyses that were most nominally different than the full mITT set: a higher proportion of composite clinical success (CCS) at sites with a financial interest and a larger decrease in the CCS proportion among nicotine uses (despite a nominally higher quantity of nicotine use in the control group). The samples sizes too low to draw firm conclusions as the study was not powered nor multiplicity controlled for these tests.

Summary of Risks

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. In the pivotal clinical trial, secondary surgical interventions were a component of the primary composite endpoint. There was a higher proportion of SSIs in the PearlMatrix™ Bone Graft arm versus the Control arm (9.1% versus 2.7%) at 24 months. Device-related SAEs were also a component of the primary composite endpoint. There was a similar proportion of 5.7% in the PearlMatrix™ Bone Graft arm (8/141) versus 4.7% in the Control arm (7/149), a difference of 1.0% (95% CI -4.1, 6.1). There were similar rates of all AEs and all SAEs between arms.

There are several sources of uncertainty in the assessment of safety. Device/procedure -related SAEs include both device-related and procedure-related SAEs grouped. The proportion of subjects with any device/procedure-related SAEs was higher in the PearlMatrix™ Bone Graft arm: 26.2% in the PearlMatrix™ Bone Graft arm (37/141) and 13.4% in the Control arm (20/149), a difference of 12.8% (95% CI 3.7, 21.9). This finding was driven by procedure-related SAEs: 26.2% in the PearlMatrix™ Bone Graft arm (37/141) and 13.4% in the Control arm (20/149), a difference of 12.8% (95% CI 3.7, 21.9). Among these procedure-related SAEs, the proportion of subjects in the Infections and Infestations group was 7.8% in the PearlMatrix™ Bone Graft arm (11/141) and 2.7% in the Control arm (4/149), a difference of 5.1% (95% CI -0.1, 11.2). The SAEs were adjudicated by an independent data monitoring committee (DMC); the separation of SAEs into device relatedness and procedure relatedness relies on clinical judgment.

1. Patient Perspective
   This submission did not include formal patient preference information (PPI) which did not serve as part of the basis of the decision to approve or deny the PMA for this device. The primary endpoint incorporated the patient perspective by its use of a patient reported outcome measure (PRO) as one component of the composite primary endpoint, ODI.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The assessment of the safety and effectiveness of the device are based on nonclinical laboratory and animal studies as well as data collected in the pivotal clinical study conducted to support PMA approval. Taken together, 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, which specifically mitigate the risks or uncertainties in benefits and risks described above.

XV. CDRH DECISION

CDRH issued an approval order on June 18, 2025.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XVI. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVII. REFERENCES

N/A