SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Filler, recombinant human bone morphogenetic protein, collagen scaffold, osteoinduction
Device Trade Name:	Infuse™ Bone Graft
Device Product Code:	NEK
Applicant's Name and Address:	Medtronic Sofamor Danek 1800 Pyramid Place Memphis, TN 38132
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P000058/S096
Date of FDA Notice of Approval:	February 13, 2026

Breakthrough Device: Granted breakthrough device status on April 6, 2024, because the use of the combination product at one or two adjacent levels in transforaminal lumbar interbody fusion (TLIF) procedures represents a novel application of an existing technology that provides for more effective treatment of irreversibly debilitating human disease.

The original PMA, P000058, was approved on July 2, 2002, and is indicated for "spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L4-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history, function deficit and/or neurological deficit and radiographic studies. These DDD patients may also have up to Grade I spondylolisthesis at the involved level. InFUSE™ Bone Graft/LT-CAGE™ devices are to be implanted via an anterior open or an anterior laparoscopic approach. Patients receiving the InFUSE™ Bone Graft/ LT-CAGE™ Lumbar Tapered Fusion Device should have had at least six months of nonoperative treatment prior to treatment with the InFUSE™ Bone Graft/LT-CAGE™ device." The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for Infuse™ Bone Graft.

II. INDICATIONS FOR USE

Infuse™ Bone Graft with an FDA cleared intervertebral body fusion device and metallic screw-and-rod system is indicated for use in a transforaminal lumbar interbody fusion (TLIF) surgical approach at one or two adjacent levels from L2-S1 in the treatment of symptomatic degenerative disc disease (DDD) confirmed by patient history and radiographic studies and having at least six months of nonoperative treatment attempted prior to treatment with Infuse™ Bone Graft.

III. CONTRAINDICATIONS

Infuse™ Bone Graft is contraindicated for patients with:

- A known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen, or to other components of the formulation or with an allergy to titanium, titanium alloy, or polyetheretherketone.
- Known history of resected or extant tumor in the vicinity, or in patients with any active malignancy or undergoing treatment for a malignancy.
- Patients who are skeletally immature or <22 years of age.
- Current or future pregnancy. The potential effects of rhBMP-2 on the human fetus have not been evaluated.
- Patients with an active infection at the operative site.

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

Infuse™ Bone Graft consists of two components – a recombinant human bone morphogenetic protein solution and a collagen sponge which acts as a carrier for the bone morphogenetic protein and as a scaffold for new bone formation. These components must be used as a system. The bone morphogenetic protein solution component must not be used without the carrier/scaffold component or with a carrier/scaffold component different from the one described in this document.

Infuse™ Bone Graft consists of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2, known as dibotermin alfa) placed on an absorbable collagen sponge (ACS). Infuse™ Bone Graft induces new bone tissue at the site of implantation. Based on data

from non-clinical studies, the bone formation process develops from the outside of the implant towards the center until the entire Infuse™ Bone Graft is replaced by trabecular bone.

rhBMP-2, an osteoinductive growth factor, is the active agent in Infuse™ Bone Graft. It consists of a disulfide-linked dimeric protein molecule with two major subunit species of 114 and 131 amino acids. Each subunit is glycosylated at one site with high-mannose-type glycans. rhBMP-2 is produced by a genetically engineered Chinese hamster ovary cell line.

rhBMP-2 and excipients are lyophilized. Upon reconstitution, each milliliter of rhBMP-2 solution contains: 1.5mg of rhBMP-2; 5.0mg sucrose, NF; 25mg glycine, USP; 3.7mg L-glutamic acid, FCC; 0.1mg sodium chloride, USP; 0.1mg polysorbate 80, NF; and 1.0mL of sterile water. The reconstituted rhBMP-2 solution has a pH of 4.5; is clear, colorless to slightly yellow; and is essentially free from plainly visible particulate matter. The concentration of rhBMP-2 is 1.5mg/ml.

The absorbable collagen sponge (ACS) is a soft, white, pliable, absorbent implantable matrix for rhBMP-2. ACS is made from bovine Type I collagen obtained from the deep flexor (Achilles) tendon. The ACS acts as a carrier for the rhBMP-2 and acts as a scaffold for new bone formation.

Figure 1. Left: Infuse™ Bone Graft (X-small kit); Right: Image of wetted and rolled Infuse™ Bone Graft sponge to facilitate delivery.

Each kit contains all the components necessary to prepare Infuse™ Bone Graft: the rhBMP-2, which must be reconstituted; sterile water; absorbable collagen sponge(s); syringes with needles; and instructions for preparation. The number of each item may vary depending on the size of the kit (see Table 1 below).

Table 1: Infuse Bone Graft kit sizes for one-level and two-level TLIF procedures

		Infuse™ Bone Graft Kit Description					
	Volume (rhBMP-2 dose)	XX small	X small	Small	Medium	Large	Large II
		0.7 cc (1.05 mg)	1.4 cc (2.1 mg)	2.8 cc (4.2 mg)	4.2 cc (8.4 mg)	8 cc (12 mg)	8 cc (12 mg)
		Total number of required kits to achieve dose					
ONE-LEVEL TLIF Procedure	2.1 mg rhBMP-2 per level	2 kits	1 kit	1/2 kit	1/4 kit	1/6 kit	1/6 kit
	4.2 mg rhBMP-2 per level	4 kits	2 kits	1 kit	1/2 kit	1/3 kit	1/3 kit
TWO-LEVEL TLIF Procedure	2.1 mg rhBMP-2 per level	4 kits	2 kits	1 kit	1/2 kit	1/3 kit	1/3 kit
	4.2 mg rhBMP-2 per level	8 kits	4 kits	2 kits	1 kit	2/3 kit	2/3 kit

The rhBMP-2 is provided as a lyophilized powder in vials delivering 1.05 mg to 12 mg of protein. After appropriate reconstitution, the concentration of rhBMP-2 is 1.5mg/mL. The solution is then applied to the provided ACS. Infuse™ Bone Graft is prepared at the time of surgery and allowed a prescribed amount of time (no less than 15 minutes and no more than 2 hours) before placement at the site of implantation. The Instructions for Preparation contains complete details on preparation of Infuse™ Bone Graft.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several non-surgical and surgical alternatives for the treatment of symptomatic lumbar degenerative disc disease (DDD). Non-surgical alternatives may include physical therapy, activity modification, and pharmacologic pain management. When non-operative managements cease to be effective, there are several surgical alternatives, which include, but are not limited to, surgical decompression alone and surgical decompression with spinal instrumentation and fusion. Each option has its own advantages and disadvantages. Patients should discuss risks, benefits and alternatives to all treatment options with their physicians.

VII. MARKETING HISTORY

Infuse™ Bone Graft has been marketed in dozens of countries under the names of Infuse™ Bone Graft or InductOs®. The product has not been withdrawn from any of these countries for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of potential adverse events (e.g., complications) associated with the use of Infuse™ Bone Graft when used with a FDA cleared intervertebral body fusion device and

metallic screw-and-rod system 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 lumbar interbody fusion (TLIF) approach; and (3) those associated with the use of bone graft, include those pertaining to Infuse 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 TLIF surgery (one- and two-levels) 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) / Chronic Regional Pain Syndrome (CRPS)
- 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, acquired (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

<u>Potential adverse effects associated with the use of Infuse™ Bone Graft include:</u>

- Allergic/immune reaction to the components of Infuse™ Bone Graft

For the specific adverse events that occurred in the clinical study, please see **Section X** below.

IX. SUMMARY OF NON-CLINICAL STUDIES

Technological characteristics of Infuse™ Bone Graft have not changed since approval rendered in P000058. Data presented in P000058 were adequate to address necessary characterization of the properties and performance of the Infuse™ Bone Graft. A summary of the preclinical studies conducted in support of Infuse™ Bone Graft is available in the SSED for P000058 on the CDRH website.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of Infuse™ Bone Graft for treatment of symptomatic degenerative disc disease (DDD) for use in TLIF procedures with intervertebral body fusion device and metallic screw-and-rod systems in one or two levels from L2-S1 for patients with at least six months of nonoperative treatment. The clinical study was conducted in the US and China under IDE G180160. 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 December 19, 2019, and April 15, 2025. The database for this Panel Track PMA Supplement reflected data collected through April 15, 2025, and included 480 patients. There were 53 investigational sites. The study is ongoing, and continuation is planned until all enrolled, randomized and implanted patients achieve 24 months follow-up after operative intervention.

The study was a prospective, randomized, controlled, single (subject)-blinded multi-center clinical study. The objective of the study was to evaluate whether Infuse™ Bone Graft (used in two different volumes) at 1 or 2 lumbar spinal levels was noninferior in overall success and superior in fusion at 24 months to local autologous bone when applied in instrumented TLIF with use of an interbody fusion device and supplemental fixation in subjects with symptomatic lumbar degenerative disc disease having undergone at least 6 months of conservative treatment. Subjects were randomized 1:1:1 into 3 groups (2 investigational and 1 control) consisting of Infuse™ Bone Graft 2.1 mg/level; Infuse™ Bone Graft 4.2 mg/level; or local bone autograft. All subjects received an FDA-cleared intervertebral body fusion device and metallic screw-and-rod system and local autograft with optional mineralized cancellous allograft implanted in the interbody space. Two level subjects received the same volume of Infuse™ Bone Graft at both levels. One TLIF interbody fusion device was used per level. When used, Infuse™ Bone Graft was placed in the anterior and contralateral portion of the disc space relative to the interbody fusion device surrounded with autograft and optionally

supplemented with allograft. All bone grafting was in the interbody space alone, without grafting in the posterolateral space.

A Bayesian adaptive design was used, which allowed for the early termination of enrollment for either early success or early futility. The early success criterion based on the posterior probabilities of success on Overall Success (>0.96) and Radiographic Fusion Success (>0.975) was met at the first interim analysis, so the study stopped enrolling. Submitted data includes all outcome data, in particular the 12-month and 24-month Overall Success and Radiographic Fusion Success outcomes. All subjects will be followed to the 24-month visit for the final analysis.

The primary outcome measure for the noninferiority hypothesis was Overall Success, a subject-level composite endpoint consisting of both effectiveness and safety measurements. To achieve Overall Success at 24 months, a subject must have met success criteria for each of the five components at 24 months: Radiographic Fusion Success, Oswestry Disability Index (pain/disability status), Neurological Status, no serious adverse events (SAEs) related to the TLIF grafting material or interbody device, and no secondary surgeries classified as failure. Radiographic Fusion Success, a co-primary study endpoint and the primary outcome measure for the superiority hypothesis, required CT-evidence of bridging bone and no evidence of motion as defined by less than 2 mm translational motion and less than 3° in angular motion at each treated level on flexion/extension radiographs.

Secondary endpoints included time to fusion; ODI, leg pain, back pain, and neurological success; secondary surgeries up to 24 months classified as failure; and interbody device- or grafting material-related SAEs up to 24 months.

A core laboratory performed image analysis (Medical Metrics, Inc., Houston TX). An independent Data Monitoring Committee (DMC) oversaw the progress and accumulation of the data. A Clinical Events Committee (CEC) reviewed data for final classification for adjudication parameters. The CEC conducted a medical review and classification adjudication for relatedness and severity of all adverse events (AEs) and additional surgical procedures.

1) Key Clinical Inclusion and Exclusion Criteria

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

- Had radiographic evidence of degenerative disease of the lumbosacral spine in one or two adjacent levels (L2 to S1) that resulted in radiculopathy secondary to nerve root compression.
- Had radiographic evidence of degenerative disease of the lumbosacral spine, including at least one of the following:

a. Instability up to and including Grade 2 spondylolisthesis/retrolisthesis
b. Stenosis, or narrowing, of the lumbar spinal canal and/or intervertebral foramen requiring significant decompression leading to segmental instability, or
c. Recurrent disc herniation.

- Had preoperative Oswestry Disability Index (ODI) score ≥ 35.
- Was at least 18 years of age and skeletally mature at the time of surgery.
- Had not responded to non-operative treatment for a period of six months.
- Planned treatment with TLIF procedure with intervertebral fusion device and posterior supplemental fixation at 1- or 2-levels.

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

- Prior surgical procedure at the involved or adjacent spinal levels (e.g., fusion, arthroplasty, and/or other non-fusion procedures). Prior discectomy and/or laminectomy at the target or adjacent levels was allowed.
- Planned use of an internal or external bone growth stimulator.
- Lumbar scoliosis > 30 degrees.
- Morbidly obese, as defined by a body mass index (BMI) > 40.
- Presence of active malignancy or prior history of malignancy (non-invasive basal cell carcinoma of the skin and non-invasive squamous cell carcinoma localized only to the skin was allowed).
- Overt or active bacterial infection, either local to surgical space or systemic.
- Autoimmune disease, which in the investigator's opinion, is known to affect bone metabolism or the spine.
- Any endocrine or metabolic disorder, which in the investigator's opinion, is known to affect osteogenesis.
- Known exposure to any recombinant proteins used for bone formation.
- Known hypersensitivity or allergy to any components of the study treatments including but not limited to bone morphogenetic proteins (BMPs); injectable collagen; protein pharmaceuticals bovine collagen products; and/or instrumentation materials (e.g., titanium, titanium alloy, cobalt chrome, cobalt chrome alloy, or polyetheretherketone [PEEK]).
- Pregnant or nursing. Females of child-bearing potential had to agree not to become pregnant for 24 months following surgery.

2) Follow-up Schedule

All subjects were scheduled to return for follow-up examinations at 6 weeks and 3, 6, 12, and 24 months after surgery, then annually until the last subject enrolled in the study has reached 24 months after surgery. All subjects followed the same schedule of events, shown in **Table 2**.

Table 2: Schedule of Events

	Pre-Perioperative		Post-operative						
Procedure	**Preop: Baseline[4]**	**Surgery/ Hospital Discharge**	**6 wks 42 days ±14 days**	**3 mo 90 days ±30 days**	**6 mo 180 days ±30 days**	**12 mo 365 days ±60 days**	**24 mo 730 days ±60 days**	**Annual Visits[5] (36,48,60 mo) 1095, 1460, 1825 days ±120 days**	**Unscheduled Visit**
Inclusion/ Exclusion criteria	X								
Informed Consent	X								
Demographics	X								
Screening Log	X								
Medical History	X								
Surgical History (Lumbar only)	X								
Randomization	X								
Preoperative Pregnancy Test[1]	X								
DEXA[2]	X								
Device Identification		X							
Device Tracking		X							
Surgery Data		X							
Hospital Discharge		X							
ODI – Oswestry Disability Index[3]	X		X	X	X	X	X	X	
Back & Leg Pain Questionnaire	X		X	X	X	X	X	X	
EQ-5D-5L Questionnaire	X		X	X	X	X	X	X	
Subject Satisfaction			X	X	X	X	X	X	
Neurological Status	X		X	X	X	X	X		
Medications	X	X	X	X	X	X	X	X	X
Adverse Event (if any)		X	X	X	X	X	X	X	X
Additional Surgery (if any)		X	X	X	X	X	X	X	X
Device Deficiency		X	X	X	X	X	X	X	X

	Pre-Perioperative		Post-operative						
Procedure	**Preop: Baseline**[4]	**Surgery/ Hospital Discharge**	**6 wks 42 days ±14 days**	**3 mo 90 days ±30 days**	**6 mo 180 days ±30 days**	**12 mo 365 days ±60 days**	**24 mo 730 days ±60 days**	**Annual Visits**[5] **(36,48,60 mo) 1095, 1460, 1825 days ±120 days**	**Unscheduled Visit**
(if any)									
Protocol Deviation (if any)	X	X	X	X	X	X	X	X	X
Radiographic Procedures									
X-Ray Anterior/Posterior[6]	X	X	X	X	X	X	X		
X-Ray A/P Ferguson (only if L5-S1)	X	X	X	X	X	X	X		
X-Ray Lateral	X	X	X	X	X	X	X		
X-Ray Flexion/Extension	X			X	X	X	X		
CT (high resolution axial, sagittal and coronal reformatting)[7]	CT or MRI[8]					X	X		

1. A pregnancy test will be administered to all female subjects of child-bearing potential within 3 days prior to surgery.
2. Not all subjects will require a DEXA scan. A DEXA Scan will only need to be obtained if the subject had a prevalent fragility fracture but has not had a T-score assessed within 12 months prior to enrollment.
3. The ODI is a subject reported outcome which is also considered part of the primary endpoint; please double check the questionnaire is completed accurately prior to the end of the subject visit.
4. The pre-operative assessments should be obtained within 3 months prior to the date of surgery. Pre-existing radiographs within 3 months prior to enrollment are acceptable and should not be repeated for study purposes.
5. Visits will be performed annually until the end of the study (i.e., until the final subject enrolled completes his/her 24-month visit), or the subject has completed their 5-year visit, whichever comes first.
6. For levels between L2 and L5 (or L6, if applicable).
7. CT not required after the 24-month postoperative evaluation.
8. A Baseline CT or MRI will only need to be obtained if the subject does not have a CT or MRI within 12 months of enrollment for the investigator's inclusion criteria assessment.

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 endpoints were Overall Success and Radiographic Fusion Success, assessed during the 24-month visit:

- Overall Success (subject must have met success criteria for each of the following five components):
  - Radiographic Fusion Success
  - ODI success (at least a 15-point improvement from baseline)

    - Neurological success (improvement or maintenance from baseline in all following four domains: motor and sensory function, reflexes and straight leg raise)
    - No Serious Adverse Events (SAEs) related to TLIF grafting material or intervertebral body fusion device
    - No additional surgeries at index level(s) related to TLIF grafting material or intervertebral body fusion device
- Radiographic Fusion Success
    - Bridging bone success based on CT assessment
    - No evidence of motion as defined by less than 2mm translational motion and less than 3° in angular motion at each treated level (flexion/extension radiographs).

In addition, adverse events (AEs) were evaluated during and after surgery and tabulated as to the nature and frequency of AEs, additional surgical procedures, and a subject's neurological status, if applicable. An independent Data Monitoring Committee (DMC) monitored the safety of the investigational treatments, as well as the effectiveness performance.

The secondary objectives included:

- assessing whether statistical difference exists between the investigational groups and the control group for the secondary endpoints listed below; and
- demonstrating superiority in Overall Success at 24 months postoperatively for the investigational group as compared to the control group if noninferiority is achieved.

For the secondary objectives, the multiplicity due to multiple endpoints was controlled using the gatekeeping method. The gatekeeping was performed separately for each dose that met the success criteria on the primary endpoints. As long as the noninferiority criteria were met for an endpoint, the sequential testing procedure proceeded to test noninferiority of the next endpoint in the hierarchy. The hierarchy is listed below for the secondary endpoints:

(1) Time to fusion
(2) Secondary surgeries up to 24 months that are classified as failure
(3) ODI Success at 24 months
(4) Leg pain success at 24 months
(5) SAEs up to 24 months that are "related" to TLIF grafting material or interbody device
(6) Back pain success at 24 months
(7) Neurological success at 24 months

Tests for noninferiority were performed at a 1-sided 5% level while tests for superiority were performed at a 1-sided 2.5% level.

B. Accountability of PMA Cohort

At the time of PMA application review, 684 patients were enrolled, and consented in the clinical study, of which 480 patients were randomized and treated (379 one-level patients, 101 two-level patients). Of the randomized and treated population, the 379 one-level patients were comprised of 149 patients from outside the US (OUS) and 230 patients were from US sites. The two-level patients were comprised of 31 patients OUS and 70 patients from US sites.

The follow-up rate of the randomized and treated populations pooled by levels from all sites at the time of the interim analysis for PMA application review was 84.4% one-level patients and 78.2% two-level patients achieving 12 months of follow-up after operative intervention, and 62.5% one-level patients and 61.4% two-level patients achieving 24 months of follow-up after operative intervention. The follow-up rate of the as-treated populations pooled by levels from all sites at the time of this interim analysis for PMA application review was 83.9% one-level patients and 80.2% two-level patients achieving 12 months of follow-up after operative intervention, and 62.2% one-level patients and 62.5% two-level patients achieving 24 months of follow-up after operative intervention.

No further enrollment is occurring, but the study will continue until all enrolled, consented, randomized and treated subjects have been followed for 24 months after operative intervention.

The analysis populations are described below.

- Primary Dataset (As Randomized and Treated; ART): used as the primary dataset for the main statistical analyses. The ART dataset included subjects who were enrolled, randomized and received treatment. Subjects were analyzed according to the treatment to which they were randomized.

- As Treated Dataset (AT): used for safety evaluation. This dataset included all subjects who were enrolled, randomized, and received treatment. Subjects were analyzed according to the treatment received.

- Per-Protocol (PP): This dataset included subjects who were enrolled, randomized, received the randomized treatments, and did not have any major protocol deviation. Two PP datasets were derived; one for deviations assessed per the protocol version in place at the time of the event and one that assessed the event according to the criteria in the final version of the protocol. The PP dataset considered for the interim evaluation at the time of PMA application

was the PP dataset that considered protocol deviations according to the criteria in the final version of the protocol.

Figure 1 conveys the enrollment, allocation, and analysis of the subjects.

Figure 1: Process of enrollment, allocation, and analysis of subjects

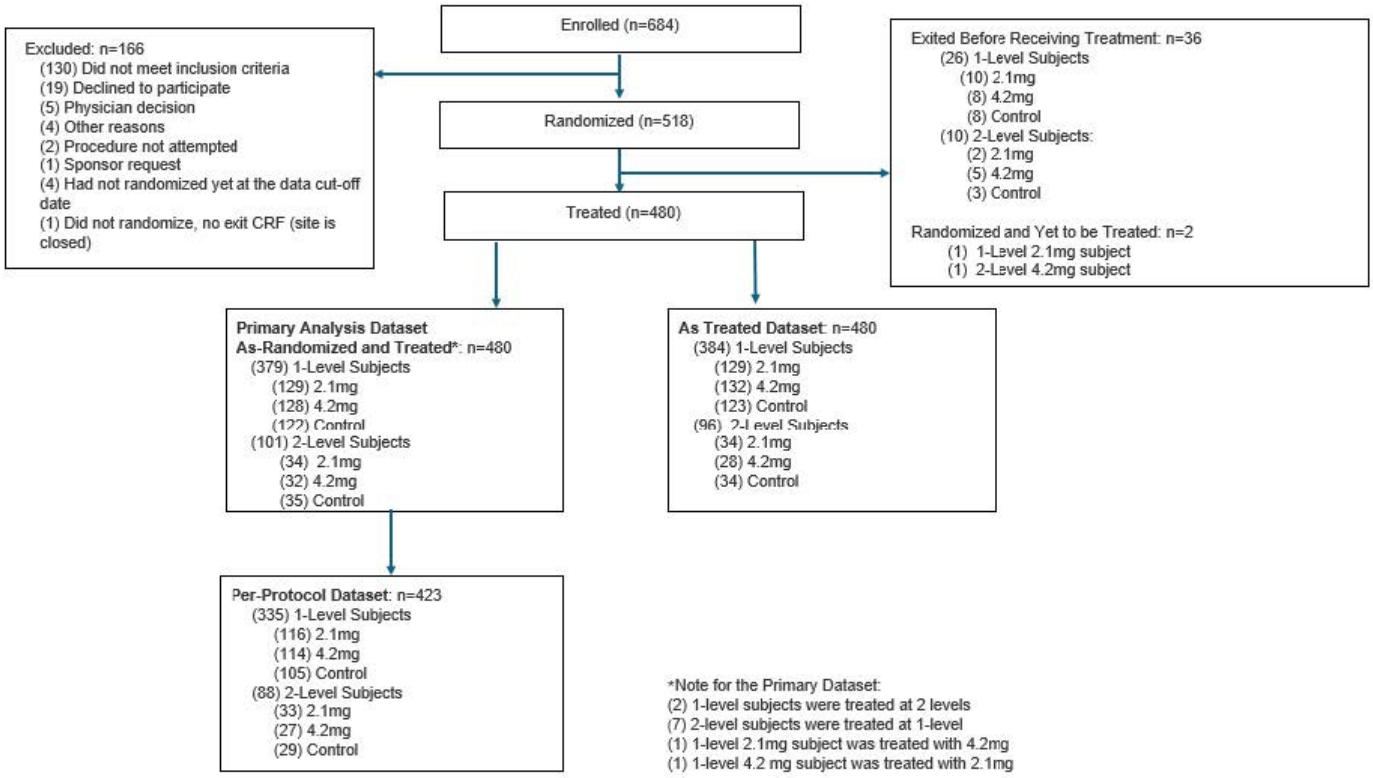


Table 3: Summary of accountability by treatment group based on all subjects

	One-level Subjects (N = 129, 128, 122 for 2.1 mg, 4.2 mg and Ctrl)																	
	Surgery			6 Weeks			3 Months			6 Months			12 Months			24 Months		
	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl
Number of Patients	129	128	122	129	128	122	129	128	122	129	128	122	129	128	122	129	128	122
Patients Not Due for the Visit [a]	0	0	0	3	3	5	6	4	6	13	10	8	21	21	17	51	47	44
Cumulative Withdrawals	0	0	0	0	0	0	0	0	1	0	0	2	0	1	2	1	2	3
Cumulative Deaths	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	1	0
Cumulative Lost to Follow-up	0	0	0	0	0	0	0	0	0	0	3	2	0	4	2	1	5	3
Cumulative Other Reasons (including Sponsor Request)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient Not Yet Overdue [b]	0	0	0	0	1	0	2	4	1	3	0	3	5	5	4	3	7	2
Expected [c]	129	128	122	126	124	117	121	120	114	112	115	107	102	97	97	72	66	70
Evaluated of Expected [d]	129	128	122	125	121	115	119	113	110	110	113	105	99	97	95	72	64	70
Percent of Follow-up (%)	100.0	100.0	100.0	99.2	97.6	98.3	98.3	94.2	96.5	98.2	98.3	98.1	97.1	100.0	97.9	100.0	97.0	100.0

	Two-level Subjects (N = 34, 32, 35 for 2.1 mg, 4.2 mg and Ctrl)																	
	Surgery			6 Weeks			3 Months			6 Months			12 Months			24 Months		
	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl
Number of Patients	34	32	35	34	32	35	34	32	35	34	32	35	34	32	35	34	32	35
Patients Not Due for the Visit [a]	0	0	0	0	1	1	2	2	2	4	6	5	7	8	7	11	13	15
Cumulative Withdrawals	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Cumulative Deaths	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cumulative Lost to Follow-up	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Cumulative Other Reasons (including Sponsor Request)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient Not Yet Overdue [b]	0	0	0	0	0	0	0	0	1	0	0	0	0	0	3	1	0	2
Expected [c]	34	32	35	34	31	34	32	30	32	30	26	30	27	24	25	20	19	17
Evaluated of Expected [d]	34	32	35	34	31	34	32	30	31	30	26	29	26	24	25	19	19	16
Percent of Follow-up (%)	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	96.9	100.0	100.0	96.7	96.3	100.0	100.0	95.0	100.0	94.1

[a] Patients whose lower bound of the visit window is after the cut off date (4/15/2025).
[b] Patients who has not completed follow-up visit and the upper bound of visit window is after the cut off date (4/15/2025).
[c] Expected = (Enrolled and Included in the Analysis) – (Not due for the visit) - (Cumulative Deaths + Cumulative LTF + Cumulative Withdrwal + Cumulative Other) - (Not Yet Overdue).
[d] Patients who have any observed clinical data except AE in a given study period.

Table 4: Summary of accountability by treatment group based on subjects from OUS

	One-level Subjects (N = 49, 51, 49 for 2.1 mg, 4.2 mg and Ctrl)																	
	Surgery			6 Weeks			3 Months			6 Months			12 Months			24 Months		
	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl
Number of Patients	49	51	49	49	51	49	49	51	49	49	51	49	49	51	49	49	51	49
Patients Not Due for the Visit [a]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	8	6
Cumulative Withdrawals	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cumulative Deaths	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Cumulative Lost to Follow-up	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cumulative Other Reasons (including Sponsor Request)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient Not Yet Overdue [b]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	1
Expected [c]	49	51	49	49	51	49	49	51	49	49	51	49	49	51	49	40	40	42
Evaluated of Expected [d]	49	51	49	49	49	48	49	50	48	47	51	48	49	51	49	40	39	42
Percent of Follow-up (%)	100.0	100.0	100.0	100.0	96.1	98.0	100.0	98.0	98.0	95.9	100.0	98.0	100.0	100.0	100.0	100.0	97.5	100.0
	Two-level Subjects (N = 14, 7, 10 for 2.1 mg, 4.2 mg and Ctrl)																	
	Surgery			6 Weeks			3 Months			6 Months			12 Months			24 Months		
	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl
Number of Patients	14	7	10	14	7	10	14	7	10	14	7	10	14	7	10	14	7	10
Patients Not Due for the Visit [a]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1	1
Cumulative Withdrawals	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cumulative Deaths	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cumulative Lost to Follow-up	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Cumulative Other Reasons (including Sponsor Request)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient Not Yet Overdue [b]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Expected [c]	14	7	10	14	7	10	14	7	10	14	7	10	14	7	10	10	6	9
Evaluated of Expected [d]	14	7	10	14	7	10	14	7	10	14	7	10	13	7	10	10	6	8
Percent of Follow-up (%)	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	92.9	100.0	100.0	100.0	100.0	88.9

[a] Patients whose lower bound of the visit window is after the cut off date (4/15/2025).
[b] Patients who has not completed follow-up visit and the upper bound of visit window is after the cut off date (4/15/2025).
[c] Expected = (Enrolled and Included in the Analysis) – (Not due for the visit) - (Cumulative Deaths + Cumulative LTF + Cumulative Withdrwal + Cumulative Other) - (Not Yet Overdue).
[d] Patients who have any observed clinical data except AE in a given study period.

Table 5: Summary of accountability by treatment group based on subjects from US

	One-level Subjects (N = 80, 77, 73 for 2.1 mg, 4.2 mg and Ctrl)																	
	Surgery			6 Weeks			3 Months			6 Months			12 Months			24 Months		
	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl
Number of Patients	80	77	73	80	77	73	80	77	73	80	77	73	80	77	73	80	77	73
Patients Not Due for the Visit [a]	0	0	0	3	3	5	6	4	6	13	10	8	21	21	17	43	39	38
Cumulative Withdrawals	0	0	0	0	0	0	0	0	1	0	0	2	0	1	2	1	2	3
Cumulative Deaths	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	0	0
Cumulative Lost to Follow-up	0	0	0	0	0	0	0	0	0	0	3	2	0	4	2	1	5	3
Cumulative Other Reasons (including Sponsor Request)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient Not Yet Overdue [b]	0	0	0	0	1	0	2	4	1	3	0	3	5	5	4	2	5	1
Expected [c]	80	77	73	77	73	68	72	69	65	63	64	58	53	46	48	32	26	28
Evaluated of Expected [d]	80	77	73	76	72	67	70	63	62	63	62	57	50	46	46	32	25	28
Percent of Follow-up (%)	100.0	100.0	100.0	98.7	98.6	98.5	97.2	91.3	95.4	100.0	96.9	98.3	94.3	100.0	95.8	100.0	96.2	100.0

	Two-level Subjects (N = 20, 25, 25 for 2.1 mg, 4.2 mg and Ctrl)																	
	Surgery			6 Weeks			3 Months			6 Months			12 Months			24 Months		
	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl
Number of Patients	20	25	25	20	25	25	20	25	25	20	25	25	20	25	25	20	25	25
Patients Not Due for the Visit [a]	0	0	0	0	1	1	2	2	2	4	6	5	7	8	7	9	12	14
Cumulative Withdrawals	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Cumulative Deaths	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cumulative Lost to Follow-up	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cumulative Other Reasons (including Sponsor Request)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient Not Yet Overdue [b]	0	0	0	0	0	0	0	0	1	0	0	0	0	0	3	0	0	2
Expected [c]	20	25	25	20	24	24	18	23	22	16	19	20	13	17	15	10	13	8
Evaluated of Expected [d]	20	25	25	20	24	24	18	23	21	16	19	19	13	17	15	9	13	8
Percent of Follow-up (%)	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	95.5	100.0	100.0	95.0	100.0	100.0	100.0	90.0	100.0	100.0

[a] Patients whose lower bound of the visit window is after the cut off date (4/15/2025).
[b] Patients who has not completed follow-up visit and the upper bound of visit window is after the cut off date (4/15/2025).
[c] Expected = (Enrolled and Included in the Analysis) – (Not due for the visit) - (Cumulative Deaths + Cumulative LTF + Cumulative Withdrawal + Cumulative Other) - (Not Yet Overdue).
[d] Patients who have any observed clinical data except AE in a given study period.

C. Study Population Demographics and Baseline Parameters

Key demographic information is summarized in the following table for one-level and two-level subjects (**Table 6**). There were no statistically significant differences across groups.

Table 6: Summary of demographic information by treatment group based on all subjects

Variable	One-Level Subjects (N = 379)			Two-Level Subjects (N = 101)		
	Infuse 2.1 (N = 129)	Infuse 4.2 (N = 128)	Control (N = 122)	Infuse 2.1 (N = 34)	Infuse 4.2 (N = 32)	Control (N = 35)
Age at Randomization (years)						
Number of Subjects with Data Available (n)	129	128	122	34	32	35
Mean (SD)	60.9 (10.4)	61.8 (11.2)	59.5 (9.5)	63.1 (8.0)	61.4 (11.3)	63.2 (8.7)
Median	60.8	62.8	59.9	64.0	64.0	64.4
Min-Max	32.2-80.8	30.6-82.4	30.6-78.3	47.8-74.7	26.9-78.3	39.6-78.1
BMI (kg/m^2)						
Number of Subjects with Data Available (n)	129	128	122	34	32	35
Mean (SD)	28.1 (5.2)	28.7 (4.9)	28.2 (4.8)	28.1 (3.9)	29.7 (4.9)	30.8 (5.1)
Median	27.0	27.9	27.3	27.9	30.0	30.2
Min-Max	17.4-39.8	17.6-40.0	18.0-39.0	21.3-36.7	20.1-38.4	21.8-39.8
Gender (m/n, %)						
Female	78/129 (60.5%)	77/128 (60.2%)	71/122 (58.2%)	16/34 (47.1%)	15/32 (46.9%)	23/35 (65.7%)
Male	51/129 (39.5%)	51/128 (39.8%)	51/122 (41.8%)	18/34 (52.9%)	17/32 (53.1%)	12/35 (34.3%)
Ethnicity (m/n, %)						
Hispanic or Latino	5/129 (3.9%)	5/123 (4.1%)	8/115 (7.0%)	2/32 (6.3%)	1/29 (3.4%)	4/34 (11.8%)
Not Hispanic or Latino	124/129 (96.1%)	118/123 (95.9%)	107/115 (93.0%)	30/32 (93.8%)	28/29 (96.6%)	30/34 (88.2%)
Race ** (m/n, %)						
American Indian or Alaska Native	0/129 (0.0%)	0/128 (0.0%)	0/122 (0.0%)	0/34 (0.0%)	0/32 (0.0%)	0/35 (0.0%)
Asian	49/129 (38.0%)	51/128 (39.8%)	50/122 (41.0%)	14/34 (41.2%)	7/32 (21.9%)	10/35 (28.6%)
Black or African American	10/129 (7.8%)	5/128 (3.9%)	9/122 (7.4%)	1/34 (2.9%)	2/32 (6.3%)	4/35 (11.4%)
Native Hawaiian or Other Pacific Islander	0/129 (0.0%)	1/128 (0.8%)	0/122 (0.0%)	0/34 (0.0%)	0/32 (0.0%)	0/35 (0.0%)
White	68/129 (52.7%)	70/128 (54.7%)	58/122 (47.5%)	18/34 (52.9%)	21/32 (65.6%)	20/35 (57.1%)
Other	2/129 (1.6%)	2/128 (1.6%)	5/122 (4.1%)	1/34 (2.9%)	2/32 (6.3%)	1/35 (2.9%)
Highest Level of Education Attained (m/n, %)						
< High School	38/129 (29.5%)	39/128 (30.5%)	37/122 (30.3%)	8/34 (23.5%)	6/32 (18.8%)	9/35 (25.7%)

Variable	One-Level Subjects (N = 379)			Two-Level Subjects (N = 101)		
	Infuse 2.1 (N = 129)	Infuse 4.2 (N = 128)	Control (N = 122)	Infuse 2.1 (N = 34)	Infuse 4.2 (N = 32)	Control (N = 35)
High School	22/129 (17.1%)	26/128 (20.3%)	24/122 (19.7%)	6/34 (17.6%)	8/32 (25.0%)	8/35 (22.9%)
> High School	69/129 (53.5%)	63/128 (49.2%)	61/122 (50.0%)	20/34 (58.8%)	18/32 (56.3%)	18/35 (51.4%)
Primary Payer Source (m/n, %)						
Medicaid	8/129 (6.2%)	4/128 (3.1%)	5/122 (4.1%)	0/34 (0.0%)	2/32 (6.3%)	2/35 (5.7%)
Medicare	31/129 (24.0%)	39/128 (30.5%)	25/122 (20.5%)	8/34 (23.5%)	10/32 (31.3%)	12/35 (34.3%)
Self Pay	4/129 (3.1%)	3/128 (2.3%)	2/122 (1.6%)	1/34 (2.9%)	1/32 (3.1%)	0/35 (0.0%)
Other	86/129 (66.7%)	82/128 (64.1%)	90/122 (73.8%)	25/34 (73.5%)	19/32 (59.4%)	21/35 (60.0%)
Preoperative Working Status (m/n, %)						
Not Working	88/129 (68.2%)	95/128 (74.2%)	81/122 (66.4%)	24/34 (70.6%)	23/32 (71.9%)	25/35 (71.4%)
Working	41/129 (31.8%)	33/128 (25.8%)	41/122 (33.6%)	10/34 (29.4%)	9/32 (28.1%)	10/35 (28.6%)
Tobacco/Nicotine Usage (m/n, %)						
Current	12/129 (9.3%)	12/128 (9.4%)	11/122 (9.0%)	2/34 (5.9%)	1/32 (3.1%)	5/35 (14.3%)
Former	28/129 (21.7%)	28/128 (21.9%)	30/122 (24.6%)	12/34 (35.3%)	12/32 (37.5%)	9/35 (25.7%)
Never	89/129 (69.0%)	88/128 (68.8%)	81/122 (66.4%)	20/34 (58.8%)	19/32 (59.4%)	21/35 (60.0%)

Table 7: Summary of demographic information by treatment group based on subjects from OUS

Variable	One-Level Subjects (N = 149)			Two-Level Subjects (N = 31)		
	Infuse 2.1 (N = 49)	Infuse 4.2 (N = 51)	Control (N = 49)	Infuse 2.1 (N = 14)	Infuse 4.2 (N = 7)	Control (N = 10)
Age at Randomization (years)						
Number of Subjects with Data Available (n)	49	51	49	14	7	10
Mean (SD)	59.6 (9.3)	57.9 (11.1)	56.9 (10.5)	61.6 (8.5)	56.5 (14.4)	61.6 (10.4)
Median	60.5	57.7	56.1	59.1	57.4	62.3
Min-Max	35.0-76.7	30.6-77.8	30.6-78.3	47.8-74.7	26.9-68.2	39.6-72.0
BMI (kg/m^2)						
Number of Subjects with Data Available (n)	49	51	49	14	7	10
Mean (SD)	24.3 (3.1)	25.6 (3.4)	25.1 (3.4)	25.9 (2.1)	26.2 (4.8)	26.3 (2.6)
Median	23.4	25.5	25.1	25.4	24.7	25.5
Min-Max	17.4-33.2	17.6-36.1	18.0-32.9	23.1-31.8	20.1-33.2	23.4-30.5
Gender (m/n, %)						

Variable	One-Level Subjects (N = 149)			Two-Level Subjects (N = 31)		
	Infuse 2.1 (N = 49)	Infuse 4.2 (N = 51)	Control (N = 49)	Infuse 2.1 (N = 14)	Infuse 4.2 (N = 7)	Control (N = 10)
Female	31/49 (63.3%)	33/51 (64.7%)	28/49 (57.1%)	6/14 (42.9%)	4/7 (57.1%)	7/10 (70.0%)
Male	18/49 (36.7%)	18/51 (35.3%)	21/49 (42.9%)	8/14 (57.1%)	3/7 (42.9%)	3/10 (30.0%)
Ethnicity (m/n, %)						
Hispanic or Latino	0/49 (0.0%)	0/50 (0.0%)	0/47 (0.0%)	0/14 (0.0%)	0/7 (0.0%)	0/10 (0.0%)
Not Hispanic or Latino	49/49 (100%)	50/50 (100%)	47/47 (100%)	14/14 (100%)	7/7 (100%)	10/10 (100%)
Race ** (m/n, %)						
American Indian or Alaska Native	0/49 (0.0%)	0/51 (0.0%)	0/49 (0.0%)	0/14 (0.0%)	0/7 (0.0%)	0/10 (0.0%)
Asian	49/49 (100%)	51/51 (100%)	49/49 (100%)	14/14 (100%)	7/7 (100%)	10/10 (100%)
Black or African American	0/49 (0.0%)	0/51 (0.0%)	0/49 (0.0%)	0/14 (0.0%)	0/7 (0.0%)	0/10 (0.0%)
Native Hawaiian or Other Pacific Islander	0/49 (0.0%)	0/51 (0.0%)	0/49 (0.0%)	0/14 (0.0%)	0/7 (0.0%)	0/10 (0.0%)
White	0/49 (0.0%)	0/51 (0.0%)	0/49 (0.0%)	0/14 (0.0%)	0/7 (0.0%)	0/10 (0.0%)
Other	0/49 (0.0%)	0/51 (0.0%)	0/49 (0.0%)	0/14 (0.0%)	0/7 (0.0%)	0/10 (0.0%)
Highest Level of Education Attained (m/n, %)						
< High School	31/49 (63.3%)	34/51 (66.7%)	33/49 (67.3%)	8/14 (57.1%)	4/7 (57.1%)	6/10 (60.0%)
High School	8/49 (16.3%)	5/51 (9.8%)	4/49 (8.2%)	1/14 (7.1%)	0/7 (0.0%)	2/10 (20.0%)
> High School	10/49 (20.4%)	12/51 (23.5%)	12/49 (24.5%)	5/14 (35.7%)	3/7 (42.9%)	2/10 (20.0%)
Primary Payer Source (m/n, %)						
Medicaid	0/49 (0.0%)	0/51 (0.0%)	0/49 (0.0%)	0/14 (0.0%)	0/7 (0.0%)	0/10 (0.0%)
Medicare	0/49 (0.0%)	0/51 (0.0%)	0/49 (0.0%)	0/14 (0.0%)	0/7 (0.0%)	0/10 (0.0%)
Self Pay	0/49 (0.0%)	2/51 (3.9%)	1/49 (2.0%)	0/14 (0.0%)	0/7 (0.0%)	0/10 (0.0%)
Other	49/49 (100%)	47/51 (92.2%)	47/49 (95.9%)	14/14 (100%)	7/7 (100%)	10/10 (100%)
Preoperative Working Status (m/n, %)						
Not Working	41/49 (83.7%)	43/51 (84.3%)	41/49 (83.7%)	12/14 (85.7%)	6/7 (85.7%)	10/10 (100%)
Working	8/49 (16.3%)	8/51 (15.7%)	8/49 (16.3%)	2/14 (14.3%)	1/7 (14.3%)	0/10 (0.0%)
Tobacco/Nicotine Usage (m/n, %)						
Current	2/49 (4.1%)	2/51 (3.9%)	4/49 (8.2%)	1/14 (7.1%)	1/7 (14.3%)	1/10 (10.0%)
Former	2/49 (4.1%)	4/51 (7.8%)	5/49 (10.2%)	2/14 (14.3%)	0/7 (0.0%)	0/10 (0.0%)
Never	45/49 (91.8%)	45/51 (88.2%)	40/49 (81.6%)	11/14 (78.6%)	6/7 (85.7%)	9/10 (90.0%)

Table 8: Summary of demographic information by treatment group based on subjects from US

Variable	One-Level Subjects (N = 230)			Two-Level Subjects (N = 70)		
	Infuse 2.1 (N = 80)	Infuse 4.2 (N = 77)	Control (N = 73)	Infuse 2.1 (N = 20)	Infuse 4.2 (N = 25)	Control (N = 25)
Age at Randomization (years)						
Number of Subjects with Data Available (n)	80	77	73	20	25	25

Variable	One-Level Subjects (N = 230)			Two-Level Subjects (N = 70)		
	Infuse 2.1 (N = 80)	Infuse 4.2 (N = 77)	Control (N = 73)	Infuse 2.1 (N = 20)	Infuse 4.2 (N = 25)	Control (N = 25)
Mean (SD)	61.7 (10.9)	64.4 (10.5)	61.2 (8.5)	64.1 (7.6)	62.8 (10.2)	63.9 (8.1)
Median	61.9	65.6	61.3	65.8	64.5	64.4
Min-Max	32.2-80.8	43.1-82.4	42.4-77.9	50.0-73.4	38.4-78.3	51.5-78.1
BMI (kg/m^2)						
Number of Subjects with Data Available (n)	80	77	73	20	25	25
Mean (SD)	30.5 (4.9)	30.8 (4.7)	30.3 (4.5)	29.7 (4.1)	30.7 (4.5)	32.6 (4.7)
Median	30.8	31.0	31.2	29.0	30.8	33.3
Min-Max	19.8-39.8	20.6-40.0	20.3-39.0	21.3-36.7	21.0-38.4	21.8-39.8
Gender (m/n, %)						
Female	47/80 (58.8%)	44/77 (57.1%)	43/73 (58.9%)	10/20 (50.0%)	11/25 (44.0%)	16/25 (64.0%)
Male	33/80 (41.3%)	33/77 (42.9%)	30/73 (41.1%)	10/20 (50.0%)	14/25 (56.0%)	9/25 (36.0%)
Ethnicity (m/n, %)						
Hispanic or Latino	5/80 (6.3%)	5/73 (6.8%)	8/68 (11.8%)	2/18 (11.1%)	1/22 (4.5%)	4/24 (16.7%)
Not Hispanic or Latino	75/80 (93.8%)	68/73 (93.2%)	60/68 (88.2%)	16/18 (88.9%)	21/22 (95.5%)	20/24 (83.3%)
Race ** (m/n, %)						
American Indian or Alaska Native	0/80 (0.0%)	0/77 (0.0%)	0/73 (0.0%)	0/20 (0.0%)	0/25 (0.0%)	0/25 (0.0%)
Asian	0/80 (0.0%)	0/77 (0.0%)	1/73 (1.4%)	0/20 (0.0%)	0/25 (0.0%)	0/25 (0.0%)
Black or African American	10/80 (12.5%)	5/77 (6.5%)	9/73 (12.3%)	1/20 (5.0%)	2/25 (8.0%)	4/25 (16.0%)
Native Hawaiian or Other Pacific Islander	0/80 (0.0%)	1/77 (1.3%)	0/73 (0.0%)	0/20 (0.0%)	0/25 (0.0%)	0/25 (0.0%)
White	68/80 (85.0%)	70/77 (90.9%)	58/73 (79.5%)	18/20 (90.0%)	21/25 (84.0%)	20/25 (80.0%)
Other	2/80 (2.5%)	2/77 (2.6%)	5/73 (6.8%)	1/20 (5.0%)	2/25 (8.0%)	1/25 (4.0%)
Highest Level of Education Attained (m/n, %)						
< High School	7/80 (8.8%)	5/77 (6.5%)	4/73 (5.5%)	0/20 (0.0%)	2/25 (8.0%)	3/25 (12.0%)
High School	14/80 (17.5%)	21/77 (27.3%)	20/73 (27.4%)	5/20 (25.0%)	8/25 (32.0%)	6/25 (24.0%)
> High School	59/80 (73.8%)	51/77 (66.2%)	49/73 (67.1%)	15/20 (75.0%)	15/25 (60.0%)	16/25 (64.0%)
Primary Payer Source (m/n, %)						
Medicaid	8/80 (10.0%)	4/77 (5.2%)	5/73 (6.8%)	0/20 (0.0%)	2/25 (8.0%)	2/25 (8.0%)
Medicare	31/80 (38.8%)	39/77 (50.6%)	25/73 (34.2%)	8/20 (40.0%)	10/25 (40.0%)	12/25 (48.0%)
Self Pay	4/80 (5.0%)	1/77 (1.3%)	1/73 (1.4%)	1/20 (5.0%)	1/25 (4.0%)	0/25 (0.0%)
Other	37/80 (46.3%)	33/77 (42.9%)	42/73 (57.5%)	11/20 (55.0%)	12/25 (48.0%)	11/25 (44.0%)
Preoperative Working Status (m/n, %)						
Not Working	47/80 (58.8%)	52/77 (67.5%)	40/73 (54.8%)	12/20 (60.0%)	17/25 (68.0%)	15/25 (60.0%)
Working	33/80 (41.3%)	25/77 (32.5%)	33/73 (45.2%)	8/20 (40.0%)	8/25 (32.0%)	10/25 (40.0%)
Tobacco/Nicotine Usage (m/n, %)						
Current	10/80 (12.5%)	10/77 (13.0%)	7/73 (9.6%)	1/20 (5.0%)	0/25 (0.0%)	4/25 (16.0%)

Variable	One-Level Subjects (N = 230)			Two-Level Subjects (N = 70)		
	Infuse 2.1 (N = 80)	Infuse 4.2 (N = 77)	Control (N = 73)	Infuse 2.1 (N = 20)	Infuse 4.2 (N = 25)	Control (N = 25)
Former	26/80 (32.5%)	24/77 (31.2%)	25/73 (34.2%)	10/20 (50.0%)	12/25 (48.0%)	9/25 (36.0%)
Never	44/80 (55.0%)	43/77 (55.8%)	41/73 (56.2%)	9/20 (45.0%)	13/25 (52.0%)	12/25 (48.0%)

Baseline clinical endpoints are summarized in **Table 9** for one-level and two-level subjects. There were no statistically significant differences across groups except for Neurological Status where there was a difference in the percentage of patients with abnormal motor functions (Infuse 2.1: 41.2% (14/34), Infuse 4.2: 12.5% (4/32), and Control: 26.5% (9/34) (**Table 9**). Baseline clinical endpoints are also shown by subjects from OUS sites (**Table 10**) and US sites (**Table 11**).

Table 9: Summary of baseline clinical endpoints by treatment group based on all subjects

Variable	One-Level Subjects (N = 379)			Two-Level Subjects (N = 101)		
	Infuse 2.1 (N = 129)	Infuse 4.2 (N = 128)	Control (N = 122)	Infuse 2.1 (N = 34)	Infuse 4.2 (N = 32)	Control (N = 35)
ODI						
Number of Subjects with Data Available (n)	129	128	122	34	32	35
Mean (SD)	54.4 (12.2)	53.9 (10.6)	53.4 (11.8)	52.2 (11.0)	56.8 (10.0)	56.5 (12.3)
Median	52.0	54.0	52.0	51.1	58.0	56.0
Min-Max	35.6-84.0	36.0-78.0	36.0-90.0	38.0-76.0	36.0-76.0	36.0-84.0
Back Pain						
Number of Subjects with Data Available (n)	129	128	122	34	32	35
Mean (SD)	6.6 (2.4)	6.4 (2.2)	6.6 (2.1)	6.8 (2.5)	7.1 (1.9)	7.3 (2.1)
Median	7.0	7.0	7.0	7.0	7.5	8.0
Min-Max	1-10	1-10	1-10	2-10	2-10	3-10
Leg Pain						
Number of Subjects with Data Available (n)	129	128	122	34	32	35
Mean (SD)	7.0 (2.0)	6.7 (2.0)	6.6 (2.2)	7.5 (1.7)	7.1 (1.8)	7.7 (1.8)
Median	7.0	7.0	7.0	7.0	7.5	8.0
Min-Max	3-10	1-10	1-10	1-10	2-10	2-10
Neurological Status						
Motor Functions (m/n, %)						
Abnormal	47/129 (36.4%)	42/126 (33.3%)	31/122 (25.4%)	14/34 (41.2%)	4/32 (12.5%)	9/34 (26.5%)
Normal	82/129 (63.6%)	84/126 (66.7%)	91/122 (74.6%)	20/34 (58.8%)	28/32 (87.5%)	25/34 (73.5%)
Sensory Functions (m/n, %)						

Variable	One-Level Subjects (N = 379)			Two-Level Subjects (N = 101)		
	Infuse 2.1 (N = 129)	Infuse 4.2 (N = 128)	Control (N = 122)	Infuse 2.1 (N = 34)	Infuse 4.2 (N = 32)	Control (N = 35)
Abnormal	41/129 (31.8%)	43/126 (34.1%)	39/122 (32.0%)	15/34 (44.1%)	9/32 (28.1%)	8/34 (23.5%)
Normal	88/129 (68.2%)	83/126 (65.9%)	83/122 (68.0%)	19/34 (55.9%)	23/32 (71.9%)	26/34 (76.5%)
Reflexes (m/n, %)						
Abnormal	39/129 (30.2%)	33/126 (26.2%)	31/122 (25.4%)	19/34 (55.9%)	10/32 (31.3%)	12/34 (35.3%)
Normal	90/129 (69.8%)	93/126 (73.8%)	91/122 (74.6%)	15/34 (44.1%)	22/32 (68.8%)	22/34 (64.7%)
Straight Leg Raise (m/n, %)						
Abnormal	43/129 (33.3%)	49/126 (38.9%)	44/122 (36.1%)	13/34 (38.2%)	7/32 (21.9%)	10/34 (29.4%)
Normal	86/129 (66.7%)	77/126 (61.1%)	78/122 (63.9%)	21/34 (61.8%)	25/32 (78.1%)	24/34 (70.6%)

Table 10: Summary of baseline clinical endpoints by treatment group based on subjects from OUS

Variable	One-Level Subjects (N = 149)			Two-Level Subjects (N = 31)		
	Infuse 2.1 (N = 49)	Infuse 4.2 (N = 51)	Control (N = 49)	Infuse 2.1 (N = 14)	Infuse 4.2 (N = 7)	Control (N = 10)
ODI						
Number of Subjects with Data Available (n)	49	51	49	14	7	10
Mean (SD)	54.1 (11.4)	56.1 (8.5)	56.5 (10.3)	54.3 (10.7)	62.4 (9.7)	57.5 (14.0)
Median	52.0	57.8	55.6	53.7	66.0	57.0
Min-Max	35.6-82.0	37.8-70.0	36.0-82.2	42.0-75.6	50.0-76.0	36.0-84.0
Back Pain						
Number of Subjects with Data Available (n)	49	51	49	14	7	10
Mean (SD)	4.8 (2.1)	5.2 (2.1)	5.4 (1.9)	5.9 (2.6)	6.7 (2.2)	5.5 (2.1)
Median	5.0	5.0	5.0	5.5	6.0	5.0
Min-Max	1-10	1-10	1-9	2-10	3-10	3-10
Leg Pain						
Number of Subjects with Data Available (n)	49	51	49	14	7	10
Mean (SD)	6.2 (1.8)	5.6 (1.8)	5.8 (2.0)	6.9 (2.1)	7.1 (1.2)	7.7 (1.6)
Median	6.0	6.0	5.0	7.0	7.0	7.5
Min-Max	3-10	1-10	2-10	1-9	6-9	6-10
Neurological Status						
Motor Functions (m/n, %)						
Abnormal	24/49 (49.0%)	17/51 (33.3%)	18/49 (36.7%)	7/14 (50.0%)	1/7 (14.3%)	4/10 (40.0%)

Variable	One-Level Subjects (N = 149)			Two-Level Subjects (N = 31)		
	Infuse 2.1 (N = 49)	Infuse 4.2 (N = 51)	Control (N = 49)	Infuse 2.1 (N = 14)	Infuse 4.2 (N = 7)	Control (N = 10)
Normal	25/49 (51.0%)	34/51 (66.7%)	31/49 (63.3%)	7/14 (50.0%)	6/7 (85.7%)	6/10 (60.0%)
Sensory Functions (m/n, %)						
Abnormal	23/49 (46.9%)	19/51 (37.3%)	19/49 (38.8%)	10/14 (71.4%)	3/7 (42.9%)	3/10 (30.0%)
Normal	26/49 (53.1%)	32/51 (62.7%)	30/49 (61.2%)	4/14 (28.6%)	4/7 (57.1%)	7/10 (70.0%)
Reflexes (m/n, %)						
Abnormal	16/49 (32.7%)	12/51 (23.5%)	13/49 (26.5%)	7/14 (50.0%)	3/7 (42.9%)	6/10 (60.0%)
Normal	33/49 (67.3%)	39/51 (76.5%)	36/49 (73.5%)	7/14 (50.0%)	4/7 (57.1%)	4/10 (40.0%)
Straight Leg Raise (m/n, %)						
Abnormal	18/49 (36.7%)	17/51 (33.3%)	13/49 (26.5%)	6/14 (42.9%)	1/7 (14.3%)	1/10 (10.0%)
Normal	31/49 (63.3%)	34/51 (66.7%)	36/49 (73.5%)	8/14 (57.1%)	6/7 (85.7%)	9/10 (90.0%)

Table 11: Summary of baseline clinical endpoints by treatment group based on subjects from US

Variable	One-Level Subjects (N = 230)			Two-Level Subjects (N = 70)		
	Infuse 2.1 (N = 80)	Infuse 4.2 (N = 77)	Control (N = 73)	Infuse 2.1 (N = 20)	Infuse 4.2 (N = 25)	Control (N = 25)
ODI						
Number of Subjects with Data Available (n)	80	77	73	20	25	25
Mean (SD)	54.7 (12.7)	52.3 (11.7)	51.4 (12.3)	50.8 (11.3)	55.3 (9.7)	56.1 (11.8)
Median	52.0	50.0	48.0	50.6	57.8	56.0
Min-Max	36.0-84.0	36.0-78.0	36.0-90.0	38.0-76.0	36.0-70.0	38.0-80.0
Back Pain						
Number of Subjects with Data Available (n)	80	77	73	20	25	25
Mean (SD)	7.7 (1.8)	7.1 (1.9)	7.4 (1.9)	7.5 (2.3)	7.2 (1.9)	8.0 (1.7)
Median	8.0	7.0	8.0	8.0	8.0	8.0
Min-Max	1-10	2-10	2-10	3-10	2-10	4-10
Leg Pain						
Number of Subjects with Data Available (n)	80	77	73	20	25	25
Mean (SD)	7.6 (1.9)	7.4 (1.7)	7.1 (2.1)	7.9 (1.3)	7.0 (1.9)	7.7 (2.0)
Median	8.0	7.0	7.0	8.0	8.0	8.0
Min-Max	3-10	2-10	1-10	6-10	2-10	2-10
Neurological Status						
Motor Functions (m/n, %)						
Abnormal	23/80 (28.8%)	25/75 (33.3%)	13/73 (17.8%)	7/20 (35.0%)	3/25 (12.0%)	5/24 (20.8%)
Normal	57/80 (71.3%)	50/75 (66.7%)	60/73 (82.2%)	13/20 (65.0%)	22/25 (88.0%)	19/24 (79.2%)
Sensory Functions (m/n, %)						

Variable	One-Level Subjects (N = 230)			Two-Level Subjects (N = 70)		
	Infuse 2.1 (N = 80)	Infuse 4.2 (N = 77)	Control (N = 73)	Infuse 2.1 (N = 20)	Infuse 4.2 (N = 25)	Control (N = 25)
Abnormal	18/80 (22.5%)	24/75 (32.0%)	20/73 (27.4%)	5/20 (25.0%)	6/25 (24.0%)	5/24 (20.8%)
Normal	62/80 (77.5%)	51/75 (68.0%)	53/73 (72.6%)	15/20 (75.0%)	19/25 (76.0%)	19/24 (79.2%)
Reflexes (m/n, %)						
Abnormal	23/80 (28.8%)	21/75 (28.0%)	18/73 (24.7%)	12/20 (60.0%)	7/25 (28.0%)	6/24 (25.0%)
Normal	57/80 (71.3%)	54/75 (72.0%)	55/73 (75.3%)	8/20 (40.0%)	18/25 (72.0%)	18/24 (75.0%)
Straight Leg Raise (m/n, %)						
Abnormal	25/80 (31.3%)	32/75 (42.7%)	31/73 (42.5%)	7/20 (35.0%)	6/25 (24.0%)	9/24 (37.5%)
Normal	55/80 (68.8%)	43/75 (57.3%)	42/73 (57.5%)	13/20 (65.0%)	19/25 (76.0%)	15/24 (62.5%)

A summary of the surgical indications and key surgical information is provided in **Table 12**. No statistical differences were noted except for the levels treated in the two-level subject group, for the mean length of hospital stay, and distribution of treatment level (**Table 12**). Surgical indications and select surgical information are also shown for OUS (**Table 13**) and US subjects (**Table 14**).

Table 12: Summary of surgical indication and surgical information by treatment group based on all subjects

Variable	One-Level Subjects (N = 379)			Two-Level Subjects (N = 101)		
	Infuse 2.1 (N = 129)	Infuse 4.2 (N = 128)	Control (N = 122)	Infuse 2.1 (N = 34)	Infuse 4.2 (N = 32)	Control (N = 35)
Primary Diagnosis (m/n, %)						
Instability	46/129 (35.7%)	53/128 (41.4%)	46/122 (37.7%)	8/34 (23.5%)	7/32 (21.9%)	8/35 (22.9%)
Recurrent Disc Herniation	12/129 (9.3%)	11/128 (8.6%)	8/122 (6.6%)	2/34 (5.9%)	2/32 (6.3%)	2/35 (5.7%)
Stenosis	71/129 (55.0%)	64/128 (50.0%)	68/122 (55.7%)	24/34 (70.6%)	23/32 (71.9%)	25/35 (71.4%)
Has the subject had previous lumbar spinal surgery (m/n, %)	16/129 (12.4%)	20/128 (15.6%)	24/122 (19.7%)	1/34 (2.9%)	6/32 (18.8%)	4/35 (11.4%)
Mean (SD) Operation Time, minutes	174.1 (66.8)	175.1 (69.8)	166.5 (56.4)	221.4 (43.7)	221.1 (61.7)	203.9 (51.2)
Mean (SD) Total Estimated Blood Loss (mL)	161.3 (148.1)	157.0 (125.0)	152.2 (112.0)	281.8 (159.4)	265.6 (282.0)	269.4 (237.9)
Mean (SD) Length of Hospital Stay (days)	3.4 (2.1)	3.5 (2.2)	3.6 (2.6)	4.7 (2.8)	3.3 (1.9)	3.7 (2.4)
Treatment Level (m/n, %) *						
L2-L3	0/129 0.0%)	1/128 (0.8%)	0/122 (0.0%)	---	---	---
L3-L4	4/129 (3.1%)	6/128 (4.7%)	7/122 (5.7%)	0/34 (0.0%)	1/32 (3.1%)	0/35 (0.0%)
L4-L5	102/129 (79.1%)	91/128 (71.1%)	91/122 (74.6%)	0/34 (0.0%)	3/32 (9.4%)	3/35 (8.6%)
L5-S1	23/129 (17.8%)	30/128 (23.4%)	21/122 (17.2%)	---	---	---
L5-L6	0/129 (0.0%)	0/128 (0.0%)	1/122 (0.8%)	---	---	---
L2-L3; L3-L4	---	---	---	1/34 (2.9%)	0/32 (0.0%)	0/35 (0.0%)

Variable	One-Level Subjects (N = 379)			Two-Level Subjects (N = 101)		
	Infuse 2.1 (N = 129)	Infuse 4.2 (N = 128)	Control (N = 122)	Infuse 2.1 (N = 34)	Infuse 4.2 (N = 32)	Control (N = 35)
L3-L4; L4-L5	0/129 (0.0%)	0/128 (0.0%)	2/122 (1.6%)	19/34 (55.9%)	17/32 (53.1%)	8/35 (22.9%)
L4-L5; L5-S1	---	---	---	14/34 (41.2%)	11/32 (34.4%)	24/35 (68.6%)
Surgical Access (m/n, %)						
Minimally Invasive (i.e. Metrx or Quadrant)	53/129 (41.1%)	53/128 (41.4%)	49/122 (40.2%)	5/34 (14.7%)	6/32 (18.8%)	4/35 (11.4%)
Open	76/129 (58.9%)	75/128 (58.6%)	73/122 (59.8%)	29/34 (85.3%)	26/32 (81.3%)	31/35 (88.6%)
Mean (SD) Volume of Local Bone Autograft Implanted (cc)	6.7 (5.3)	6.1 (4.0)	7.0 (5.5)	Sup: 8.6 (6.6) Inf: 8.3 (6.1)	Sup: 8.1 (4.9) Inf: 7.5 (4.7)	Sup: 9.0 (5.6) Inf: 10.5 (5.7)
Mean (SD) Volume of Allograft Bone Implanted (cc)	9.3 (7.6)	9.8 (7.5)	11.0 (9.3)	Sup: 8.2 (10.4) Inf: 11.5 (14.1)	Sup: 8.7 (5.7) Inf: 9.2 (5.5)	Sup: 6.9 (3.4) Inf: 8.8 (1.5)

* Two subjects were randomized as one-level subject, but two levels were treated, seven subjects were randomized as two-level subjects, but only one level was treated.

Table 13: Summary of surgical indication and surgical information by treatment group based on subjects from OUS

Variable	One-Level Subjects (N = 149)			Two-Level Subjects (N = 31)		
	Infuse 2.1 (N = 49)	Infuse 4.2 (N = 51)	Control (N = 49)	Infuse 2.1 (N = 14)	Infuse 4.2 (N = 7)	Control (N = 10)
Primary Diagnosis (m/n, %)						
Instability	16/49 (32.7%)	18/51 (35.3%)	16/49 (32.7%)	0/14 (0.0%)	0/7 (0.0%)	2/10 (20.0%)
Recurrent Disc Herniation	1/49 (2.0%)	3/51 (5.9%)	2/49 (4.1%)	1/14 (7.1%)	1/7 (14.3%)	0/10 (0.0%)
Stenosis	32/49 (65.3%)	30/51 (58.8%)	31/49 (63.3%)	13/14 (92.9%)	6/7 (85.7%)	8/10 (80.0%)
Has the subject had previous lumbar spinal surgery (m/n, %)	2/49 (4.1%)	3/51 (5.9%)	3/49 (6.1%)	1/14 (7.1%)	1/7 (14.3%)	0/10 (0.0%)
Mean (SD) Operation Time, minutes	176.2 (66.9)	173.5 (66.6)	169.2 (54.7)	219.3 (56.5)	214.4 (43.0)	180.7 (47.2)
Mean (SD) Total Estimated Blood Loss (mL)	191.8 (96.7)	196.7 (89.1)	204.3 (89.0)	350.7 (158.9)	400.0 (152.8)	285.0 (137.5)
Mean (SD) Length of Hospital Stay (days)	5.0 (1.2)	4.8 (1.1)	5.2 (1.2)	6.9 (2.7)	5.7 (1.3)	5.3 (1.6)
Treatment Level (m/n, %) *						
L3-L4	1/49 (2.0%)	0/51 (0.0%)	2/49 (4.1%)	---	---	---
L4-L5	36/49 (73.5%)	36/51 (70.6%)	35/49 (71.4%)	0/14 (0.0%)	1/7 (14.3%)	0/10 (0.0%)
L5-S1	12/49 (24.5%)	15/51 (29.4%)	10/49 (20.4%)	---	---	---
L5-L6	0/49 (0.0%)	0/51 (0.0%)	1/49 (2.0%)	---	---	---
L3-L4; L4-L5	0/49 (0.0%)	0/51 (0.0%)	1/49 (2.0%)	8/14 (57.1%)	5/7 (71.4%)	2/10 (20.0%)
L4-L5; L5-S1	---	---	---	6/14 (42.9%)	1/7 (14.3%)	8/10 (80.0%)
Surgical Access (m/n, %)						
Minimally Invasive (i.e. Metrx or Quadrant)	16/49 (32.7%)	19/51 (37.3%)	17/49 (34.7%)	1/14 (7.1%)	1/7 (14.3%)	0/10 (0.0%)
Open	33/49 (67.3%)	32/51 (62.7%)	32/49 (65.3%)	13/14 (92.9%)	6/7 (85.7%)	10/10 (100%)

Variable	One-Level Subjects (N = 149)			Two-Level Subjects (N = 31)		
	Infuse 2.1 (N = 49)	Infuse 4.2 (N = 51)	Control (N = 49)	Infuse 2.1 (N = 14)	Infuse 4.2 (N = 7)	Control (N = 10)
Mean (SD) Volume of Local Bone Autograft Implanted (cc)	5.6 (5.0)	5.2 (4.1)	5.5 (4.5)	Sup: 6.6 (6.1) Inf: 7.8 (7.0)	Sup: 5.7 (3.4) Inf: 6.0 (5.2)	Sup: 9.0 (8.2) Inf: 12.9 (9.3))
Mean (SD) Volume of Allograft Bone Implanted (cc)	2.0 (0.0)	3.2 (1.8)	2.7 (0.7)	Sup: 3.3 (1.4) Inf: 1.0 (NA)	Sup: 4.7 (1.5) Inf: 3.0 (NA)	Sup: 5.3 (3.1) Inf: 8.0 (NA)
* One subject was randomized as one-level subject, but two levels were treated; One subject was randomized as two-level subjects, but only one level was treated;						

Table 14: Summary of surgical indication and surgical information by treatment group based on subjects from US

Variable	One-Level Subjects (N = 230)			Two-Level Subjects (N = 70)		
	Infuse 2.1 (N = 80)	Infuse 4.2 (N = 77)	Control (N = 73)	Infuse 2.1 (N = 20)	Infuse 4.2 (N = 25)	Control (N = 25)
Primary Diagnosis (m/n, %)						
Instability	30/80 (37.5%)	35/77 (45.5%)	30/73 (41.1%)	8/20 (40.0%)	7/25 (28.0%)	6/25 (24.0%)
Recurrent Disc Herniation	11/80 (13.8%)	8/77 (10.4%)	6/73 (8.2%)	1/20 (5.0%)	1/25 (4.0%)	2/25 (8.0%)
Stenosis	39/80 (48.8%)	34/77 (44.2%)	37/73 (50.7%)	11/20 (55.0%)	17/25 (68.0%)	17/25 (68.0%)
Has the subject had previous lumbar spinal surgery (m/n, %)	14/80 (17.5%)	17/77 (22.1%)	21/73 (28.8%)	0/20 (0.0%)	5/25 (20.0%)	4/25 (16.0%)
Mean (SD) Operation Time, minutes	172.8 (67.2)	176.0 (72.3)	164.7 (57.8)	222.8 (33.5)	223.0 (66.6)	213.2 (50.7)
Mean (SD) Total Estimated Blood Loss (mL)	142.6 (170.1)	130.6 (138.4)	117.2 (112.8)	233.5 (144.6)	228.0 (300.3)	263.2 (270.0)
Mean (SD) Length of Hospital Stay (days)	2.4 (1.8)	2.6 (2.3)	2.5 (2.7)	3.2 (1.6)	2.6 (1.5)	3.0 (2.4)
Treatment Level (m/n, %) *						
L2-L3	0/80 (0.0%)	1/77 (1.3%)	0/73 (0.0%)	---	---	---
L3-L4	3/80 (3.8%)	6/77 (7.8%)	5/73 (6.8%)	0/20 (0.0%)	1/25 (4.0%)	0/25 (0.0%)
L4-L5	66/80 (82.5%)	55/77 (71.4%)	56/73 (76.7%)	0/20 (0.0%)	2/25 (8.0%)	3/25 (12.0%)
L5-S1	11/80 (13.8%)	15/77 (19.5%)	11/73 (15.1%)	---	---	---
L2-L3; L3-L4	---	---	---	1/20 (5.0%)	0/25 (0.0%)	0/25 (0.0%)
L3-L4; L4-L5	0/80 (0.0%)	0/77 (0.0%)	1/73 (1.4%)	11/20 (55.0%)	12/25 (48.0%)	6/25 (24.0%)
L4-L5; L5-S1	---	---	---	8/20 (40.0%)	10/25 (40.0%)	16/25 (64.0%)
Surgical Access (m/n, %)						
Minimally Invasive (i.e. Metrx or Quadrant)	37/80 (46.3%)	34/77 (44.2%)	32/73 (43.8%)	4/20 (20.0%)	5/25 (20.0%)	4/25 (16.0%)
Open	43/80 (53.8%)	43/77 (55.8%)	41/73 (56.2%)	16/20 (80.0%)	20/25 (80.0%)	21/25 (84.0%)
Mean (SD) Volume of Local Bone Autograft Implanted (cc)	7.3 (5.4)	6.7 (3.9)	8.0 (5.9)	Sup: 9.9 (6.7) Inf: 8.6 (5.7)	Sup: 8.7 (5.1) Inf: 7.9 (4.6)	Sup: 9.0 (4.2) Inf: 9.7 (3.9)
Mean (SD) Volume of Allograft Bone Implanted (cc)	10.2 (7.5)	11.1 (7.5)	13.0 (9.3)	Sup: 17.8 (14.6) Inf: 16.8 (15.2)	Sup: 10.3 (6.0) Inf: 10.4 (5.1)	Sup: 7.8 (3.5) Inf: 9.0 (1.7)
* One subject was randomized as one-level subject, but two levels were treated; six subjects were randomized as two-level subjects, but only one level was treated.						

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety for PMA application was based on the "As Treated" (AT) cohort at 24 months after operative intervention. For the PMA application analysis, the AT cohort (N = 480) was comprised of 384 1-level subjects and 96 2-level subjects. The 1-level subjects had 129, 132 and 123 subjects in the 2.1 mg, 4.2 mg, and control cohorts. The 2-level subjects had 34, 28 and 34 subjects in the 2.1 mg, 4.2 mg, and control cohorts. The 24 month follow up rate of the AT population pooled by levels from all sites at the time of this interim analysis for PMA application review was 62.2% one-level patients and 62.5% two-level patients. Adverse events were reviewed and adjudicated for relatedness and severity by an independent clinical events committee (CEC). Cumulative rate of adverse events at the time of PMA application are reported in **Table 15** to **Table 28**.

Adverse events that occurred in the PMA clinical study

For one-level subjects, the 24-month cumulative AE rate was 88.6% in the Infuse 2.1 mg group, 89.8% in the Infuse 4.2 mg group, and 87.5% in the Control group (**Table 15**). There were no statistically significant differences in the 24-month cumulative AE rates between the Infuse groups (2.1 mg or 4.2 mg) and Control group for cumulative AE rate (**Table 15**, **Table 17**).

For one-level subjects, the 24-month cumulative SAE rate was 27.2% in the Infuse 2.1 mg group, 41.3% in the Infuse 4.2 mg group, and 24.6% in the Control group **(Table 15**). The 24-month cumulative rate of procedure related SAEs was 11.2% for the Infuse 2.1 mg group, 19% for the Infuse 4.2 mg group, and 8.3% for the Control group for a statistically significant difference in procedure related SAEs for the 4.2 mg group at 24 months after operative intervention compared to the control (p=0.032) (**Table 15**). When compared to control at 24 months for the 1-level subjects, the Infuse 4.2 mg group had a statistically significantly higher number of SAEs classified as "musculoskeletal and connective tissue disorders" (p = 0.017) and "general disorders and administration site conditions" (p = 0.008) (**Table 19, Table 23, Table 27**).

Otherwise, for one-level subjects at 24 months, there were no other statistically significant differences amongst the 2.1 mg, 4.2 mg, and control groups for AEs or SAEs related to surgical construct, or for AEs or SAEs related to study procedure for the 2.1 mg group compared to control, or for AEs related to study procedure for the 4.2 mg group compared to control (**Table 21, Table 23, Table 25, Table 27**).

Reported adverse events of heterotopic ossification (HO) were captured under the MedDRA Preferred Terms extra skeletal ossification, vertebral osteophyte, or exostosis. Eleven AEs in 10 subjects (3 events in 3 subjects in the Infuse 2.1 mg group, 6 events in 5 subjects in the Infuse 4.2 mg group, and 2 events in 2 subjects in the

Control group) reported under these Preferred Terms were adjudicated by the Clinical Events Committee (CEC) to be "related" to the bone graft material. Seven of these events were radiographic observations of HO in subjects who had no clinical sequelae. One subject (Infuse 4.2 mg group) experienced radiculopathy classified as a serious adverse event (SAE) that resulted in a secondary surgical procedure. A CT assessment of HO was also conducted by the independent imaging core lab with an adjudication process. HO was more frequently observed with the Infuse 2.1 and 4.2 mg groups (one-level: Infuse 2.1 mg: 87.0% (60/69), Infuse 4.2 mg: 96.7% (59/61), Control: 56.7% (38/67)). These results, however, did not correlate with radiculopathy-related adverse event as there were no statistically significant differences in radiculopathy-related adverse events between groups.

Three deaths were reported in the study: one from the Infuse 2.1 mg group and two from the Infuse 4.2 mg group. None of the deaths were related to the TLIF grafting material, interbody device, or posterior-fixation. Causes of death were cardiac arrest (Infuse 4.2 mg – one-level), rectal cancer (Infuse 4.2 mg – one-level), and necrotizing pancreatitis (Infuse 2.1 mg – one-level).

Table 15: Adverse Event (AE) rates in the AT Population by severity and relatedness for 1-level subjects

Adverse Event Type n- # of Patients % - Cumulative Adverse Event Rate*	One-Level Subjects (N = 129, 132, 123 for 2.1 mg, 4.2 mg and Ctrl)											
	Up to 12 months						Up to 24 Months					
	Infuse 2.1 mg (N = 129)		Infuse 4.2 mg (N = 132)		Control (N = 123)		Infuse 2.1 mg (N = 129)		Infuse 4.2 mg (N = 132)		Control (N = 123)	
	n	%	n	%	n	%	n	%	n	%	n	%
Subjects Having Any Adverse Events	94	80.3	109	89.8	95	85.4	98	88.6	109	89.8	96	87.5
Subjects Having Any Serious Adverse Events	21	19.1	35	30.3	20	19.5	26	27.2	41	41.3	23	24.6
Subjects Having Any Adverse Events Related to Surgical Construct**	39	33.9	43	35.7	37	33.7	42	38.6	47	42.6	38	35.5
• Related to TLIF Grafting Material/Interbody Device	38	33.2	42	34.9	37	33.7	41	38.0	45	40.1	38	35.5
- Related to TLIF Grafting Material	38	33.2	40	33.2	36	32.6	41	38.0	43	38.4	38	36.1
- Related to Interbody Device	37	32.4	40	33.4	36	32.8	40	37.3	43	38.7	37	34.6
• Related to Posterior Fixation	37	32.3	38	31.8	35	31.6	40	37.0	42	38.6	36	33.4
Subjects Having Any Serious Adverse Events Related to Surgical Construct**	2	2.3	7	6.2	4	4.1	4	5.7	10	11.5	4	4.1
• Related to TLIF Grafting Material/Interbody Device	1	1.1	5	4.4	3	3.2	3	4.6	7	8.0	3	3.2
- Related to TLIF Grafting Material	0	0.0	3	2.8	3	3.2	2	3.4	5	6.5	3	3.2
- Related to Interbody Device	1	1.1	5	4.4	1	1.2	3	4.6	7	8.0	1	1.2
• Related to Posterior Fixation	1	1.1	5	4.7	2	2.1	3	4.5	7	8.3	2	2.1

Adverse Event Type n- # of Patients % - Cumulative Adverse Event Rate*	One-Level Subjects (N = 129, 132, 123 for 2.1 mg, 4.2 mg and Ctrl)											
	Up to 12 months						Up to 24 Months					
	Infuse 2.1 mg (N = 129)		Infuse 4.2 mg (N = 132)		Control (N = 123)		Infuse 2.1 mg (N = 129)		Infuse 4.2 mg (N = 132)		Control (N = 123)	
	n	%	n	%	n	%	n	%	n	%	n	%
Subjects Having Any Procedure Related Adverse Events	69	57.2	81	63.9	66	57.6	73	64.9	83	67.6	67	59.3
Subjects Having Any Procedure Related Serious Adverse Events	9	7.8	19	15.4	9	8.3	11	11.2	21	19.0	9	8.3
*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.												

For two-level subjects, the 24-month cumulative AE rate was 83.6% in the Infuse 2.1 mg group, 94.1% in the Infuse 4.2 mg group, and 85.2% in the Control group (**Table 16)**. There were no statistically significant differences in the 24-month cumulative AE rates between the Infuse groups (2.1 mg or 4.2 mg) and Control group for cumulative AE rate (**Table 16, Table 18, Table 22**).

For two-level subjects, the 24-month cumulative SAE rate was 36.2% in the Infuse 2.1 mg group, 37.4% in the Infuse 4.2 mg group, and 26.8% in the Control group. The difference in SAE rates between the 2.1 mg group (p = 0.535) and the 4.2 mg group (p = 0.677) did not meet statistical significance when compared to control (**Table 16, Table 20, Table 24**).

The only other group meeting statistical significance for the two – level subjects was the 2.1 mg group compared to control (p =0.047) for subjects having any adverse events related to study procedure, which was 80.6% in the Infuse 2.1 mg group, 77.0% in the Infuse 4.2 mg group, and 61.0% in the Control group (**Table 16, Table 26, Table 28**).

Table 16: Adverse Event (AE) Rates in the AT Population by severity and relatedness for 2-level subjects

Adverse Event Type n - # of Patients % - Cumulative Adverse Event Rate*	Two-Level Subjects (N = 34, 28, 34 for 2.1 mg, 4.2 mg and Ctrl)											
	Up to 12 months						Up to 24 Months					
	Infuse 2.1 mg (N = 34)		Infuse 4.2 mg (N = 28)		Control (N = 34)		Infuse 2.1 mg (N = 34)		Infuse 4.2 mg (N = 28)		Control (N = 34)	
	n	%	n	%	n	%	n	%	n	%	n	%
Subjects Having Any Adverse Events	26	78.1	22	82.3	25	85.2	27	83.6	23	94.1	25	85.2
Subjects Having Any Serious Adverse Events	6	17.9	5	21.7	5	18.2	9	36.2	7	37.4	6	26.8
Subjects Having Any Adverse Events Related to Surgical Construct	16	48.1	12	46.7	14	45.8	17	54.2	15	65.5	15	54.1
• Related to TLIF Grafting Material/Interbody Device	15	45.7	12	46.7	13	42.0	15	45.7	15	65.5	15	57.5
- Related to TLIF Grafting Material	15	45.7	11	43.2	13	42.0	15	45.7	14	63.2	15	57.5

Adverse Event Type n - # of Patients % - Cumulative Adverse Event Rate*	Two-Level Subjects (N = 34, 28, 34 for 2.1 mg, 4.2 mg and Ctrl)											
	Up to 12 months						Up to 24 Months					
	Infuse 2.1 mg (N = 34)		Infuse 4.2 mg (N = 28)		Control (N = 34)		Infuse 2.1 mg (N = 34)		Infuse 4.2 mg (N = 28)		Control (N = 34)	
	n	%	n	%	n	%	n	%	n	%	n	%
- Related to Interbody Device	14	42.9	12	46.7	13	42.1	14	42.9	15	65.5	15	57.5
• Related to Posterior Fixation	14	42.3	11	42.5	14	45.8	15	48.8	14	61.6	15	54.1
Subjects Having Any Serious Adverse Events Related to Surgical Construct	2	5.9	0	0.0	1	4.9	2	5.9	1	7.4	1	4.9
• Related to TLIF Grafting Material/Interbody Device	1	2.9	0	0.0	1	4.9	1	2.9	1	7.4	1	4.9
- Related to TLIF Grafting Material	1	2.9	0	0.0	1	4.9	1	2.9	1	7.4	1	4.9
- Related to Interbody Device	1	2.9	0	0.0	1	4.9	1	2.9	1	7.4	1	4.9
• Related to Posterior Fixation	2	5.9	0	0.0	1	4.9	2	5.9	1	7.4	1	4.9
Subjects Having Any Adverse Events Related to Study Procedure	25	74.1	17	63.8	17	51.2	26	80.6	19	77.0	18	61.0
Subjects Having Any Serious Adverse Events Related to Study Procedure	5	14.7	2	7.6	3	11.1	6	21.0	2	7.6	3	11.1
*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.												

Table 17: AEs up to 24 months in AT population for 1-level subjects by System Organ Class (SOC)

System Organ Classes (SOC)	One-Level Subjects (N = 384)					
	Up to 24 Months					
	Infuse 2.1 (N = 129)		Infuse 4.2 (N = 132)		Control (N = 123)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Patients Who Had Any Adverse Events	98	88.6	109	89.8	96	87.5
Injury, Poisoning And Procedural Complications	43	38.6	52	45.3	43	40.0
Musculoskeletal And Connective Tissue Disorders	42	38.4	60	52.2	46	44.5
Infections And Infestations	36	37.8	38	36.7	38	39.3
Nervous System Disorders	35	33.6	41	34.7	35	32.0
Gastrointestinal Disorders	17	17.7	19	19.9	15	14.0
Renal And Urinary Disorders	11	12.0	10	8.7	11	10.8
Vascular Disorders	10	11.9	14	14.1	2	1.8
General Disorders And Administration Site Conditions	8	6.4	15	14.6	8	6.7
Investigations	7	6.3	6	6.7	7	6.3
Blood And Lymphatic System Disorders	5	5.2	1	0.8	5	4.2
Respiratory, Thoracic And Mediastinal Disorders	4	4.5	10	9.9	7	6.6
Skin And Subcutaneous Tissue Disorders	4	4.4	6	6.2	4	4.0

System Organ Classes (SOC)	One-Level Subjects (N = 384)					
	Up to 24 Months					
	Infuse 2.1 (N = 129)		Infuse 4.2 (N = 132)		Control (N = 123)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Psychiatric Disorders	5	4.1	6	6.3	8	7.2
Eye Disorders	4	3.6	3	4.2	2	1.9
Ear And Labyrinth Disorders	2	2.6	3	3.2	0	0.0
Metabolism And Nutrition Disorders	3	2.5	7	6.1	9	9.3
Surgical And Medical Procedures	2	2.5	1	0.8	2	2.0
Congenital, Familial And Genetic Disorders	2	2.1	0	0.0	1	1.0
Cardiac Disorders	2	2.0	4	3.6	5	6.1
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	2	1.8	6	7.5	6	7.0
Reproductive System And Breast Disorders	2	1.7	6	6.0	5	5.4
Hepatobiliary Disorders	1	1.1	2	3.8	3	3.0
Product Issues	1	0.9	1	0.8	2	2.2
Immune System Disorders	1	0.8	1	0.8	0	0.0
Endocrine Disorders	0	0.0	0	0.0	0	0.0

*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.

Table 18: Summary of AEs up to 24 months in AT population for 2-level subjects by System Organ Class (SOC)

System Organ Classes (SOC)	Two-Level Subjects (N = 96)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 34)		Infuse 4.2 (N = 28)		Control (N = 34)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Patients Who Had Any Adverse Events	27	83.6	23	94.1	25	85.2
Injury, Poisoning And Procedural Complications	21	73.2	9	33.6	10	34.4
Musculoskeletal And Connective Tissue Disorders	18	59.5	12	53.6	14	47.2
Infections And Infestations	14	51.1	7	35.3	11	41.5
Nervous System Disorders	11	35.8	16	66.0	10	40.0
Gastrointestinal Disorders	8	28.2	5	20.8	4	20.5
Vascular Disorders	6	24.1	4	21.0	2	6.3
General Disorders And Administration Site Conditions	7	21.0	5	23.0	5	21.9
Renal And Urinary Disorders	4	21.0	3	13.5	2	8.0
Metabolism And Nutrition Disorders	6	18.1	0	0.0	4	24.0
Reproductive System And Breast Disorders	2	12.9	1	7.4	1	7.7
Cardiac Disorders	3	10.5	0	0.0	3	11.1
Blood And Lymphatic System Disorders	3	8.8	3	11.9	0	0.0

System Organ Classes (SOC)	Two-Level Subjects (N = 96)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 34)		Infuse 4.2 (N = 28)		Control (N = 34)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Skin And Subcutaneous Tissue Disorders	3	8.8	2	8.3	2	9.8
Product Issues	1	6.7	0	0.0	3	17.4
Investigations	2	6.2	3	12.1	3	10.8
Psychiatric Disorders	2	6.1	0	0.0	4	20.4
Ear And Labyrinth Disorders	1	4.3	1	4.3	1	3.3
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	1	4.3	1	7.4	1	3.3
Endocrine Disorders	1	3.2	0	0.0	0	0.0
Eye Disorders	1	3.0	1	4.9	1	7.7
Respiratory, Thoracic And Mediastinal Disorders	1	2.9	1	7.4	3	9.7
Congenital, Familial And Genetic Disorders	0	0.0	1	7.4	1	8.0
Hepatobiliary Disorders	0	0.0	0	0.0	0	0.0
Immune System Disorders	0	0.0	1	4.3	0	0.0

*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.

Table 19: SAEs up to 24 months in AT population for 1-level subjects by System Organ Class (SOC)

SOC	One-Level Subjects (N = 384)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 129)		Infuse 4.2 (N = 132)		Control (N = 123)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Patients Who Had Any Serious Adverse Events	26	27.2	41	41.3	23	24.6
Musculoskeletal And Connective Tissue Disorders	7	9.6	14	18.4	4	4.8
Infections And Infestations	3	3.8	4	4.5	5	5.6
Injury, Poisoning And Procedural Complications	4	3.5	8	9.0	5	6.6
Nervous System Disorders	3	2.9	11	11.9	3	2.8
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	2	2.0	3	4.0	2	2.1
Vascular Disorders	2	1.9	2	1.9	0	0.0
Gastrointestinal Disorders	2	1.8	4	4.7	5	6.0
Ear And Labyrinth Disorders	1	1.7	0	0.0	0	0.0
Product Issues	1	1.1	1	0.9	1	1.2
Metabolism And Nutrition Disorders	1	0.9	0	0.0	2	1.6

SOC	One-Level Subjects (N = 384)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 129)		Infuse 4.2 (N = 132)		Control (N = 123)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Psychiatric Disorders	1	0.9	0	0.0	0	0.0
Cardiac Disorders	1	0.8	2	1.7	3	3.5
General Disorders And Administration Site Conditions	1	0.8	7	8.0	0	0.0
Skin And Subcutaneous Tissue Disorders	1	0.8	0	0.0	0	0.0
Surgical And Medical Procedures	1	0.8	1	0.8	1	1.2
Eye Disorders	0	0.0	1	1.2	0	0.0
Hepatobiliary Disorders	0	0.0	0	0.0	1	1.2
Investigations	0	0.0	0	0.0	1	0.8
Renal And Urinary Disorders	0	0.0	2	1.6	0	0.0
Reproductive System And Breast Disorders	0	0.0	1	1.9	0	0.0
Respiratory, Thoracic And Mediastinal Disorders	0	0.0	0	0.0	2	1.6

*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.

Table 20: SAEs up to 24 months in AT population for 2-level subjects by System Organ Class (SOC)

SOC	Two-Level Subjects (N = 96)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 34)		Infuse 4.2 (N = 28)		Control (N = 34)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Patients Who Had Any Serious Adverse Events	9	36.2	7	37.4	6	26.8
Injury, Poisoning And Procedural Complications	6	25.9	3	15.3	1	4.9
Musculoskeletal And Connective Tissue Disorders	4	20.1	1	3.6	2	11.4
Nervous System Disorders	1	6.7	2	9.2	1	3.0
Renal And Urinary Disorders	1	6.7	0	0.0	0	0.0
Reproductive System And Breast Disorders	1	6.5	0	0.0	0	0.0
Gastrointestinal Disorders	1	3.0	1	4.9	0	0.0
Infections And Infestations	1	3.0	2	14.8	0	0.0
Cardiac Disorders	1	2.9	0	0.0	1	4.9
Metabolism And Nutrition Disorders	1	2.9	0	0.0	2	11.1
Respiratory, Thoracic And Mediastinal Disorders	1	2.9	1	7.4	1	8.0

SOC	Two-Level Subjects (N = 96)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 34)		Infuse 4.2 (N = 28)		Control (N = 34)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Eye Disorders	0	0.0	1	4.9	0	0.0
General Disorders And Administration Site Conditions	0	0.0	1	4.0	0	0.0
Investigations	0	0.0	0	0.0	0	0.0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	0	0.0	0	0.0	1	3.7
Skin And Subcutaneous Tissue Disorders	0	0.0	1	7.1	0	0.0
Vascular Disorders	0	0.0	1	7.1	0	0.0

*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.

Table 21: AEs related to surgical construct up to 24 months in AT population for 1-level subjects by System Organ Class (SOC)

SOC	One-Level Subjects (N = 384)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 129)		Infuse 4.2 (N = 132)		Control (N = 123)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Patients Who Had Any Adverse Events Related To Surgical Construct	42	38.6	47	42.6	38	35.5
Nervous System Disorders	22	21.7	20	16.7	15	13.5
Musculoskeletal And Connective Tissue Disorders	21	18.4	27	23.4	21	19.7
Injury, Poisoning And Procedural Complications	9	9.7	7	9.1	14	15.3
Investigations	3	2.8	1	0.8	5	4.6
Product Issues	1	0.9	1	0.8	2	2.2
Blood And Lymphatic System Disorders	1	0.8	0	0.0	0	0.0
Renal And Urinary Disorders	1	0.8	1	0.8	0	0.0
General Disorders And Administration Site Conditions	0	0.0	2	2.7	2	1.7

Table 22: AEs related to surgical construct up to 24 months in AT population for 2-level subjects by System Organ Class (SOC)

SOC	Two-Level Subjects (N = 96)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 34)		Infuse 4.2 (N = 28)		Control (N = 34)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Patients Who Had Any Adverse Events Related To Surgical Construct	17	54.2	15	65.5	15	54.1
Injury, Poisoning And Procedural Complications	10	38.2	2	9.8	5	22.4
Musculoskeletal And Connective Tissue Disorders	10	33.5	5	27.1	11	37.4
Nervous System Disorders	6	19.2	12	55.0	7	28.6
Product Issues	1	6.7	0	0.0	3	17.4
Investigations	1	3.2	2	8.3	2	7.4
General Disorders And Administration Site Conditions	1	2.9	0	0.0	0	0.0
Vascular Disorders	1	2.9	0	0.0	0	0.0
Infections And Infestations	0	0.0	0	0.0	1	3.0
Renal And Urinary Disorders	0	0.0	0	0.0	1	4.9

*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.

Table 23: SAEs related to surgical construct up to 24 months in AT population 1-level subjects by System Organ Class (SOC)

SOC	One-Level Subjects (N = 384)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 129)		Infuse 4.2 (N = 132)		Control (N = 123)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Patients Who Had Any Serious Adverse Events Related To Surgical Construct	4	5.7	10	11.5	4	4.1
Musculoskeletal And Connective Tissue Disorders	3	4.5	4	4.9	0	0.0
Product Issues	1	1.1	1	0.9	1	1.2
General Disorders And Administration Site Conditions	0	0.0	1	1.9	0	0.0
Injury, Poisoning And Procedural Complications	0	0.0	1	1.9	2	2.1
Investigations	0	0.0	0	0.0	1	0.8
Nervous System Disorders	0	0.0	4	4.2	0	0.0

*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.

Table 24: SAEs related to surgical construct up to 24 months in AT population 2-level subjects by System Organ Class (SOC)

	Two-Level Subjects (N = 96)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 34)		Infuse 4.2 (N = 28)		Control (N = 34)	
SOC	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Patients Who Had Any Serious Adverse Events Related To Surgical Construct	2	5.9	1	7.4	1	4.9
Injury, Poisoning And Procedural Complications	2	5.9	0	0.0	1	4.9
Musculoskeletal And Connective Tissue Disorders	0	0.0	1	7.4	0	0.0
Nervous System Disorders	0	0.0	1	7.4	0	0.0

*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.

Table 25: AEs related to study procedure up to 24 months in AT population 1-level subjects by System Organ Class (SOC)

	One-Level Subjects (N = 384)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 129)		Infuse 4.2 (N = 132)		Control (N = 123)	
SOC	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Patients Who Had Any Adverse Events Related To Study Procedure	73	64.9	83	67.6	67	59.3
Injury, Poisoning And Procedural Complications	34	28.8	40	33.6	36	32.2
Nervous System Disorders	26	25.4	27	22.2	22	19.3
Musculoskeletal And Connective Tissue Disorders	26	22.7	38	32.5	28	25.8
General Disorders And Administration Site Conditions	6	4.7	10	8.9	6	5.0
Investigations	4	3.6	1	0.8	7	6.3
Gastrointestinal Disorders	4	3.1	2	1.5	6	5.0
Blood And Lymphatic System Disorders	3	2.4	1	0.8	4	3.3
Infections And Infestations	3	2.4	4	3.1	2	1.7
Renal And Urinary Disorders	2	1.6	5	3.8	4	3.3
Respiratory, Thoracic And Mediastinal Disorders	2	1.6	2	1.5	3	2.5
Vascular Disorders	2	1.6	5	3.8	0	0.0
Product Issues	1	0.9	1	0.8	2	2.2

SOC	One-Level Subjects (N = 384)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 129)		Infuse 4.2 (N = 132)		Control (N = 123)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Metabolism And Nutrition Disorders	1	0.8	4	3.1	1	0.8
Psychiatric Disorders	1	0.8	1	0.8	1	0.8
Skin And Subcutaneous Tissue Disorders	1	0.8	3	2.3	0	0.0
Surgical And Medical Procedures	1	0.8	1	0.8	1	0.8
Cardiac Disorders	0	0.0	2	1.5	0	0.0
Reproductive System And Breast Disorders	0	0.0	0	0.0	1	0.8
*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.						

Table 26: AEs related to study procedure up to 24 months in AT population 2-level subjects by System Organ Class (SOC)

SOC	Two-Level Subjects (N = 96)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 34)		Infuse 4.2 (N = 28)		Control (N = 34)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Patients Who Had Any Adverse Events Related To Study Procedure	26	80.6	19	77.0	18	61.0
Injury, Poisoning And Procedural Complications	20	69.8	6	21.7	9	29.1
Musculoskeletal And Connective Tissue Disorders	14	44.8	7	33.3	12	44.2
Nervous System Disorders	9	30.5	14	62.3	9	36.0
General Disorders And Administration Site Conditions	6	17.8	3	11.9	3	10.8
Metabolism And Nutrition Disorders	5	14.7	0	0.0	1	3.0
Infections And Infestations	4	12.0	3	10.9	2	6.1
Gastrointestinal Disorders	4	11.8	2	7.2	1	3.0
Blood And Lymphatic System Disorders	3	8.8	1	3.6	0	0.0
Product Issues	1	6.7	0	0.0	3	17.4
Skin And Subcutaneous Tissue Disorders	2	5.9	1	3.6	1	4.9
Investigations	1	3.2	1	4.0	2	7.4
Cardiac Disorders	1	2.9	0	0.0	1	3.0
Psychiatric Disorders	1	2.9	0	0.0	0	0.0
Respiratory, Thoracic And Mediastinal Disorders	1	2.9	0	0.0	2	6.0
Vascular Disorders	1	2.9	2	7.3	1	3.0

SOC	Two-Level Subjects (N = 96)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 34)		Infuse 4.2 (N = 28)		Control (N = 34)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Renal And Urinary Disorders	0	0.0	0	0.0	1	4.9

*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.

Table 27: SAEs related to study procedure up to 24 months in AT population 1-level subjects by System Organ Class (SOC)

SOC	One-Level Subjects (N = 384)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 129)		Infuse 4.2 (N = 132)		Control (N = 123)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Patients Who Had Any Serious Adverse Events Related To Study Procedure	11	11.2	21	19.0	9	8.3
Musculoskeletal And Connective Tissue Disorders	4	5.3	4	4.9	2	1.8
Injury, Poisoning And Procedural Complications	3	2.3	4	4.2	2	2.0
Product Issues	1	1.1	1	0.9	1	1.2
General Disorders And Administration Site Conditions	1	0.8	4	4.2	0	0.0
Nervous System Disorders	1	0.8	5	4.9	2	1.6
Surgical And Medical Procedures	1	0.8	1	0.8	0	0.0
Vascular Disorders	1	0.8	1	0.8	0	0.0
Cardiac Disorders	0	0.0	1	0.8	0	0.0
Gastrointestinal Disorders	0	0.0	0	0.0	1	0.8
Infections And Infestations	0	0.0	1	0.8	1	0.8
Investigations	0	0.0	0	0.0	1	0.8
Metabolism And Nutrition Disorders	0	0.0	0	0.0	1	0.8
Renal And Urinary Disorders	0	0.0	1	0.8	0	0.0
Respiratory, Thoracic And Mediastinal Disorders	0	0.0	0	0.0	2	1.6

*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.

Table 28: SAEs related to study procedure up to 24 months in AT population 2-level subjects by System Organ Class (SOC)

	Two-Level Subjects (N = 96)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 34)		Infuse 4.2 (N = 28)		Control (N = 34)	
SOC	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Patients Who Had Any Serious Adverse Events Related To Study Procedure	6	21.0	2	7.6	3	11.1
Injury, Poisoning And Procedural Complications	4	15.6	1	3.6	1	4.9
Musculoskeletal And Connective Tissue Disorders	1	6.7	1	3.6	0	0.0
Nervous System Disorders	1	6.7	1	7.4	1	3.0
Infections And Infestations	1	3.2	0	0.0	0	0.0
Cardiac Disorders	1	2.9	0	0.0	0	0.0
Metabolism And Nutrition Disorders	1	2.9	0	0.0	1	3.0
Respiratory, Thoracic And Mediastinal Disorders	1	2.9	0	0.0	0	0.0
General Disorders And Administration Site Conditions	0	0.0	1	4.0	0	0.0

*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.

Table 29 and **Table 30** summarize secondary surgeries up to 24 months by treatment group for one- and two-level subjects. For one-level subjects, the 24-month cumulative of secondary surgeries was 18.3% for the Infuse 2.1 mg group, 30.4% for the Infuse 4.2 mg group, and 26.4% for the control group (numerical difference does not reach statistical significance). One subject in the Infuse 2.1 group and one subject in the Infuse 4.2mg group had removal surgery. Two subjects in the Infuse 2.1 group, four subjects in the Infuse 4.2 mg group, and two subjects in the control group had additional surgery classified as failure (numerical difference does not reach statistical significance).

For two-level subjects, the 24-month cumulative of secondary surgeries was 28.1% for the Infuse 2.1 mg group, 30.1% for the Infuse 4.2 mg group, and 19.8% for the control group (numerical difference does not reach statistical significance). There was one subject classified as a failure in the control group.

Table 29: Secondary surgeries up to 24 months in AT population 1-level subjects

	One-Level Subjects (N = 384)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 129)		Infuse 4.2 (N = 132)		Control (N = 123)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Subjects Having Any Additional Surgery	17	18.3	29	30.4	24	26.4
Removal	1	1.1	1	0.8	0	0.0
Reoperation	3	2.4	5	5.0	3	2.5
Revision	1	1.7	1	0.9	1	1.2
Non-Target Lumbar Surgery	1	1.1	4	5.0	2	2.2
Other**	11	12.3	19	20.8	18	21.1
Subjects Having Any Additional Surgery Classified As Failure	2	2.9	4	4.4	2	2.0

*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.

**Medra v. 26.0 System Organ Classifications: Cardiac disorders, Congenital, familial and genetic disorders, Eye disorders, Gastrointestinal disorders, General disorders and administration site conditions, Hepatobiliary disorders, Injury, poisoning and procedural complications, Investigations, Musculoskeletal and connective tissue disorders, Neoplasms benign, malignant and unspecified (incl cysts and polyps), Nervous system disorders, Renal and urinary disorders, Reproductive system and breast disorders, Skin and subcutaneous tissue disorders, Surgical and medical procedures, Vascular disorders.

Table 30: Secondary surgeries up to 24 months in AT population 2-level subjects

	Two-Level Subjects (N = 96)					
	up to 24 Months [0-911 days)					
	Infuse 2.1 (N = 34)		Infuse 4.2 (N = 28)		Control (N = 34)	
	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*	#Patients	Cumulative Rate (%)*
Subjects Having Any Additional Surgery	6	28.1	6	30.1	5	19.8
Removal	0	0.0	0	0.0	0	0.0
Reoperation	1	3.2	0	0.0	0	0.0
Revision	0	0.0	0	0.0	1	4.9
Non-Target Lumbar Surgery	1	6.7	1	7.4	0	0.0
Other**	4	19.2	6	30.1	5	19.8
Subjects Having Any Additional Surgery Classified As Failure	0	0.0	0	0.0	1	4.9

*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.

**Medra v. 26.0 System Organ Classifications: Cardiac disorders, Congenital, familial and genetic disorders, Eye disorders, Gastrointestinal disorders, General disorders and administration site conditions, Hepatobiliary disorders, Injury, poisoning and procedural complications, Investigations, Musculoskeletal and connective tissue disorders, Neoplasms benign, malignant and unspecified (incl cysts and polyps), Nervous system disorders, Renal and urinary disorders, Reproductive system and breast disorders, Skin and subcutaneous tissue disorders, Surgical and medical procedures, Vascular disorders.

2. Effectiveness Results

The analysis of effectiveness for PMA application was based on the "As Randomized and Treated" (ART) cohort at 24 months after operative intervention. For the PMA application analysis, the ART cohort (N = 480) was comprised of 379 1-level subjects and 101 2-level subjects. The 1-level subjects had 129, 128, and 122 subjects in the 2.1 mg, 4.2mg, and control cohorts. The 2-level subjects had 34, 32, and 35 subjects in the 2.1 mg, 4.2 mg and control cohorts. The 24-month follow up rate of the ART population pooled by levels from all sites at the time of this interim analysis for PMA application review was 62.2% of one-level patients and 62.5% of two-level patients. Effectiveness outcomes at the time of PMA application are reported in **Table 31** and **Table 32**.

Primary Endpoint – Clinical Composite Success

The primary endpoint was a co-primary endpoint consisting of non-inferiority of Overall Success and superiority of Radiographic Fusion Success compared to control for either Infuse™ Bone Graft group (2.1 mg or 4.2 mg) at 24 months after operative intervention. Each individual subject was determined to achieve Overall Success if they met all of the following five (5) measures of safety and effectiveness at 24 months:

- At least a 15-point improvement in ODI from baseline;
- Radiographic Fusion Success as evaluated by an independent radiology core lab (see criteria below);
- Neurological success, defined as an improvement or maintenance from baseline in all following four domains: motor and sensory function, reflexes and straight leg raise);
- No serious adverse events related to TLIF grafting material or intervertebral body fusion device; and
- No additional surgeries at index level(s) related to TLIF grafting material or intervertebral body fusion device.

Radiographic Fusion Success was defined as:

- Presence of bridging bone via CT assessment
- No evidence of motion as defined by ≤ 2 mm translational motion and -≤ 3° in angular motion at each treated level (flexion/extension radiographs).
- For 2-level subjects, fusion had to be met at both levels individually

Overall Success for one-level subjects at 24 months was 68.6%, 70.1% and 53.6% in the Infuse 2.1 mg, Infuse 4.2 mg, and Control groups, respectively,

Overall Success for two-level subject at 24 months was 57.9%, 60.0% and 20.0% in the Infuse 2.1 mg, Infuse 4.2 mg, and Control groups, respectively.

Radiographic Fusion Success for one-level subjects at 24 months was 87.5%, 90.0% and 61.8% in the Infuse 2.1 mg, Infuse 4.2 mg, and Control groups, respectively.

Radiographic Fusion Success for two-level subject at 24 months was 78.9%, 86.7% and 43.8% in the Infuse 2.1 mg, Infuse 4.2 mg, and Control groups, respectively.

Table 31: Clinical Composite (Overall Success) in the ART population by treatment group

	One-Level Subjects (N = 129, 128, 122 for 2.1 mg, 4.2 mg and Ctrl)						Two-Level Subjects (N = 34, 32, 35 for 2.1 mg, 4.2 mg and Ctrl)					
	12 Months			24 Months			12 Months			24 Months		
Variable	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**
ODI Success	89/97 (91.8%)	87/97 (89.7%)	87/93 (93.5%)	67/71 (94.4%)	62/64 (96.9%)	65/70 (92.9%)	22/26 (84.6%)	21/24 (87.5%)	21/25 (84.0%)	17/19 (89.5%)	14/18 (77.8%)	14/16 (87.5%)
Radiographic Fusion Success	**66/96 (68.8%)**	**72/94 (76.6%)**	**48/90 (53.3%)**	**63/72 (87.5%)**	**54/60 (90.0%)**	**42/68 (61.8%)**	**19/24 (79.2%)**	**18/24 (75.0%)**	**11/25 (44.0%)**	**15/19 (78.9%)**	**13/15 (86.7%)**	**7/16 (43.8%)**
Neurological Success	81/96 (84.4%)	91/95 (95.8%)	85/95 (89.5%)	60/71 (84.5%)	57/63 (90.5%)	63/70 (90.0%)	21/26 (80.8%)	19/23 (82.6%)	21/25 (84.0%)	16/19 (84.2%)	16/19 (84.2%)	12/15 (80.0%)
SAEs that are related to TLIF grafting material or interbody device	1	5	3	3	7	3	1	0	1	1	1	1
Secondary surgeries that are classified as failure	1	3	2	2	4	2	0	0	1	0	0	1
Overall Success[a]	**56/97 (57.7%)**	**60/96 (62.5%)**	**42/91 (46.2%)**	**48/70 (68.6%)**	**47/67 (70.1%)**	**37/69 (53.6%)**	**14/26 (53.8%)**	**13/23 (56.5%)**	**8/25 (32.0%)**	**11/19 (57.9%)**	**9/15 (60.0%)**	**3/15 (20.0%)**

[a]Overall Success: satisfy all the following criteria
(1) ODI Success
(2) Radiographic Fusion Success (by CT assessment)
(3) Neurological Success
(4) No serious adverse events that are "related" to TLIF grafting material or interbody device
(5) No secondary surgeries that are classified as failure

At the time of the interim analysis for PMA application, 62.5% one-level patients and 61.4% two-level patients achieved 24 months of follow-up after operative intervention. For patients who had not achieved 24 months of follow-up, but had 12-month data available, their 24-month outcomes were imputed from their 12-month data using a beta-binomial imputation model.

Consideration of the totality of observed and imputed data outcomes for the ART population was adequate to substantiate the non-inferiority of Overall Success and superiority of Radiographic Fusion Success are achieved with a probability of >0.999 for both the 2.1 mg and the 4.2 mg ART cohorts as compared to the control group in the ART population. The summary of Bayesian inference for the co-primary endpoints based on the ART population is presented in **Table 32**.

Table 32: Posterior Probabilities of Noninferiority of Overall Success and Superiority of Fusion Succes, both at 24 Months for Primary Endpoints (ART population)

Variable	Posterior Probabilities**				Posterior Mean Difference** (95% BCI*)	
	Noninferiority Compared to the Ctrl (delta=0.10)		Superiority Compared to the Ctrl		24 Months	
	2.1 mg	4.2 mg	2.1 mg	4.2 mg	2.1 mg - Ctrl	4.2mg - Ctrl
	One-Level Subjects (N = 129, 128, 122 for 2.1 mg, 4.2 mg and Ctrl)					
Overall Success	>0.999	>0.999			0.141 (0.003, 0.276)	0.213 (0.075, 0.346)
Radiographic Fusion Success			>0.999	>0.999	0.228 (0.106, 0.347)	0.273 (0.155, 0.390)
	Two-Level Subjects (N = 34, 32, 35 for 2.1 mg, 4.2 mg and Ctrl)					
Overall Success	>0.999	>0.999			0.140 (0.003, 0.277)	0.218 (0.077, 0.355)
Radiographic Fusion Success			>0.999	>0.999	0.249 (0.113, 0.391)	0.303 (0.166, 0.448)

*BCI: Bayesian Credible Interval

** Based on 62.5% one-level patients and 61.4% two-level patients achieved 24 months of follow up, and beta-binomial imputation model for patients who have not achieved 24 months of follow up.

3. Secondary Effectiveness and Safety Outcomes

a. Time to fusion

Figure 2 and **Figure 3** are the Kaplan-Meier curves for time to fusion by treatment group for one-level and two-level subjects, respectively, illustrating the median number of days to achieve fusion. For one-level subjects, the median number of days to achieve fusion was lower for the Infuse 2.1 mg and Infuse 4.2 mg groups (379 and 363 days, respectively) than the Control group (405 days). For two-level subjects, the median number of days to achieve fusion was lower for the Infuse 2.1 mg and Infuse 4.2 mg groups (358 and 376 days, respectively) than the Control group (734 days). For both one- and two-level subjects, treatment with either Infuse 2.1 mg or Infuse 4.2 mg allowed for a faster time to fusion compared to control for the population analyzed for PMA application.

Figure 2: Time to Fusion Kaplan-Meier curve for one-level subjects

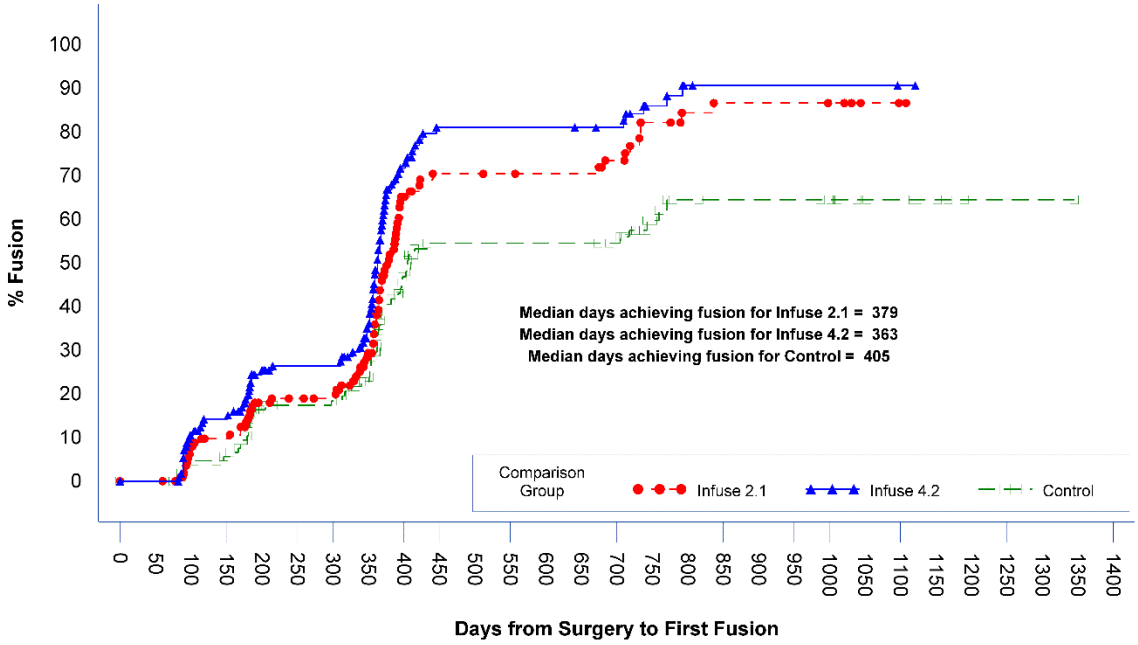
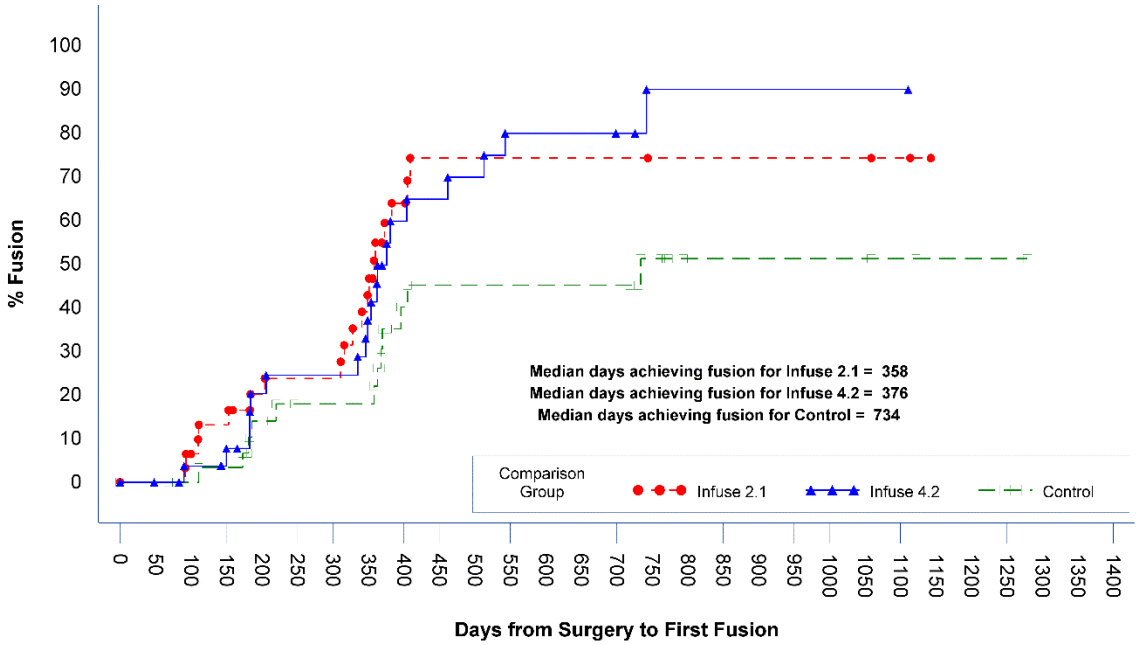


Figure 3: Time to Fusion Kaplan-Meier curve for two-level subjects



b. Secondary surgeries up to 24 months that are classified as failure

Any additional surgical procedure having "possible," "probable," or "causal relationship" with the TLIF grafting material or intervertebral body fusion device was considered to be "related" to the TLIF grafting material or intervertebral body fusion device and classified as a "failure." The relatedness of these adverse events was determined by an independent CEC.

At the time of PMA application, the rate of 1-level subjects at 24 months having any secondary surgery classified by CEC as a failure was 2.9% in the Infuse 2.1 mg group, 4.4% in the Infuse 4.2 mg group, and 2.0% in the Control group (**Table 29**).

At the time of PMA application, the rate of 2-level subjects at 24 months having any secondary surgery classified by CEC as a failure was 0.0% in the Infuse 2.1 mg group, 0.0% in the Infuse 4.2 mg group, and 4.9% in the Control group (**Table 30**).

c. ODI success at 24 months

At the time of PMA application, for one-level subjects at 24 months, 94.4%, 96.9%, and 92.9% of subjects in the Infuse 2.1 mg, Infuse 4.2 mg, and Control groups, respectively, achieved ODI success (**Table 31**).

At the time of PMA application, for two-level subjects at 24 months, 89.5%, 77.8%, and 87.5% of subjects in the Infuse 2.1 mg, Infuse 4.2 mg, and Control groups, respectively, achieved ODI success (**Table 31**).

d. Leg pain success at 24 months

Success for leg pain was defined as at least 30% improvement from the pre-operative score. At the time of PMA application, for one-level subjects at 24 months, 90.1%, 89.1%, and 85.7% of subjects in the Infuse 2.1 mg, Infuse 4.2 mg, and Control groups, respectively, achieved leg pain success (**Table 33**).

At the time of PMA application, for two-level subjects at 24 months, 84.2%, 77.8%, and 93.8% of subjects in the Infuse 2.1 mg, Infuse 4.2 mg, and Control groups, respectively, achieved leg pain success (**Table 33**).

Table 33: Leg pain success by treatment group

	One-Level Subjects (N = 129, 128, 122 for 2.1 mg, 4.2 mg and Ctrl)														
	6 Weeks			3 Months			6 Months			12 Months			24 Months		
Variable	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**
LEG Pain Success[a]	102/123 (82.9%)	100/121 (82.6%)	89/113 (78.8%)	102/116 (87.9%)	95/113 (84.1%)	88/110 (80.0%)	87/109 (79.8%)	87/111 (78.4%)	87/105 (82.9%)	80/97 (82.5%)	81/97 (83.5%)	79/93 (84.9%)	64/71 (90.1%)	57/64 (89.1%)	60/70 (85.7%)

	Two-Level Subjects (N = 34, 32, 35 for 2.1 mg, 4.2 mg and Ctrl)														
	6 Weeks			3 Months			6 Months			12 Months			24 Months		
Variable	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**
LEG Pain Success[a]	28/33 (84.8%)	24/30 (80.0%)	27/33 (81.8%)	27/32 (84.4%)	26/28 (92.9%)	29/31 (93.5%)	28/30 (93.3%)	24/25 (96.0%)	27/29 (93.1%)	23/26 (88.5%)	21/24 (87.5%)	25/25 (100%)	16/19 (84.2%)	14/18 (77.8%)	15/16 (93.8%)

[a] Success: (Preop Score - Postop Score)/(Preop Score) >= 30%.

e. <u>SAEs up to 24 months that are related to the TLIF grafting material or interbody device</u>

At the time of PMA application, for one-level subjects, the 24-month cumulative rate of SAEs related to the TLIF graft material / interbody device was 4.6% for the Infuse 2.1 mg group, 8.0% for the Infuse 4.2 mg group, and 3.2% for the Control group. For 1-level subjects, the rate of SAEs related to the TLIF Grafting material for the same group was 3.4% for the Infuse 2.1 mg group, 6.5% for the Infuse 4.2 mg group, and 3.2% for the Control group. The differences in 24-month cumulative rate of collective SAEs related to TLIF graft material/interbody device or individually related to "TLIF grafting material", "Interbody device" or "posterior fixation" individually at the time of interim analysis for PMA application did not achieve statistical significance for the numerical differences between the groups. (**Table 15**).

At the time of PMA application, for two level subjects, the 24-month cumulative rate of SAEs related to the TLIF graft material / interbody device was 2.9% for the Infuse 2.1 group, 7.4% for the Infuse 4.2 group, and 4.9% for the Control group. For 2-level subjects, the differences in 24-month cumulative rate of SAEs related to the TLIF grafting material/interbody device at the time of interim analysis for PMA application did not achieve statistical significance for the numerical differences between groups (**Table 16**).

f. <u>Back pain success at 24 months</u>

Success for back pain was defined as at least 30% improvement from the pre-operative score. At the time of PMA application, for one-level subjects at 24 months, those in the Infuse 2.1 mg and Infuse 4.2 mg groups had higher back pain

success rates (88.7% and 90.6%, respectively) than those in the Control group (81.4%) (**Table 34**).

At the time of PMA application, for two-level subjects at 24 months, those in the Infuse 2.1 mg and Control groups (89.5% and 87.5%, respectively) had a higher back pain success rate than those in the Infuse 4.2 mg group (77.8%) (**Table 34**).

Table 34: Back pain success by treatment group

	One-Level Subjects (N = 129, 128, 122 for 2.1 mg, 4.2 mg and Ctrl)														
	6 Weeks			3 Months			6 Months			12 Months			24 Months		
Variable	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**
Back Pain Success[a]	91/123 (74.0%)	81/121 (66.9%)	92/113 (81.4%)	92/116 (79.3%)	81/113 (71.7%)	88/110 (80.0%)	88/109 (80.7%)	84/111 (75.7%)	89/105 (84.8%)	88/97 (90.7%)	78/97 (80.4%)	79/93 (84.9%)	63/71 (88.7%)	58/64 (90.6%)	57/70 (81.4%)

	Two-Level Subjects (N = 34, 32, 35 for 2.1 mg, 4.2 mg and Ctrl)														
	6 Weeks			3 Months			6 Months			12 Months			24 Months		
Variable	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**
Back Pain Success[a]	22/33 (66.7%)	22/30 (73.3%)	28/33 (84.8%)	23/32 (71.9%)	22/28 (78.6%)	26/31 (83.9%)	26/30 (86.7%)	19/25 (76.0%)	22/29 (75.9%)	23/26 (88.5%)	20/24 (83.3%)	22/25 (88.0%)	17/19 (89.5%)	14/18 (77.8%)	14/16 (87.5%)

[a] Success: (Preop Score - Postop Score)/(Preop Score) >= 30%.

g. Neurological success

The overall neurological success was defined as maintenance or improvement in four key neurological assessments: motor function, sensory function, reflexes, and straight leg raise at a postoperative time period as compared to the corresponding elements before surgery (preoperative).

At the time of PMA application ,the neurological success rate at 24 months was 85.3% in Infuse 2.1 mg, 92.2% in Infuse 4.2 mg, and 91.3% in the Control group for one-level subjects, and 84.2% in Infuse 2.1 mg, 83.3% in Infuse 4.2 mg, and 78.6% in the Control group for two-level subjects (**Table 31**).

4. Subgroup Analyses

Several subgroup analyses were conducted for the primary endpoint of Overall Success and Radiographic Fusion Success at 24 months. The pre-defined subgroup analyses include the ones based on the following analyses: a) primary indication (e.g., instability, recurrent disc herniation, or stenosis), b) type of intervertebral body cage utilized, c) use of nicotine at baseline, and d) long-term usage of NSAIDs at baseline. The study was not specifically powered for these subgroups. Of these subgroup

analyses, none had a statistically significant effect on Overall Success or Radiographic Fusion Success.

5. Region Sensitivity Analysis: OUS versus US Clinical Outcomes

In addition to the subgroup analyses outlined above, the region sensitivity analysis was carried out for subjects treated outside of the US (OUS) versus subjects treated in the US for the primary endpoints. OUS subjects from three investigational sites in China collectively contributed 37.5% of data utilized to generate the analysis of safety and effectiveness for the PMA application. **Table 35** is the summary of Overall Success by region based on the ART population, while **Table 36** and **Table 37** is the summary of adverse events by region based on the AT population for one- and two-level patients.

Table 35: Clinical Composite (Overall Success) in the ART population by Region: OUS versus US

	One-Level Subjects (N = 379)											
	12 Months						24 Months					
	OUS Sites (N = 149)			US Sites (N = 230)			OUS Sites (N = 149)			US Sites (N = 230)		
Variable	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**
ODI success	48/49 (98.0%)	50/51 (98.0%)	48/49 (98.0%)	41/48 (85.4%)	37/46 (80.4%)	39/44 (88.6%)	40/40 (100%)	39/39 (100%)	41/42 (97.6%)	27/31 (87.1%)	23/25 (92.0%)	24/28 (85.7%)
Radiographic fusion success	36/49 (73.5%)	37/50 (74.0%)	25/47 (53.2%)	30/47 (63.8%)	35/44 (79.5%)	23/43 (53.5%)	33/40 (82.5%)	33/36 (91.7%)	28/41 (68.3%)	30/32 (93.8%)	21/24 (87.5%)	14/27 (51.9%)
Neurological success	49/49 (100%)	51/51 (100%)	48/49 (98.0%)	32/47 (68.1%)	40/44 (90.9%)	37/46 (80.4%)	40/40 (100%)	38/38 (100%)	41/42 (97.6%)	20/31 (64.5%)	19/25 (76.0%)	22/28 (78.6%)
SAEs that are related to TLIF grafting material or interbody device	0	1	0	1	4	3	0	1	0	3	6	3
Secondary surgeries that are classified as failure	0	1	0	1	2	2	0	1	0	2	3	2
Overall Success[a]	36/49 (73.5%)	36/50 (72.0%)	24/47 (51.1%)	20/48 (41.7%)	24/46 (52.2%)	18/44 (40.9%)	33/40 (82.5%)	33/37 (89.2%)	28/41 (68.3%)	15/30 (50.0%)	14/30 (46.7%)	9/28 (32.1%)
	Two-Level Subjects (N = 101)											
	12 Months						24 Months					
	OUS Sites (N = 31)			US Sites (N = 70)			OUS Sites (N = 31)			US Sites (N = 70)		
	2.1 mg	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**	**2.1 mg**	**4.2 mg**	**Ctrl**
ODI success	12/13 (92.3%)	7/7 (100%)	9/10 (90.0%)	10/13 (76.9%)	14/17 (82.4%)	12/15 (80.0%)	8/10 (80.0%)	6/6 (100%)	7/8 (87.5%)	9/9 (100%)	8/12 (66.7%)	7/8 (87.5%)
Radiographic fusion success	9/13 (69.2%)	6/7 (85.7%)	5/10 (50.0%)	10/11 (90.9%)	12/17 (70.6%)	6/15 (40.0%)	7/10 (70.0%)	4/4 (100%)	3/8 (37.5%)	8/9 (88.9%)	9/11 (81.8%)	4/8 (50.0%)
Neurological success	12/13 (92.3%)	5/6 (83.3%)	9/10 (90.0%)	9/13 (69.2%)	14/17 (82.4%)	12/15 (80.0%)	9/10 (90.0%)	6/6 (100%)	7/8 (87.5%)	7/9 (77.8%)	10/13 (76.9%)	5/7 (71.4%)
SAEs that are related to TLIF grafting material or interbody device	1	0	0	0	0	1	1	0	0	0	1	1
Secondary surgeries that are classified as failure	0	0	0	0	0	1	0	0	0	0	0	1
Overall Success[a]	7/13 (53.8%)	4/6 (66.7%)	4/10 (40.0%)	7/13 (53.8%)	9/17 (52.9%)	4/15 (26.7%)	5/10 (50.0%)	4/4 (100%)	2/8 (25.0%)	6/9 (66.7%)	5/11 (45.5%)	1/7 (14.3%)

[a]Overall Success: satisfy all the following criteria
(1) ODI Success
(2) Radiographic Fusion Success (by CT assessment
(3) Neurological Success
(4) No serious adverse events that are “related” to TLIF grafting material or interbody device
(5) No secondary surgeries that are classified as failure

Table 36: Adverse Events up to 24 Months by Region OUS versus US for 1-level subjects (As Treated Dataset)

Adverse Event n - # of Patients % - Cumulative Adverse Event Rate	One-Level Subjects (N = 384)											
	OUS Sites (N = 149)						US Sites (N = 235)					
	2.1 mg (N = 49)		4.2 mg (N = 52)		Ctrl (N = 48)		2.1 mg (N = 80)		4.2 mg (N = 80)		Ctrl (N = 75)	
	n	%	n	%	n	%	n	%	n	%	n	%
Subjects Having Any Adverse Events	38	82.3	43	83.3	39	83.1	60	93.2	66	97.4	57	92.5
Subjects Having Any Serious Adverse Events	6	12.7	8	17.0	5	11.8	20	41.5	33	66.0	18	36.8
Subjects Having Any Adverse Events Related to Surgical Construct	6	13.1	10	20.7	9	19.8	36	62.0	37	63.8	29	49.7
• Related to TLIF Grafting Material/Interbody Device	6	13.1	10	20.7	9	19.8	35	61.3	35	58.5	29	49.7
- Related to TLIF Grafting Material	6	13.1	10	20.7	9	19.8	35	61.3	33	54.6	29	51.6
- Related to Interbody Device	5	11.2	8	16.9	9	19.8	35	61.3	35	58.8	28	47.8
• Related to Posterior Fixation	5	11.2	7	15.1	8	16.7	35	60.0	35	59.8	28	49.6
Subjects Having Any Serious Adverse Events Related to Surgical Construct	0	0.0	1	1.9	0	0.0	4	12.3	9	21.6	4	8.1
• Related to TLIF Grafting Material/Interbody Device	0	0.0	1	1.9	0	0.0	3	10.2	6	14.7	3	6.4
- Related to TLIF Grafting Material	0	0.0	1	1.9	0	0.0	2	7.7	4	12.4	3	6.4
- Related to Interbody Device	0	0.0	1	1.9	0	0.0	3	10.2	6	14.7	1	2.5
• Related to Posterior Fixation	0	0.0	0	0.0	0	0.0	3	9.8	7	16.8	2	4.1
Subjects Having Any Adverse Events Related to Study Procedure	26	54.6	29	57.1	24	50.9	47	76.7	54	78.3	43	68.5

Table 37:Adverse Events up to 24 Months by Region: OUS versus US for 2-level subjects (As Treated Dataset)

Adverse Event n - # of Patients % - Cumulative Adverse Event Rate*	Two-Level Subjects (N = 96)											
	OUS Sites (N = 31)						US Sites (N = 65)					
	2.1 mg (N = 14)		4.2 mg (N = 6)		Ctrl (N = 11)		2.1 mg (N = 20)		4.2 mg (N = 22)		Ctrl (N = 23)	
	n	%	n	%	n	%	n	%	n	%	n	%
Subjects Having Any Adverse Events	9	64.3	5	83.3	9	81.8	18	100.0	18	100.0	16	81.8
Subjects Having Any Serious Adverse Events	1	7.1	1	28.6	1	9.1	8	63.0	6	40.2	5	42.5
Subjects Having Any Adverse Events Related to Surgical Construct	6	42.9	2	33.3	1	9.1	11	66.0	13	73.3	14	89.7
• Related to TLIF Grafting Material/Interbody Device	6	42.9	2	33.3	1	9.1	9	48.5	13	73.3	14	92.4
- Related to TLIF Grafting Material	6	42.9	2	33.3	1	9.1	9	48.5	12	70.9	14	92.4
- Related to Interbody Device	5	35.7	2	33.3	1	9.1	9	49.2	13	73.3	14	92.4
• Related to Posterior Fixation	4	28.6	1	16.7	1	9.1	11	66.4	13	73.3	14	89.7
Subjects Having Any Serious Adverse Events Related to Surgical Construct	1	7.1	0	0.0	0	0.0	1	5.0	1	9.5	1	9.1
• Related to TLIF Grafting Material/Interbody Device	1	7.1	0	0.0	0	0.0	0	0.0	1	9.5	1	9.1
- Related to TLIF Grafting Material	1	7.1	0	0.0	0	0.0	0	0.0	1	9.5	1	9.1
- Related to Interbody Device	1	7.1	0	0.0	0	0.0	0	0.0	1	9.5	1	9.1
• Related to Posterior Fixation	1	7.1	0	0.0	0	0.0	1	5.0	1	9.5	1	9.1
Subjects Having Any Adverse Events Related to Study Procedure	9	64.3	5	83.3	4	36.4	17	100.0	14	75.2	14	86.3
Subjects Having Any Serious Adverse Events Related to Study Procedure	1	7.1	0	0.0	1	9.1	5	33.3	2	9.8	2	14.0

6. Pediatric Extrapolation

   In this premarket application, existing clinical data were 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 203 investigators of which none were full-time or part-time employees of the sponsor and nine (9) principal investigators, and seven (7) sub-investigators 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: None
- Significant payment of other sorts: Sixteen (16) investigators across eleven (11) clinical sites
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in sponsor of covered study: None

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses did not detect outlier trends or clinical outcomes attributable to sites with known financial interests/arrangements.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Protocol Deviations

At the time of PMA application, for one-level subjects, total major protocol deviations (10.1%, 10.9%, and 13.9% for Infuse 2.1 mg, Infuse 4.2 mg, and Control groups, respectively) were due to study treatment deviations (incorrect surgical technique or prolonged medication use) (**Table 38**).

At the time of PMA application, for two-level subjects, total major protocol deviations (5.9%, 15.6%, and 17.0% for the Infuse 2.1 mg, Infuse 4.2 mg, and Control groups, respectively) for the Infuse 2.1 mg group were due to study treatment deviations (incorrect surgical technique or prolonged medication use). For the Infuse 4.2 mg and Control groups, total major protocol deviations occurred due to the randomization procedure not being followed (**Table 38).**

Table 38: Summary of major protocol deviations

	One-Level Subjects (N = 379)					
	Infuse 2.1 mg (N = 129)		Infuse 4.2 mg (N = 128)		Control (N = 122)	
Major Protocol Deviation*	**Event**	**Patient (n%)**	**Event**	**Patient (n%)**	**Event**	**Patient (n%)**
Eligibility criteria not met	0	0/129 (0.0%)	0	0/128 (0.0%)	0	0/122 (0.0%)

Enrolled subject did not meet enrollment criteria	2	2/129 (1.6%)	0	0/128 (0.0%)	3	3/122 (2.5%)
Randomization procedure not followed	3	3/129 (2.3%)	1	1/128 (0.8%)	2	2/122 (1.6%)
Study treatment deviation	11	9/129 (7.0%)	26	13/128 (10.2%)	15	13/122 (10.7%)
Incorrect surgical technique	4	4/9 (44.4%)	4	4/13 (30.8%)	2	2/13 (15.4%)
Prolonged medication use	7	6/9 (66.7%)	22	9/1 (69.2%)	13	11/13 (84.6%)
Total	16	13/129 (10.1%)	27	14/128 (10.9%)	20	17/122 (13.9%)

	Two-Level Subjects (N = 101)					
	Infuse 2.1 mg (N = 34)		**Infuse 4.2 mg (N = 32)**		**Control (N = 35)**	
Major Protocol Deviation*	**Event**	**Patient (n%)**	**Event**	**Patient (n%)**	**Event**	**Patient (n%)**
Eligibility criteria not met	0	0/34 (0.0%)	0	0/32 (0.0%)	2	2/35 (5.7%)
Enrolled subject did not meet enrollment criteria	0	0/34 (0.0%)	0	0/32 (0.0%)	1	1/35 (2.9%)
Randomization procedure not followed	0	0/34 (0.0%)	4	4/32 (12.5%)	3	3/35 (8.6%)
Study treatment deviation	3	2/34 (5.9%)	4	1/32 (3.1%)	0	0/35 (0.0%)
Incorrect surgical technique	2	2/2 (100%)	0	0/1 (0.0%)	0	-
Prolonged medication use	1	1/2 (50.0%)	4	1/1 (100%)	0	-
Total	3	2/34 (5.9%)	8	5/32 (15.6%)	6	6/35 (17.1%)

* Major protocol deviation was based on the final clinical investigation protocol reviewed at time of PMA application

XII. 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.

XIII. CONCLUSIONS DRAWN FROM CLINICAL STUDY

A. Effectiveness and Clinical Composite Conclusions

1. Primary Endpoints

Overall Success

- Results Based on Primary Dataset - As Randomized and Treated

The rates for Overall Success at 24 months were respectively 48/70 (68.6%), 47/67 (70.1%), and 37/69 (53.6%) for the Infuse 2.1 mg, Infuse 4.2 mg, and Control groups within 1-level subjects. For 2-level subjects, the rates for Overall Success were 11/19 (57.9%), 9/15 (60.0%) and 3/15 (20.0%) for the Infuse 2.1 mg, Infuse 4.2 mg, and Control groups. These values were statistically

determined to meet the primary objective of the study of non-inferiority for clinical composite success of both the 2.1 mg and the 4.2 mg cohorts compared to the control at 24 months after operative intervention.

Radiographic Fusion Success

- Results Based on Primary Dataset - As Randomized and Treated

  The rates for Radiographic Fusion Success at 24 months were respectively 63/72 (87.5%), 54/60 (90.0%), and 42/68 (61.8%) for the Infuse 2.1 mg, Infuse 4.2 mg and Control groups, within 1-level subjects. For 2-level subjects, the rates for Radiographic Fusion Success at 24 months were 15/19 (78.9%), 13/15 (86.7%) and 7/16 (43.8%), respectively for the Infuse 2.1 mg, Infuse 4.2 mg and Control groups. These values were statistically determined to meet the co-primary objective of the study of superiority of Radiographic Fusion Success of both the 2.1 mg and the 4.2 mg cohorts compared to the control at 24 months after operative intervention.

B. Safety Conclusions

The safety analysis of the product is based on adverse event (AE) data collected in the clinical study conducted to support PMA approval. All the subjects who were enrolled, randomized, and received treatment were included in adverse event collection. AEs were monitored over the 24-month reporting period and reviewed/adjudicated by an independent CEC for classification of relatedness and severity. The subjects were grouped by the treatment they received, which was defined in the protocol as the As Treated dataset.

For one-level subjects, the 24-month cumulative AE rate was 88.6% in the Infuse 2.1 mg group, 89.8% in the Infuse 4.2 mg group, and 87.5% in the Control group.

The 24-month cumulative SAE rate was higher in the Infuse 4.2 mg group (41.3%) compared to the Control group (24.6%, $p<0.05$), but none of the individual rates of SAEs in the Infuse groups (2.1 mg or 4.2 mg) had any significant differences compared to the individual rates in the Control group.

For AEs and SAEs that were related to the surgical construct, the cumulative rate at 24 months had no statistical differences between the Infuse groups (2.1 mg or 4.2 mg) and the Control group.

For two-level subjects, the 24-month cumulative AE rate was 83.6% in the Infuse 2.1 mg group, 94.1% in the Infuse 4.2 mg group, and 85.2% in the Control group. The cumulative rates at 24 months in the Infuse 2.1 mg or Infuse 4.2 mg group were not statistically different compared to that of the Control group in regard to AEs, SAEs, or any AEs/SAEs related to TLIF Grafting Material/Interbody Device.

C. Benefit-Risk Determination

Summary of Benefits

The probable benefits of the product are based on data collected in a clinical study conducted to support PMA approval. A primary benefit of Infuse™ Bone Graft when used with an intervertebral fusion device, supplemental fixation, local autograft and optionally supplemented with allograft in one- and two-level TLIF procedures is its significantly higher probability of achieving radiographic fusion success compared to the same construct without Infuse™ Bone Graft. For one-level subjects at 24 months, more subjects in the Infuse 2.1 and Infuse 4.2 groups achieved radiographic fusion success (87.5% and 90.0%, respectively) than the Control group (61.8%). For two-level subjects at 24 months, more subjects in the Infuse 2.1 and Infuse 4.2 groups achieved radiographic fusion success (78.9% and 86.7%, respectively) than the Control group (43.8%). In additional to higher probability of radiographic fusion success for both 1- and 2-level TLIF patients, use of Infuse™ Bone Graft in TLIF demonstrated a shorter time to fusion. Finally, TLIF patients who had Infuse™ Bone Graft compared to TLIF patients with the same construct without Infuse™ Bone Graft were non-inferior to the control based on clinical composite success outcomes and superior in radiographic fusion success at 24 months after operative intervention. Sources of uncertainty in the assessment of benefits of Infuse™ Bone Graft include the comparatively low rate of radiographic fusion success in the control arm for those with 24 months data reviewed for this PMA application, the question of representativeness of the OUS subset cohort to the US general population, and the incomplete follow up of the entirety of the enrolled cohort. (~62% of anticipated overall study data available for review).

Summary of Risks

The probable risks of the device are based on data collected in a clinical study conducted to support PMA approval. Infuse™ Bone Graft has been approved for use in lumbar spine fusion procedures since 2002 (P000058, approved July 2, 2002). Known risks of the device are included in the Instructions for Use and include exuberant and heterotopic bone formation and local or systemic allergic reaction to the product or its components. No unanticipated risks were identified in the pivotal clinical trial conducted to support this PMA application for use of Infuse™ Bone Graft in TLIF procedures.

The assessment of safety in the PMA study included an evaluation of reported adverse events (AEs) and safety endpoints for subjects undergoing TLIF procedures with Infuse™ Bone Graft at one or two lumbar levels. AEs were monitored over the 24-month reporting period and reviewed/adjudicated by an independent CEC for classification of relatedness and severity. Cumulative rates of AEs were found to be similar across all treatment groups (Infuse 2.1 mg, Infuse 4.2 mg, and Control). The

rate of severe adverse events (SAEs) was higher in the Infuse 4.2 mg group (41.3%) compared to the Control group (24.6%). However, none of the individual rates of SAEs in the Infuse groups showed any significant differences compared to the individual rates in the Control group. Heterotopic ossification was more frequently observed in the Infuse groups, but no correlation was identified between radiographic observation of HO and reported adverse events (AEs) that could potentially result from HO. Rates of secondary surgeries were similar across all groups.

Sources of uncertainty in the assessment of safety included those mentioned in the assessment of benefits, specifically the comparatively low rate of radiographic fusion success in the control arm, the question of representativeness of an OUS subset cohort to the US general population, and the incomplete follow-up of the entirety of the enrolled cohort. (~62% of anticipated overall study data available for review). Additionally for the risk assessment of Infuse™ Bone Graft, there was uncertainty in the discrepancy in reported rates of device and procedure AEs in the OUS cohort compared to the US cohort. Also specific to uncertainty in risk assessment based on the data collected for the PMA application, is the protocol deviation rate of >10%, although these deviations were found equally amongst all three studied populations (2.1 mg, 4.2 mg and control) for both 1- and 2-level patients.

D. Overall Conclusions

The data in this application supports the reasonable assurance of safety and effectiveness of this product when used in accordance with the indications for use. The assessment of the safety and effectiveness of the product are based on previous nonclinical laboratory and animal studies as well as data collected in the pivotal clinical study conducted to support PMA approval of Infuse™ Bone Graft, in combination with an intervertebral fusion device, local autograft and supplemental allograft chips at one or two levels in transforaminal lumbar interbody fusion (TLIF) procedures. Taken together, the data demonstrate that Infuse™ Bone Graft, has 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.

XII. CDRH DECISION

CDRH issued an approval order on February 13, 2026. The final clinical conditions of approval cited in the approval order are described below. The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820), which was in effect at the time of the inspection. As of February 2, 2026, the revised part 820, referred to as the Quality Management System Regulation (QMSR), is effective.

XIII. 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.

XIV. REFERENCES

Not applicable.