TITLE:

Clinical Outcomes Associated With the Use of ViviGen® for the Treatment of Lumbar Degenerative Disc Disease

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Study Protocol and Statistical Analysis Plan

Clinical Outcomes Associated with the use of ViviGen® in Conjunction with Posterolateral Fusion for the Treatment of Lumbar Degenerative Disc Disease

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Introduction

DePuy Synthes, Inc. is proposing a prospective randomized interventional outcomes study of clinical safety and fusion rates in subjects who have received standard-of-care one or two-level posterolateral lumbar fusion surgery with instrumentation using ViviGen® Cellular Bone Matrix on-label for the treatment of degenerative disc disease.

Background and Significance

Nearly half of the estimated 500,000 bone grafting procedures performed annually in the United States involve spine fusion.[1] Traditionally, autologous bone grafts are used to repair damaged bone caused by trauma, infection, malignancy, degenerative disease and congenital deformity. However, harvesting of bone autograft is an invasive procedure that can lead to significant donor site morbidity.[2]

Bone graft substitute (BGS) materials offer an alternative to autograft bone capable of supporting new bone growth, while avoiding or minimizing the frequent co-morbidities associated with autograft harvest from the iliac crest.[3-5] Allograft bone has been used successfully for more than two decades as a first-generation alternative to autograft bone. While traditional processed allograft bone can be difficult to shape, shows variable resorption characteristics, and variable biological activity, ViviGen® Cellular Bone Matrix has addressed these issues in their product. While containing all the properties required for bone formation, it additionally has a consistency that allows it to hold shape in a putty-like consistency.[6] ViviGen® Cellular Bone Matrix can be molded into a specific form that allows proper placement, positioning and formation during posterolateral lumbar fusion.[6]

Description of ViviGen®[6]

ViviGen® is manufactured by DePuy Synthes, Inc. (West Chester, Pennsylvania). ViviGen® Cellular Bone Matrix is comprised of cryopreserved viable cortical cancellous bone matrix and demineralized bone. ViviGen® Cellular Bone Matrix is a Human Cells, Tissues, and Cellular and Tissue-based Product (HCT/P) as defined by the U.S. Food and Drug Administration in 21 CFR 1271.3. ViviGen® Cellular Bone Matrix is processed from donated human tissue, resulting from the generous gift of an individual or his/her family.

ViviGen® Cellular Bone Matrix contains all of the properties required for bone formation being that it is osteoconductive, osteoinductive and osteogenic. Safety of ViviGen® Cellular Bone Matrix is defined by every lot is aseptically processed and final product is tested for sterility using USP standards. Packaging and handling is beneficial in that all four sizes of ViviGen® Cellular Bone Matrix will thaw in less than 5 minutes, which is vital for cell viability, in that the ported pouch allows for the quick and efficient removal of the cryopreservation media and rinsing solutions. ViviGen® Cellular Bone Matrix maximizes cell viability by modes of processing that is focused on protecting viable lineage committed bone cells from recovery to implantation.

Objective

The objective of this study is to perform a prospective, randomized, controlled clinical trial to compare radiographic fusion rates and patient reported outcomes, including pain and function preoperatively and postoperatively, using Depuy ViviGen® Cellular Bone Matrix mixed with

cortical/cancellous allograft in conjunction with an approved Depuy Synthes pedicle screw system compared to autograft mixed with cortical/cancellous allograft in conjunction with the same DePuy Synthes pedicle screw system used for a one or two- level posterolateral lumbar fusion.

Methodology

Study Design

This is a prospective randomized, non-blinded, controlled study. Patients with a diagnosis of degenerative disc disease and/or up to grade I spondylolisthesis and planning to undergo a 1- or 2-level instrumented posterolateral lumbar fusion surgery between L1-S1 will be screened. If eligible and the subject meets all the inclusion criteria and none of the exclusion criteria, the subject will be approached about study participation by the surgeon. If the subject agrees to participate, the consent process will be initiated by the study coordinator. Once the patient has been consented; data including medical history, neurological exam, patient questionnaires (VAS, ODI, SF-36) will be collected. Randomization will occur once a surgery date has been scheduled so the appropriate instrumentation can be boarded accordingly. A randomization envelope will reveal randomization treatment group. The envelopes will be generated in a 1:1 fashion and be randomly allocated to an assigned study identification number. Subjects will be randomized to either: 1) treatment arm where the investigator will use an FDA approved/cleared DePuy Synthes spinal pedicle screw system with ViviGen® Cellular Bone Matrix mixed with cortical/cancellous allograft or the 2) control arm where the investigator use the same DePuy Synthes spinal pedicle screw system with local autologous bone graft mixed with cortical/cancellous allograft. Both treatment groups represent standard of care lumbar fusion surgeries using two types of bone graft options to create the arthrodesis as comparators.

Once the lumbar fusion surgery has taken place as planned; data will be collected regarding the surgery performed, including operative time, amount of bone graft used, spinal system used, length of hospital stay, and adverse events/complications.

Study subjects will be followed up at 6-weeks, 3-months, 6-months, and 12-months postoperatively at the private practice or clinic. During these routine (standard of care) postoperative visits, subjects will complete questionnaires (VAS, ODI, SF-36, patient satisfaction) and have neurological exam (lumbar spine exam, see appendix 1) completed by the investigator. Adverse events related to device and/or procedure will be evaluated as each postoperative visit. AP and lateral x-rays will be performed at all visits with flexion and extension x-rays added at baseline, 3-months, 6-months, and 12-months. A CT scan of the lumbar spine will be performed during the 12-month postoperative time frame at the Beaumont-RO Imaging Center. Radiographic analysis will be performed and evaluated for fusion status as evidenced by bony bridging, presence of radiolucency, and development of pseudoarthrosis at each follow-up visit.

This study design reflects the current standard of care for lumbar spinal stenosis, degenerative disc disease and lumbar degenerative spondylolisthesis. Lumbar fusion surgery using pedicle screw fixation with autograft and allograft bone grafting options is treatment of choice after conservative (non-surgical) therapies have been implemented and failed.

Statistical Analysis

The sample size will consist of 40 patients; 20 in each treatment arm. The primary hypothesis is that the probability of achieving fusion using ViviGen bone graft is not clinically inferior to using autograft and allograft in lumbar fusion at 12-months post-surgery. Using a one-sided test and fusion rate of 86%, there is a 0.80 probability of 0.80 of finding a difference for 60 patients. A 10% dropout rate was considered. Forty patients may result in low statistical power; however, this may be increased by 10 in each arm once enrollment has obtained and if needed, and upon agreement with study sponsor. Enrollment of 40 reflects the current allotted grant/budget per the study sponsor for this project.

There are other studies that analyzed demineralized bone matrix in two-year fusion outcomes for lumbar spinal fusions that used a similar size population (range between 13 and 28 patients) to the proposed enrollment for this study, as demonstrated in *Vaccaro et al (2007)* and *Kang et al* (2012). Power calculation for the primary outcome of bone fusion was obtained using PASS 15. An 86% fusion rate (Kang et al) was assumed with a 10% dropout rate for both arms.

Secondary endpoints (VAS, ODI, SF-36, neurological status, and fusion) will be quantified to detect changes longitudinally from baseline through 12-months post-surgery.

Study Population and Inclusion/Exclusion Criteria

Patients with a diagnosis of spinal stenosis, degenerative disc disease and/or up to grade I spondylolisthesis and planning to undergo a 1or 2-level instrumented posterolateral lumbar fusion surgery between L1-S1 will be asked to participate in the study. If eligible, the consent process will be initiated by the study coordinator

A subject may be included if the following criteria are met:

1. ≥18 years of age
2. Able to provide consent
3. Is undergoing standard of care one or two-level instrumented posterolateral fusion at the level between L1-S1
4. Has diagnosis of spinal stenosis, degenerative disc disease and/or up to Grade 1 spondylolisthesis
5. Requires decompression at intended fusion level (multi-level decompression allowed L1-S1)
6. Has failed 6-weeks or more of conservative, non-operative treatment
7. Has back and/or radicular lumbar symptoms with ODI (Oswestry Disability Index) score of ≥ 30 preoperatively.

A subject will be excluded if any of the following criteria are met:

1. Any prior lumbar fusion surgery
2. Requires fusion of more than two levels
3. Requires an interbody fusion based on relevant diagnosis and factors (such as foraminal stenosis, degree of spondylolisthesis, spinal deformity, disc space collapse, and subject's age) as determined by investigator
4. BMI > 40

5. Active systemic infection or infection at operative site
6. History of an osteoporotic fracture and/or vertebral body fracture
7. Is currently being treated with chemotherapy, radiation, immunosuppression or chronic steroid therapy
8. History of osteoporosis, osteopenia, or osteomalacia that would contraindicate spinal surgery
9. Psychological or physical condition in the opinion of the investigator that would interfere with subject self-assessments
10. History of neurological condition in the opinion of the investigator that may affect lumbar function and pain assessments
11. Subjects with a history of cancer must be disease free for at least 3 years
12. Pregnant, or plans on becoming pregnant

Intervention

Treatment arm/group: 20 subjects undergoing open, one or two-level instrumented posterolateral lumbar fusion surgery using ViviGen Cellular Bone Matrix mixed with cortical/cancellous allograft and DePuy Synthes pedicle screw system.
Control arm/group: 20 subjects undergoing open, one or two-level posterolateral lumbar fusion surgery using local autograft mixed with cortical/cancellous allograft and DePuy Synthes pedicle screw system.

Data and Safety Monitoring

The PI and study team (including sub-investigators, clinical research manager) will be responsible for data and safety monitoring. All adverse events will be reviewed to determine relatedness to the product and reported to sponsor as necessary (if related to product and unanticipated according to risk profile). The data will be reviewed for maintenance of confidentiality and integrity as well as the data collection process. The data and safety review will take place every six months from the date of the first patient enrolled into the study or after every ten patients enrolled whichever comes first.

Adverse Events

Relevant adverse events (those related to the study device, the surgical procedure, or the lumbar spine) will be recorded in this study. All adverse events will be reviewed for relatedness and expectedness by the PI on a case by case basis and per Data and Safety Monitoring guidelines.

Protocol Deviations

The investigators are responsible for documenting all protocol deviations, including an explanation for why the deviation occurred. All protocol deviations will be recorded and submitted to the IRB per policy.

Outcomes

Primary Endpoint

- Successful lumbar fusion as measured by CT scan and flexion/extension x-rays at 12-months; as evidenced by bony bridging, presence of radiolucency, no development of pseudoarthrosis

Secondary Endpoints

- Improvement in patient reported outcomes as measured by VAS (≥ 2-point improvement), ODI (≥ 15-point improvement), SF-36 (≥ 15-point improvement) from baseline to 12-months.
- No new or worsening neurological (motor and sensory) deficit as compared to baseline through 12-months. No revision surgery and/or development of pseudoarthrosis by month 12.
- No occurrence of adverse events related to device by month 12.

Subject Screening and Enrollment

Patients who have already planned a decompressive lumbar laminectomy and fusion surgery will be approached about potential study participation. If the patient wishes to proceed with study participation, the study coordinator will go through the informed consent process. After the consent process has been completed, the subject will be further screened for eligibility and given the subject questionnaires to complete.

Screen Failures

If the subject does not meet all inclusion criteria or meets one of the exclusion criteria after signing consent, then the subject will be considered a screen failure and therefore, not enrolled into the study. The subject will also be considered a screen failure and not enrolled in the study if there is a change in surgical treatment based on the surgeon's observations and best practice intraoperatively.

Withdrawals

A subject who withdraws consent prior to study completion will be removed from the study and no longer followed. The surgery, instrumentation, and bone grafts are FDA approved and cleared and considered standard of care. The subjects may follow-up as needed and per standard of care at their own discretion if they decide to no longer participate in the study.

The reasons for voluntary withdrawal or discontinuation of study subjects will be documented. If during the course of the clinical study, a study subject is non-responsive to attempts to schedule follow-up visits, communication methods such as phone calls, emails, mail, or other means as appropriate in an attempt schedule an appointment or determine if the subject has moved, died, or otherwise become lost to follow-up.

Summary and Rationale of Proposed Study

The purpose of this study is to collect on-label safety and efficacy data where ViviGen® Cellular Bone Matrix is applied to posterolateral lumbar fusion with DePuy Synthes pedicle screw system. It is expected that this study will contribute to the compilation of clinical data required

to demonstrate the ability of ViviGen® Cellular Bone Matrix to promote safe, effective and timely spine fusion in patients who undergo posterolateral lumbar fusion surgery. The results of this study will lead to further analysis (i.e. comparison to historical data of other marketed bone graft products, as well as, to local bone alone).

References

1. Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. *Spine* 27, S26-S31 (2002).

2. Kim, D et al. Prospective study of iliac crest bone graft harvest site pain and morbidity. *Spine* 9, 886-892 (2009).

3. Betz, R. Limitations of autograft and allograft: new synthetic solutions. *Orthopedics* 25, s561-s570 (2002).

4. Gazdag, A; Lane, J; Glaser, D; Forster, R. Alternatives to autogenous bone graft: efficacy and indications. *J Am.Acad.Orthop.Surg.* 3, 1-8 (1995).

5. DeCoster, T; Gehlert, R; Mikola, E; Pirela-Cruz, M. Management of post-traumatic segmental bone defects. *J Am.Acad.Orthop.Surg.* 12, 28-38 (2004).

6. DePuy Synthes. https://www.depuysynthes.com/hcp/spine/products/qs/vivigen-cellular-bone-matrix. Copyright DePuy Synthes 2014-2017. DePuy Synthes Biomaterials Division 1302 Wrights Lane East, West Chester, Pennsylvania 19380.

7. Vaccaro AR, Stubbs HA, Block JE. Demineralized bone matrix composite grafting for posterolateral spinal fusion. Orthopedics. 2007 Jul; 30(7): 567-70.

8. Kang J, An H, Hilibrand A, Yoon ST, Kavanagh E, Boden S. Grafton and local bone have comparable outcomes to iliac crest bone in instrumented single-level lumbar fusions. Spine. 2012 May 20;37(12):1083-91.

Study Synopsis

Sponsor	DePuy Synthes
Protocol Version	Version 1.5 Date 06.04.2018
Study Title	Clinical Outcomes Associated with the use of ViviGen® in Conjunction with Posterolateral Fusion for the Treatment of Lumbar Degenerative Disc Disease
Site	Beaumont Health – Royal Oak (William Beaumont Hospital)
Study Design	Prospective, randomized, interventional outcomes study
Study Duration	Approximately 4 years (enrollment of first subject to the last follow-up visit)
Enrollment Number	Total: 40 20 – ViviGen treatment arm 20 – Control arm
Treatment Arm	20 subjects undergoing one or two-level instrumented posterolateral lumbar fusion surgery using ViviGen Cellular Bone Matrix mixed with cortical/cancellous allograft and DePuy Synthes pedicle screw system
Control Arm	20 subjects undergoing open, one or two-level posterolateral lumbar fusion surgery using local autograft mixed with cortical/cancellous allograft and Depuy Synthes pedicle screw system.
Study Objectives	• *Primary Objective:* 1. To evaluate bone fusion using ViviGen Cellular Bone Matrix for one or two-level instrumented posterolateral lumbar fusion surgery • *Secondary Objectives:* 1. To evaluate VAS, ODI, SF-36 and patient satisfaction scores postoperatively compared to baseline/preoperative. 2. Evaluate the occurrence of procedure and/or device related adverse events

Study Endpoints	*Primary Endpoint:* • Successful lumbar bone fusion as measured by CT scan and flexion/extension x-rays at 12-months; as evidenced by bony bridging, presence of radiolucency, no development of pseudoarthrosis *Secondary Endpoints:* • Improvement in patient reported outcomes as measured by VAS (≥ 2-point improvement), ODI (≥ 15-point improvement), SF-36 (≥ 15 point improvement) from baseline to 12-months. • No new or worsening neurological (motor and sensory) deficit as compared to baseline through 12-months. No revision surgery and/or development of pseudoarthrosis by month 12. • No occurrence of adverse events related to device by month 12.
Inclusion Criteria	A subject may be included if the following criteria are met: 1. ≥18 years of age 2. Able to provide consent 3. Is undergoing standard of care one or two-level instrumented posterolateral fusion at the level between L1-S1 4. Has diagnosis of spinal stenosis, degenerative disc disease and/or up to Grade 1 spondylolisthesis 5. Requires decompression at intended fusion level (multi-level decompression allowed L1-S1) 6. Has failed 6-weeks or more of conservative, non-operative treatment 7. Has back and/or radicular lumbar symptoms with ODI (Oswestry Disability Index) score of ≥ 30 preoperatively.
Exclusion Criteria	A subject will be excluded if any of the following criteria are met: 1. Any prior lumbar fusion surgery 2. Requires fusion of more than two levels 3.Requires an interbody fusion based on relevant diagnoses and factors (such as foraminal stenosis, degree of spondylolisthesis, spinal deformity, disc space collapse, and subject's age) as determined by investigator 3. BMI > 40 4. Active systemic infection or infection at operative site 5. History of an osteoporotic fracture and/or vertebral body fracture 6. Is currently being treated with chemotherapy, radiation, immunosuppression or chronic steroid therapy 7. History of osteoporosis, osteopenia, or osteomalacia that would contraindicate spinal surgery 8. Psychological or physical condition in the opinion of the investigator that would interfere with subject self-assessments 9. History of neurological condition in the opinion of the investigator that may affect lumbar function and pain assessments 10. Subjects with a history of cancer must be disease free for at least 3 years 11. Pregnant, or plans on becoming pregnant

Study Summary	All subjects who sign an IRB approved consent form are considered in active screening to determine eligibility. Once a subject is consented, the following visits will take place: Baseline (≤ 60 days of surgery): • Medical history • Neurological exam (Lumbar Spine Exam, appendix 1) • Demographics • VAS, ODI, SF-36 questionnaires • Lumbar spine x-rays AP/lateral, flexion/extension or as done per standard of care • Randomization Surgical Visit: • Surgery performed • Operative Time • Amount of Bone Graft used • Pedicle Screw System used • Length of Hospital Stay • Adverse Events/Complications 6-week Visit (± 2 weeks): • VAS, ODI, SF-36, patient satisfaction questionnaires • Neurological Exam • Lumbar AP/Lateral x-rays • Adverse Events 3-month Visit (± 3 weeks): • VAS, ODI, SF-36, patient satisfaction questionnaires • Neurological Exam • Lumbar AP/Lateral and flexion/extension x-rays • Adverse Events 6-month Visit (± 1 month): • VAS, ODI, SF-36, patient satisfaction questionnaires • Neurological Exam • Lumbar AP/Lateral and flexion/extension x-rays • Adverse Events 12-month Visit (± 2 months): • VAS, ODI, SF-36, patient satisfaction questionnaires • Neurological Exam • Lumbar AP/Lateral and flexion/extension x-rays • CT scan of the lumbar spine without contrast • Evaluate fusion status • Adverse Events