K2M Post Market Clinical Study Protocol

The Fusion Rate with K2M VESUVIUS® Demineralized Fibers used with K2M EVEREST® Spinal System Compared to Autologous Bone Graft with Posterior Stabilization

Clinical Protocol CA-003

Revision 1

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Sponsor: **K2M, Inc.**
600 Hope Parkway SE
Leesburg, VA 20175

Contact: **Marissa Conrad**
Director of Clinical Affairs
Office: 866-526.4171
Fax: 877-594-7206
spineclinical@stryker.com
www.k2m.com

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1 PROTOCOL SYNOPSIS

Primary Objective: To evaluate the perioperative and post-operative radiographic and patient outcome variables with the K2M VESUVIUS® Demineralized Fibers when used with the K2M EVEREST® Spinal System as compared to literature reported outcomes using autograft with posterior stabilization in the treatment of spinal stenosis, spondylolisthesis (grade 1 or 2), and/or degenerative disc disease.

Study Design: Prospective, non-randomized (single arm) multi-center study

Follow-Up Evaluations: Clinical evaluations will be conducted at initial post-op, 3 months, 6 months, 12 months, and 24 months post-procedure. Adverse events will be monitored continuously.

Outcome Assessments: Outcome measurements include the following:

- Qualitative Radiographic and CT Assessments
    - Fusion Assessment
    - Device Status
- Oswestry Disability Index (ODI)
- Back, Hip/Buttock, and Leg Pain 10cm Visual Analog Scale (VAS)
- SF-12v2 Health Survey
- Operative Assessments
    - Estimated Blood Loss
    - Length of Operation
    - Time of Anesthesia
- Length of Hospital Stay
- Functional and Economic Status and Return to Work/School
- Use of Narcotics Post-Surgery
- Patient Satisfaction

Safety Assessment: Safety will be assessed by:

- The evaluation of all adverse events including but not limited to device related, procedure related, and additional serious adverse events

Study Subjects: Patients eligible for study enrollment will require pedicle screw fixation for posterior stabilization as an adjunct to fusion at one or two spinal levels (contiguous) for spinal stenosis, spondylolisthesis (grade 1 or 2), and/or degenerative disc disease (DDD). Qualified patients will be confirmed by history and radiographic assessment. Subjects under evaluation will be ≥ 18 years old at time of enrollment.

Device Evaluation Group: VESUVIUS Demineralized Fibers (distributed by K2M, Inc. for LifeNet Health) used with the EVEREST Spinal System (K2M, Inc.) cleared for marketing and distribution under 510(k) K133944.

Comparative Group: Historical, literature control of traditional spinal fusion intervention with posterior stabilization instrumentation and autograft.

Sample Size:

Two-hundred four (204) total subjects at up to 15 clinical sites, geographically distributed throughout the US. Sites are considered a Principal Investigator and their Sub-Investigators who are covered by a single Institutional Review Board's (IRB's) oversight and approval.

Subject enrollment will be capped so that no single site contributes more than approximately 15% of the cases.

Investigator Selection:

- Appropriate patient population for trial indication
- The Investigator must have completed a minimum of three surgeries using the EVEREST Spinal System. If a surgeon does not have experience with this, their first three (3) patients will be considered roll-in patients and the results from these patients will be analyzed against the entire cohort to determine if a learning curve exists. If a surgeon has previously completed three (3) surgeries using the EVEREST Spinal System, there will be no stratification of their data.
- Experience in clinical trial execution
- Dedicated research infrastructure
- Local institutional review board (IRB) for research oversight or ability to use central IRB
- Standard of Care (SOC) compatible with protocol requirements
    - Radiographic imaging per protocol
    - Use/Collection of patient reported outcome measures – ODI; Back, Hip/Buttock, and Leg VAS; SF-12v2
    - Follow-up evaluations at initial post-op, 3 months, 6 months, 12 months, and 24 months
- Insofar as possible, sites for the study will be distributed regionally and by type of institution and level of investigator experience, patient volume and research experience so that any unanticipated and potentially prognostic factors may then be balanced both geographically and demographically in the study

2 INTRODUCTION

2.1 Study Purpose

The purpose of this study is to evaluate fusion status and patient outcomes observed from use of the VESUVIUS Demineralized Fibers with the EVEREST Spinal System as compared to the literature reported outcomes of spinal fusion using autograft with posterior stabilization.

2.2 Background and Significance

Degenerative disc disease is a spinal condition caused by the breakdown of intervertebral discs. As a result of aging, the spine begins to show signs of wear and tear as the discs dry out and shrink. These age-related changes can lead to arthritis, disc herniation, or spinal stenosis, which can put pressure on the spinal cord and nerves and may cause back pain. Spinal fusion is often utilized as the final treatment after conservative method attempts have failed.

Although iliac crest graft is the gold standard for assisting instrumented fusion, alternatives to obviate the morbidity of graft harvest have become available. Specifically, the VESUVIUS Demineralized Fibers will be used in conjunction with the EVEREST Spinal System and results will be compared to those reported in literature after the utilization of autograft and posterior stabilization.

2.3 Device Description

VESUVIUS Fibers are sterile freeze-dried allografts that are processed from donated human tissue, resulting from the gift of an individual or his/her family. The EVEREST polyaxial screw provides an increased range of motion and features a CoCr head to minimize head splay, optimized dual lead thread designed to increase fixation in bone, an Easy-to-Start set screw facilitating set screw introduction, and the ability to accept both 5.5 mm and 6.0 mm diameter rods. Both K2M products are indicated for the uses described herein.

The EVEREST Spinal System was cleared for marketing under 510(k) K133944. The VESUVIUS Demineralized Fibers are a Human Cell and Tissue Based Product (HCT/P) that is distributed by K2M, Inc. for LifeNet Health.

2.4 Surgical Procedure

Implantation of the EVEREST Spinal System (K2M, Inc., Leesburg, VA) should be performed along with a posterolateral/transverse process fusion using VESUVIUS Demineralized Fibers (K2M, Inc., Leesburg, VA) as a graft extender. Implantation is performed according to the standard of care of the Investigator, and in accordance with K2M's Instructions for Use and Surgical Technique Manual for the EVEREST Spinal System and for the VESUVIUS Demineralized Fibers. The use of an interbody spacer is optional. If an interbody spacer is used, a biocompatible PEEK cage must be implanted using the transforaminal lumbar interbody fusion (TLIF) technique. Refer to Section 8.3, for further details of the surgical technique.

2.5 Indications for Use

VESUVIUS Demineralized Fibers are allograft material indicated for implantation in bony voids for tissue repair and are not intrinsic to the stability of the construct. Allograft is commonly used as a bone graft extender to augment insufficient volumes of local autograft. The EVEREST Spinal System may be used in conjunction with the RANGE® (MESA® and DENALI®) Spinal Systems, all of which are cleared for the following indications: Non-cervical fixation as an adjunct to fusion for the following indications: degenerative disc disease (defined as back pain of discogenic origin with degeneration of the disc confirmed by history and radiographic studies); spondylolisthesis; trauma (i.e., fracture or dislocation); spinal stenosis; curvatures (i.e., scoliosis, kyphosis and/or lordosis); tumor; pseudoarthrosis; and/or failed previous fusion.

Except for hooks, when used as an anterolateral thoracic/lumbar system the Everest Spinal System may also be used for the same indications as an adjunct to fusion. When used for posterior non-cervical pedicle screw fixation in pediatric patients the Everest Spinal System implants are indicated as an adjunct to fusion to treat adolescent idiopathic scoliosis. These devices are to be used with autograft and/or allograft. Pediatric pedicle screw fixation is limited to a posterior approach.

2.6 Benefits and Risks

2.6.1 Potential Benefits

There is no guarantee that the subject will experience any immediate or direct benefits with the use of the EVEREST Spinal System and/or the VESUVIUS Demineralized Fibers or for taking part in this study.

2.6.2 Potential Risks

Potential risks include those associated with any spinal surgery resulting in neurological, cardiovascular, respiratory, gastrointestinal compromise, or death. A full listing of potential risks of the device and the surgical procedure can be found in **Section 9.5 Potential Risks and Anticipated Adverse Events**.

2.7 Mitigation of Risks

Operative and acute periprocedural risks for the patients enrolled in this study are mitigated by restricting the use of the device to skilled neurological and orthopedic spine surgeons trained and experienced in the proper surgical technique to implant the respective device. Long-term risks such as device failure or pseudoarthrosis are mitigated by proper patient selection and implanting the device in accordance with the Surgical Technique Manual for the EVEREST Spinal System and use of the surgical instruments provided by K2M and by following accepted standard of care in this population for spinal fusion surgery.

3 INVESTIGATOR/SITE SELECTION

The Investigators selected to participate in this clinical study will be responsible for conducting the study according to the requirements of the protocol. Each site will have a designated Principal Investigator and may have Sub-Investigators. Investigators/sites will be selected for participation in the study according to the following criteria:

The Investigator/Site must have:

- Expertise in clinical areas relevant to the study, including a background in spine surgery, sufficient experience in clinical research and an adequate patient population with adult spine disorders
- Completed a minimum of three (3) surgeries using the EVEREST Spinal System. If a surgeon does not have experience with these, their first three (3) patients will be considered roll-in patients and the results from these patients will be analyzed against the entire cohort to determine if a learning curve exists. If a surgeon has previously completed three (3) surgeries using the EVEREST Spinal System, there will be no stratification of their data.
- Experience in participating in clinical studies and have adequate personnel and a dedicated research infrastructure including a Study Coordinator to adequately perform the tasks required by the clinical protocol
- Local institutional review board (IRB) for research oversight or ability to use central IRB
- A practice in a medical facility equipped appropriately to fulfill the surgical and patient contact requirements of the study
- A standard of care (SOC) compatible with or capable of complying with the protocol requirements including but not limited to:
    - Radiographic imaging per protocol
    - Use/Collection of patient reported outcome measures – ODI; Back, Hip/Buttock, and Leg VAS; SF-12v2
    - Follow-up evaluations at initial post-op, 3 months, 6 months, 12 months, and 24 months
- (Be willing to) sign a Clinical Research Agreement and abide by the agreement for the duration of the study.
- (Be willing to) provide financial disclosure; including updating the disclosure during the study if the financial status changes

The Investigators and practices in this trial are representative of the general user population of this type of device. Insofar as possible, sites for the study will be distributed regionally and by type of institution and level of investigator experience, patient volume and research experience so that any unanticipated and potentially prognostic factors may then be balanced both geographically and demographically in the study.

3.1 Investigator Training

Training sessions in proper surgical technique and trial performance for the Principal Investigator, all Sub-Investigators and research coordinators will be provided by the sponsor prior to initiation of the study at each site.

4 STUDY METHODS

4.1 Study Design

Prospective, non-randomized (single arm) multi-center study to evaluate the perioperative and post-operative radiographic and patient outcome variables of the VESUVIUS Demineralized Fibers and the EVEREST Spinal System compared to literature reported outcomes for traditional autograft and posterior stabilization treatment of spinal stenosis, spondylolisthesis, and/or degenerative disc disease (DDD).

4.2 Treatment Group

Patients treated with the VESUVIUS Demineralized Fibers and EVEREST system that had/were:

- Diagnosis of spinal stenosis, spondylolisthesis (grade 1 or 2), and/or degenerative disc disease (DDD). Qualified patients will be confirmed for inclusion by patient history and radiographic studies.
- One or two contiguous levels requiring surgical intervention between L1-S1
- Skeletally mature and ≥ 18 years old at time of enrollment

4.3 Control Group – Comparative Data

Literature reported outcomes of adult patients (≥ 18 years old) with surgical intervention utilizing autograft and posterior stabilization for the treatment of spinal stenosis, spondylolisthesis and/or DDD.

4.4 Sample Size

Two-hundred four (204) total subjects at up to 15 clinical sites, geographically distributed throughout the US. Sites are considered a Principal Investigator and their Sub-Investigators who function under the same institution and/or are covered by a single Institutional Review Board's (IRB's) oversight and approval.

Subject enrollment will be capped so that no single site contributes more than approximately 15% of the cases.

5 STUDY OBJECTIVES/OUTCOMES

5.1 Primary Study Objective

The primary study objective is:

5.1.1 Radiographic Assessment of Fusion

Radiographic assessments by CT scan at the 12 month visit and AP, lateral, Flex/Ext and oblique x-rays at the 12 and 24 month visits include overall assessment of fusion. Fusion will be graded by an independent radiologist taking into account signs such as:

- Bony Bridging
- Radiolucency
- Development of Pseudoarthrosis

5.2 Primary Safety Objectives

The primary safety objectives are:

- The evaluation of all adverse events including device related, procedure related and additional serious adverse events.
- Additional surgical intervention at the operative site including supplemental fixation, revision and/or device removal

All adverse events will be documented on a continuous basis and reviewed by K2M Clinical Research Staff. Information regarding all device failures including implant breakage, subsidence, migration, or expulsion will be captured.

5.2.1 Device and Procedure Adverse Events

Device and procedure adverse events will be documented and reported to the sponsor, including the need for removals, revisions, re-operations or supplemental fixation required to modify the device.

5.3 Secondary Objectives

Secondary objectives are expected to further define the safety and patient outcomes for effectiveness of the K2M device. Secondary objectives include:

5.3.1 Oswestry Disability Index

The Oswestry Disability Index (ODI) is one of the principal condition-specific outcome measures used in the management of spinal disorders. The ODI is the most commonly used outcome measure in patients with low back pain. It has been extensively tested, showed good psychometric properties, and applicable in a wide variety of settings. This patient-reported outcome measure is a 10 item questionnaire that evaluates disability and functional impairment associated with back problems. This validated instrument includes items that relate to subjective symptomatology and activities of daily living (pain intensity, personal care, lifting, walking, sitting, standing, sex life, traveling). Each item is scored from 0 up to 5, with higher scores corresponding to greater disability. A total ODI score is determined by adding the scores of the individual questions and dividing that total by the maximum possible score (i.e., 50 if all questions are answered) to yield a percentage. Therefore, the ODI score ranges from 0% to 100%.

5.3.2 Visual Analog Scale

The severity of back, hip/buttock, and leg pain will each be evaluated in all study subjects using a 10-cm visual analog scale (VAS). The study will employ a 15% improvement for success.

5.3.3 Health-Related Quality of Life

Health-related quality of life will be evaluated in all study subjects using the SF-12v2 Health Survey. This shortened and simplified version of the SF-36 makes the questionnaire less ambiguous for patients. It has a self-administered form that makes it easy to read and complete, and that reduces missing responses. The physical and mental component summary scales, referred to as PCS-12 and MCS-12 will be evaluated against published normative values and a 15% improvement in these scores will be used as an assessment of success.

5.3.4 Radiographic Assessments

Qualitative radiographic assessment of the post-operative AP, lateral and oblique images will be performed by an independent radiologist. Radiographic assessments being performed include, but are not limited to:

- Posterior/Transverse process fusion, Right side (by level)
- Posterior/Transverse process fusion, Left side (by level)
- Anterior fusion, if TLIF procedure done, by level
- Overall fusion by level
- Device Condition
- Device Subsidence
- Device Migration

5.3.5 Patient Satisfaction

At the 12 month and 24 month follow-up visits, subjects will be asked whether they were satisfied with the outcome of their surgery (Yes/No) and whether they would repeat the operation (Yes/No).

5.3.6 Surgery Time

The length of the surgical procedure from the initial incision to final closure will be captured from the Anesthesia Record.

5.3.7 Anesthesia Time

The length of time the patient is under anesthesia will be captured from the Anesthesia Record.

5.3.8 Estimated Blood Loss

The amount of blood loss over the entire length of the surgery, documented on the Anesthesia Record will be captured.

5.3.9 Length of Hospital Stay

The length of hospital stay from the date of admission to the date of discharge will be calculated.

5.3.10 Functional and Economic Status and Return to Work/School

The subject's economic and functional status as well as ability to and the time it takes for the subject to be cleared to return to work/school, as judged by the Investigator, from the date of surgery will be documented. Economic and functional status will be assessed using the Prolo Scale as modified by Voorhies in 2007.[1]

[1] Voorhies RM, Jiang X, Thomas N "Predicting outcome in the surgical treatment of lumbar radiculopathy using the pain drawing score, McGill short form pain questionnaire, and risk factors including psychosocial issues and axial joint pain." Spine J, 2007 7:516–524

5.3.11 Use of Narcotics Post-Surgery

The types and dosages of any narcotics taken by the patient post-surgery will be documented.

6 STUDY ENDPOINT

6.1 Primary Study Endpoint

The endpoint of this study is the fusion status at 24 months.

7 STUDY POPULATION

7.1 Sample Size

A total of two-hundred four (204) total subjects at up to 15 clinical sites, geographically distributed throughout the US, will be enrolled.

7.2 Inclusion and Exclusion Criteria

To be eligible to participate in the study, a subject must meet all of the Inclusion Criteria and none of the Exclusion Criteria.

Inclusion Criteria

1. Diagnosis of spinal stenosis; spondylolisthesis (grade 1 or 2); and/or degenerative disc disease (DDD) with one or two contiguous levels requiring fusion and adjunctive posterior stabilization between L1-S1. Qualified patients will be confirmed for inclusion by patient history and radiographic studies
2. Willing and able to comply with the requirements of the protocol including follow-up requirements
3. Willing and able to sign a study specific informed consent
4. Skeletally mature and ≥ 18 years old at time of enrollment

Exclusion Criteria

1. Previous spine surgery at the index level

(This is not intended to exclude previous microdiscectomies, microlaminotomies and other procedures that do not violate the disc space or that have not destabilized the spine, see also #2.)

2. Previous posterior spine surgery (e.g., posterior decompression) that destabilizes the lumbar spine

(*Previous posterior spine surgery is intended to exclude destabilization at the target levels for the EVEREST surgical procedure. For example, previous laminectomies at the index levels will be excluded*.)

3. Active systemic infection or infection at the operative site
4. Co-morbid medical conditions of the spine or upper/lower extremities that may affect the lumbar spine neurological and/or pain assessment
5. Metabolic bone disease such as osteoporosis and osteopenia that contraindicates spinal surgery
6. History of an osteoporotic fracture
7. History of an endocrine or metabolic disorder (e.g., Paget's disease) known to affect bone and mineral metabolism
8. Taking medications that may interfere with bony/soft tissue healing including chronic steroid use

(*Chronic steroid use is defined as any oral/systemic steroid use (this does not include inhaled, nasal, or topical steroids) for greater than 6 contiguous weeks within 3 months of the date of surgery; and /or >5 mg per day of oral steroids used daily within 2 weeks of the date of surgery.)*

9. Known allergy to titanium or cobalt chrome
10. Rheumatoid arthritis or other autoimmune disease or a systemic disorder such as HIV, active hepatitis B or C, or fibromyalgia
11. Insulin-dependent type 1 or type 2 diabetes

12. Medical condition (e.g., unstable cardiac disease, cancer) that may result in patient death or have an effect on outcomes prior to study completion
13. Pregnant, or intends to become pregnant, during the course of the study
14. Severe obesity (Body Mass Index > 40)
15. Physical or mental condition (e.g., psychiatric disorder, senile dementia, Alzheimer's disease, alcohol or drug addiction) that would interfere with patient self-assessment of function, pain, or quality of life.
16. Involved in current or pending spinal litigation where permanent disability benefits are being sought
17. Incarcerated at the time of study enrollment
18. Current participation in an investigational study that may impact study outcomes

7.3 Study Duration

Study subjects will be expected to participate in this study for 24 months following surgery, with follow-up evaluations at initial post-op, 3 months, 6 months, 12 months, and 24 months.

8 STUDY ENROLLMENT/EVALUATIONS

8.1 Patient Screening and Enrollment

Consecutive patients who potentially meet the study inclusion and exclusion criteria will be screened for eligibility. The screening process will be as follows:

- Consecutive patients are potentially eligible for entry into the study based on their age and whether their medical condition appears to generally fit the characteristics specific to this study.
- Patients who agree to enter the study must sign the approved informed consent form.
- A patient is considered enrolled in the study after signing the IRB approved informed consent. Consented patients complete the remainder of the screening process to confirm study eligibility. Patients who do not fulfill the screening criteria are considered Screening Failures and will be documented on the Screening and Enrollment Log. Screening failures will not count against the total number of subjects eligible for analysis.
- Diagnostic imaging studies (standing x-rays) MUST be completed within 180 days of the planned surgery. For diagnostic purposes, an optional pre-op MRI may also be done, per surgeon's standard of care, but does not serve as a substitute for standing x-rays.
- Subject self-assessment questionnaires must be completed within 90 days of the planned date of surgery.
- Subjects who have signed the informed consent and fulfilled the Inclusion/Exclusion criteria are then scheduled for surgery.
- If study surgery is unable to be completed within 90 days of the date of screening, the patient self-assessment questionnaires must be repeated and the site must assess whether any imaging studies need to be repeated (these must be dated within 180 days of surgery). If any imaging study is outside the screening window and has to be repeated, the subject must be exited from the study, re-consented, and assigned a new Subject ID number for re-screening. The Screening Log will provide a means to identify the original Subject ID number for any subjects who are rescreened.

If, after qualifying for the study and before surgery, the subject experiences a significant change in his/her clinical presentation, the changes should be noted in the source documents and any screening tests and imaging repeated if medically indicated. The patient self-assessment questionnaires must be repeated. This subject need not be re-consented to continue the study if any repeated tests are medically indicated. The subject needs not be exited from the study unless the Investigator believes it is in the subject's best medical interest to do so or that the subject no longer meets the eligibility criteria for the study. The following should be considered when evaluating whether or not the change in clinical presentation is considered significant: an increase in related pain of approximately 3 points (on VAS scale from 0-10), a change in the location of the pain, deteriorating neurological status or other conditions where repeat radiographic studies may be necessary. The objective is to ensure that the patient still meets the eligibility criteria based on the medical judgment of the surgeon.

The Subject ID number will be used to capture de-identified information. For this study, the following standardized format will be used: *Site Identifying Number (2 digits)-Subject Identifying Number (3 digits)*. Your site identifying number will be assigned by the Sponsor, and the subject identifying number should start with 001 and continue accordingly during patient enrollment. For example, if the site identifying number issued to you is Site 03, and you are enrolling your second patient into the study, their Subject ID would be 03-002. A Patient Information Log will be provided to you to keep as a cross reference for study subjects.

8.2 Pre-Operative Evaluation

All subjects will complete the ODI, VAS, and SF-12v2 questionnaires within 90 days prior to the scheduled surgery. All patient questionnaires should be completed during the visit, preferably prior to the patient interacting with the Investigator or other clinical staff. A pertinent medical history will be documented and all subjects will undergo a standard neurological examination including assessments of sensation, motor function, and reflexes.

8.2.1 Pre-Operative Assessment

- Informed consent
- Inclusion/exclusion criteria
- Demographics
- Pertinent history and physical including current symptoms, height, weight, and tobacco use
- Functional, Economic and Work/school status
- Current medication for spine problem
- Neurological Examination
    - AP and Lateral x-rays, (must be completed within 180 days of planned date of surgery)
    - MRI (optional per standard of practice within 180 days of planned date of surgery)
- Oswestry Disability Index; Back, Hip/Buttock, and Leg VAS; and SF-12v2 (within 90 days of planned date of surgery)

8.3 Hospitalization/Surgical Technique/Discharge

Subjects will be admitted to the hospital according to the Investigator's standard for an instrumented posterolateral fusion in conjunction with a TLIF surgery. Prophylactic antibiotics, preoperative planning, patient positioning and anesthesia will be carried out in accordance with the institution's and Investigator's standard of care.

Surgical Approach. The surgeon performs a midline incision and standard posterior exposure to decorticate the transverse processes bilaterally to accommodate graft for the posterior fusion. The spinous processes and interspinous ligaments can usually be left intact, which minimizes epidural scarring and provides a larger surface area for the posterior fusion.

After exposure, the EVEREST Spinal System pedicle screws are placed bilaterally in accordance with K2M's Instructions for Use and Surgical Technique Manual. Fluoroscopy or other strategies may be used to aid in proper screw positioning. Distraction may then be performed using the surgeon's preferred method to open the posterior portion of the disc space, if needed.

Transforaminal Lumbar Interbody Fusion (TLIF). For the TLIF procedure, access to the disc space is gained via a triangular working window. The window is formed by the traversing nerve root and thecal sac on the medial side, the exiting nerve root from the proximal vertebral level on the lateral side, and the superior aspect of the pedicle of the distal vertebra forms the base of the triangle. The surgeon performs a laminotomy, laminectomy and/or facetectomy (partial or total) along with removal of the ligamentum flavum to provide access to the disc space. Care should be taken to preserve the facets as much as possible and remove only enough bone as needed to provide access for introduction of the interbody spacer and to decompress and mobilize the nerve root as necessary. If decompression of the contralateral side of the spinal canal is required, the TLIF procedure can be modified to include a central laminectomy.

After exposure of the posterior aspect of the disc, an incision is made in the annulus through which the discectomy and endplate preparation are performed. Endplate preparation consists of removal of the cartilaginous endplate down to bleeding bone. The interbody spacer (a biocompatible PEEK spacer of the surgeon's choice) is then introduced.

The TLIF approach with the EVEREST Spinal System also allows for auxiliary procedures for decompression of the spinal cord, correction of spondylolisthesis, correction of disc space collapse or mild kypohsis, as may be medically indicated.

Once the interbody implant is in place and bone graft added to the disc space, distraction is released and compression is applied to the pedicle screw to load the anterior implant and restore lordosis to the spine.

Posterolateral/Transverse Process Fusion and use of VESUVIUS Demineralized Fibers. For each level of the posterolateral fusion, local bone (amount used is to be estimated and recorded) is supplemented with VESUVIUS Demineralized Fibers and bone marrow aspirate (BMA)[2]. The Fibers and BMA are to be combined in a 3:2 volumetric ratio (i.e., a minimum of 15cc Fibers and 10ml BMA are required for a one-level case). If BMA volumes are insufficient to achieve a 3:2 ratio, BMA may be supplemented with venous-line blood. The bone graft, extended with a minimum of 15cc VESUVIUS Fibers and 10ml BMA per level, is then evenly distributed to the right and left lateral gutters. Local bone may be obtained from the levels to be fused, as well as from no more than one additional level of decompression above the target level(s).

The interspinous ligament, if preserved, will serve to prevent graft migration into the exposed portion of the spinal canal and foramen. Care must be taken when placing graft on the ipsilateral intertransverse region to avoid allowing graft to enter the spinal canal or compress the exiting nerve root. Before closure, inspect the neurologic elements to ensure that no graft material has fallen into the spinal canal.

[2] Obtained from the anterior iliac crest and/or vertebral body (refer to detailed instructions provided in Appendix 1 of this protocol)

Surgical Close and Recovery. Standard procedures and precautions are to be followed for closure of the surgical incision and postoperative recovery. The patient is typically mobilized out of bed the day after surgery; bracing is not required but can be used according to surgeon preference. The subject may be instructed to return to normal activity at the discretion of the Investigator.

Additional post-operative restrictions may be imposed according to the standard of care normally utilized by the Investigator. In addition, subjects should be instructed to notify the Investigator if experiencing untoward events including but not limited to noticeable pain, numbness, tingling, or weakness that does not decrease with rest, swelling of the lower extremities that does not decrease, or increased pain, erythema, edema or drainage from the surgical incision. The Investigator should then determine if an evaluation is warranted.

A Subject may be withdrawn from the study intra-operatively at the discretion of the Investigator if unexpected findings/occurrences dictate deviation from the intended study procedure. Justification for an intra-operative withdrawal and alternative surgical procedure must be fully documented in the subject's medical record and on the Study Exit case report form.

8.3.1 Surgery/Hospital Discharge Evaluation

Surgery Data – Data points required on the Operative case report form must be documented at the time of surgery, including intra-operative adverse events.

- Date of Hospital Admission
- Date of Surgery
- Date of Hospital Discharge
- Implanting Surgeon
- Implanted System Details (screw and rod size, connector use, etc.)
- Surgery Detail/Concomitant Procedures
- Surgery Time (initial incision to closure)
- Anesthesia Time
- Perioperative Antibiotic Use
- Estimated Blood Loss
- Quantity of VESUVIUS Demineralized Fibers, Bone Marrow Aspirate and Local Bone Used
- Adverse Event Assessment

If the patient experienced an adverse event(s) during the hospitalization it should be documented and recorded on an Adverse Event case report form.

8.4 Post-Operative Follow-Up Visits

All subjects will be required to return for follow-up visits at initial post-op, 3 months, 6 months, and 12 months, and 24 months post-procedure. (A "wound check only" visit does not require data collection unless there is an adverse event. Then this would be captured as an Unscheduled Visit, and an Adverse Event CRF would be completed.)

Data collected at each follow-up visit must be confirmable by source documents and the appropriate case report forms must be completed. All patient questionnaires should be completed at the visit, preferably prior to the patient interacting with the Investigator or other clinical staff. Post-operative follow-up visit requirements are as follows:

8.4.1 Follow-Up Evaluation Data – Post-op through 24 Months

- Functional, Economic and Work/school Status (including release for return to work/school) (initial post-op, 3 month, 6 month, 12 month, and 24 month)
- Current Symptoms (all visits)
- Medication (taken for spine problem since last contact) (initial post-op, 3 month, 6 month, 12 month, and 24 month)
- Neurological Examination (initial post-op, 3 month, 6 month, 12 month, and 24 month)
- AP, Lateral, Oblique and Flex/Ext x-rays (6 month, 12 month, and 24 month)
- Oswestry Disability Index (initial post-op, 3 month, 6 month, 12 month, and 24 month)
- Back, Hip/Buttock, and Leg VAS (initial post-op, 3 month, 6 month, 12 month, and 24 month)
- SF-12v2 (initial post-op, 3 month, 6 month, 12 month, and 24 month)
- Adverse Event Assessment (all visits)
- CT Scan (12 month)
- Patient Satisfaction (12 month, 24 month)
- Study Exit

8.5 Unscheduled Follow-up Evaluation

Subjects may return to the clinic at a time point that is not a scheduled follow-up visit. If the Investigator determines that the return visit is related to the study device, procedure or surgery, the Unscheduled Visit portion of the Post-Operative Follow-Up case report form should be completed. If a subject requires a device or procedure related re-operation including supplemental fixation, revision and/or device removal as a result of an unscheduled visit the Sponsor should be notified immediately and an Adverse Event case report form should also be completed.

8.6 Schedule of Subject Evaluations

Interval → **Assessment ↓**	Pre-op	Operative/ Discharge	Initial F/U (discharge-8 weeks post-op)	3 Month F/U (± 2 weeks)	6 Month F/U (± 1 month)	12 Month F/U (± 2 months)	24 Month F/U (±2 months)	Unscheduled Visit
Informed Consent	X							
Inclusion/Exclusion	X							
Demographics	X							
Pertinent History	X							
Current Symptoms / Complaints & Findings	X		X	X	X	X	X	
Functional, Econ., Work/school Status	X		X	X	X	X	X	
Medications for Spine Problems	X		X	X	X	X	X	
Neurological Examination	X		X	X	X	X	X	
ODI	X		X	X	X	X	X	
Back, Hip/Buttock, and Leg VAS	X		X	X	X	X	X	
SF-12v2	X		X	X	X	X	X	
Patient Satisfaction						X	X	
Hospitalization and Surgery Data		X						
Adverse Event Assessment		X	X	X	X	X	X	X
AP & Lateral x-rays	X				X	X	X	If needed
Flex/Ext x-rays					X	X	X	
Oblique (right, left) x-rays					X	X	X	
CT Scan						X		
Study Exit							X	

8.7 Pregnancy During Study Participation (as appropriate)

If a subject becomes pregnant during the study, the sponsor should be notified as soon as possible. The subject will remain in the study, but during the pregnancy the study follow-up visit(s) will be modified to exclude the X-ray imaging requirements. At follow-up visits after the pregnancy, the required X-rays should again be performed. Information related to the pregnancy and outcome should be maintained by the site and documented by the Sponsor in monitoring reports during periodic visits.

8.8 Protocol Deviations

The Protocol must be followed closely, and the Investigators should not deviate from the protocol unless in the opinion of the Investigator a deviation from the protocol is in the best interest of safety for the subject. A deviation from the protocol should be reported to the sponsor as soon as possible after the deviation is noted. In addition, during routine monitoring visits the monitor may determine a protocol deviation and initiate the protocol deviation process. All protocol deviations must be documented on a Protocol Deviation case report form. For the scientific integrity of the study, protocol deviations must be kept at a minimum. If the site has an unacceptable number of protocol deviations that cannot be explained due to patient safety, the issue will be discussed with the site and corrective action will be considered.

In the event a patient questionnaire is not completed during a visit, permission may be obtained from the Sponsor to have the questionnaire mailed into the site within a reasonable amount of time.

8.9 Subject Lost to Follow-Up

Every attempt will be made to have all subjects complete the follow-up visit schedule as specified in the protocol. A subject will not be considered lost to follow-up unless efforts to obtain compliance are unsuccessful. If a subject misses a follow-up visit, the site must document attempts to contact the subject by phone twice. If both contact attempts are unsuccessful, a certified letter from the Investigator must be sent to the subject's last known address indicating the subject's commitment to the study and site contact information to arrange a visit. If the subject does not respond, only then will the subject be considered lost to follow-up. If a subject is lost to follow-up, a Study Exit case report form, including a full description of the attempts to locate the subject, must be completed.

8.10 Subject Withdrawal

Subjects have the right to withdraw their consent at any time during the study. If a subject requests to withdraw from the study, all information regarding the subject's withdrawal and disposition must be recorded in the subject's medical record. A Study Exit case report form, including a full description of the circumstances related to the withdrawal, must be completed.

8.11 Study Case Report Forms

The Sponsor will provide Case Report Forms (CRFs) to the sites for the study. Visit or evaluation specific as well as additional CRFs to complete as needed are included. Data should be entered with a black pen on the specified locations of the CRFs. If an error is made on a CRF, the incorrect entry should be crossed out with a single horizontal line, the correct entry written next to it, and the correction initialed and dated by the person making the correction. Copies of the CRFs for the study are included as an appendix to the protocol.

List of Case Report Forms

- Inclusion/Exclusion
- Pre-operative
- Operative/Discharge
- Follow-up form covering:
  - Initial Post-Op Follow-up Visit (discharge to 8 weeks post-op)
  - 3 Month Follow-up Visit ± 2 weeks

  - 6 Month Follow-up Visit ± 1 month
  - 12 Month Follow-up Visit ± 2 months
  - 24 Month Follow-up Visit ± 2 months
  - Unscheduled Visit
- Subject Questionnaires including Oswestry Disability Index; Back, Hip/Buttock, and Leg Visual Analog Scale (VAS); SF-12v2; and Patient Satisfaction
- Adverse Event
- Protocol Deviation
- Study Exit

9 ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event

An Adverse Event (AE) is defined as any untoward medical occurrence in a subject undergoing surgery in this trial which does not necessarily have a causal relationship with this intervention. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the one of the devices, whether or not the event is considered causally related to the use of the device. Any worsening of a pre-existing condition or illness is considered an AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention that could impact the study's surgical outcomes, and/or if the Investigator considers them to be AEs.

9.1.2 Serious Adverse Event

Any AE that results in one or more of the following is considered a Serious Adverse Event (SAE): death, life threatening situation, inpatient hospitalization, persistent or significant disability/incapacity, and other medically important events. Definitions of SAEs are:

Death: the subject dies during participation in the study.

Life threatening situation: the subject is at risk of death at the time of the event, but does not refer to the hypothetical risk of death if the AE were more severe or were to progress.

Inpatient hospitalization: a subject requires hospitalization or prolongation of an existing hospitalization, including medical or surgical intervention to prevent permanent impairment to a body structure or body function during participation in a clinical study.

Persistent or significant disability/incapacity: any AE having an outcome that is associated with a substantial disruption of the ability to carry out normal life functions. This includes the inability to work, but is not intended to include transient interruptions of daily activities.

Other medically important events: important medical events that may not result in death, be life-threatening, or require hospitalization (including emergency room visits) but may be considered a serious AE when, based upon medical judgment, they may jeopardize the subject.

Reports of all Serious Adverse Events (SAEs), as classified by the Investigator, will be reviewed on a periodic basis by the Medical Monitor.

9.1.3 Subsequent Surgical Interventions

The cause for subsequent surgical interventions should be listed as a serious adverse event.

Subsequent surgical interventions are classified as follows:

Revision: a procedure that adjusts or in any way modifies the original implant configuration. A revision may also include adjusting the position of the original configuration.

Removal: a procedure where all of the original system configuration are removed with or without replacement.

Supplemental Fixation: a procedure in which additional instrumentation not under study in the protocol is implanted.

Reoperation: any surgical procedure at the involved level that does not require removal, modification, or addition of any components to the system.

9.2 Adverse Event Reporting

Any AE that occurs during the subject's participation in the study will be recorded on the Adverse Event case report form. Pre-existing medical conditions or symptoms occurring prior to the initiation of the study will not be reported as AEs but a worsening of a pre-existing medical condition or symptom will be reported as an AE. Pain, neurological status and functional impairment should be considered AEs when a subject's complaint for any of these symptoms results in an unscheduled visit or when a subject presents with new or worsening symptoms as compared to a previous visit.

All AEs will be followed until the event is resolved or considered to be stable. Relevant source documentation must be available to confirm the occurrence of an AE and must be provided to the sponsor upon request.

9.2.1 Serious Adverse Event Reporting

Independent of the relationship to the study device or procedure, the site must report SAEs to the Sponsor immediately upon becoming aware of the events and subsequently submit the appropriate CRFs within 10 working days. SAEs will be investigated and reported to the FDA if they fall within the appropriate guidelines for Medical Device Reporting (MDR). The site must also report SAEs to the reviewing Institutional Review Board (IRB) according to IRB requirements.

The site must confirm the SAE in appropriate source documents and provide detailed information pertaining to the event to the sponsor and reviewing IRB if requested.

9.3 Adverse Event Severity

The Investigator will be asked to characterize the severity of each AE as mild, moderate or severe. The assessment is subjective and the Investigator will use medical judgment to compare the reported AE to similar types of events observed in clinical practice. Guidelines for AE severity assessment are as follows:

Mild: The AE is transient and easily tolerated by the subject. No medical treatment required.

Moderate: The AE causes the subject discomfort and interrupts the subject's usual activities. Medical treatment required to alleviate or lessen the impact of this untoward condition.

Severe: The AE causes considerable interference with the subject's usual activities may be incapacitating and may require hospitalization. See **Section 9.1.3 Serious Adverse Events**.

9.4 Adverse Event Association

The relationship of all AEs to the device, the procedure or general surgery will be classified by the Investigator as not related, possibly related, probably related or definitely related.

Not related: The AE is due to an underlying or concurrent illness or effect of another device, drug or intervention and is not related to the study device, procedure or general surgery.

Possibly related: The causal and/or temporal relationship to the study device, procedure or general surgery, is equally or less likely than other plausible explanations.

Probably related: The causal and/or temporal relationship to the study device, procedure or general surgery, is likely or significantly more likely than other plausible explanations.

Definitely related: A clinical event that can only be attributed to the device, procedure or general surgery.

9.5 Potential Risks and Anticipated Adverse Events

9.5.1 General Surgery Risks

General surgical risks are but may not be limited to:

- Airway obstruction
- Anaphylaxis

- Anesthesia related
- Atelectasis
- Blood clots, including pulmonary emboli
- Cardiac arrest
- Cardiac, other
- CVA
- Death
- Decompensation
- Deep vein thrombosis
- Epidural fibrosis
- Epidural hematoma or bleeding
- Excessive blood loss
- Hemorrhage, possibly requiring blood transfusion
- Infection, deep wound
- Infection, superficial wound
- Infection, urinary tract
- Infection, other
- Myocardial infarction
- Phlebitis
- Pleural effusion
- Pneumonia
- Pneumothorax
- Poor tissue healing
- Retained sponge
- Septicemia
- Suture abscess
- Transfusion reaction
- Vascular or blood vessel injury
- Wound dehiscence

9.5.2 Posterior Fusion Surgery Risks

Posterior Fusion surgical risks are but may not be limited to:

- Allergic reaction to the implant/retractor materials
- Bowel and bladder dysfunction
- Disc height loss
- Dural tear, with or without CSF leak
- Dysesthesia or numbness
- Erosion due to implant
- Failure to relieve symptoms including unresolved pain
- Foreign body reaction
- Kyphosis or hyperextension
- Loss of spine flexibility
- Muscle and tissue injury or damage
- Nerve injury
- Nerve root injury
- Osteolysis
- Pain, new onset
- Pain, unresolved
- Paralysis
- Pseudoarthrosis
- Sexual dysfunction
- Spinal cord damage
- Spinal degradation
- Spinous process fracture
- Surgical intervention at incorrect level
- Thigh pain
- Tingling
- Vertebral body fracture
- Weakness

9.5.3 K2M Device Risks

Risks specific to the VESUVIUS Demineralized Fibers and EVEREST system are but may not be limited to:

- Bone graft migration
- Bone graft subsidence
- Device instability
- Device malposition
- Device migration
- Device subsidence
- Disengagement – from bone
- Disengagement – screw/rod interface
- Foreign body reaction
- Hook/rod interface disengagement
- Material degradation
- Prominent implants
- Rod breakage
- Screw back-out
- Screw breakage
- Screw/rod interface slide
- Set screw loosening

10 SITE REGULATORY REQUIREMENTS

10.1 Institutional Review Board (IRB) Approval

Prior to enrolling subjects in the study, site IRB approval must be obtained according to 21 CFR Part 56. IRB approval must be maintained by the site throughout the study. The IRB approval letter(s) must be maintained in the study files at all times.

10.2 Study Specific Informed Consent

A study specific sample informed consent will be provided to each site prior to the IRB process. The sample informed consent should be used as a template for creating the IRB specific informed consent. Prior to submission of the proposed informed consent to the reviewing IRB, the Sponsor must review the informed consent for completeness according to the protocol and according to 21 CFR Part 50. Potential study subjects should be offered informed consent according to the process outlined in **Section 8.1, Patient Screening and Enrollment**.

Patients must not be offered informed consent until written proof of IRB approval is attained. The patient should be given the opportunity to take home a copy of the informed consent to review and discuss with family members or acquaintances prior to signing. Potential study subjects must also be given the opportunity to discuss the procedure, risks, benefits, alternative treatments and study requirements prior to signing the informed consent. Patients should be informed that they are free to refuse participation in this study and refusal will not affect their medical treatment. If patients elect to participate, it should be made clear that they may withdraw from the study for any reason and at any time without prejudicing further care.

A copy of the signed and dated IRB approved informed consent should be given to all subjects.

10.3 Regulatory Documents

Prior to patient enrollment, the following documents must be provided to the Sponsor and be on file at the site:

- Curriculum vitae and copy of medical license for Principal and Sub-Investigators
- IRB approval letter and IRB roster
- IRB approved Informed Consent Form
- Signed Clinical Research Agreement
- Signed Investigators agreement for Principal and Sub-Investigators, as required
- Finalized budget agreement
- Financial disclosures for the Principal and Sub-Investigators
- Site Initiation documentation

11 SITE VISIT/MONITORING PROCEDURES

Monitoring of the study will be a continuous process conducted in accordance with 21 CFR 812.46 and applicable Sponsor procedures. Monitoring will be performed by qualified clinical research personnel, or designees, of K2M.

11.1 Site Qualification Visit

Prior to selecting an Investigator for participation in the study a Qualification visit will be performed. The purpose of the visit is to confirm that the Investigator/investigative site has adequate staff, including a designated Study Coordinator, and facilities to perform the study according to the requirements of the protocol.

11.2 Study Initiation Visit

Prior to enrolling subjects at a study site, a Site Initiation Visit will be performed. The purpose of the visit is to confirm that the site continues to be qualified for participation and to review the Investigator/site responsibilities and requirements for the study. Site training will be performed and will include:

- Review of the clinical protocol and data collection process
- Monitoring requirements
- IRB requirements
- Informed Consent process
- Review of site records

11.3 Periodic Monitoring Visits

Periodic site monitoring visits will be performed during the study by a designated study monitor assigned by the Sponsor. The purposes of the visits are to confirm compliance to the protocol, review regulatory documents, accurate and complete records are being maintained and to compare source documents to completed CRFs for completeness and consistency. The initial monitoring visit to a site will be scheduled soon after the first 2 to 5 patients are enrolled in the study and may occur prior to the first surgery. The frequency of subsequent visits will be dependent upon the rate of enrollment and site performance on previous monitoring visits. If possible, monitoring visits will be performed at least quarterly. Specific assessments during a monitoring visit include:

- Continued site acceptability
- Compliance to the protocol
- IRB approval status
- Use of the approved informed consent
- Adequacy of source documents
- Complete and accurate CRFs
- Reporting of adverse events
- Protocol deviations
- Site records

If it is determined during a monitoring visit that there are significant non-compliance issues at a site, including adherence to the protocol or applicable regulatory requirements, the issues will be discussed with the Investigator and Study Coordinator and the site will be instructed how to gain compliance. If continued non-compliance is detected on a subsequent monitoring visit, it may be necessary to terminate site participation in the study.

11.4 Final Close-Out Visit

At the completion of the last long-term follow-up visit at each site a final close-out visit will be performed. The purpose of the visit will be to:

- Reconcile all outstanding data queries
- Review site records
- Review the records retention requirements for the study
- Review the final IRB requirements for the study

12 STATISTICAL METHODS

12.1 Study Design

Prospective, single arm, multi-center study with historical controls to evaluate radiographic and clinical outcome variables of the VESUVIUS Demineralized Fibers and the EVEREST Spinal System compared to literature reported outcomes for patients with spinal stenosis, spondylolisthesis, and/or degenerative disc disease treated using traditional autograft with posterior stabilization. Subjects undergoing fusion with the VESUVIUS Demineralized Fibers and the EVEREST Spinal System may also receive an interbody spacer (using the TLIF technique) based on the physician's standard of care.

12.2 Study Hypotheses

The primary study endpoint is the rate of fusion at 24 months. The primary hypothesis of this trial is that the fusion rate with the VESUVIUS Demineralized Fibers and the EVEREST Spinal System combination is non-inferior to the fusion rate achieved and reported with the traditional fusion utilizing autograft and posterior stabilization.

A PubMed literature review was conducted to assemble relevant publications utilizing results from posterior fusion surgeries incorporating osteobiologics. Searches included all peer-reviewed journals published between January 2000 and April 2013. Sample sizes, patient populations, evaluated variables, results, and recorded complications were assessed for each selected article. Only articles describing the use of autograft in comparable patient populations were incorporated into the results. The following table gives the fusion rates found during the literature review:

Papers*	Number of Cases	Number of Fusions	Fusion Rate
Paper 1[1]	81	44	54.3%
Paper 2A[2]	39	34	87.2%
Paper 2B	35	29	82.9%
Paper 3[3]	36	15	41.7%
Paper 4[4]	45	33	73.3%
Paper 5A[5]	21	19	90.5%
Paper 5B	22	20	90.9%
Paper 6A[6]	10	10	100.0%
Paper 6B	10	10	100.0%
Paper 7A[7]	47	44	93.6%
Paper 7B	48	42	87.5%
Paper 8A[8]	42	31	73.8%
Paper 8B	42	24	57.1%
Pooled	478	355	74.3%

* Refer to Appendix 2 for references

A total of 355 successes in 478 subjects gives an overall fusion rate of 74.3%. The hypotheses to be tested for this primary endpoint are as follows:

H_O: $P_{K2M} \leq P_0 - \delta$
H_A: $P_{K2M} > P_0 - \delta$

where P_{K2M} is the success rate of the VESUVIUS Demineralized Fibers and the EVEREST Spinal System combination, P_0 is the literature success rate of 74.3% and δ is the non-inferiority margin of 10% against the historical success rate.

12.3 Sample Size

A total sample size of 204 was selected for the study. Assuming the actual fusion success rate of the VESUVIUS Demineralized Fibers and the EVEREST Spinal System combination is the same as the historical rate (74.3%) and using a one-sided 0.05 exact binomial test to evaluate the hypothesis in section 12.2 (H_0: $P_{K2M} \leq 0.643$), a sample size of 173 provides >80% power. To account for 15% drop out, one will need a sample size of 172. However, the sample size was increased to 204 to account for safety considerations. A sample size of 204 provides >80% power to see at least one serious adverse event that occurs in 0.8% of the population and 87% power to see a serious adverse event that occurs in 1.0% of the population. Thus, a sample size of 204 provides reasonable assurance that an uncommon serious adverse event would be seen in the study should one exist.

Subject enrollment will be capped so that no single site contributes more than approximately 15% of the cases.

12.4 Analysis Populations

Analysis Populations are defined as follows:

- The Intent-to-Treat (ITT) population includes all enrolled subjects.
- The Per-Protocol population includes all enrolled subjects who have no major protocol violations (defined as not meeting inclusion/exclusion criteria or not being consented properly).

The fusion analysis will be performed on the ITT population. Analysis of the per-protocol population will be confirmatory of the ITT analysis. The safety analysis will be performed on the ITT population.

12.5 Analysis of Primary Endpoint

The primary study endpoint will be evaluated by a one-sided exact test of the VESUVIUS Demineralized Fibers and the EVEREST Spinal System combination success rate against the literature success rate of 74.3% with a non-inferiority margin of 10% at a significance level of 0.05. If the lower bound to the exact one-sided 95% Confidence Interval of the VESUVIUS Demineralized Fibers and the EVEREST Spinal System combination success rate is greater than 64.3%, the primary endpoint will have been met.

12.6 Safety Analyses

Incidence rates of adverse events will be provided descriptively in tabular form for each study groups for the overall adverse event rate, serious adverse event rates, revision rates, removal rates, etc. at each follow-up interval.

12.7 Supplementary Analysis

Other ancillary variables such as demographics, baseline variables, surgical variables and post-op pain medication usage will be summarized by mean, standard deviation, median (if appropriate), and range for continuous measures, and frequency and percent for categorical measures. Descriptive statistics and graphical methods such as bar graphs, box and whiskers plots, and star plots may be employed to compare subjects' clinical outcomes to baseline values (pre-operative) and the prospective and historical study groups simultaneously for multiple variables.

Descriptive statistics or graphical methods will also be used to explore the impact of any covariates of interest, e.g., presence or absence of anterior spacer on the prospectively collected outcome data.

12.8 Methods to Minimize Bias

This trial includes several well-validated patient-reported outcome measures (i.e., ODI, VAS, and SF-12v2). When providing follow-up self-reports of these outcomes, subjects will remain blinded to their previous responses on these instruments so as to not bias their current reports. With respect to the SF-12v2, previously published validation studies have shown that the results of this instrument, particularly the physical functioning domains, are not substantially affected by non-specific study effects such as placebo. When conducting follow-up neurological examinations, every effort will be made to blind the investigators to the ratings provided at earlier

intervals. Investigational sites will be restricted from enrolling more than approximately 15% of the study cohort. Radiographic evaluations will be conducted by an independent central radiologist.

We will evaluate the subjects from each site to assess poolability of the data. Sites will be examined for adherence to the requirements of the protocol, baseline demographic and relevant clinical characteristics.

13 SITE RESPONSIBILITIES

13.1 Investigator

Principal Investigators selected by K2M to participate in this clinical study assume overall responsibility for the performance of the study at the site.

Specifically, the Investigator will assume the overall responsibility for:

- Obtaining IRB approval
- Conducting the study according to the clinical protocol and applicable, federal, state and local regulations and the signed Clinical Research Agreement
- Providing financial disclosure according to federal regulations
- Proper execution of the approved informed consent
- Protecting the rights, safety and welfare of study subjects
- Appropriate source documents to verify study data
- Reviewing and signing all CRFs for subjects enrolled in the study
- Oversight and training of site staff given study related responsibilities

13.2 Study Coordinator

The Study Coordinator is designated by the Investigator to assume site management responsibilities. Specifically, the Study Coordinator is responsible for:

- Managing the IRB submission and approval process
- Managing study activities according to the clinical protocol and applicable, federal, state and local regulations and the signed Clinical Research Agreement
- Ensuring proper execution of the approved informed consent
- Protecting the rights, safety and welfare of study subjects
- Maintaining appropriate source documents to verify study data
- Ensuring that CRFs are complete, reviewed and signed by the Investigator at the completion of patient contacts and before scheduled monitoring visits
- Management of additional staff members given study related responsibilities

If the Investigator designates a replacement Study Coordinator at any time during the performance of the study, the Sponsor must be notified immediately. A Sponsor designee will arrange to visit the site as soon after the notification as is feasible to ensure that the replacement Study Coordinator has the ability and is adequately trained to function in that capacity.

14 RECORDS AND REPORTS

All Sponsor and site records may be subject to regulatory inspection and must be retained for a period of 2 years following, a) the date the investigation is completed or terminated, or b) the records are no longer required to support a regulatory submission, whichever is longer. The Sponsor will notify the site in regard to length of record retention at the completion of the study.

14.1 Investigator/Site Records

Investigator/site records must be maintained and updated as necessary. Records will be reviewed during the site initiation visit and on subsequent monitoring visits to ensure adequacy and completeness of records. Investigator/site records include, but may not be limited to:

- Original and all subsequent IRB approval letters
- Original and all subsequent (if applicable) approved informed consents
- IRB Roster
- IRB updates/reports as required by reviewing IRB
- Final protocol and subsequent (if applicable) protocol amendments
- Other required reports
- Relevant correspondence between the Investigator, IRB and K2M
- Signed Clinical Research Agreement
- Investigators Agreement for Principal and Sub-Investigators, as required
- Financial Disclosure Documents
- Copies of Curriculum Vitae for the Investigator and Sub-Investigators
- Site Signature & Responsibility Log
- Site Monitoring Log
- Signed Informed Consents
- Completed Case Report Forms

14.2 Investigator/Site Reports

The Investigator/site is responsible for the preparation and submission of reports to the Sponsor, IRB and applicable Regulatory agencies. The following reports are required:

Serious Adverse Events: Submitted to the Sponsor within 10 working days of first learning of the event and to the reviewing IRB as required

Withdrawal of IRB approval: Sponsor must be notified within 5 working days

IRB Updates/Reports: Submitted to the reviewing IRB as required

Failure to Obtain Informed Consent: Submitted to the Sponsor and reviewing IRB within 5 working days after realizing the failure

Final Report: Submitted as required to the reviewing IRB

14.3 Sponsor Records

The Sponsor will maintain site specific study files including:

- Copy of the original and all subsequent IRB approval letters
- Copy of the original and all subsequent (if applicable) approved informed consents
- IRB Roster
- Copy of IRB updates/reports as required by reviewing IRB
- Other required reports
- Relevant correspondence between the Investigator, IRB and K2M
- Signed Clinical Research Agreement
- Investigators Agreement for Principal and Sub-Investigators, as required
- Clinical Research Agreement and Investigators Agreement template, as applicable
- Financial Disclosure Documents
- Copies of Curriculum Vitae for the Investigator and Sub-Investigators
- Copies of site approved recruitment and patient information documents
- Site Initiation Report
- Site Monitoring Reports
- Completed Case Report Forms

In addition, the Sponsor will maintain a Study Central File including, but not limited to:

- Final protocol and subsequent (if applicable) protocol amendments
- Investigator agreement template
- Master recruitment and patient information documents (if applicable)
- Composite listing of adverse events
- Data and data analysis
- Interim (if applicable) and final summary

14.4 Sponsor Reports

The Sponsor is responsible for the preparation and submission of reports to the site and applicable Regulatory agencies. The following reports are required:

Serious Adverse Events: Submitted to the FDA only if they meet the requirements for MDR reporting

Final Report: Submitted to all sites upon completion of the study and final data analysis

Reports not listed may be made by the Sponsor to Regulatory agencies and to the sites if additional notifications are necessary.

15 PUBLICATION POLICY

Data resulting from the conduct of this study are considered confidential information. Abstracts, book chapters, peer-reviewed manuscripts and other publications (all of which are "Publications") resulting from the study can originate from the Sponsor or from Investigators participating in the study; provided, however, any Publications shall be governed by and in compliance with the terms of Section VIII of the Clinical Evaluation Research Agreement.

APPENDIX 1 – Bone Marrow Aspiration & Hydration of VESUVIUS Demineralized Fibers

NOTE: VESUVIUS Fibers are packaged in quantities of 2, 5, 15, and 30 cc; use this to help estimate the volume of local bone used

Bone marrow aspiration from the **posterior or anterior iliac crest** is performed as follows:

1. Locate site for aspiration of bone marrow.
2. Using sterile technique, prepare surgical site and anesthetize the area.
3. With a scalpel, make incision in the skin above the area from which the bone marrow is to be aspirated.
4. Hold needle with proximal end in palm and index finger against the shaft near the tip. This position stabilizes the needle and enhances needle control.
5. Introduce needle through prepared incision site.
6. Use gentle, but firm pressure to advance the needle. Rotate needle in alternating clockwise-counterclockwise motion, or gently tap the needle handle with a mallet. In general, decreased resistance is encountered upon entrance into the marrow cavity.
7. Remove stylet by rotating upper section of handle and pulling stylet straight out.
8. Screw the distal end of the included syringe into the proximal hub of the bone-marrow aspiration needle. Ensure a firm fit, but do not over-tighten.
9. Apply suction by withdrawing syringe plunger to draw bone marrow asparite (BMA) into the syringe. NOTE: If using a multi-fenestrated bone-marrow aspiration needle, withdraw no more than 10ml BMA from each harvest site. If using a non-fenestrated bone-marrow aspiration needle, withdraw no more than 2ml BMA from each harvest site.
10. VESUVIUS Demineralized Fibers graft material and BMA should be combined in a 3:2 volumetric ratio (approximately 15cc Fibers and 10ml BMA required for a one-level case). Supplement the BMA with venous-line blood if BMA volumes are insufficient to achieve a 3:2 ratio. NOTE: A 1:1 ratio of Fibers:BMA tends to yield an overly wetted final graft construct. This mixture is added to extend local bone for grafting.
11. Disengage syringe containing the aspirated bone marrow and immediately transfer the aspirated bone marrow from the syringe onto the VESUVIUS Demineralized Fibers. Dispose of the needle in accordance with applicable laws and regulations.

Marrow aspiration from the **vertebral body** is performed as follows:

1. Access the vertebral body via transpedicular technique.
2. Use gentle, but firm pressure to advance the needle through the pedicle into the vertebral body. Rotate needle in alternating clockwise-counterclockwise motion, or gently tap the needle handle with a mallet. In general, decreased resistance is encountered upon entrance into the marrow cavity.
3. Remove stylet by rotating upper section of handle and pulling stylet straight out.
4. Screw the distal end of the included syringe into the proximal hub of the bone-marrow aspiration needle. Ensure a firm fit, but do not over-tighten.
5. Apply suction by withdrawing syringe plunger to draw bone marrow aspirate (BMA) into the syringe. NOTE: If using a multi-fenestrated bone-marrow aspiration needle, withdraw up to 8ml BMA from each pedicle (16ml total from each vertebral body). If using a non-fenestrated bone-marrow aspiration needle, eight discrete 2ml aspirations can be harvested from each vertebral level – four

from the right and four from the left pedicle, using a coaxial transpedicular technique. Collect aspirates from each of four vertebral depths, one at the superficial depth just beyond the origin of the pedicle from the back of the vertebral body (30mm) and the others from the subsequent depths of 35mm, 40mm, and 45mm of cannula insertion. This technique will yield up to 16ml of bone-marrow aspirate from each vertebral body.

6. VESUVIUS Demineralized Fibers graft material and BMA should be combined in a 3:2 volumetric ratio (approximately 15cc Fibers and 10ml BMA required for a one-level case). Supplement the BMA with venous-line blood if BMA volumes are insufficient to achieve a 3:2 ratio. NOTE: A 1:1 ratio of Fibers:BMA tends to yield an overly wetted final graft construct. This mixture is added to extend local bone for grafting.
7. Disengage syringe containing the aspirated bone marrow and immediately transfer the aspirated bone marrow from the syringe onto the VESUVIUS Demineralized Fibers. Dispose of the needle in accordance with applicable laws and regulations.

APPENDIX 2 – SAP References

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