VTI InterFuse® S vs. InterFuse® T for the treatment of scoliosis and degenerative disc disease: protocol for a multicenter post-market study

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Background and objectives: VTI InterFuse® S and InterFuse® T are the interbody fusion devices used in spinal fusion procedures to relieve the pain of patients with scoliosis and degenerative disc disease through maintaining foraminal height and decompression. The aim of this study is to investigate the therapeutic effects of the VTI InterFuse® S and InterFuse® T on scoliosis and degenerative disc disease.

Design: A prospective, two-arm, multicenter, post-market trial.
Methods: A total of 200 eligible patients (18–19 years old) with scoliosis and/or degenerative disc disease and a planned fusion of at least 5 levels were recruited from 10 clinical sites. The patients will be assigned to receive T interbody fusion treatment with the InterFuse® S or InterFuse® T interbody fusion devices.
Outcome measures: The following outcome measures will be observed during 24-month follow-up: interbody fusion assessed by CT scan (primary outcome measure), and Visual Analog Scale and Oswestry Disability Index, and the Scoliosis Research Society Outcomes Instrument scores (secondary outcome measures).
Discussion: This study will provide direct evidence for the intelligent use of VTI InterFuse® S and InterFuse® T interbody fusion devices in the treatment of scoliosis and/or degenerative disc disease.

Ethics and dissemination: The study will receive approval from the institutional review board at each site and will be conducted in accordance with the ethical principles of the Declaration of Helsinki. Results will be presented at national and international meetings and submitted for publication to peer-reviewed journals.


Keywords: clinical trial; interbody infusion; interbody infusion device; scoliosis; degenerative disc disease; post-market study

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INTRODUCTION

Since the spine is a cooperative system of elements, it follows that altering the structure and mechanics at one location could significantly increase stress at adjacent disc levels, leading to a progression of disc degeneration (See Figures 1 and 2).

Early in the degenerative process, most patients will “self prescribe” treatments such as non-prescription pain medications, rest, heat or bracing to reduce pain and allow

Strengths and limitations

• This trial will be the first prospective post-market study on the two types of interbody infusion devices VTI InterFuse® S and InterFuse® T.
• Small sample size.
• Non-randomized trial design may increase the risk of bias in study results.
healing. Those that seek medical attention in the early stages of their disease may receive any of the above plus stronger medications including oral or epidural cortisone, physical therapy, chiropractic care and other conservative non-operative treatments.

If conservative treatment does not relieve the patient’s pain, the surgeon may progress to one of two main types of surgical methods: decompression and fusion.

Decompression is performed to relieve pressure on nerve elements by excision of disc material, or removing bone that is compressing a nerve. In the traditional posterior approach, open discectomy surgery requires removal of a small portion of lamina and ligament with an incision into the posterior annulus. Discectomy techniques are usually successful in relieving radicular pain caused by a herniated disc. However, such surgery alone is unable to restore the nucleus to its original load sharing capacity and makes long-term results more questionable. Ultimately, progressive disc narrowing, increased compressive stress on the annulus, advanced degeneration and spinal stenosis may evolve over the years after the surgery.

Spinal fusion is performed to stop the motion of a painful vertebral motion segment, which in turn should decrease or eliminate the pain generated from this area. Eighty percent of the axial force on the spine is transmitted across the vertebral bodies while twenty percent is transmitted by the posterior elements (facet joints). Thus, anterior column support and stability are critical in obtaining a successful fusion. Fusion is typically achieved by several methods all of which include the use of bone graft material with or without some form of interbody implant. A common procedure is to use pedicle fixation devices in conjunction with interbody fixation devices to attain fusion. The science behind spinal fusions continues to evolve. Many procedures have become minimally invasive, and make use of new technologies, which in turn reduce hospital stays and improve patient outcomes.

Scoliosis – In some adult patients the degenerative process progresses to produce scoliosis or a medial/lateral curvature of the spine when viewed from the back. Some of these adult deformity patients have a congenital tendency toward scoliosis while others develop scoliosis secondary to trauma, degenerative changes or osteoporotic fractures (Figure 3). While scoliosis may not be painful, many of these adult deformity patients develop neuro compressive symptoms that result in significant back and/or leg pain. Interrupting this degenerative process and relieving their pain often requires multi-level surgery resulting in a long fusion construct. Extending the long fusion construct to the pelvis requires a strong base at the L₅–S₁ and L₄–₅ levels. With 80% of the axial forces on the spine normally transmitted across the vertebral endplates a congruent, large footprint interbody device with maximal endplate contact is biomechanically necessary to optimize the successful reconstructive process. The basic premise of this study is that a large footprint posterior interbody fusion device will provide superior fusion and stability results at the base of a long fusion construct.
Primary endpoints for the study will be:

- Fusion
- Subsidence
- Migration
- Hardware loosening
- Disc height pre- & post-instrumentation
- Lordosis restoration

Secondary endpoints for the study will be:

- Visual analog scale (VAS) scores
- Scoliosis Research Society (SRS-22) Outcomes Instrument scores
- Length of stay
- Re-admission rate
- Re-operation rate

Study objectives
The primary objective of this prospective, post-market study is to collect data to assess the long term outcome of a broad contact modular interbody device in the form of the InterFuse® S and InterFuse® T device in patients undergoing long construct fusion for degenerative disc disease (DDD) and/or scoliosis. While there is no concurrent control population, there is ample historical control data to be used for comparison.

Methods/Design

Study design
This is a prospective, two-arm, multicenter, post-market trial. The study will include 200 patients recruited from 10 clinical sites, and provide a prospective evaluation of the InterFuse “T” and/or InterFuse “S” Interbody Fusion System. Primary endpoints will be assessed at 12 and 24 months post-surgery. All patients enrolled in the study will be followed for 24 months.

Site selection
The investigational sites selected to participate in this study will be dependent on the investigator at each site having the necessary resources to fulfill the clinical research requirements outlined in the protocol. These resources include adequate patient population and facilities and support staff to perform the clinical evaluation according to all applicable requirements.

Investigator selection
The investigators selected to participate in this study are qualified orthopaedic or neurosurgeons experienced in spine surgery. The investigator will be required to sign an Investigators Agreement (Additional file 1) detailing their responsibility in the study including obtaining institutional review board (IRB) approval for the study, adherence to the protocol and all relevant regulations, and any relevant IRB requirements.

If the investigator is found by the sponsor to be non-compliant, appropriate action will be taken immediately to obtain compliance to the approved protocol. If non-compliance remains an issue appropriate action up to and including withdrawal from the study may be taken.

Patient selection
The protocol includes skeletally mature patients both male and female, 18 to 89 years old, with DDD and/or scoliosis and a planned fusion of at least five levels. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies.

Patients may also have up to a grade I spondylolisthesis or retrolisthesis at the involved level(s). Patient should have completed at least 6 months of non-operative treatment. Patients may have had a previous non-fusion surgery at the involved spinal level(s). In addition to the InterFuse® S and InterFuse® T interbody fusion devices, patients will receive supplemental internal spinal fixation systems, e.g., pedicle screws (standard procedure for interbody implants).

Inclusion criteria

- The patients has a planned fusion construct of at least five levels and will have the InterFuse (S) or (T) planned for L_{5–S_{1} } and/or L_{4–5}.
- The patient has documented conservative (non-operative) treatment for at least 6 months.
- The patient has a VAS score of ≥ 6 for Back and/or Leg.
- The patient has an Oswestry Disability Index ≥ 40%.
- The patient is at least 18 years of age and skeletally mature.
- The general condition of the patient is appropriate for surgery, as evaluated by the Investigator.
- The patient is willing and able to comply with study requirements.
- The patient has agreed to participate in the study.

Exclusion criteria

- The patient has undergone any prior interbody implants at L_{4–5} or L_{5–S_{1} }. Previous non-fusion surgery at the proposed treatment level(s) is acceptable.
- The patient has osteoporosis or severe osteopenia as determined by the Investigator. A clinical score calculator may be utilized for females over 40 years of age.
- The patient has grade 2 or higher spondylolisthesis or retrolisthesis at the affected level(s).
- The patient has known neoplastic disease other than skin cancer.
- The patient has a body mass index (BMI) of greater than
40 kg/m².
• The patient has an active infection.
• The patient is pregnant or is planning on becoming pregnant in the next 2 years.
• The patient is mentally ill or has a history of drug abuse or severe depression/psychosocial issues.
• The patient has a known allergy to polyether ether ketone, stainless steel or tantalum.
• The patient is currently enrolled in an investigational spine study.
• The patient has rheumatoid arthritis, ankylosing spondylitis or other autoimmune disease.
• The patient has symptomatic fibrous arachroiditis.

Sample size
A total of 200 subjects will be enrolled over a planned 6-month recruitment period. Enrollment will occur at 10 clinical sites.

Device description
• InterFuse® S and InterFuse® T
  K # for S
  K080673
  K091988
  K093675
• K# for T
  K110226
  K110227

Study evaluations
Patient data
Patients are required to undergo a thorough pre-operative evaluation prior to surgery and return for follow-up evaluations according to a pre-determined follow-up schedule. The pre-operative evaluation includes confirmation at least 6 months of conservative treatment. Pre-operative, operative and follow-up data will be collected on case report forms provided by the sponsor. All patients will be followed for at least 24 months once enrolled in the study. Table 1 summarizes the follow up visits and evaluations.

All patients are required to return for scheduled follow-up at 6 weeks (± 2 weeks), 3 months (± 1 month), 6 months (± 1 month), 12 months (± 2 months) and 24 months (± 2 months). In addition to scheduled follow-up visits, the patients should be instructed to contact the Investigator at any time during the follow-up period if he/she has questions or concerns relating to the implantation of the device.

Case Report Forms for the study include:
• Screening
• VAS and ODI
• Zurich Claudication, SRS-22 and the Short-form 36 Health Status Questionnaire (SF-36)
• Inclusion-exclusion
• Hospital discharge
• Treatment
• X-ray imaging
• CT imaging (optional)
• Follow up
• Protocol deviations
• Adverse event

Screening evaluation
All patients considered for enrollment must undergo a thorough pre-operative evaluation prior to scheduled implantation of the InterFuse® S and InterFuse® T device. The evaluation includes the collection of demographic information, medical history, low back physical examination, imaging evaluation, and patient completion of pain/functional and optional well-being test instruments.

<table>
<thead>
<tr>
<th>Table 1: Evaluations performed at each patient contact</th>
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</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
</tr>
<tr>
<td>Informed consent</td>
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<tr>
<td>Inclusion/exclusion</td>
</tr>
<tr>
<td>Medical history</td>
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<tr>
<td>Previous spine surgeries</td>
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<tr>
<td>Medication history</td>
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<tr>
<td>Neurological exam</td>
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<tr>
<td>Physical exam</td>
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<tr>
<td>Outcome questionnaires</td>
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<tr>
<td>X-ray</td>
</tr>
<tr>
<td>CT scans</td>
</tr>
<tr>
<td>Adverse event</td>
</tr>
</tbody>
</table>
Patient demographics
Patient demographics collected include gender, body mass index and occupational status.

Medical history
General medical history and information relating to the patient’s lower back pain history will be obtained.

Physical examination
A physical examination, specific to patients with spinal deformity, will be done.

Imaging evaluations
Imaging evaluations include a standard anteroposterior and lateral neutral and lateral flexion/extension X-rays. The standard X-rays will be used to confirm diagnosis and to provide additional information on the overall condition of the spine to assist in appropriate patient selection. CT scans will be conducted at 12- and 24-month visits, and will be graded for fusion success using the classification systems derived from those described by Fogel et al.¹⁷

Patient questionnaires
Patients are required to complete the Outcome Questionnaires prior to surgery. Patients will also be asked to complete the outcome questionnaires (ODI, VAS, Zurich Claudication, SRS-22 and SF-36) prior to surgery, at the 6-week, 3-, 6-, 12- and 24-month visits.

Final diagnosis
The Investigator will determine the affected level(s) requiring surgery.

Post-operative care
The post-operative rehabilitation plan should be explained and agreed to by the patient during the pre-operative assessment period. The suggested post-operative care plan is outlined in the surgical technique.

Operative evaluation
If a patient presents for surgery with an active infection, or other medical condition that precludes surgery at this time, the procedure should be delayed until the infection or medical condition is treated and resolved.

If the Investigator is not an experienced user of the InterFuse® S and InterFuse® T devices, a VTI representative will be present as needed for surgeries to provide technical guidance to the Investigator. Surgical data, including surgical preparation, surgical technique and InterFuse® S or InterFuse® T device placement will be collected.

Surgical preparation
Surgical preparation data include date of surgery, type of anesthesia used and length of procedure; patient should be in a neutral or slight flexion, prone position on a lumbar frame.

Device surgical technique
The Investigator should generally follow the InterFuse® S and InterFuse® T surgical technique guides for implanting the device. Any deviations from the surgical technique must be thoroughly documented on the operative case report form.

Visualization with C-arm fluoroscopy is used throughout the implant procedure in both anteroposterior and lateral planes and oblique planes as necessary. Direct visualization may be used to supplement fluoroscopy.

Follow-up visits
See Table 2 for required CT imaging follow-up.

### Table 2: The required CT images

<table>
<thead>
<tr>
<th>Image</th>
<th>Patient position</th>
<th>Image acquired or reconstructed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transverse</td>
<td>Supine</td>
<td>Yes</td>
</tr>
<tr>
<td>Coronal reconstruction</td>
<td>Supine</td>
<td>Yes</td>
</tr>
<tr>
<td>Sagittal reconstruction</td>
<td>Supine</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Note: Images shall be taken of the lumbar spine. Slices of ≤3 mm in thickness shall be acquired or reconstructed and preferably slices of 1 mm thickness will be acquired or reconstructed at the level of implant.

Unscheduled visits
In addition to scheduled follow-up visits, the patient should be instructed to contact the Investigator at any time during the follow-up period if he/she has questions or concerns relating to the implantation of the device. If the patient returns to the clinic for evaluation related to his/her participation in the study, a follow-up visit evaluation should be performed and recorded on the Follow-Up Visit Form.

Adverse events
Definitions

### Adverse event
As defined in ISO 14155-1¹⁸ an adverse event is “any untoward medical occurrence in a subject whether it is considered related to the device or not.” Any current/baseline condition that is recorded as a pre-existing condition is not an adverse event unless there is a change in its nature, or it worsens in intensity or duration. All adverse events that occur during the course of the study until the completion of the final follow-up visit, whether observed by the inves-
The description of the adverse event will include the date of onset, seriousness, causal relationship to the investigational product and/or the procedure, any treatment required, and the outcome of the event. The Investigator will follow each subject who experiences an adverse event until the event resolves. In the unusual circumstance that an adverse event has not resolved by the time of the subject’s completion of the study, an explanation will be entered on the appropriate CRF. Such a circumstance may be determined to be a permanent condition, and will be documented as such.

Serious adverse event
According to ISO 14155-1 an adverse event is categorized as serious if it:
• Requires hospitalization ≥ 24 hours or requires prolongation of an existing hospitalization;
• Results in permanent impairment of a body structure or body function;
• Results in a medical or surgical intervention to prevent permanent damage to a body structure or body function;
• Is life threatening; or
• Results in death.

All serious device related adverse events must be recorded on the Adverse Event Case Report Form and reported to the sponsor as soon as possible. Upon receipt of a serious device related adverse event, the sponsor will immediately conduct an evaluation of the event.

Adverse device effect (ADE)
As defined in ISO 14155-1 an ADE is “any untoward and unintended response to a medical device.” This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. This definition also includes any event that is the result of a user error.

Serious adverse device effect (SADE)
As defined in ISO 14155-1 a SADE is “an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.” If the Investigator becomes aware of a serious adverse event, they will notify the sponsor within 24 hours of awareness.

Unanticipated serious adverse device event (USADE)
An USADE is “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subject.” Any event that it considered an unanticipated serious adverse device effect will be reported within 10 days to regulatory authorities, all investigators and IRBs.

Determining relationship to the device
The investigator will also evaluate the relationship to the InterFuse® S or InterFuse® T device according to the following definitions:

| Related | The adverse event follows a reasonable timing from implantation (or attempted implantation) of the device and the possibilities of factors other than the device, such as underlying disease, concomitant drugs, or concurrent treatment are excluded. This includes an adverse event that occurs during the implant procedure. |
| Not Related | The adverse event has no timing relationship from implantation of the device, or it can be explained by other factors, including underlying disease, concomitant medication, or concurrent treatment. |

Radiographic evaluation
An independent radiographic evaluation will be conducted on X-rays taken preoperatively and postoperatively according to the evaluation schedule. Anteroposterior and lateral neutral radiographs will be obtained at each visit. CT of the lumbar spine will be taken postoperatively at 12 and 24 months. All radiographs will be reviewed and evaluated by an independent reviewer.

Preoperative radiographic assessment
Preoperative films will be examined to determine if the patient is an appropriate candidate for treatment with the InterFuse® Device. Anteroposterior, lateral, flexion/extension radiographs, will be used to make this determination. Postoperative radiographic assessment
The postoperative assessment will evaluate parameters that will be used to determine function of the involved segment(s) of the lumbar spine. This will be conducted by an independent radiologist. Elements to be evaluated include:
• Fusion
• Bridging bone
• Implant subsidence
• Implant migration
• Loosening of supplement internal spinal fixation, e.g., pedicle screws

Data analysis
Results obtained from the study will be tabulated and ana-
lyzed, using common statistical software packages. Patients without any follow-up examination as required by the study protocol will be listed separately.

Descriptive statistic reports will be presented according to:
- Demographic and pre-operative assessments
- Operative assessments
- Radiographic evaluations
- Complications
- Re-operation and revision surgeries

Frequency and percent distributions will be presented for qualitative observations, whereas the mean, median, standard deviation, minimum and maximum, will be presented for quantitative variables. The changes in VAS, ODI, Zurich Index, SRS 22 and SF-36 over the course of the study will be tabulated.

Appropriate statistical tests will be performed under the guidance of a statistician as applicable.

An initial report will be written when all patients recruited into the study have completed their 12 month follow-up assessment. A final report will be prepared after all patients have completed their 24-month follow-up assessment.

### Administrative requirements

#### Regulatory obligations

#### Changes to the protocol, regulatory procedures

Amendments to the protocol will be submitted to the investigators and IRBs for review and/or approval prior to instituting any changes.

#### Deviations from the investigational plan

All departures from the protocol must be reported on the appropriated CRFs.

#### Planned deviations

If any unusual circumstances arise that may justify a departure from the protocol, the sponsor will be contacted by the investigator immediately. A joint decision between the investigator and sponsor will be made as to whether the protocol may be modified for that subject. The reason for the decision must be documented in writing.

#### Unplanned deviations

If a departure from the protocol occurs during the course of a procedure, such as in an emergency, a report will be sent to the sponsor as soon as possible, but no later than five working days after the procedure. Additionally, protocol deviations will be reported to the IRB as required.

#### Study termination

Upon notification of study termination, the investigator must immediately discontinue any planned implantation of the InterFuse® S or InterFuse® T devices. All subjects with implanted InterFuse® S or InterFuse® T devices must be monitored throughout the duration of the follow-up period as specified by the protocol. The study may be terminated by the investigator, the sponsor, or the IRB.

**By the investigator**

If, in the investigator’s opinion, there are reasons not to continue with this study, termination will be reported to VTI within 5 working days in the form of a written statement that fully documents the reasons for the action.

**By the sponsor**

If VTI chooses to suspend or terminate the study, appropriate notification will be given to the investigator.

**By the IRB**

If the IRB decides to withdraw approval for the study, the investigator or IRB must inform VTI as soon as possible but no later than five working days from the date of the decision.

### Responsibilities of the IRB

The IRB has the main responsibility to oversee the welfare of the subjects entered into this study. The IRB, by its approval of the informed consent form, also ensures that the potential subjects are aware of the benefits and risk of participation in the study. The written IRB approval of the protocol and the consent form to be used must be given to the investigator prior to the study initiation. If applicable, written IRB approval of any subject information material or any advertisements must also be obtained prior to their use.

### Sponsor obligations

The sponsor must assume the following responsibilities and must keep the required records.

The sponsor agrees to:
- Provide the investigator with the necessary information (protocol and IFU) and training required to conduct the post market study.
- Inform the investigator and the IRB of all new information that may affect the decision to continue participation in the study.
- Send a qualified monitor to the site, as necessary, to inspect the records and ensure that the study is being conducted in compliance with the applicable regulations.
- Conduct an evaluation of any USADE and report the result of such evaluation to all reviewing IRBs and all participating investigators within 10 working days of first receiving notice of the event.
Investigator documents

The following documents will be provided to VTI by the investigator prior to initiation of the study.

- A signed and dated Investigator Agreement.
- Current (within 1 year) curriculum vitae of the principal investigator and all co-investigators.
- A copy of the approval letter by the IRB for the study protocol and the informed consent.

Investigator obligations

Upon signing the Investigator Agreement, the investigator agrees to assume the following responsibilities, to keep the required records, and to file the required reports in a timely manner.

The investigator agrees to:

- Conduct the investigation in compliance with the signed agreement, the investigational plan, and applicable regulations. Changes to the protocol will only be made after approval by the sponsor and the supervising IRB, or when necessary to protect the safety, rights or welfare of a subject.
- Conduct the investigation in compliance with the IRB.
- Personally conduct or supervise the investigation.
- Read and understand the information in the protocol and IFU.
- Be aware of the potential risks and side effects of the device.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations.
- Protect the rights, safety and welfare of research subjects. This is an FDA cleared device being used in a post market study
- Complete all CRFs for each subject in a timely manner.
- Assure initial and continuing review of the investigation by an IRB.

Monitoring

Clinical monitors for this study will be representatives of the sponsor. All responsibilities designated to any clinical research organization will be detailed in the monitoring plan. The monitors are trained to perform all monitoring requirements per the established monitoring plan including the assurance of investigator compliance, protocol adherence and data accuracy as well as any other monitoring functions according to this protocol.

Ethics and dissemination

IRB approval

IRB approval will be obtained prior to study initiation at each site. The name and address of the IRB and the name of the chairman must be kept on file at the site and a copy provided to VTI. A copy of the approval notification and the approved study specific patient informed consent must also be kept on file at the site and a copy provided to VTI prior to the enrollment of patients. The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki (Additional file 2).

Informed consent

Before a subject participates in the study, his or her written informed consent must be obtained. The subject will be asked to read a consent form, approved by the IRB. The investigator will inform the subject of the purpose of the study, proposed duration and follow-up schedule. The investigator will discuss the foreseeable risks involved as well as the potential benefits that may result from the use of the device as outlined in the study specific informed consent form.

The subject will be informed that his or her medical records will be subject to review by the sponsor’s representatives. This health information will be used during the analysis of the results of the clinical study, but the confidentiality of the subject will be maintained at all times.

The subjects will be informed by the investigator that they are free to refuse participation in this study at any time without compromising further medical care.

A signed and dated Informed Patient Consent form must be obtained by the investigator from the subject prior to commencement of any study required procedure. A copy of the signed and dated informed consent form will be provided to the patient and the original will be filed with the subject records at the investigator’s office. The subjects will be notified if the study is terminated.

Use of information and publication

The sponsor encourages the Investigator to publish and present the results of this study in peer-reviewed journals and at national and international conferences. The investigator will submit for publication the results of this study in a peer-reviewed journal to be agreed jointly with the sponsor at the earliest possible time after completion of the study. The investigator and the sponsor will together ensure that early release of data or prior presentation of data will not be made in such a way that it may prejudice future publication. The sponsor reserves the right to jointly review draft publications and presentations arising from this study. Draft publications and presentations should be submitted to the sponsor for review and approval not less than 30 days before submission, such approval not to be unreasonably withheld or unduly delayed. Approval will only be delayed beyond 30 days for protection of intellectual property and in any case would not exceed 90 days.
**TRIAL STATUS**

Recruitment for the study is ongoing.

**Author contributions**

All authors participated in the design of the clinical trial, the manuscript elaboration and have agreed on the final version of the manuscript.

**Conflicts of interest**

None declared.

**Declaration of interest**

This protocol contains confidential information and is limited in its distribution to Investigational Staff intending to conduct the study and Institutional Review Boards charged with approving the study.

**Declaration of patient consent**

The authors certify that they will obtain all appropriate patient consent forms. In the form, the patients will give their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Data sharing statement**

No data is reported in the article.

**Plagiarism check**

Checked twice by iThenticate.

**Peer review**

Externally peer reviewed.

**Open access statement**

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**Additional file**

Additional file 1: Investigator Agreement.

Additional file 2: Declaration of Helsinki.

**REFERENCES**


