ABYRX

IRB Approved at the
Protocol Level
Jan 08, 2019

A Prospective, Multicenter, Randomized, Controlled Clinical Investigation of MONTAGE in Adults with Spinal Deformity Undergoing Pedicle Subtraction Osteotomy

PROTOCOL NUMBER:	ABYRX- MONTAGE 001-2017
PRINCIPAL INVESTIGATOR(S):	William Lavelle, MD
INDICATION:	Hemostasis after Pedicle Subtraction Osteotomy for Adult Spinal Deformity
PRODUCT:	MONTAGE
DEVELOPMENT PHASE:	Phase 4 – Post-market
SPONSOR:	Abryx, Inc. 1 Bridge Street, Suite 121, Irvington, NY 10533
MEDICAL MONITOR:	Jan Lessem, M.D., Ph.D., FACC Consultant Medical Officer ABYRX Mobile: 857-891-6525

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List of Abbreviations

AE	Adverse Event
cm	Centimeter
CRA	Clinical Research Associate
CRF	Case Report Form
FDA	U.S. Food & Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
in	Inch
IRB	Institutional Review Board
ITT	Intention-to-Treat
ODIv2.1a	Oswestry Disability Index version 2.1a
QoL	Quality-of-Life
SAE	Serious Adverse Event
SRS-22	Scoliosis Research Society -22 Outcomes
UADE	Unexpected Adverse Device Effect
VAS	Visual Analog Scale back and leg pain

SUMMARY

Title:	A Prospective, Multicenter, Randomized, Controlled Clinical Investigation of MONTAGE in Adults with Spinal Deformity undergoing Pedicle Subtraction Osteotomy
Short Title:	MONTAGE in PSO for Adult Spinal deformity
Protocol Number:	Montage 001-2017
Phase:	Phase 4-postmarketing
Methodology:	Prospective, randomized, open, controlled study
Study Duration:	2 years from entry of last subject
Follow-up:	2 years
Study Centers:	Multicenter study with up to 4-6 centers
Objectives:	Primary: To assess the safety and effectiveness of MONTAGE in reducing post-operative blood loss Secondary: To assess the PSO stability
Number of Subjects:	50 subjects
Diagnosis and Main Inclusion Criteria:	1. Presence of spinal deformity requiring a PSO 2. Patients aged 18-80 and 3. Non-smokers (must have quit smoking 6 months prior to surgery) and current smokers
Study Product, Dose, Regimen:	After surgically creating the wedged PSO defect, prior to closure of the osteotomy, patients will be randomized 1:1 to receive either MONTAGE applied to the cut surfaces for the osteotomy site or no hemostatic material.
Duration of Administration:	1 application during surgery
Reference Therapy:	Standard of care – no bone hemostat.

End-points and Statistical Methodology:

Efficacy Endpoint:	The primary efficacy outcome variable for the study is the amount of post-operative bleeding compared between patients randomized 1:1 to MONTAGE or standard of care (no bone hemostat). Blood loss will be measured indirectly by formulae that provide an estimate through changes in hematocrit. A 2-sided “t” test will be used for the analysis.
Safety Endpoints:	Consistent with the standard of care, successful reconstruction of the osteotomy site requires observation of the residual angle of the osteotomy and any gap that may be present. In order to demonstrate that the use of Montage does not negatively impact the desired outcome, any residual gap will be measured in millimeters and compared between the groups. This will be done by including a CT scan performed at 1-year post surger A 2-sided “t” test will be used for the analysis. NRS back pain and NRS leg pain, SRS-22 and Oswestry Disability Index (ODIv2.1a) will be compared between the two groups and also reported as secondary outcome scores. Descriptive statistics will be reported.

PROTOCOL APPROVAL

Date	,,
....	William Lavalle, MD
....	……………………………………………………
Date	Jan Lessem, MD, Ph.D
	Consultant Medical Officer ABYRX

INVESTIGATOR AGREEMENT

The signing of this protocol by the Investigator signifies that the contents have been laid down in full agreement and that the trial will be conducted according Good Clinical Practice and to the procedures described.

....	....
Date	***<Investigator>***

1. INTRODUCTION

1.1 STATEMENT OF INTENT

The design, conduct and reporting of this trial shall be undertaken in compliance with the protocol, ICH/GCP and all appropriate regulatory requirements.

1.2 TITLE

A Prospective, Multicenter, Randomized, Controlled Clinical Investigation of MONTAGE in Adults with Spinal Deformity undergoing Pedicle Subtraction Osteotomy

1.3 BACKGROUND INFORMATION

PEDICLE SUBTRACTION OSTEOTOMY - ASSOCIATED BLOOD LOSS

Pedicle Subtraction osteotomy (PSO) is a surgical option for treating several spinal deformities. It has been utilized in alignment disorders of the fused spine, in the lumbar spine to treat large sagittal deformities and in patients with ankylosing spondylitis with thoracolumbar kyphotic deformity (1).

PSO is a procedure most commonly performed in the lumbar and thoracic spinal regions. PSO is often avoided in the distal lumbar spine because the risk of the neurologic injury is greater and fewer fixation points are available. It has been suggested that some of the ideal candidates for PSO are those patients with a substantial sagittal imbalance > 10 to 12 cm, with a sharp angular kyphosis and patients who have circumferential fusion along multiple segments. For most patients with ankylosing spondylitis, PSO could be the treatment of choice. The procedure involves surgical excision of a wedge of bone from the posterior spine (osteotomy). The two cut edges are then drawn together by a system of screws and rods designed to apply compression and thus reduce the unnatural forward curvature of the spine.

PSO typically results in substantial loss of blood (as much as 2L) with a significant portion of the loss likely occurring at the osteotomy surfaces post-surgically. Blood loss-associated morbidities can be direct, including hypotension, organ damage (particularly cardiac, pulmonary, renal) and coagulopathy. Excessive blood loss also may require allogeneic blood transfusion, which may further result in acute lung injury, hypersensitivity reactions, infections, and immune suppression. Another concern with regard to post-operative bleeding in spinal surgery is the risk of spinal epidural hematoma formation, which might lead to spinal cord or cauda equina compression. Therefore, the control of peri-operative blood loss is considered a critical issue by spine surgeons (2,3,5).

A variety of methods have been proposed for the reduction of blood loss during or immediately after spine surgery, including preoperative use of erythropoietin, autologous blood, cell salvage, intra-operative controlled hypotension, and the use of anti-fibrinolytic drugs (6). Bone hemostats have traditionally not been part of the standard of care to promote hemostasis probably because most available options (e.g., bone wax) are nonabsorbable and thus might interfere with fusion at the osteotomy site.

<u>MONTAGE</u>

MONTAGE is a settable (hardening) bioabsorbable polymer and hydroxyapatite/beta tricalcium phosphate based putty, used in the control of bleeding from bone during spine, orthopedic, craniomaxillofacial, thoracic and other surgical procedures.

It is easy to manipulate and typically results in immediate and complete cessation of bleeding at the bony defect. The putty hardens within minutes after application, remaining secure in place, without being dislodged or dissolved during the early stages of bone formation. In animal studies, the use of MONTAGE has not been shown to interfere with bone healing or fusion (7).

MONTAGE putty was implanted in rabbit diaphyseal femoral defects (N=12) and each defect was evaluated after 4 weeks by histopathology (8). The microscopic evaluation demonstrated no significant signs of inflammation or fibrosis, while there was indication that new bone formation occurred. MONTAGE is fully absorbed within approximately 1 year and is replaced with endogenous bone.

MONTAGE settable putty is FDA cleared as a bone hemostat in skeletal surgical procedures.

1.4 OBJECTIVES

The primary objective of this study is to evaluate the difference in postoperative bleeding between two study groups, FDA cleared MONTAGE and standard of care (no bone hemostat), and the extent to which any transfusion is needed and blood loss is measured through drop in hematocrit (HCT), as well as wound drain output, if utilized. As an exploratory evaluation of the primary endpoints a calculation will be made of blood loss for the first 7 days following surgical procedure as assessed by a multivariate combination of these measures of blood loss.

The secondary objective is the stability of the construct, as measured by whether the correction has maintained stability at 1-year and 2-years post surgery. Each incidence of instability will be categorized as belonging to one of the following groups: 1) hardware malplacement, 2) loosening or dislodegment, 3) nonunion or nonfusion with hardware fracture 4) nonunion or nonfusion without hardware fracture and 5) perihardware fracture.

Each osteotomy site will be assessed using X-rays and with computed tomography (CT) scans – performed at 12 months post surgery. Failure of fusion will be determined to be present if an area of bone apposition lucency greater than 2mm in thickness is present.

Secondary objectives will also include:

- The formation of new bone, as measured by CT scans at 1-year post surgery,

- Evaluation of Visual Analog Scale (VAS) back and leg pain, Oswestry Disability Index (ODIv2.1a), and SRS-22 scores, which will be recorded during the study and compared between the two groups.

- Evaluation of work status.

-Antifibrinolytics use and type will be recorded during the study and compared between the two groups

2. INVESTIGATIONAL PRODUCT/TREATMENT

2.1 DESCRIPTION OF INVESTIGATIONAL PRODUCT UNDER TEST

MONTAGE is a settable (hardening) bioabsorbable polymer and hydroxyapatite/beta tricalcium phosphate based putty, used in the control of bleeding from bone during spine, orthopedic, craniomaxillofacial, thoracic and other surgical procedures, and has been FDA cleared.

It is easy to manipulate and in all instances, as reported in preclinical studies, resulted in immediate and complete cessation of defect bleeding. The putty hardens within minutes after application, remaining secure in place, without being dislodged or dissolved.

In rabbit diaphyseal femoral defects (N=12), MONTAGE putty was implanted; and after 4 weeks each defect was evaluated by histopathology. The microscopic evaluation demonstrated no significant signs of inflammation or fibrosis, while there was indication that new bone formation occurred.

MONTAGE has been used in many clinical settings, including during spinal and sternotomy procedures. Long-term follow-up in various settings has not demonstrated any adverse events of significance. (9, 10, 11, 12).

2.2 PACKAGING AND LABELING

MONTAGE will be supplied terminally sterilized in individual packaged units of 5cc (10grams). MONTAGE should be stored at room temperature.

2.3 METHOD OF DISTRIBUTION

Delivery of all study materials (e.g. product, CRFs, etc.) to the study centers will be arranged by the Sponsor's Clinical Research Associates (CRA).

2.4 ACCOUNTABILITY

The investigator or designated individual will maintain inventories that will detail receipt, use, return and collection of Montage trial supplies by the company. The use inventory log will be used to document which products (batch, expiry, and quantity) were used on which subjects for traceability.

3. TRIAL SUBJECT POPULATION

3.1 NUMBER OF SUBJECTS

A multicenter study will be undertaken in the US, with up to 4-6 centers contributing 50 patients (maximum of 20 patients per center). A sample size of 25 randomly assigned patients per study group (50 subjects in total) was calculated to detect a clinically significant treatment effect of MONTAGE (90% power; alpha = 0.05, 2-sided; 10% lost-to-follow up). This calculation was performed with the assumption that subjects within the control group lose on average 1,500 mL (+/- 500mL) of blood postoperatively while subjects within the treatment group will lose 1,000 mL of blood postoperatively.

3.2 SUBJECT SOURCES

Adult subjects referred to hospital or community-based clinics for treatment of spinal deformity will be eligible for the study.

3.3 SELECTION CRITERIA

The following criteria must be met before a subject is recruited to the trial:

3.3.1 Inclusion Criteria

1. Subject is at least 18 years old, and not more than 80 years old.

2. Presence of spinal deformity requiring a PSO at a single site level, such as for patients with thoracolumbar kyphotic deformity, sagittal imbalance, and spinal global malalignment.

3. Non-smokers (have proven to quit smoking for at least 6 months prior to surgery) and current smokers

3. Female subjects of childbearing potential must be willing to use acceptable methods of contraception (birth control pills, barriers, or abstinence). A pregnancy test at the Week 0 visit must be administered, and must be negative, for inclusion into the study.

4. Subject understands and is willing to participate in the clinical study and can comply with required visits and the follow-up regimen.

5. Subject has read and signed the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved Informed Consent Form before screening procedures are undertaken.

3.3.2 Exclusion Criteria

1. Subjects whose spinal deformity is deemed by the investigator to be of such severity that a possible surgical intervention would be either harmful or not warranted.

2. Subjects with morbid obesity (i.e. a Body Mass Index [BMI] ≥ 40).

3. Subjects who have a known allergy to the components of MONTAGE.

4. Subjects who are non-mobile (i.e. not ambulatory, or have significant impairment of their mobility making them completely bedridden).

5. Subjects who, in the opinion of the investigator, show evidence of infection, cellulitis, and/or osteomyelitis.

6. Subjects with abnormally low platelets, abnormal coagulation parameters, or with documented bleeding disorders, including a prior history of excessive bleeding during surgery.

6. Subjects with a history of a malignancy, not in remission for five years or more, or a newly diagnosed malignancy, treated with cytotoxic therapies or radiation therapy.

7. Subjects on any investigational drug(s) within 30 days preceding randomization (i.e. Week 0); or subject or physician anticipates use of any of these therapies by the subject during the course of the study.

8. Subjects with:

   (ii) Alcohol abuse as recorded by an average daily intake of > 4 units in females, > 5 units in males (i.e. 1 oz. of spirit, glass of wine, or can of beer per unit).

   (iii) Drug abuse as evidenced by the subject's use of illegal drugs or prescription drugs that have not been prescribed for him/her.

9. Subjects with one or more medical conditions, as determined by medical history, including renal, hepatic, hematologic, active auto-immune or immune diseases that, in the opinion of the Investigator, would make the subject an inappropriate candidate for this study.

10. Subjects with a history of osteoporosis, as defined by imaging, or on medication for osteoporosis or documented fracture of fragility (Hip fracture, osteoporotic compression fracture, distal radius fracture). If there are any concerns these may be arbitrated by the study PI.

11. Subject has previously participated in any MONTAGE trial.

12. Subjects who are unable to understand the aims and objectives of the trial and/or unwilling to return for the follow-up examinations..

3.4 WITHDRAWAL

Subjects may drop out or be withdrawn at their own request. Although subjects need not give a reason for requesting withdrawal from the trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

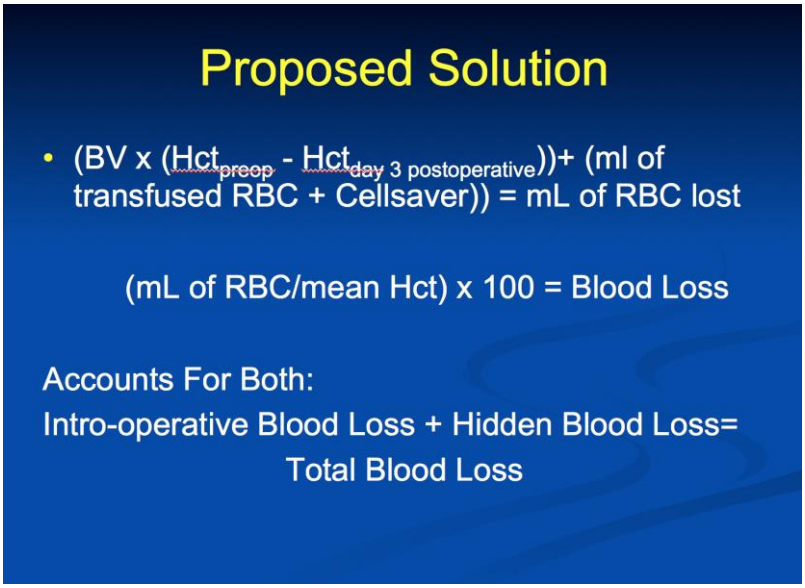
4. TRIAL DESIGN AND METHODOLOGY

4.1 TRIAL DESIGN

This study will be an open, prospective, multicenter, randomized, and controlled study to evaluate the effects of MONTAGE® on blood loss and maintenance of the PSO corrective surgical procedure.
Patients will be randomized to receive either standard of care (no bone hemostat) or MONTAGE. Within each study group, patients will be stratified according to their smoking status (non-smokers versus current smokers).

4.1.1 PRIMARY OBJECTIVE

To assess the effectiveness of MONTAGE in reducing blood loss in the first week after surgery. A formula will be used to calculate blood loss during the post-surgical period up until day 7 or hospital discharge (whichever comes first). The following formula from the Harms Study Group, shown at day 3 as an example, will be used and comparisons of blood loss between the two groups will be calculated.



4.1.2 SAFETY OBJECTIVES

Safety objectives will include:

- Evaluation of the repaired osteotomy by measuring displacement of the edges of the bone under compression. The angular measurement is the angle between the superior endplate of the vertebral body below the PSO and the inferior endplate of the vertebral body above the PSO. Consistent with the standard of care, successful reconstruction of the osteotomy site requires observation of the residual

angle of the osteotomy and any gap that may be present. In order to demonstrate that the use of Montage does not negatively impact the desired outcome, any residual gap will be measured in millimeters and compared between the groups. This will be done by including a CT scan performed at 1-year post surger A 2-sided “t” test will be used for the analysis.

- To demonstrate that Montage does not interfere with the repair, evaluation of the formation of new bone, as measured by CT scans at 1-year post surgery.

- Evaluation using the VAS back pain and leg pain, Oswestry Disability Index (ODIv2.1a) and SRS-22, which will be recorded during the study and reported as outcomes scores, and compared between the two groups.

-Antifibrinolytics use and type will be recorded during the study and compared between the two groups

4.2 TREATMENT METHODOLOGY

MONTAGE will be used only at a focal site where the osteotomy is performed. It will be applied to the edges of the spine defect after removal of the wedge. MONTAGE will be applied immediately prior to placing the osteotomy site under compression prior to its hardening so as to ensure no interference with compression against the osteotomy edges. Participating investigators, at their discretion, may use autograft and allograft bone void fillers for the other parts of the spine fusion as part of standard of care.

A teaching video will be used to ensure strict adherence to the study procedure at all sites.

Hematological parameters, such as Hb, Hematocrit, RBC, WBC, platelet counts, MCV, MCHC, and differential counts will be recorded and compared between the groups at baseline, immediate post-surgery, and daily up until day 7 or discharge (whichever comes first).

All standard-of-care blood values, including CBC, electrolytes, liver function and kidney function tests during the initial hospital admission will be recorded and analyzed at certified laboratories.

Consistent radiographic parameters will be used to evaluate the angular measurements between the superior endplate of the vertebral body below the PSO and the one above it.

All radiographic images will be read by two reviewers, without knowledge of treatment groups (i.e., blinded).

The radiographic techniques that will be employed in this study are X-rays and CT scans of the thoracolumbar spine without contrast, focusing on the vertebral segments above the osteotomy, the osteotomy segment itself, and the spinal area just below the osteotomy procedure. All images during the study will be read by the same two reviewers.

4.2.1 Screening and Pre-Treatment Regimen

4.2.1.1 Visit #1: Screening Evaluation and Enrollment (Week -2)

- Signed written Informed Consent Form will be obtained.
- Subjects will be enrolled according to the Inclusion and Exclusion criteria listed above.
- Subject demographics, medical history, and vital signs will be recorded.

- A blood sample will be drawn from the subject for analysis of hematological and biochemical parameters at a central laboratory consistent with the study institutions preoperative workup
- Subjects will undergo pre-operative imaging using CT and radiographs, which are based on standard of care.
- Patient’s co-morbidities will be scored using the Charlson Comorbidity index, the ASA score as well as ISSG severity scores.

- A list of pain medications with dosing will be recorded
- VAS back and leg pain, ODIv2.1a and SRS-22 scores will be collected as a baseline.

4.2.2 Randomization

The randomization will occur with the participating center contacting the central study data repository after submitting preoperative subject data; random assignment will be generated by computer. Patients will be randomized to either PSO with MONTAGE or standard of care

4.2.3 Treatment

4.2.3.1 Visit #2: Treatment Phase (Week 0)

The patient will undergo the surgical intervention, excising a bone wedge from the vertebral body followed by a closure of the defect and re-apposition of the bony edges, creating the correction. Just prior to closure of the osteotomy, either MONTAGE or no bone hemostat will be placed on the surface of the cut bone.
Operative parameters, including surgery time (duration of surgery) level of the osteotomy and type of surgery, as well as intra-operative blood loss will be recorded.
The use of anti-fibrinolytics will be recorded.
Regular blood values, including Hb, Hematocrit, RBC, WBC, platelet count, MCV, MCHC and differential counts will be performed on each post operative day while subject is in the hospital, up until day 7.
Number of blood transfusions as well as any wound drain output will also be recorded.

4.2.3.2 Visit #3: Follow-up Visit (Week 2)

Radiographs- standing ap and lateral scoli xrays will be completed and centrally read by independent evaluators.
VAS back and leg, ODIv2.1a and SRS-22 scores will be collected.
Current Pain medications/dosing will be collected.
Adverse Events will be recorded.

4.2.3.3 Visit #4: Follow-up Visit (Week 6)

Radiographs- standing ap and lateral scoli xrays will be completed and centrally read by independent evaluators.
VAS back and leg, ODIv2.1a and SRS-22 scores will be collected
Current Pain medications/dosing will be collected.
Angular correction and gap will be measured.
Regular blood chemistry, including Hb, Hematocrit, RBC, WBC, Platelet count, MCV, MCHC and differential counts will be performed (as clinically indicated).
Adverse Events will be recorded

4.2.3.4 Visit #5: Follow-up Visit (Week 12)

Radiographs- standing ap and lateral scoli xrays will be completed and centrally read by independent evaluators.
VAS back and leg, ODIv2.1a and SRS-22 scores will be collected
Current Pain medications/dosing will be collected.
Work Status will be recorded
Angular correction and gap will be measured.
Adverse Events will be recorded.

4.2.3.5 Visit #6: Follow-up Visit (Week 24)

Radiographs- standing ap and lateral scoli xrays will be completed and centrally read by independent evaluators.
VAS back and leg, ODIv2.1a and SRS-22 scores will be collected
Current Pain medications/dosing will be collected.
Work Status will be recorded
Angular correction and gap will be measured.
Adverse Events will be recorded.

4.2.3.6 Visit #7: Follow-up visit (Week 52)

Radiographs- standing ap and lateral scoli xrays will be completed and centrally read by independent evaluators.
VAS back and leg, ODIv2.1a and SRS-22 scores will be collected
Current pain medications/dosing will be collected.
Angular correction and gap will be measured.
A CT scan will be taken to evaluate screw loosening and other measures of bone healing.
Adverse Events will be recorded.

4.2.3.7 Visit #8: Follow-up visit (Week 104)

Radiographs standing ap and lateral scoli xrays will be completed and centrally read by independent evaluators.
VAS back and leg, ODIv2.1a and SRS-22 scores will be collected
Current Pain medications/dosing will be collected.
Angular correction and gap will be measured.
Adverse Events will be recorded.

5. ADVERSE EVENTS (DEFINITIONS AND REPORTING)

All adverse events reported spontaneously by the subject/or in response to questioning or observation by the investigator will be recorded.

5.1 ADVERSE EVENT

An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, or disease temporally associated with the use of the study products, or worsening of a pre-existing condition, whether or not it is considered related to the study treatment. All AEs and intercurrent illnesses must be recorded in the subject's medical records and on the CRF.

Adverse events will be defined as those events that occur after signing the informed consent until the final study visit. A description of the AE along with the onset date, end date, severity, action taken, treatment, outcome, likely cause, and relationship to the study products will be recorded in the CRF.

Local and systemic AEs associated with each treatment arm will be tabulated and compared. AEs will be elicited through direct questioning, subject reports, and physical examination.

An abnormal laboratory test result is not by itself considered to be an AE unless the Investigator considers the finding of clinical significance that should be reported in such a manner.

5.1.1 Reporting of Adverse Events

The Investigator will be responsible for assessing the relationship of the adverse event to the investigational product, and the seriousness and expectedness of the adverse event at the time of occurrence. A medically

qualified person appointed by the Sponsor will also assess this, once the Sponsor has been notified of an AE. All adverse events that occur during the trial will be documented on the supplied adverse event forms.

AEs and serious adverse events (SAEs) reported during the study, or SAEs reported within 30 days of the end of the study, will be followed to resolution of the AE/SAE or, within thirty days from the end of the study, a further and final assessment of the outcome will be made.

Each AE will be categorized as “serious” or “not serious” based on the definition of an SAE. An SAE is defined as an AE resulting in at least one of the outcomes described in Section 5.2.

The severity of AEs will be classified as “mild”, “moderate”, or “severe”, based on the following definitions:

- Mild: Awareness of sign, symptom, or event, but easily tolerated; does not interfere with usual daily activities or tasks.
- Moderate: Discomfort enough to cause interference with usual daily activity; may warrant therapeutic intervention.
- Severe: Incapacitating; inability to perform usual activities and daily tasks; significantly affects clinical status; requires therapeutic intervention.

AEs will be assigned a relationship (causality) to the study products. The Investigator will be responsible for determining the relationship between an AE and the study product. The type of event, organ system affected, and timing of onset of the event will be factors in assessing the likelihood that an AE is related to the treatment. Relationship of AEs to study products will be classified as follows:

- Not Related: No relationship exists between the AE and the treatment. The event is attributed to a pre-existing medical condition or an intercurrent event unrelated to the study product.
- Possibly Related: Follows the treatment, but may have developed as a result of an underlying clinical condition or treatments/interventions unrelated to the study product.
- Probably Related: Follows the treatment, but is unlikely to have developed as a result of the subject’s underlying clinical condition or other treatment or other interventions.
- Definitely Related: Follows the treatment and physical evidence shows a convincing relationship to the treatment.
- Unknown: Follows the treatment, but unable to determine the relationship to the treatment.

5.1.2 Subject Follow-up

Subjects who experience an AE will be followed until the AE has resolved, if possible.

5.2 SERIOUS ADVERSE EVENT

A SAE will be defined as any untoward medical occurrence that occur after signing the informed consent until the Final Evaluation that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect,
- Other (event not covered by SAE categories but in the investigator's opinion, should be considered serious).

Important medical events that may not result in death, be immediately life threatening, or require hospitalization may be considered an SAE when, based upon medical judgment, if they may jeopardize the subject and require intervention to prevent one of the outcomes listed above.

5.2.1 Reporting Serious Adverse Events

The Investigator must report all SAEs (including any subject deaths) occurring during the study (from informed consent until the Final Evaluation). Once the Investigator becomes aware of an SAE, he/she must e-mail (preferred method of communication) or telephone the Sponsor within 24 hours:

Dr Jan Lessem, M.D., Ph.D
Consultant Medical Officer

Telephone (home): 786-916-2860
Telephone (Sweden; May through August): +46-431-360167
Telephone (mobile): 857-891-6525
Email: jlessem@clinstrat.com

The Investigator is responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

5.3 UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

An unanticipated adverse device effect is defined as 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 relates to the rights, safety, or welfare of subjects.

5.3.1 Reporting UADEs

The Investigator must report all UADEs (including any subject deaths) occurring during the study (from informed consent until the Final Evaluation). Once the Investigator becomes aware of an UADE, he/she must e-mail (preferred method of communication) or telephone the Sponsor within 24 hours:

Dr Jan Lessem, M.D., Ph.D
Consultant Medical Officer

Telephone (home) : 786-916-2860
Telephone (Sweden): 0431-360167
Telephone (mobile): 857-891-6525
Email: jlessem@clinstrat.com

6. STATISTICAL DESIGN

6.1 DESIGN

This is a parallel group, randomized, open, multicenter, prospective study in subjects with spinal deformities requiring a PSO procedure at a single level. Patients will be randomized 1:1 to receive either MONTAGE or no bone hemostat. Within each randomization study group, patients will be stratified according to their smoking status (non-smokers versus current smokers).

The primary objective of this study is the evaluation of post-operative blood loss in the week following surgery.

The secondary outcome will be the stability of the construct, as measured by the gap between the repaired osteotomy edges. In addition, observations will be made regarding whether the hardware repair has been maintained, and if the screws have loosened, and if the inserted rods are intact. Each repair complication will be categorized as belonging to one of the following groups: 1) hardware malplacement, 2) loosening or dislodegment, 3) nonunion or nonfusion with hardware fracture 4) nonunion or nonfusion without hardware fracture 5) peri-hardware fracture. These complications will be measured with imaging, including CT scans performed at 1-year. Fusion failure will be determined to be present if an area of perihardware lucency greater than 2 mm in thickness is present.

Malplacement of hardware will be considered present when an abnormal hardware position with hardware impingement on an important structure such as nerve or vessel is present.

Other secondary objectives will include:

- The formation of new bone at the osteotomy site, measured in mms at 1-year post surgery at the osteotomy site.

- VAS back and leg, Oswestry Disability Index (ODIv2.1a), and SRS-22 scores which will be recorded during the study and reported as outcomes scores, and compared between the two groups.

-Analysis of the MONTAGE/vertebral body interface, evaluating whether bony substitution has occurred at 1-year post-surgery. The presence or absence of bony resorption around the MONTAGE will also be reviewed.

-The use and type of antifibrinolytics will be compared between the two groups.

6.2 SAMPLE SIZE

A total of 50 subjects will be recruited to this study, with 1:1 randomization, stratified to ensure equal distribution of smokers and non-smokers within each group.

6.3 ANALYSIS PLAN

The statistical analysis will be performed in conjunction with Abyrx. Analyses will be conducted on the Intention-to-Treat population (ITT), with additional Per Protocol analyses. All significance tests will be two-sided; p-values will be provided with $P(H_0) < 0.05$ indicating a significant difference.

All other analyses with respect to demographic and clinical parameters will be reported with descriptive statistics.

6.3.1 Subject Analysis Sets

The Intention-to-Treat population (ITT) is defined as all subjects receiving study treatment.

6.3.2 Secondary Variables and Analyses

Several secondary analyses will be carried out; the results of any secondary analyses are exploratory.

6.3.3 Safety

All AEs and medications information will be listed in full. The AE information, including the responses for severity, seriousness, relationship to investigational product, unexpected, and outcome, will be summarized in a table by treatment.

6.3.4 Other Data Summaries

The following variables will be summarized in tables by treatment and overall, using descriptive statistics:

- Reasons for discontinuing participation.
- Treatment duration (by reason for discontinuing participation).
- Reasons for study discontinuation
- Study duration.

7. ADDITIONAL INFORMATION

7.1 USE OF ADDITIONAL MEDICAL SERVICES

A radiological laboratory will be used as appropriate. All CT scans will be interpreted by two independent reviewers.

A Certified laboratory will be used for all hematological and chemistry measurements.

7.2 SOURCE DATA VERIFICATION (SDV)

To enable SDV of the trial data, direct access to the subjects' medical records/data and source notes documentation will be granted to the trial monitor and to auditor(s), IRB(s)/IEC(s) and regulatory authority(-ies), by the subject and institution/Investigator.

The following data in the Consent form and the CRF will be checked for 100% of subjects, against the source notes documentation/medical records/data:

- Consent Form
- Identity Number
- Subject Initials
- Date of Birth
- Sex
- Date of Subject Entry and Completion/Withdrawal from the Trial
- CRF Assessment Dates
- Adverse Events
- Therapy Modifications

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7.3 TRIAL MONITORING

The Trial Monitor will telephone and visit the centers at initiation and then as frequently as is deemed necessary. At a minimum, there will be one interim audit and a close-out audit.

7.4 USE OF TRIAL FINDINGS

The Sponsor, in conjunction with the principal investigator (PI), will prepare an analysis and a report of the results of the trial. The PI shall have the right to include the material contained in this report in relevant articles for scientific journals or presentations at scientific meetings provided that 30 days prior to such publication by the Investigator the Investigator shall submit a copy of the publication or presentation paper to the Sponsor for verification of factual data contained in the publication or presentation paper. The Sponsor shall advise the PI as soon as reasonably practical of any perceived discrepancies within the publication or presentation paper. The Sponsor has the right to modify the presentation/publication if in the opinion of the Sponsor it is likely to be in conflict with the requirements of the regulatory authorities regarding the regulatory status of the product in any of its international markets. The PI and Sponsor shall conduct good faith discussions with the aim of resolving any discrepancies within 21 days of receipt of the proposed publication or presentation paper. The PI shall provide a revised copy (if any) of the publication or presentation paper to the Sponsor prior to publication.

8. ETHICAL AND LEGAL ISSUES

8.1 GOOD CLINICAL PRACTICES (GCP)

The trial will be performed in accordance with the current ICH Good Clinical Practice Guidance for Industry, the Declaration of Helsinki (revised version of Somerset West, Republic of South Africa, 1996), applicable FDA regulations including 21 CFR 50, Protection of Human Subjects and 21CFR 56, Institutional Review Boards and applicable EU regulations including European Commission Directives 2001/20/EC and 2005/28/EC.

8.2 APPROVAL OF PROTOCOL

Before the start of the trial, the investigator will sign the Approval and Agreement page (Section 9) and will submit the trial protocol to the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

The first subject will not be enrolled in the trial until the Trial Monitor has received a copy of the ethics approvals in which the protocol is mentioned by name and number.

8.3 CONFIDENTIALITY

The subject will be identified throughout the evaluation and documentation by the numbers allocated to them during the trial and by their initials. The subjects will be told that all trial findings will be stored on computer and handled in strictest confidence. No record of a subject's name will be kept by the sponsor company.

The signed informed consent forms remain with the investigators. By signing this protocol, the investigators agree to obtain a correctly completed informed consent form from each subject included in the trial. They also agree to keep the forms for 15 years and will allow these to be inspected on request.

8.4 INSURANCE/FINANCIAL

Public/Products Liability Insurance has been purchased by Abyrx. and incorporates coverage for personal injury in respect of clinical trials. The Sponsor agrees to implement in good faith the ABPI guidelines regarding compensation for injury arising in the course of clinical trials. Indemnity and Financial agreements between the Sponsor and the trial center are appended separately.

8.5 SUBJECT CONSENT

Before being admitted to the clinical trial, the subject must have consented to participate, after the nature, scope and possible consequences of the trial have been explained in an understandable form. The subject should be informed of the following aspects:

1. That the trial involves research, a description of the aims of the trial and how it will be organized and the expected duration of the subject's participation.

2. The type of treatment and the way in which the subjects will be allocated to treatment (i.e. by 1:1 randomization).

3. The positive effects which can be expected of the test material.

4. Any negative effects possibly attributable to the test material.

5. Alternative therapeutic approaches.

6. The freedom to ask for further information at any time.

7. The extent, if any, to which confidentiality of records identifying the subjects will be maintained and that the Regulatory Authorities may inspect the records.

8. That participation is voluntary and that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

9. The existence of adequate subject insurance coverage.

The subject's consent must be confirmed by the signature of the Investigator or designated personnel, and subject. The Sponsor will supply the investigator with an adequate number of informed consent forms. The investigator will not undertake any medical measures related to the clinical trial until valid consent has been obtained.

9. REFERENCES

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APPENDIX I
Montage Time/Events Table

Interval	Baseline/ Screening	Operative/ Discharge	Week 2	Week 6	Week 12	Week 24	Week 52	Week 104
Range	Within 30 days of Surgery	N/A	+/- 4 days	+/- 2 wks	+/- 2 wks	+/-3 wks	+/- 6 wks	+/- 6 wks
Consent	X							
Randomization	X							
Treatment		X						
Physical (neuro) Exam	X		X	X	X	X	X	X
Medical History	X							
Charlson Comorbidity index, ASA and ISSg	X							
VAS	X		X	x	X	X	X	X
ODI	X		X	X	X	X	X	X
SRS-22	?		X	X	X	X	X	X
Work Status	X			X	X	X	X	X
Medications	X	X	X	X	X	X	X	X
Smoking Status	X		X	X	X	X	X	X
Blood Chemistry (Hb, Hct, RBC, WBC, Platelet count, MCV, MCHC and differentials	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
SAE/AE		X	X	X	X	X	X	X
Operative data collection		X						
IMAGING								
Radiographs	X		X	X	X	X	X	X
CT Scan	X						X	
Angular Correction and gap measurement					X	X	X	X

[1]to be completed if standard of care

v.3.22.18

APPENDICES A-C HAVE BEEN ADDED TO THE DOCUMENT FOR ABYRX USE ONLY AND DO NOT HAVE ANY IMPACT ON THE PROTOCOL.

Appendix A: Essential Clinical Investigation Documents Prior to Clinical Investigation

Doc #	Title	Purpose/Comments	Reference to Standard	Included (with date)
A1	Investigators Brochure (IB)	Describes the investigational device, including instructions for device use.	5.5, Annex B	
A2	Clinical Investigation Plan (CIP)	Describes the clinical investigation design and procedures.	5.4, Annex A	
A3	Sample of labelling attached to the investigational device	Confirms appropriate labelling.	5.10	
A4	Principal Investigators current CV, ***signed and dated***	Identifies the principal investigator. The site has CVs for principal investigators at that site; the sponsor has CVs for principal investigators from all investigation sites.	4.5.2(e), 9.2(a), Annex D.13(c)	
A5	Current CV of key members of the investigation site team, ***signed and dated***	Identifies the key members of the investigation site team. The site has CVs for key members of investigation site team at that site.	9.2 (a)	
A6	CV or other qualification documentation of individuals other than those cited in A4 and A5, who materially contribute to the clinical investigation, ***signed and dated***	Documents qualification of all other parties involved in clinical investigation.	5.1, 8.2.1, 8.2.4.3	
A7	Log of principal investigator and key members of investigation site team at each investigation site	Documents the attribution of responsibilities, with signature, title, and responsibilities in the clinical investigation.	6.2, 8.2.1(e), 8.2.4.5 (b)	
A8	List of investigation sites	Evidences who is conducting the clinical investigation, with names and addresses.	Annex A 1.4	
A9	Ethics committee (EC) notification, correspondence and opinion/approval	Gives evidence that a qualified, independent EC has reviewed the clinical investigation.	4.5.3, 6.1, 8.2.2(g), 9.4	
A10	EC voting list for the clinical investigation	Provides evidence that the investigator is not part of the voters (dependent on regulatory requirements).	4.5.3	
A11	Regulatory authority notification, correspondence and approval (where required)	Verifies information provided to regulatory authorities. Confirms notification or approval.	6.1, 8.2.2(f)	

Doc #	Title	Purpose/Comments	Reference to Standard	Included (with date)
A12	Signed agreement between principal investigator(s)/investigation site(s) and sponsor	Demonstrates understanding of each party's respective responsibilities.	5.9, 8.2.1(a), 8.2.2(e)	
A13	Signed agreements between sponsors and third parties, e.g. CRO, core laboratories	Demonstrates understanding of each party's responsibilities.	5.9, 8.2.1(a)	
A14	Financial agreements, if separate from agreements on responsibilities	Provides evidence of financial arrangements between investigator/ investigation site and sponsor (can be kept separate from other site files).	8.2.2(e)	
A15	Insurance certificates, if applicable	Gives evidence that compensation to subject(s) for clinical investigation-related injuries will be available.	4.3, 4.5.2(j), 8.2.2(d)	
A16	Shipping records for investigational devices	Verifies physical possession of devices.	6.9, 8.2.2(c), 8.2.3(a), 8.2.4.5(l), 9.6(k)	
A17	Shipping records for clinical investigation-related documents and materials	Verifies physical shipment of documents and materials.	8.2.2(c)	
A18	Sample of approved informed consent forms, information for the subjects and advertisements, including translations	Gives evidence of the content of the informed consent forms and of the information provided to the subject during the clinical investigation.	4.5, 4.7, 8.2.2(a)	
A19	Randomization list for randomized clinical investigations	Verifies that randomization has been followed. Depending on the design of the clinical investigation, the list might not be available at the investigation site for blinded/masked clinical investigations.	6.8.1	
A20	Decoding procedures for blinded/masked clinical investigations, where applicable	Might not take place on the investigation site depending on study design.	6.8.1, Annex A6.1(a), A16(b)	
A21	Investigation site selection report	Verifies that qualifications of investigator and investigation site have been reviewed.	5.8, 8.2.1(b), 8.2.4.3, 8.2.4.7	
A22	Clinical investigation initiation monitoring report	Verifies that investigator and investigation site team have been trained to device use and CIP compliance	6.2, 8.2.4.7	
A23	Follow-up letter further to clinical investigation initiation monitoring; correspondence with the investigation site	Identifies any findings and actions to the investigation site.	8.2.4.7	

Doc #	Title	Purpose/Comments	Reference to Standard	Included (with date)
A24	Case Report Forms (CRF)	Blank set to evidence toe content of data being collected	5.6, Annex C	
A25	Adverse Event Forms	Documents all adverse events as required by the standard (Forms may or may not be part of CRF)	5.6, 6.4.1, Annex C	
A26	Device Deficiency Forms	Document all device deficiencies (Forms may or may not be part of CRF)	5.6, 6.4.2, Annex C	
A27	Name/Contact information of Monitor(s)	Document the person who has ensured continuing compliance of the clinical investigation.	5.1, 8.2.1 (a) 8.2.1 (f) Annex D.13(e)	
A28	Training Records	Provides evidence that investigator(s) have been trained in the use of the investigational device and all relevant aspects of the clinical investigation.	8.2.1(g)	
A29	Disclosure of conflicts of interest	Documentation of conflicts of interest, e.g. financial.	8.2.1(d), 9.2(c)	

Appendix B: Essential Clinical Investigation Documents During Clinical Investigation

Doc #	Title	Purpose/Comments	Reference to Standard	Included (with date)
B1	Investigators Brochure (IB) amendments, if any	Documents changes to the IB	6.5.1	
B2	Clinical Investigation Plan (CIP) amendments, if any	Documents changes to the CIP	6.5.1	
B3	Sample of amendments to informed consent form		6.5.1	
B4	Ethics Committee (EC) opinion/approval of any amendments		4.5.4(d), 4.5.5(a), 8.2.3(b), 8.2.4.5(m), 9.4(c)	
B5	Notices or approvals to regulatory authorities of any amendments, where required	Verifies information provided to authorities, confirms notification of approval	6.1, 8.2.2(f), 8.2.2(h)	
B6	***New*** Principal Investigators current CV, ***signed and dated***	Identifies the principal investigator. The site has CVs for principal investigators at that site; the sponsor has CVs for principal investigators from all investigation sites.	4.5.2(e), 9.2(a), Annex D.13(c)	
B7	CV of ***new*** key members of the investigation site team, ***signed and dated***	Identifies the key members of the investigation site team. The site has CVs for key members of investigation site team at that site.	9.2 (a)	
B8	Shipping records and investigational device accountability records		6.9, 8.2.2(c), 8.2.3(a), 8.2.4.5(l), 9.6(k)	
B9	Shipping records for clinical investigation-related documents and materials		8.2.4.4(a)	
B10	Monitoring visit reports	Provides summary of key findings to the principal investigator	8.2.3(d), 8.2.4.7	
B11	Correspondence related to the clinical investigation, including emails, letters, meeting notes, and phone reports		8.2.3(b), 8.2.4.5(m), 9.6(o)	

Doc #	Title	Purpose/Comments	Reference to Standard	Included (with date)
B12	Updated log of principal investigator and key members of investigation site team at each investigation site, including signature, title, and responsibility in the clinical investigation	Documents the attribution of responsibilities	6.2, 8.2.1(e), 8.2.4.5 (b)	
B13	Signed, dated, and fully executed informed consent forms	Verifies that informed consent has been given	4.7.1, 7.4, 8.2.4.5(f), 9.5	
B14	Source documents		6.5.3, 6.8.2, 9.6(o), 9.7(f)	
B15	CRFs, fully executed	Evidences what data were collected and that their authenticity has been verified by the PI	6.3, 6.8.1, 6.8.2, 8.2.4.5(i), 9.6(j)	
B16	Reports of adverse events, adverse device effects, and device deficiencies	Documents the occurrence and resolution of adverse events and adverse device effects	6.4, 8.2.4.5(j)(k), 8.2.5, 9.8, Annex D 13(g)	
B17	CRF corrections	Gives evidence of any changes, additions, or corrections made to CRFs after data were initially recorded	6.8, 8.2.4.5(i), 9.6(j)	
B18	Reports of adverse events or device deficiencies by sponsor to regulatory authorities or by the PI, where applicable	Filing in investigation sites only where national regulations require notification by the PI	6.4, 7.1, 8.2.5, 9.8	
B19	Reports of adverse events by the PI or the sponsor to the EC, where required		4.5.4	
B20	Reports by sponsor to investigators of adverse events occurring at other investigation sites		8.2.5	
B21	Interim or annual reports by PI to EC, where applicable		4.5.4, 8.2.3(b), 8.2.4.5(m), 9.4, 9.8	
B22	Subject screening log		6.5.2	
B23	Subject identification log		6.5.2	

Doc #	Title	Purpose/Comments	Reference to Standard	Included (with date)
B24	Accountability logs of all the investigational devices at the investigational site, where appropriate		6.9, 8.2.3(a), 8.2.4.5(l), 9.6(k)	
B25	Updated Name/Contact information of Monitor(s), where applicable	Document the person who has ensured continuing compliance of the clinical investigation.	8.2.1 (a) 8.2.1 (f) Annex D.13(e)	
B26	Disclosure of conflicts of interest	Documentation of conflicts of interest, e.g. financial.	8.2.1(d), 9.2(c)	

Appendix C: Essential Clinical Investigation Documents After Clinical Investigation

Doc #	Title	Purpose/Comments	Reference to Standard	Included (with date)
C1	Investigational device accountability at each investigation site		6.9, 7.2(a), 9.6(k)(o)	
C2	Documentation of investigational device return/disposal, where applicable	Documents the proper disposal of biohazardous materials or other materials that require special disposal	6.9, 7.2(a), 9.6(k)	
C3	Completed subject identification log		6.5.2	
C4	Audit certificate (If required or conducted)		6.11, 8.1, Annex D.13(h)	
C5	Close out monitoring report		8.2.4.7	
C6	Notification of clinical investigation close out to the Ethics Committee by principal investigator(s) or sponsor, where required		4.5.4, 7.1, 7.2, 8.2.6(d), 9.4	
C7	Notification of the clinical investigation close out to the regulatory authorities by the principal investigator(s) or sponsor, where required		7.1, 7.2, 8.2.6(d)	
C8	Sponsor's statistical analyses and clinical investigation report		7.3, 8.2.6, Annex D	