FERRING
PHARMACEUTICALS

Protocol (consolidated protocol incorporating amendment 2)

Title of trial: A multi-center, randomized, pivotal study evaluating AMPLEX compared to autogenous bone graft in subjects indicated for arthrodesis surgery involving the hindfoot or ankle
NCT number: NCT03028415
Sponsor trial code: 000226
Date: 14 March 2018

CLINICAL TRIAL PROTOCOL

A Multi-Center, Randomized, Pivotal Study Evaluating AMPLEX® Compared To Autogenous Bone Graft in Subjects Indicated for Arthrodesis Surgery Involving the Hindfoot or Ankle

Trial Code: 000226
Consolidated Protocol Incorporating Amendment 2.0

IDE Number:	G150153
Investigational Device:	AMPLEX® (B2A® Enhanced Ceramic Granules)
Indication:	AMPLEX is indicated for use as an alternative to autograft in hindfoot and ankle fusion procedures that require supplemental graft material, including tibiotalar, talocalcaneal, talonavicular and calcaneocuboid fusions
Phase:	Pivotal IDE
Name and Address of Sponsor:	*Ferring International Pharmascience Center U.S., Inc. (FIPCUS)* *100 Interpace Parkway* *Parsippany, NJ 07054* *1-973-796-1600*
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

A Multi-Center, Randomized, Pivotal Study Evaluating AMPLEX Compared To Autogenous Bone Graft in Subjects Indicated for Arthrodesis Surgery Involving the Hindfoot or Ankle

SIGNATORY INVESTIGATOR(S)

[redacted]

TRIAL SITE(S)

Up to a total of 50 centers; 35-40 US centers and 10-15 Canadian centers

PLANNED TRIAL PERIOD	CLINICAL PHASE
Study Start-up: 6 months Subject Enrollment: 18 months Treatment and Follow-up: 18 months Study Closeout: 4 months	Pivotal

OBJECTIVE

To demonstrate that AMPLEX is non-inferior to autogenous bone graft (ABG) for bone fusion in a population indicated for single, double, or triple hindfoot arthrodesis or ankle arthrodesis surgery with supplemental graft material.

ENDPOINTS

Primary Efficacy Endpoint

- Proportion of subjects who meet all the following criteria for the Subject Performance Composite (SPC) Endpoint at 52 weeks:
  - Improvement in pain on weight-bearing at fusion site (≥ 20 mm reduction from baseline on 100 mm VAS)
  - Absence of significant graft harvest site pain (< 20 mm on 100 mm VAS)
  - Improvement in Foot and Ankle Ability Measure Activities of Daily Living subscale (FAAM-ADL) (≥ 8 points improvement from baseline)
  - Absence of device related or procedure related SAEs (up to Week 52)
  - Absence of secondary surgical or nonsurgical interventions intended to promote fusion (up to Week 52)

Key Secondary Endpoint

- Proportion of subjects who meet the following criteria for Computerized Tomography (CT) radiographic fusion success at 52 weeks:
  - Radiographic evidence of fusion by CT scan (≥ 50% bone bridging across the joint space for the full complement of joints in the absence of secondary surgical or nonsurgical interventions intended to promote fusion)

Secondary Endpoints

- Proportion of subjects achieving CT radiographic fusion success at 12 and 24 weeks (in the absence of secondary surgical or nonsurgical interventions intended to promote fusion)
- Change from baseline in pain on weight-bearing at fusion site at 12, 24, and 52 weeks (≥ 20 mm reduction from baseline on 100 mm VAS)
- ABG harvest site pain at 2, 6, 12, 24, and 52 weeks (< 20 mm on 100 mm VAS)
- Change from baseline in FAAM-ADL at 12, 24, and 52 weeks
- SPC at 12 and 24 weeks
- Change from baseline in Short Form-12 (SF-12) at 24 and 52 weeks

Safety Endpoints

- Frequency, severity and seriousness of Adverse Events (AEs)
- Device or Procedure Related SAEs
- Secondary surgical intervention including revision, removal, reoperation or supplemental fixation
- Subsidence, device migration, nonunion, osteolysis and/or heterotopic ossification in the area surrounding the implant site by radiographic assessment
- Presence of anti-B2A antibodies (Ab) in serum

Pharmacokinetic Assessment

- Plasma B2A levels at Days 1, 2, 4, 7, and 15
- AUC, AUCt, % AUC extrap, Cmax, Tmax, t½, lamda z, CL/F, Vz/F for B2A

METHODOLOGY

The study will be conducted at up to a total of 50 centers; 35-40 US centers and 10-15 Canadian centers, following approval by appropriate oversight and regulatory agencies [Institutional

Review Board (IRB) and Food and Drug Administration, USA (FDA) or the local Research Ethics Board (REB) and Health Canada, respectively]. Following appropriate informed consent procedures, subjects will undergo screening evaluations to determine eligibility before randomization.

Prior to surgery, each subject will have baseline information collected which will include medical history, injury/disease etiology, diagnosis, clinical laboratory assessments (including serum for anti-B2A antibody analysis), pain and disability assessments, in addition to radiographic imaging.

At the screening/pre-operative visit anterior/posterior (A/P), lateral and oblique X-rays will be collected. Historical X-rays, taken up to 24 weeks prior to the planned date of surgery, will also be accepted provided they are inclusive of A/P, lateral and oblique views and are available in a readily copied format [e.g., electronic images on Compact Disc (CD)]. These pre-operative X-rays will be the baseline for subsequent safety evaluation.

As part of eligibility determination, the Investigator will review any relevant diagnostic imaging results and comorbidities to ensure that subjects meet the appropriate eligibility criteria and that ankle or hindfoot arthrodesis surgery with supplemental graft material is indicated. Eligible subjects will be randomized as close to the procedure as possible, preferably on the day of the surgery.

Approximately 480 subjects will be randomized to one of two treatment groups in a 2:1 ratio (320 AMPLEX: 160 ABG).

Surgeries will be performed by board-certified/board eligible orthopedic surgeons. Perioperative prophylactic antibiotics will be administered before surgical incision in accordance with investigational site guidelines. Standard anesthesia procedures will be used. Standard surgical technique will be employed to gain access to each fusion site and to ensure rigid fixation of the fusion site. The joint will be exposed and prepared as per standard practice (please refer to the Surgical Manual for more details). The graft material should be placed in the joint space to minimize the chance of extrusion while maximizing bone-on-bone contact. Once the graft is placed, internal fixation screws will be placed across the joint. At least one (1) and up to three (3) screws can be used per joint. Supplemental pins and staples may be used, as well as supplemental screws and plates external to the fusion site(s). The surgical site will be closed in layers using standard surgical technique. Surgical exposure and technique will be documented on the case report form (CRF).

Subjects will be followed for 78 weeks. Post discharge clinical visits will include visits at 2, 6, 12, 24, 52, and 78 weeks. Adverse event data will be collected throughout the study. The primary endpoint will be assessed at 52 weeks.

A Pharmacokinetic (PK) assessment will be conducted to assess the amount of B2A in blood (plasma) after surgery, on Days 1, 2, 4, 7, and 15, and will include a baseline, pre-procedure evaluation. The PK assessment will include a sub-set of up to approximately 30 AMPLEX subjects, allowing pharmacokinetic evaluation in at least 20 AMPLEX subjects. Both genders will be represented. Blood samples will be collected and processed to plasma for laboratory evaluation (plasma B2A concentration). Data will be descriptive in nature and report, to the extent possible, the following for plasma: AUC, AUCt, % AUC extrap, Cmax, Tmax, t½, lamda z, CL/F, Vz/F.

NUMBER OF SUBJECTS

Approximately 480 subjects will be randomized in a 2:1 ratio (Treatment: Control) with approximately 320 to receive AMPLEX and 160 to receive ABG.

CRITERIA FOR INCLUSION / EXCLUSION

Inclusion Criteria

Subjects enrolled in the study must meet the following inclusion criteria:

1. Signed written informed consent
2. Male or female at least 18 years of age but less than age 75
3. Indicated for ankle or hindfoot arthrodesis and require one of the following arthrodesis procedures:
    - Tibiotalar (ankle)
    - Talocalcaneal (subtalar)
    - Talonavicular
    - Calcaneocuboid
    - Double hindfoot (e.g., talonavicular and talocalcaneal joints)
    - Triple hindfoot (subtalar, talonavicular and calcaneocuboid joints)
4. Presents with pain on weight-bearing of at least 40 mm on a 100 mm VAS at the area indicated for arthrodesis
5. Presents with at least one comorbid risk factor (based on Baumhauer *et al* 2013) that warrant the use of supplemental autogenous bone or allograft
    - Radiographic evidence of bone defect, deficit, subsidence or subchondral cyst
    - More than one joint to be fused
    - Involvement of other adjacent or nonadjacent joints
    - Large surface area
    - Intra-articular or extra-articular deformity
    - Post-traumatic arthritis
    - Diagnosis of osteoporosis
6. The Investigator determines if the joint space(s) can be adequately filled with graft

material (AMPLEX or ABG) according to the following parameters:
  - Single hindfoot joint fusion: up to 5 cm^3
  - Double or triple hindfoot fusion: each individual joint up to 5 cm^3, but overall, not more than 10 cm^3 for the full complement of joints
  - Ankle fusion: up to 10 cm^3
7. Each fused joint can be rigidly stabilized with at least 1 and no more than 3 screws across the fusion plane. (Supplemental pins and staples may be used, as well as supplemental screws and plates external to the fusion site(s).)
8. Willing and able to comply with all study requirements including all postoperative clinical and radiographic evaluations
9. For women of childbearing potential (not post-menopausal for 12 months or surgically sterile), a urine pregnancy test with a negative result must be obtained at screening and on the day of surgery, prior to procedure. These trial participants must commit to adequate birth control (e.g., oral contraceptive, two methods of barrier birth control, or abstinence) through the 78 week follow-up

Exclusion Criteria

Participants who have or meet any of the following exclusion criteria will not be eligible for the Study:

1. Bone deficit requiring a structural graft
2. Charcot foot disease
3. Radiographic evidence of open physes
4. Prior arthroplasty, arthrodesis, major surgical repair or reconstruction of the index ankle or hindfoot joint(s)
5. Requires osteotomy or fusion of any midfoot joints
6. BMI greater than 45 kg/m^2
7. Documented medical history of, or radiographic evidence of, a bone disease (e.g. avascular necrosis) or other condition (e.g., osteolysis) that would preclude the subject from receiving screw fixation in the opinion of the surgeon
8. Requires intramedullary nail fixation or an external fixator
9. Comorbidity that would limit the ability to administer any functional measurements such as FAAM-ADL
10. Has at the time of surgery, a systemic infection or local infection at the site of surgery
11. Medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigator, would preclude participation in the study or potentially decrease survival or interfere with ambulation or rehabilitation (e.g., history of transient ischemic attack, stroke or liver disease)
12. HgbA1c level greater than or equal to 8%

13. Known hypersensitivity to any of the components of the product [e.g. B2A peptide, Hydroxyapatite (HA): beta-tricalcium phosphate (βTCP), ceramic granule]
14. Currently receiving treatment with a drug known to interfere with bone metabolism [e.g., systemic corticosteroid therapy (topical corticosteroid therapy is permissible), methotrexate]
15. Has previously received treatment with a drug known to interfere with bone metabolism [e.g., systemic corticosteroid therapy (topical corticosteroid therapy is permissible), methotrexate] and in the opinion of the investigator could continue to negatively interfere with bone metabolism or bone healing
16. History of any severe allergy or anaphylaxis, or a history of hypersensitivity to protein pharmaceuticals [e.g., monoclonal antibodies or gamma globulins, recombinant Bone Morphogenetic Proteins (BMPs)]
17. Medical condition requiring radiation, chemotherapy or immunosuppression
18. Have a prior or active history of malignancy (except for basal cell carcinoma of the skin)
19. Has a history of autoimmune disease known to effect bone metabolism. Examples include spondyloarthropathies (e.g., ankylosing spondylitis, Crohn's disease, and ulcerative colitis), Juvenile Arthritis, Grave's disease and Hashimoto's thyroiditis; Rheumatoid Arthritis is allowed.
20. Have pathological or genetic liver disease or who have clinically significant, elevated baseline liver function enzymes
21. Has obvious and/or documented alcohol or illicit drug addictions
22. Is a prisoner in a correctional institution/facility
23. Actively involved in litigation or workman's compensation
24. Has participated in clinical studies evaluating investigational devices, pharmaceuticals or biologics within 6 months of randomization
25. Requires chronic therapeutic use of NSAID during the first 6 post-operative weeks (except aspirin up to 325 mg bid for cardiovascular protection and/or DVT prophylaxis)
26. Has previously been treated with, or exposed to, therapeutic levels of synthetic or recombinant BMPs
27. Requires chronic subcutaneous or intravenous heparin therapies

INVESTIGATIONAL DEVICE

AMPLEX, the investigational device, is a synthetic bone graft substitute comprised of two parts; 1) a synthetic bone void filler (BVF) that functions as an osteoconductive scaffold and 2) a synthetic peptide (B2A) that augments osteodifferentiation.

AMPLEX is supplied in kit form (AMPLEX kit) and the components must be combined and utilized in accordance with the Instructions for Use (IFU).

AMPLEX, B2A Enhanced Ceramic Granules (AMPLEX), is the Investigational Device supplied in kit form and must be used as a system. When fully prepared according to the IFU, AMPLEX consists of osteoconductive granules (BVF) with bound synthetic B2A peptide.

The AMPLEX kit contains two sterile, non-pyrogenic components that must be used as a system:

- Part 1: Bone void filler (BVF); 1 to 2 millimeter (mm) diameter granules, 5 cm^3/vial, two (2) vials per kit
- Part 2: Lyophilized B2A Peptide Powder, 2.8 mg/vial

Part 1: BVF consists of two (2) vials of 5 cc, sterile, ceramic granules. The granules are composed of 20% HA and 80% β-TCP.

Part 2: Lyophilized B2A Peptide Powder, is formulated as a sterile product containing 2.8 mg B2A with mannitol and glycine as excipients, and is lyophilized in borosilicate glass vials. Each vial contains a white to off-white caked powder composed of highly purified B2A (acetate salt), mannitol (USP), and glycine (USP) under an atmosphere of nitrogen (nitrogen headspace gas). The vials are closed with a Daikyo V10 RB2-TR FluroTec® coated stopper and with an aluminum-based, flip-top closure.

For preparation of implant-ready AMPLEX by following the instructions in IFU, the lyophilized drug product (DP) is reconstituted in sterile water for injection (WFI). In-use stability of the reconstituted drug product has been demonstrated by measuring purity of the solution following reconstitution over a six (6) hour period. After reconstitution, a defined volume of B2A solution is withdrawn, added to the granules (BVF) and mixed according to the IFU. Implant-ready AMPLEX, with 0.225mg B2A/cm^3 granules should be used within four (4) hours of preparation.

The control material, ABG, is harvested at the discretion of the surgeon from a location other than the graft site, for example, the calcaneus, proximal tibia, distal tibia or iliac crest and administered by surgical implant.

The aggregate volume of graft material (AMPLEX or ABG) utilized in index joints will be at the discretion of the surgeon, provided the joint space(s) can be adequately filled with graft material according to the following parameters:

- Single hindfoot joint fusion: up to 5 cm^3
- Double or triple hindfoot fusion: each individual joint up to 5 cm^3, but overall, not more than 10 cm^3 for the full complement of joints
- Ankle fusion: up to 10 cm^3

ABG will be obtained from a location other than the graft site, for example, the calcaneus, proximal tibia, distal tibia, or iliac crest using standard surgical procedure. The selection of the

ABG harvest site will be at the discretion of the surgeon and based on medical judgment. The harvested bone will be cleaned of soft tissue and morselized. The volume of ABG harvested for treatment will be measured using a syringe.

DURATION OF TREATMENT

Treatment and Follow-up: 78 weeks (primary endpoint at 52 weeks)

SCHEDULE OF ASSESSMENTS

	Screening	Treatment	Follow-up					
Visit number	**V1**	**V2 Procedure**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**
Weeks	**-12**	--	**2**	**6**	**12**	**24**	**52**	**78**
Days	**Days -84 to -1**	**Day 1**	**Day 15 (+/- 3)**	**Day 43 (+/- 14)**	**Day 85 (+/- 14)**	**Day 169 (+/- 30)**	**Day 365 (+/- 30)**	**Day 547 (+/- 30)**
Informed consent	X							
Medical History/ comorbidities	X	X						
Supplemental graft requirement confirmation	X							
Eligibility criteria verification	X	X						
Physical assessment of foot/hindfoot, vital signs	X	X	X	X	X	X	X	X
Pregnancy test [1] (if applicable)	X	X						
Standard Urinalysis [2]	X							
Clin. labs: chemistry and hematology [3]	X		X	X	X			
Immunological Testing for HBV, HCV and HIV	X							
Serum for B2A Ab testing [4]	X			X	X			
Identification of target arthrodesis site	X	X						
Subject randomization [5]		X						
Arthrodesis procedure		X						
Specific intraoperative data collection [6]		X						
Graft material volumes		X						
A/P, lateral and oblique X-rays of hindfoot/ankle	X†	X [7]		X	X	X	X	X
Foot and ankle CT scan					X	X	X	
FAAM-ADL	X				X	X	X	
Weight bearing pain at fusion site VAS	X				X	X	X	

Graft Harvest site pain VAS			X	X	X	X	X	
SF-12	X					X	X	
Adverse event evaluation [8]		X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X

† At the screening/pre-operative visit, A/P, oblique and lateral X-rays will be collected (historical X-rays taken up to 24 weeks prior to the planned date of surgery will also be accepted).
[1] Pregnancy test may be performed within 24 hours of the procedure.
[2] If positive for blood, leukocytes, or nitrite, microscopic unrinalysis will be performed.
[3] HbA1c is to be performed at screening for all subjects.
[4] B2A Antibody testing may continue past the 12 week follow-up visit if there is a positive test at 12 weeks.
[5] The subject will be randomized as close to the time of surgery as possible, with the recommendation that the randomization be performed on the day of the surgical procedure.
[6] See Section 6.1.4 referencing the Surgical Manual.
[7] Perform immediately following surgery or within 1 week following the procedure.
[8] Collected from time of informed consent. Post-treatment outcomes that are evaluated as efficacy endpoints, such as pain on weight-bearing, harvest site pain, etc. will not be reported as AEs

SCHEDULE OF ASSESSMENTS FOR PK SAMPLING

	Screening	Treatment	Follow-up								
Visit number	**V1**	**V2 Procedure**	**V3***				**V4**	**V5**	**V6**	**V7**	**V8**
Weeks	**-12**	--	**2**				**6**	**12**	**24**	**52**	**78**
Days	**Days -84 to -1**	**Day 1**	**Day 2**	**Day 4**	**Day 7**	**Day 15**	**Day 43 (+/- 14)**	**Day 85 (+/- 14)**	**Day 169 (+/- 30)**	**Day 365 (+/- 30)**	**Day 547 (+/- 30)**
PK assessment [1]		X	X	X	X	X					

[1] A sub-set of up to 20 evaluable AMPLEX subjects will have a PK assessment. An additional sample of blood will be collected at pre-procedure and after surgery on Days 1, 2, 4, 7 and 15.
* Visit 3 will also consist of Days 2, 4 and 7, for which there will be an **option for blood to be collected at home by a mobile laboratory unit**.

STATISTICAL METHODS

Sample Size:

Assuming true success rates of the primary endpoint to be 60% for ABG and 62% for AMPLEX groups, respectively, 396 subjects are needed to maintain 85% power to demonstrate non-inferiority of AMPLEX to ABG with a non-inferiority margin of -12% (AMPLEX minus ABG) at a type I error rate of 1-sided 5% in a 2:1 randomization (264 for AMPLEX and 132 for ABG). To account for approximately 15% lost to follow-up, a total of 480 subjects (320 for AMPLEX and 160 for ABG) will be randomized.

Analysis Set:

Modified Intent-to-Treat (mITT) analysis set: The mITT analysis set will include all randomized subjects who have an attempted fusion of the index joint(s).

Per-protocol (PP) analysis set: The PP analysis set will consist of all randomized subjects that: [1] complete the fusion procedure and receive either AMPLEX or ABG as assigned, [2] meet critical study eligibility criteria, and [3] have no significant protocol deviations.

Efficacy Analysis:

The primary efficacy analysis will be based on the mITT population. A sensitivity analysis will be conducted for the PP population. In the analysis on the mITT population, subjects who do not receive the assigned treatment will be analyzed as randomized.

The primary efficacy endpoint will be the proportion of subjects who meet all of the following criteria for the SPC at 52 weeks:

- Improvement in pain on weight-bearing at fusion site (≥ 20 mm reduction from baseline on 100 mm VAS)
- Absence of significant graft harvest site pain (< 20 mm on 100 mm VAS)
- Improvement in Foot and Ankle Ability Measure Activities of Daily Living subscale (FAAM-ADL) (≥8 points improvement from baseline)
- Absence of device related or procedure related SAEs (up to Week 52)
- Absence of secondary surgical or nonsurgical interventions intended to promote fusion (up to Week 52)

The key secondary efficacy endpoint will be the proportion of subjects who meet the following criteria for the CT radiographic fusion success at 52 weeks:

- Radiographic evidence of fusion by CT scan (≥ 50% bone bridging across the joint space for the full complement of joints in the absence of secondary surgical or nonsurgical interventions intended to promote fusion)

The primary and key secondary efficacy endpoints will be analyzed by a fixed-sequence procedure according to the following order to maintain the overall Type 1 error rate to a one-sided 5% for non-inferiority and a one-sided 2.5% for superiority testings.

1. Non-inferiority of AMPLEX to ABG in the primary efficacy endpoint
2. Non-inferiority of AMPLEX to ABG in the key secondary efficacy endpoint
3. Superiority of AMPLEX to ABG in the key secondary efficacy endpoint
4. Superiority of AMPLEX to ABG in the primary efficacy endpoint

Testing procedure will begin with the non-inferiority in the primary efficacy endpoint, and each test will be conducted without adjustment of multiplicity as long as all preceding tests are significant. The non-inferiority will be claimed if the lower bound of the 2-sided 90% confidence interval (CI) for the difference in the proportions (AMPLEX minus ABG) is greater than -12.0%.

The superiority will be claimed if the lower bound of the 2-sided 95% CI is greater than zero. The CI will be constructed with the normal approximation to the binomial.

For the primary and key secondary analyses, the last observation carried forward (LOCF) approach will be used for subjects with missing SPC endpoint at 52 weeks.

Safety Analysis:
All safety endpoints will be descriptively summarized.

Pharmacokinetic Assessment:
Pharmcokinetic (PK) data will be descriptively tabulated and summarized for plasma AUC, AUCt, % AUC extrap, Cmax, Tmax, t½, lamda z, CL/F, Vz/F.

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LIST OF ABBREVIATIONS & DEFINITION OF TERMS

List of Abbreviations

Ab	Antibody
ABG	Autogenous Bone Graft
AE	Adverse Event
A/P	Anterior/Posterior
ALT	Alanine Transaminase
APT	Alkaline Phosphatase
ASA	Acetylsalicylic Acid
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BID	Twice daily
BMI	Body Mass Index
BMP	Bone Morphogenetic Proteins
BMP-2	Bone Morphogenetic Protein 2
BMPR	Bone Morphogenetic Protein Receptors
βTCP	Beta-Tri-Calcium-Phosphate
BVF	Bone Void Filler
cc	Cubic Centimeter
CEC	Clinical Events Committee
CD	Compact Disc
CI	Confidence Interval
cm	Centimeter
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CT	Computerized Tomography
eCRF	Electronic Case Report Form
DMC	Data Monitoring Committee
DP	Drug Product
DVT	Deep Vein Thrombosis

FAAM-ADL	Foot and Ankle Ability Measure – Activities of Daily Living
FDA	Food and Drug Administration, USA
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GMP	Good Manufacturing Practice
HA	Hydroxyapatite
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IFU	Instructions For Use
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISO	International Standard Organization
kg	Kilogram
LOCF	Last Observation Carried Forward
MCID	Minimal Clinically Important Difference
MDC	Minimal Detectable Change
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intention-to-Treat
mL	Milliliter
mm	Millimeter
NCS	Not Clinically Significant
NIH	U.S. National Institutes of Health
NLM	National Library of Medicine
NSAID	Non-Steroidal Anti-inflammatory Drug
PK	Pharmacokinetic
PP	Per-Protocol
PT	Preferred Term
REB	Research Ethics Board
REP	Radiographic Evaluation Protocol

RHPDGF	Recombinant Human Platelet-Derived Growth Factor
RHPDGF-BB	Recombinant Human Platelet-Derived Growth Factor-BB
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-12	Short Form-12
SOC	Systems Organ Class
SPC	Subject Performance Composite
SRM	Site Reference Manual
TEAE	Treatment Emergent Adverse Event
UADE	Unanticipated Adverse Device Effect
WFI	Water for Injection
WHO-Drug	World Health Organization Drug Dictionary
VAS	Visual Analog Scale

Pharmacokinetic Terms and Definitions

AUC	Area under the concentration-time curve from dosing to infinity
AUC_t	Area under the concentration-time curve from dosing up to time t, where t is the last time point at which the concentration is above the lower limit of quantification
% AUC_{extrap}	Percentage of AUC that is due to extrapolation from the last measurable concentration
C_{max}	Maximum concentration observed
CL	Clearance
F	Bioavailability
λ_z	First-order rate constant associated with the terminal (log-linear) portion of the concentration-time curve
NCA	Non-compartmental analysis
$t_{½}$	Terminal elimination half-life
t_{max}	Time of maximum observed concentration (C_{max})
V_z	Distribution volume

1 INTRODUCTION

1.1 Background

The foot and ankle articular complex must work in concert to enable normal ambulation and movement. In some individuals, either from traumatic injury or due to the degenerative effects of arthritis, motion at one or more of these joints becomes markedly painful, resulting in impaired function and quality of life.[1] When non-operative measures are no longer effective, arthrodesis is an accepted operative treatment option for patients with severe pain or disability caused by arthritis or deformity of the ankle or hindfoot.

Approximately 110,000 foot and ankle arthrodesis were performed in the United States in 2009 and this number is increasing annually because of both an aging population and the continued prevalence of contributory comorbidities.[2] Arthrodesis is designed to relieve pain and restore function associated with the numerous maladies that cause joint destruction, including trauma, diabetes, inflammatory arthridities, seronegative arthropathy, instability, malalignment, and congenital.[3-8] Although arthrodesis has long been the mainstay of surgical treatment for foot and ankle arthritis, nonunion of the intended fusion construct remains one of the most common complications resulting in morbidity and disability.[9-11] In fact, there are a number of factors associated with a higher risk for a nonunion result, including: age $\geq$ 60 years, obesity, diabetes mellitus and tobacco product use, etc., which often requires the use of bone grafting to improve fusion rates and, ultimately long-term clinical outcomes.[12]

The biological process involved in bone regeneration requires (i) osteogenic potential that is capable of directly providing cells to the newly forming bone, (ii) osteoinductive factors that are able to cause the osteoblastic differentiation of osteogeprogenitor stem cells and (iii) osteoconductive scaffold that facilitate the neovascularization and supports the ingrowth of bone.

Successful fusion surgery must engage the bone regeneration process to produce new bone to bridge the area previously occupied by the joint space and articular cartilage. To enable this process, orthopedic surgeons often will harvest bone, known as autologous bone graft (ABG), from elsewhere in the body to fill the joint.

ABG provides an effective osteoconductive scaffold for new bone formation and contains appropriate growth factors and cells to potentiate new bone formation (osteoinductive). The availability of locally-harvested bone in ankle or foot arthrodesis can be limited, therefore, a second harvest site is often required from either the iliac crest, proximal or distal tibia to facilitate the acquisition of enough bone to support the graft substitute application. Harvesting ABG, however, is associated with both short- and long-term morbidity. Complications of autograft harvest include blood loss, postoperative pain, fracture, infection, other non-infectious wound complications, heterotopic bone formation, hernia, and nerve injury.[13-16] Baumhauer and colleagues recently

reported the results of a prospective randomized study of patients undergoing ankle and hindfoot fusion procedures using ABG harvested from one of four sites (iliac crest, proximal tibia, distal tibia, and calcaneus). Clinically significant pain at the bone graft harvest site was reported by 35% of patients 3 weeks postoperatively and 18% had persistent pain up to 1 year.[17] A review of the literature suggests that the overall complication rate from tibial graft sites, although it has become a favored source for autograft material for foot and ankle surgery, is 5.5%.[18] These complications range in severity from hematoma/seroma and paresthesia to infection, fracture and invasion of the joint space.

Though advances have been made in improving the safety and efficacy of foot and ankle arthrodesis procedures by utilizing better fixation devices, more recent emphasis has been placed on the biological aspects of bone healing and the development of alternatives that eliminate the need to harvest bone graft to augment fusion.[19] AMPLEX is in development as an alternative to ABG in hindfoot and ankle fusion procedures that require supplemental graft material, including tibiotalar, talocalcaneal, talonavicular and calcaneocuboid fusions. This investigational bone graft substitute is comprised of two parts: 1) bone void filler (BVF) granules made from hydroxyapatite (HA) and beta tricalcium-phosphate (βTCP) that functions as an osteoconductive scaffold and 2) the synthetic peptide B2A that augments local osteodifferentiation. Clinical studies on AMPLEX demonstrated benefit as a bone substitute without the need for a second procedure and the resulting morbidity associated with that second procedure. In a pilot randomized study of 24 subjects comparing AMPLEX to ABG, bone fusion was similar in both groups, and the AMPLEX group demonstrated improvements in bone density, healing and patient functional capacity.[20] No device-related complications were reported.

1.2 Scientific Justification for Conducting the Trial

AMPLEX is an investigational medical device supplied in kit form (AMPLEX kit) and must be used as a system. When fully prepared, AMPLEX consists of osteoconductive ceramic granules (BVF) mixed with synthetic B2A peptide. The principal mode of action of the device is based on the osteoconductive granules that act as a scaffold for cellular ingrowth; B2A augments that action. The sterile ceramic granules, supplied by a third party vendor, are currently cleared for use as a BVF for bony voids or gaps of the skeletal system (e.g., extremities, spine and pelvis) that are not intrinsic to the stability of the bony structure. These defects may be surgically- or traumatically-created osseous defects to the bone (K063527, MBCP+).[21]

The primary mode of action of AMPLEX is achieved by the osteoconductive ceramic granules. [22-26] The granules provide a biocompatible scaffold that enables the migration, proliferation and differentiation of host pre-osteoblast cells, the basis of bone repair. B2A, a synthetic peptide, complements the action of the granules by facilitating osteodifferentiation through its actions on bone morphogenetic protein receptors (BMPRs), augmenting the cell response to local bone morphogenetic proteins (BMPs).[27-32]

The growth and differentiation of pre-osteoblasts on the ceramic granules is assisted and complemented by B2A in a cooperative process with the native osteoinductive proteins generated as a part of normal bone healing. B2A therefore acts primarily as a selective positive receptor modulator, increasing the sensitivity of cells to natural (endogenous), physiologically-active levels of BMP-2, and thereby augmenting osteodifferentiation. The augmentation of osteodifferentiation can only occur, however, when B2A and BMP-2 are each above their respective biological threshold levels. This only occurs at the implant site where the B2A-coated granules are located and where BMP-2 is up-regulated as a part of the normal bone healing process. Over time, the scaffold is naturally resorbed by the body, leaving only the newly formed bone in its place.

The control material used in this study, ABG, is harvested from a location other than the graft site, for example, the calcaneus, proximal tibia, distal tibia or iliac crest, and administered by standard surgical procedure. The selection of the ABG harvest site is at the discretion of the surgeon and based on medical judgment. The harvested bone is cleaned of soft tissue and morselized in standard fashion.

1.3 Benefit / Risk Aspects

Arthrodesis remains the most common surgical procedure for patients with debilitating ankle and hindfoot arthritis. Average nonunion rates remain high (10-15%) but can be substantially higher in patients with co-morbid factors such as diabetes and other metabolic diseases, obesity, smoking, age $\geq$ 65 and osteoporosis.[33] The data with both ABG and bone graft replacement products, particularly in light of their nearly ubiquitous use in this setting and the apparent equivalence of their fusion rates, suggest that a major differentiator is the lack of pain, dysfunction and morbidity related to graft donor sites when bone graft replacement products are utilized.

The inclusion of patient reported outcomes, functional evaluations and quality of life assessments is therefore important in evaluating the differences between these approaches. The current clinical trial was designed with this in mind, incorporating both radiologic assessment of fusion rate and validated scales to assess pain and functional outcome.[34-40]

1.4 Clinical Benefit

The proposed clinical study is designed to demonstrate that AMPLEX is non-inferior to ABG for bone fusion in a population indicated for single, double, or triple hindfoot arthrodesis or ankle arthrodesis surgery with supplemental graft material. The potential benefit to AMPLEX subjects is successful fusion of the ankle or hindfoot via an operation that is smaller in magnitude and devoid of the risks and additional pain associated with the harvesting of autogenous bone graft. Subjects who receive AMPLEX may experience the following potential benefits:

1. Similar rate of fusion compared to autograft without the additional risks of the autograft procedure (i.e., harvest site pain, longer anesthetic and longer procedure, harvest site infection, harvest site fracture, or other complications)
2. Higher rate of fusion compared to autograft without the additional risks of the autograft procedure
3. Similar or higher rate of fusion at earlier time points than autograft without the additional risks of the autograft procedure
4. Similar or larger extent of fusion as measured by trabecular bridging of bone across the fusion site.

1.5 Analysis of Increased Risks to Treatment Subjects

Pre-clinical testing and pilot studies conducted outside the United States indicate that AMPLEX should be safe and effective. However, until this is proven in a prospective, randomized clinical trial utilizing a concurrent control group comprised of subjects undergoing ankle or hindfoot fusions, subjects receiving AMPLEX may experience increased risk of:

1. Allergic reaction (local or systemic response)
2. Ectopic bone growth (bone forming outside of normal bone growth areas)
3. Abnormal cell growth (growth of tissue or cells beyond the norm)
4. Negative effects on pregnancy or fetus
5. Immune response (bodily response against foreign material)
6. Significant increase in liver enzyme measures

Table 1. Below describes these increased risks to treatment subjects and their mitigation. Additional descriptions of procedure and study related risks are provided in Appendix 1, Anticipated Adverse Events.

Table 1 Risks: Description & Mitigation

Risks	Description/Mitigation
Allergic reaction (local or systemic response)	Biocompatibility testing has been performed on the AMPLEX material demonstrating a minimal reactivity. Monitoring of study conduct and safety data will be conducted on an ongoing basis by Sponsor and Data Monitoring Committee, governed by a Charter. If these groups identify any new or unforeseen risks they will notify the Sponsor and render an opinion on potential study modifications/stopping.
Ectopic bone growth (bone forming outside	Osteoconductive materials, including allograft bone, have a risk of ectopic bone growth. The preclinical battery of in-

of normal bone growth areas)	vitro and in-vivo animal testing performed on AMPLEX has not identified any instances of exuberant bone growth. It has also not been seen in any of the feasibility clinical cases. Monitoring of study conduct and safety data will be conducted on an ongoing basis by Sponsor and Data Safety Monitoring Committee, governed by a Charter. Evidence of this would be detectable on the CT scans used to evaluate efficacy. If these groups identify any new or unforeseen risks they will notify the Sponsor and render an opinion on potential study modifications/stopping.
Abnormal cell growth (growth of tissue or cells beyond the norm)	An extensive preclinical battery of in vitro and in vivo animal testing of AMPLEX and PREFIX did not identify an impact on tumor cell growth, tumor promotion, or metastatic behavior, thus minimizing the potential for such an event to occur with the treatment device. The study enrollment criteria include an exclusion for subjects with a prior history of active malignancy with the exclusion of basal cell carcinoma of the skin. Monitoring of study conduct and safety data will be conducted on an ongoing basis by Sponsor and Data Monitoring Committee, governed by a Charter. If these groups identify any new or unforeseen risks they will notify the Sponsor and render an opinion on potential study modifications/stopping.
Negative effects on pregnancy or fetus	The preclinical testing has projected that the B2A component of AMPLEX is completely eliminated within six weeks of implantation and during that time that circulating B2A levels are quite low. Therefore, the risk of an effect on a fetus is unlikely. However, to avoid this potential risk, female subjects are excluded from the trial if they are pregnant or lactating, or intend to become pregnant during the course of this study. Monitoring of study conduct and safety data will be conducted on an ongoing basis by Sponsor and Data Monitoring Committee, governed by a Charter. If these groups identify any new or unforeseen risks they will notify the Sponsor and render an opinion on potential study modifications/stopping.
Immune response (bodily response against foreign material)	Pre-clinical and clinical immunogenicity testing during PREFIX and AMPLEX development have not demonstrated any immune reactions nor development of significant anti-B2A antibody formation.

	Although remote, based on the established data, this risk is mitigated through single exposure to AMPLEX and the protocol specified assessment of antibody response. Despite this being a remote risk, monitoring of study conduct and safety data will be conducted on an ongoing basis by Sponsor and Data Monitoring Committee, governed by a Charter. If these groups identify any new or unforeseen risks they will notify the Sponsor and render an opinion on potential study modifications/stopping
Elevated liver enzymes (from the B2A peptide)	Transient excursions in lab values, specifically liver function enzymes, have been noted in the pilot clinical studies conducted in both the treatment and control groups. After extensive consultation with various experts, it was determined that these elevations are largely related to surgery itself, concomitant medications and pre-existing conditions. Despite this being a remote risk, monitoring of study conduct and safety data will be conducted on an ongoing basis by Sponsor and Data Monitoring Committee (DMC), governed by a Charter. If these groups identify any new or unforeseen risks they will notify the Sponsor and render an opinion on potential study modifications/stopping.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

The primary objective of this pivotal study is to demonstrate that AMPLEX is non-inferior to ABG for bone fusion in a population indicated for single, double, or triple hindfoot arthrodesis or ankle arthrodesis surgery with supplemental graft material.

2.2 Endpoints

2.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects who meet all the following criteria for the Subject Performance Composite (SPC) Endpoint at 52 weeks:

- Improvement in pain on weight-bearing at fusion site (≥ 20 mm reduction from baseline on 100 mm VAS)
- Absence of significant graft harvest site pain (< 20 mm on 100 mm VAS)
- Improvement in Foot and Ankle Ability Measure Activities of Daily Living subscale (FAAM-ADL) (≥ 8 points improvement from baseline)
- Absence of device related or procedure related SAEs (up to Week 52)
- Absence of secondary surgical or nonsurgical interventions intended to promote fusion (up to Week 52)

2.2.2 Secondary Endpoints

The key secondary endpoint is the proportion of subjects achieving CT radiographic fusion success at 52 weeks:

- Radiographic evidence of fusion by CT scan (≥ 50% bone bridging across the joint space for the full complement of joints in the absence of secondary surgical or nonsurgical interventions intended to promote fusion)

The other secondary endpoints are as follows:

- Proportion of subjects achieving CT radiographic fusion success at 12 and 24 weeks (in the absence of secondary surgical or nonsurgical interventions intended to promote fusion)
- Change from baseline in pain on weight-bearing at fusion site at 12, 24, and 52 weeks (≥ 20 mm reduction from baseline on 100 mm VAS)
- ABG harvest site pain at 2, 6, 12, 24, and 52 weeks (< 20 mm on 100 mm VAS)
- Change from baseline in FAAM-ADL at 12, 24 and 52 weeks
- SPC at 12 and 24 weeks
- Change from baseline in Short Form-12 (SF-12) at 24 and 52 weeks

2.2.3 Safety Endpoints

The safety endpoints are as follows:

- Frequency, severity and seriousness of Adverse Events (AEs)
- Device or Procedure Related SAEs
- Secondary surgical intervention including revision, removal, reoperation or supplemental fixation
- Subsidence, device migration, nonunion, osteolysis and/or heterotopic ossification in the area surrounding the implant site by radiographic assessment
- Presence of anti-B2A antibodies (Ab) in serum

2.2.4 Pharmocokinetic Endpoints

- Plasma B2A levels at Days 1, 2, 4, 7, and 15
- Plasma AUC, AUCt, Cmax, Tmax, t½, CL/F, Vz/F for B2A

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Trial Design Diagram

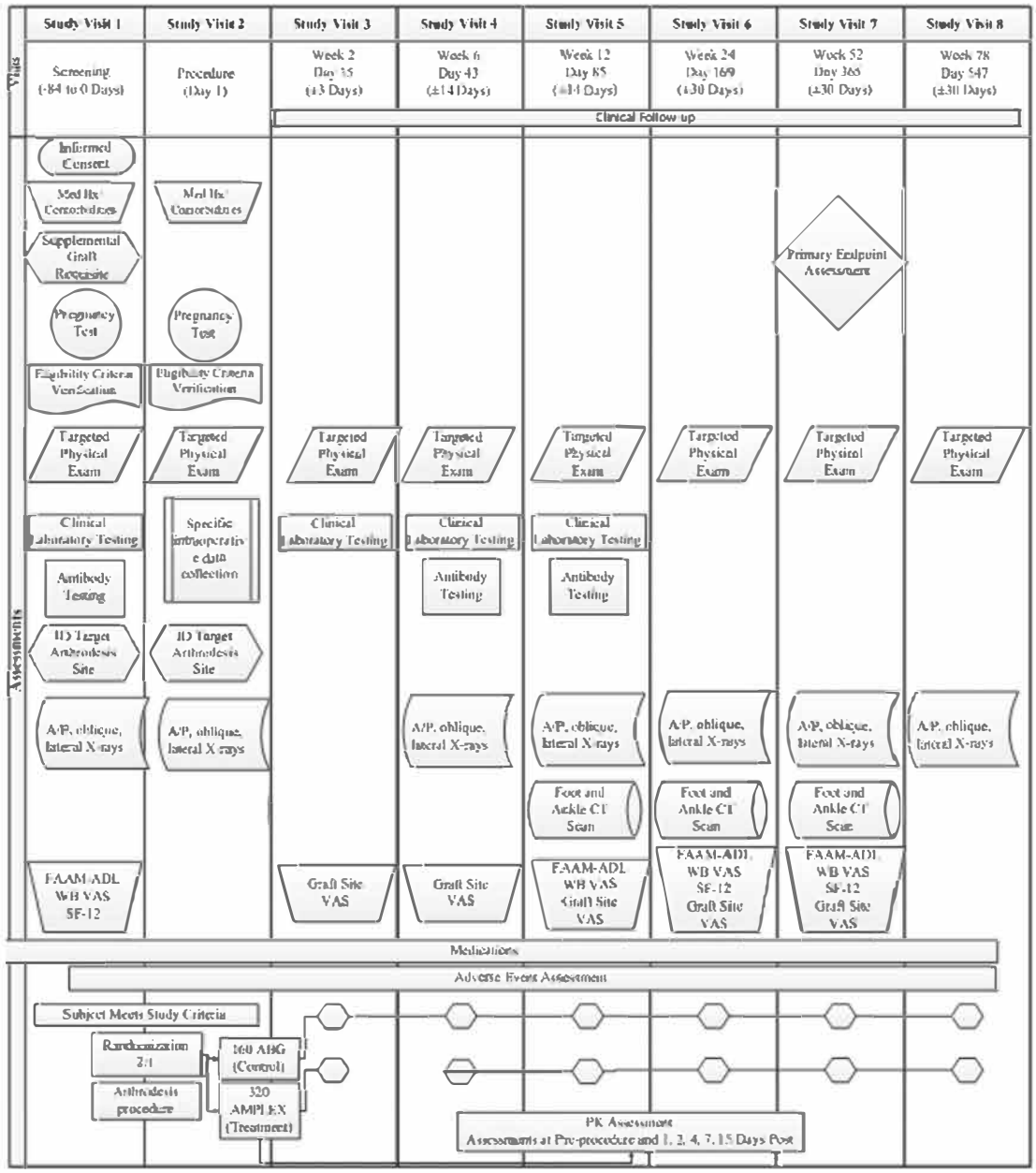

Figure 1 Trial Design Diagram

3.1.2 Trial Schedule

Investigational Device Exemption (IDE) Approval: 20 November 2015
Study Start-up: 6 months

Subject Enrollment: 18 months
Treatment and Follow-up: 18 months
Study Closeout: 4 months
Total Duration: 46 months

3.2 Planned Number of Trial Sites and Subjects

The study will be conducted at up to a total of 50 centers; 35-40 US centers and 10-15 Canadian centers, following approval by appropriate oversight committees and regulatory agencies [Institutional Review Board (IRB) and Food and Drug Administration, USA (FDA) or the local Research Ethics Board (REB) and Health Canada, respectively] with informed consent obtained from all subjects.

Approximately 480 subjects will be randomized in a 2:1 ratio (Treatment: Control) with approximately 320 to receive AMPLEX and 160 to receive ABG.

3.3 Study Oversight

3.3.1 Clinical Events Committee

An independent group of physicians that are not involved in the clinical investigations will act as the Clinical Events Committee (CEC). The CEC will be responsible for the review and adjudication of Investigator-reported events and events identified in the monitoring process. Any potential device, ancillary device or procedural related AEs, all events associated with secondary surgical intervention, and any other AEs specified in the CEC Charter will be adjudicated. Subsequent to Investigator determination of severity and relatedness of the event, the CEC shall classify each of these adverse events based on severity and association to the device and/or procedure. During the review of the events, the CEC will be blinded to the clinical site and treatment. The CEC Charter will be developed upon identification of committee members and shall include consistent definitions for each type of event and shall outline the review process.

3.3.2 Data Monitoring Committee

An independent panel of medical and biostatistics experts will serve in the capacity of Data Monitoring Committee (DMC). The DMC will periodically review clinical study data to ensure patient safety, trial integrity, and scientific rigor. DMC members will have relevant orthopedic experience and medical knowledge of the product under investigation. The DMC will develop and ratify a Charter that provides guidelines for oversight of trial safety. The Charter will define the scope and DMC's responsibilities, quorum, operating guidelines, sample template for required data analyses, pre-defined stopping rules, communication pathway to the study Sponsor, and frequency of meetings.

3.3.3 Imaging Core Laboratory

An independent imaging core laboratory will be utilized for assessment of radiographic images at each follow-up visit in which a radiographic image is obtained. A comprehensive description of the imaging methodology will be detailed in an imaging core lab Radiographic Evaluation Protocol (REP) provided in the Site Reference Manual (SRM). All radiographic imaging shall be performed in accordance with this protocol.

Prior to development of the REP, the imaging core laboratory conducted a Radiographic Image Review and Validation Assessment to determine the impact of any potential confounding factor (i.e., metallic screws in the graft site, radio-opacity of the graft material) on the ability of readability of the images and utilized the information to develop the REP.

The assessment of fusion status and device condition shall be performed by an independent imaging core lab in compliance with their REP provided in the SRM. Results of these assessments will not be adjudicated by the CEC,

3.4 Discussion of Overall Trial Design and Choice of Control Groups

3.4.1 Trial Design

This is a prospective, multi-center clinical trial in subjects (≥18 and <75 years of age) undergoing tibiotalar (ankle) arthrodesis or single, double, or triple hindfoot (talocalcaneal-, calcaneocuboid- or talonavicular-joint) arthrodesis with supplemental graft material and internal fixation with up to 3 screws per joint.

Subjects will be followed for 78 weeks. Post-discharge clinical visits will include visits at 2, 6, 12, 24, 52 and 78 weeks. Adverse event data will be collected throughout the study. The primary endpoint will be assessed at 52 weeks.

The objective of the trial is to demonstrate that AMPLEX is non-inferior to ABG for bone fusion in a population indicated for ankle arthrodesis or single, double, or triple hindfoot arthrodesis surgery with supplemental graft material. The study will be declared successful if non-inferiority of AMPLEX compared to ABG in the primary efficacy endpoint is demonstrated in the mITT analysis population within a non-inferiority margin of -12.0% at a type I error rate of 1-sided 5%.

3.4.2 Selection of Endpoints

The primary endpoint of this trial is the success in the SPC, which consists of improvement in pain on weight bearing at fusion site, absence of significant graft harvest site pain, functional improvement, absence of device related SAEs or procedure related SAEs and absence of secondary surgical or non-surgical interventions intended to promote fusion. This endpoint is considered to provide relevant assessment to determine the benefit/risk profile of the investigational device (AMPLEX) compared to the control material (ABG) used in arthrodesis surgery involving hindfoot or ankle.

Functional improvement will be measured by the FAAM-ADL. It is a reliable and valid self-assessment instrument that was specifically developed to measure physical function for subjects with foot and ankle disorders (Martin, Irrgang, Burdett, Conti, & van Swearingen, 2005). The validity evidence for test content, internal structure, score stability, and responsiveness was demonstrated in 243 subjects including 51 (21%) subjects who underwent foot and ankle related surgery (Martin, Irrgang, Burdett, Conti, & van Swearingen, 2005). The reliability and responsiveness were further demonstrated in 311 subjects who underwent elective surgery for a foot or ankle related disorder (Hung, Baumhauer, Brodsky, & al., 2014). The minimal detectable change (MDC) and minimal clinically important difference (MCID) were identified as 5.7 and 8 points (Martin, Irrgang, Burdett, Conti, & van Swearingen, 2005).

Both harvest site pain and pain on weight bearing at fusion site will be measured by the 100 mm VAS. The 100mm VAS is a reliable self-assessment instrument commonly used in the assessment of pain. The VAS has been widely used in the clinical arena and research setting (Hawker, Mian, Kendzerska, & French, 2011) and is frequently employed in patients with musculoskeletal disorders (Tubach, et al., 2012). Minimal clinically important improvement in pain has been reported for knee and hip osteoarthritis at 19.9 mm and 15.3 mm respectively (Tubach, et al., 2005, p. 31). Additionally, improvement in baseline weight-bearing pain of >20 mm has been used as a component of a subject performance composite endpoint in other studies of ankle and hindfoot fusion. (FDA Orthopaedic and Rehabilitation Devices Division, 2011 [May]) (Daniels, et al., 2015, pp. 743-746) (Baumhauer J. et al, 2014, p. 107).

CT imaging is logistically feasible, is a meaningful endpoint and has been used in past FDA studies. It reflects the proposed benefit of the therapies, the underlying clinical condition and has precedence for use. Its use is also independent of the assigned randomization and would therefore represent an objective measure of efficacy. Consistent interpretation in these complex anatomies is important in obtaining unbiased assessments, supporting the use of an independent imaging core lab with expertise in this area for image interpretation. The blinding of radiographic reviewers from clinical information further adds to the validity of the assessments. Although there may be radiographic differences observed in the treatments, the blinding of the reviewers in this trial is consistent with the current draft guidance on imaging in clinical trials.[44]

3.4.3 Blinding

The Investigator cannot be blinded to the device because of system-specific requirements for use. The independent radiologist(s) at the imaging core laboratory will remain formally blinded to the treatment assignment. In addition, PK assessment will not be performed in a blinded manner. Blinding of the subjects is not possible due to the need for a surgical incision at a secondary site in the control group. Since subjects may not be blinded due to the presence of a second surgical site for the ABG Control treatment, subjects will be blinded until after the procedure to mitigate the impact of unblinded randomization and potential subsequent withdrawal of consent prior to treatment. In this process and following appropriate informed consent procedures, subjects will undergo screening evaluations to determine eligibility before randomization. Eligible subjects will then be randomized as close to the procedure as possible.

3.4.4 Trial Population

Subjects will be ≥18 and < 75 years of age and candidates for tibiotalar (ankle) arthrodesis or single, double, or triple hindfoot (talocalcaneal-, calcaneocuboid- or talonavicular-joint) arthrodesis with supplemental graft material. Subjects shall be screened prior to randomization to ensure they meet inclusion/exclusion criteria. The screening will include a review of all imaging and critical comorbid risk factors for nonunion by the Investigator.

A Pharmacokinetic (PK) assessment will be conducted in a sub-set of subjects to assess the amount of B2A in blood (plasma) after surgery, on Days 1, 2, 4, 7, and 15, and will include a baseline, pre-procedure evaluation. The sub-set of subjects will include up to approximately 30 AMPLEX subjects, allowing pharmacokinetic evaluation in at least 20 AMPLEX subjects. Both genders will be represented. Blood samples will be collected and processed to plasma for laboratory evaluation (plasma B2A concentration).

3.4.5 Withdrawal Criteria

A study subject will be discontinued from participation in the study if:

- The Investigator feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures would not be in the best interest of the subject.
- The subject is lost to follow up. A subject will be considered "lost to follow-up" and terminated from the study when all of the following criteria have been met:
    - Failure to complete the remainder of the scheduled study visits without due cause; and
    - Documentation of three unsuccessful attempts to contact the subject via telephone and by certified mail.
- The subject wishes to withdraw their consent for participation in the study.

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

4.1.1 Inclusion Criteria

Subjects enrolled in the study must meet the following inclusion criteria:

1. Signed written informed consent
2. Male or female at least 18 years of age but less than age 75
3. Indicated for ankle or hindfoot arthrodesis and require one of the following arthrodesis procedures:
    - Tibiotalar (ankle)
    - Talocalcaneal (subtalar)
    - Talonavicular
    - Calcaneocuboid
    - Double hindfoot (e.g., talonavicular and talocalcaneal joints)
    - Triple hindfoot (subtalar, talonavicular and calcaneocuboid joints)
4. Presents with pain on weight-bearing of at least 40 mm on a 100 mm VAS at the area indicated for arthrodesis
5. Presents with at least one comorbid risk factor (based on Baumhauer *et al* 2013) that warrant the use of supplemental autogenous bone or allograft
    - Radiographic evidence of bone defect, deficit, subsidence or subchondral cyst
    - More than one joint to be fused
    - Involvement of other adjacent or nonadjacent joints
    - Large surface area
    - Intra-articular or extra-articular deformity
    - Post-traumatic arthritis
    - Diagnosis of osteoporosis
6. The Investigator determines the joint space(s) can be adequately filled with graft material (AMPLEX or ABG) according to the following parameters:
    - Single hindfoot joint fusion: up to 5 cm^3
    - Double or triple hindfoot fusion: each individual joint up to 5 cm^3, but overall, not more than 10 cm^3 for the full complement of joints
    - Ankle fusion: up to 10 cm^3
7. Each fused joint can be rigidly stabilized with at least 1 and no more than 3 screws across the fusion plane. (Supplemental pins and staples may be used, as well as supplemental screws and plates external to the fusion site(s).)
8. Willing and able to comply with all study requirements including all postoperative clinical and radiographic evaluations
9. For women of childbearing potential (not post-menopausal for 12 months or surgically sterile), a urine pregnancy test with a negative result must be obtained at screening and within 24 hours prior to procedure. These trial participants must commit to adequate birth control (e.g., oral contraceptive, two methods of barrier birth control, or abstinence) through the 78 week follow-up

4.1.2 Exclusion Criteria

Participants who have or meet any of the following exclusion criteria will not be eligible for the Study:

1. Bone deficit requiring a structural graft
2. Charcot foot disease
3. Radiographic evidence of open physes
4. Prior arthroplasty, arthrodesis, major surgical repair or reconstruction of the index ankle or hindfoot joint(s)
5. Requires osteotomy or fusion of any midfoot joints
6. BMI greater than 45 kg/m^2
7. Documented medical history of, or radiographic evidence of, a bone disease (e.g. avascular necrosis) or other condition (e.g., osteolysis) that would preclude the subject from receiving screw fixation in the opinion of the surgeon
8. Requires intramedullary nail fixation or an external fixator
9. Comorbidity that would limit the ability to administer any functional measurements such as the FAAM-ADL
10. Has at the time of surgery, a systemic infection or local infection at the site of surgery
11. Medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigator, would preclude participation in the study or potentially decrease survival or interfere with ambulation or rehabilitation (e.g., history of transient ischemic attack, stroke or liver disease)
12. HgbA1c level greater than or equal to 8%
13. Known hypersensitivity to any of the components of the product [e.g. B2A peptide, Hydroxyapatite (HA): beta-tricalcium phosphate (βTCP), ceramic granule]
14. Currently receiving treatment with a drug known to interfere with bone metabolism [e.g., systemic corticosteroid therapy (topical corticosteroid therapy is permissible), methotrexate]
15. Has previously received treatment with a drug known to interfere with bone metabolism [e.g., systemic corticosteroid therapy (topical corticosteroid therapy is permissible), methotrexate] and in the opinion of the investigator could continue to negatively interfere with bone metabolism or bone healing
16. History of any severe allergy or anaphylaxis, or a history of hypersensitivity to protein pharmaceuticals [e.g., monoclonal antibodies or gamma globulins, recombinant Bone Morphogenetic Proteins (BMPs)]
17. Medical condition requiring radiation, chemotherapy or immunosuppression
18. Have a prior or active history of malignancy (except for basal cell carcinoma of the skin)
19. Has a history of autoimmune disease known to affect bone metabolism. Examples include spondyloarthropathies (e.g., ankylosing spondylitis, Crohn's disease, and ulcerative colitis), Juvenile Arthritis, Grave's disease and Hashimoto's thyroiditis; Rheumatoid Arthritis is alowed.
20. Have pathological or genetic liver disease or who have clinically significant, elevated

baseline liver function enzymes

21. Has obvious and/or documented alcohol or illicit drug addictions
22. Is a prisoner in a correctional institution/facility
23. Actively involved in litigation or workman's compensation
24. Has participated in clinical studies evaluating investigational devices, pharmaceuticals or biologics within 6 months of randomization
25. Requires chronic therapeutic use of NSAID during the first 6 post-operative weeks (except aspirin up to 325 mg bid for cardiovascular protection and/or DVT prophylaxis)
26. Has previously been treated with, or exposed to, therapeutic levels of synthetic or recombinant BMPs
27. Requires chronic subcutaneous or intravenous heparin therapies

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Recruitment

Each Investigator will recruit subjects who are undergoing surgical treatment for hindfoot or ankle arthritis equitably in an effort to ensure to the best extent possible that the subject pool is representative in gender, race, ethnicity, and age of the population affected by the condition being studied. The Investigator or his/her designee such as the study coordinator will notify Ferring or their designee of each potential subject. The coordinator will assign each consented subject a subject identification number in consecutive, ascending, and chronological order. This number will serve as a subject's identifier on all study-related documentation.

All subjects screened for the trial will be recorded on a screening log, including subject age, sex, race and ethnicity. The reason of non-eligibility for all subjects who are deemed ineligible by the Investigator should also be recorded on the study screening log. The screening log serves as a method for Ferring or their authorized designee to ensure that there is no selection bias in the trial. Screening logs will be periodically examined to evaluate reasons for non-enrollment of women or other key demographic groups.

Once it is determined that the subject is eligible for the study, the site will inform the Ferring representative or designee of the surgery date. The subject will be randomized according to the randomization schedule for each site as close to the time of surgery as possible, with the recommendation that the randomization be performed on the day of the surgical procedure. The subject randomization number will then be recorded on the relevant CRF. The randomization number will be assigned prior to surgery in a sequential, chronological order. Randomization numbers will not be reassigned.

Evaluations performed at each study visit are summarized in Section 6: Trial Procedures. If a subject misses a visit, all reasonable efforts should be made to reschedule the missed visit within the allocated visit window. If the visit cannot be rescheduled within the allocated visit window, the site should schedule a visit with the subject as soon as possible.

4.2.2 Randomization

Once written informed consent is obtained and eligibility is confirmed the subject can be randomized. Randomization must occur prior to surgery, with a recommendation to take place on the day of surgery or as close to the procedure as possible. Subjects will not be made aware of their randomization result prior to surgery.

Subjects will be randomly assigned on a two to one (2:1) basis to either the treatment group (AMPLEX) or the control group (ABG). Randomization will be stratified by clinical center, surgical site (hindfoot vs. ankle), and nonunion risk factors (none vs. any of: obesity, diabetes, previous hindfoot/ankle surgery, or smoking history). Permuted block randomization will be performed within strata. To minimize the opportunity for the sequence to be predicted, the block size will be variable. The randomization schedules for all strata will be generated in advance by an independent statistician who is not going to be involved in the study conduct using a computerized random number generator. Investigational sites will not have access to the randomization schedules.

Administration of randomization assignments will be accomplished using an electronic system. The study coordinator or a designee will obtain the randomization assignment per the provided randomization instructions. A copy of the randomization assignment will be maintained in the subject's file.

If, between the time of randomization and the beginning of surgery, the subject becomes ineligible or withdraws, the reason for failure to treat will be recorded in the subject's study records.

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Investigational Device

AMPLEX, the investigational device, is a synthetic bone graft substitute comprised of two parts; 1) a synthetic bone void filler (BVF) that functions as an osteoconductive scaffold and 2) a synthetic peptide (B2A) that augments osteodifferentiation.

The principal mode of action of the device is based on the osteoconductive granules that act as a scaffold for cellular ingrowth; B2A augments that action. The sterile ceramic granules, supplied by a third party vendor, are currently cleared for use as a BVF for bony voids or gaps of the skeletal system (e.g., extremities, spine and pelvis) that are not intrinsic to the stability of the bony structure. These defects may be surgically- or traumatically-created osseous defects to the bone (K063527, MBCP+).[21]

AMPLEX is supplied in kit form (AMPLEX kit) and the components must be combined and utilized in accordance with the Instructions for Use (IFU).

AMPLEX, B2A Enhanced Ceramic Granules (AMPLEX), is the Investigational Device supplied in kit form and must be used as a system. When fully prepared according to the IFU, AMPLEX consists of osteoconductive granules (BVF) with bound synthetic B2A peptide.

The AMPLEX kit contains two sterile, non-pyrogenic components that must be used as a system:

- Part 1: Bone void filler (BVF); 1 to 2 millimeter (mm) diameter granules, 5 cm^3/vial, two (2) vials per kit
- Part 2: Lyophilized B2A Peptide Powder, 2.8 mg/vial

Part 1: BVF consists of two (2) vials of 5 cc, sterile, ceramic granules. The granules are composed of 20% HA and 80% β-TCP.

Part 2: Lyophilized B2A Peptide Powder, is formulated as a sterile product containing 2.8 mg B2A with mannitol and glycine as excipients, and is lyophilized in borosilicate glass vial. Each vial contains a white to off-white caked powder composed of highly purified B2A (acetate salt), mannitol (USP), and glycine (USP) under an atmosphere of nitrogen (nitrogen headspace gas). The vials are closed with a Daikyo V10 RB2-TR FluroTec® coated stopper and with an aluminum-based, flip-top closure. Each vial contains sufficient B2A to prepare both vials of Part 1 ceramic granules.

For preparation of implant-ready AMPLEX by following the instructions in IFU, the lyophilized drug product (DP) is reconstituted in sterile water for injection (WFI). In-use stability of the reconstituted drug product has been demonstrated by measuring purity of the solution following reconstitution over a six (6) hour period. After reconstitution, a defined volume of B2A solution is withdrawn, added to the granules (BVF) and mixed according to the IFU. Implant-ready AMPLEX, with 0.225mg B2A/cm^3 granules should be used within four (4) hours of preparation.

5.1.2 Non-Investigational Material

The control material, Autogenous Bone Graft (ABG), is harvested from a location other than the graft site, for example, the calcaneus, proximal tibia, distal tibia or iliac crest and administered by surgical implant.

5.1.3 Investigational Device and Non-Investigational Material

The aggregate volume of the investigational device (AMPLEX) or control material (ABG) utilized in index joints will be at the discretion of the surgeon, provided the joint space(s) can be adequately filled with graft material according to the following parameters:

- Single hindfoot joint fusion: up to 5 cm^3
- Double or triple hindfoot fusion: each individual joint up to 5 cm^3, but overall, not more than 10 cm^3 for the full complement of joints
- Ankle fusion: up to 10 cm^3

ABG will be obtained from a location other than the graft site, for example, the calcaneus, proximal tibia, distal tibia, or iliac crest using standard surgical procedure. The selection of the ABG harvest site will be at the discretion of the surgeon and based on medical judgment. The harvested bone will be cleaned of soft tissue and morselized. The volume of ABG harvested for treatment will be measured using a syringe and the amount implanted, including the treated joint(s) recorded.

5.2 Characteristics and Source of Supply

All devices are provided by Ferring Pharmaceuticals and will be handled according to the principles of Good Manufacturing Practice (GMP).

5.2.1 Investigational Device Manufacturing

Ferring Pharmaceuticals Inc. is the specification developer and legal manufacturer of AMPLEX. The components of AMPLEX are manufactured using contract manufacturers. The BVF is manufactured by Biomatlante (Nantes, France) (FDA registration #3002673655). It is noted that separately, the BVF component has been cleared by the FDA via 510k as K063527 (referred to with the trade name MBCP+). The manufacturer of B2A Drug Substance will be Bachem Inc. (Torrance, CA). Bachem Inc. is a GMP-compliant, FDA-registered and California-licensed facility that specializes in the synthesis of peptide drug substances. The manufacturer of B2A Drug Product to be utilized in pivotal clinical trials will be AAI Pharma, Charleston, SC. AAI Pharma is a GMP-compliant, FDA-registered, licensed facility that specializes in drug formulation and packaging.

5.3 Packaging and Labelling

Packaging and labelling of AMPLEX will be performed in accordance with GMP and national regulatory requirements.

5.3.1 Investigational Device Packaging

The AMPLEX kit is composed of two sterile parts:

- Part 1: BVF; 1 to 2 mm diameter granules, 5 cm^3/vial, two (2) vials per kit
- Part 2: Lyophilized B2A peptide powder, 2.8 mg/vial

An IFU is provided within the kit details the preparation of the implantable material.

Part 1 has two (2) vials per kit wherein each vial contains 5 cm^3/vial of BVF of sterile, ceramic granules housed in vials with external screw-top closures. Each unit is sealed in double Tyvek pouches and radiation sterilized.

Part 2 is a vial that contains a white to off-white caked powder composed of highly purified B2A (acetate salt), mannitol (USP), and glycine (USP) under an atmosphere of nitrogen (nitrogen headspace gas). The vials are closed with a Daikyo V10 RB2-TR FluroTec® coated stopper and with an aluminum-based, flip-top closure. Part 2 is intended for use only with Part 1 vials.

Each of the AMPLEX kit elements as described above will be packaged in a kit box. The kit box and the AMPLEX kit will be labeled with study specific labels, fulfilling requirements for investigation device. The content of the labels will be in accordance of US/Canadian requirements and Annex 13, Eudralex, Volume 4 when applicable.

Each component within the kit will carry its own label delineating a description of the component.

All study (investigational) device accountability records will be maintained by the Investigator or qualified designee, stored in a secure location and reviewed during monitoring visits by the assigned Clinical Research Associate (CRA)/monitor. If AMPLEX is prepared, but not implanted or used for whatever reason, it will be discarded per the Institution's policy and the circumstances recorded in the device accountability log/form(s).

5.3.2 Non-Investigational Material (ABG)

As ABG is being used as an active control reference in the clinical trial and is obtained during surgery, there is no packaging or labeling.

5.4 Conditions for Storage and Use

The Investigator will ensure that the investigational device will be stored in appropriate conditions in a secure location with controlled access. The storage compartment shall be monitored regularly and the temperature shall be documented.

5.4.1 Investigational Device Storage

The investigational device will only be dispensed to subjects who meet the eligibility criteria and are randomized to a treatment group in the trial.

AMPLEX should be refrigerated (2-8 degrees Celsius / 36-46 degrees Farenheit) in a secure room (e.g. hospital pharmacy). A temperature log should be maintained to confirm temperatures have not been exceeded. If stored as instructed, AMPLEX is stable for up to 1 year.

5.5 Treatment Compliance

5.5.1 Dispensing and Accountability

AMPLEX will only be dispensed to subjects who meet the eligibility criteria and are randomized to the treatment group in the trial. The Investigator (or his/her designated personnel, e.g. trial nurse) will maintain a device accountability log/form(s) detailing the dates and quantities of the investigational devices dispensed to, and used by, each subject, as well as the batch numbers. The monitor will verify the device accountability during the trial.

Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation and according to the protocol. The Sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal. The principal Investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include:

- date of receipt
- identification of each investigational device (kit lot number)
- expiry date, if applicable
- date or dates of use

- subject identification
- date on which the investigational device was returned/explanted from subject, if applicable
- date of return of unused, expired or malfunctioning investigational devices, if applicable
- date and manner of device destruction

All study (investigational) device accountability records will be maintained by the Investigator or qualified designee, stored in a secure location and reviewed during monitoring visits by the assigned CRA/monitor.

If AMPLEX is prepared, but not implanted or used for whatever reason, it will be discarded per the institution's policy and the circumstances recorded in the device accountability log/form(s). If needed (e.g., due to faulty preparation, accidental contamination, etc.), and with time permitting, a new device may be prepared according to the same randomization treatment assignment, (e.g., any given subject will be assigned a single randomization code/assignment).

At the end of the study or as frequently as deemed appropriate, all unused study (investigational) device kits should be returned to the Sponsor or its designated representative unless otherwise instructed.

5.6 Return and Destruction of Medicinal Products and Auxiliary Supplies

All opened and unused devices can be destructed at the trial site (in accordance with local requirements) after the device accountability has been finalized, verified by the monitor, and signed off by the Investigator.

Any material remaining after B2A reconstitution and preparation will be discarded according to the Institution's policy and will be recorded and documented accordingly.

At the end of the study, any remaining unopened study (investigational device) product will be shipped to Ferring or its representative for destruction unless authorized in writing by Ferring to proceed otherwise.

6 TRIAL PROCEDURES

6.1.1 Subject Recruitment

Each Investigator will recruit any subjects who meet the eligibility criteria regardless of the subjects' gender, race or ethnicity.

6.1.2 Screening/Pre-Operative Visit

The potential risks and benefits associated with participation in the study will be explained to potential study subjects. Written informed consent must be obtained before the subject can begin any study-specific procedures that are not standard of care (e.g. immunology sample collection). In addition, if governing laws require, all subjects must sign the appropriate authorization for use, collection, and disclosure of protected health information and receive a copy of their signed informed consent.

The following assessments/activities will be performed at the screening or pre-operative visit:

- Obtain informed consent and authorization to disclose and release protected health information as applicable
- Medical History:
  - Record medical history
  - Record all concomitant medications taken within the past month, including vitamins/supplements such as glucosamine and chondroitin, and pain relief medication including those that are herbal
  - Record comorbidities
- Physical Assessment:
  - Verify inclusion/ exclusion criteria
  - Record vital signs, weight, height and BMI
  - Collect standing A/P, lateral and oblique X-rays of the hindfoot or ankle (historical X-rays, taken up to 24 weeks prior to the planned date of surgery, will also be accepted)
  - Collect urine sample(s) for pregnancy test from female subjects of childbearing potential, for standard urinalysis and for microscopic urinalysis (only if required)
  - Collect four blood samples for: 1) non-fasting chemistry (including aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [APT], gamma-glutamyl transferase [GGT] bilirubin and hemaglobin [HbA1c]), 2) hematology, 3) immunogenicity testing for B2A antibodies, and 4) immunological testing (hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV]). Additional details for the collection and handling of blood samples are provided in the SRM
  - Review with the subject the instructions for, and ask the subject to complete, the FAAM-ADL Questionnaire and the weight-bearing pain VAS
  - Review the instructions for and ask the subject to complete the SF-12 Questionnaire

- Investigator Screening Assessment:
  - Review medical history and comorbidities
  - Record patient-reported VAS pain on weight-bearing at site where fusion is to be performed
  - Review available relevant diagnostic imaging results evaluations (e.g. X-rays, MRI, SPECT/CT or CT scans obtained up to 24 weeks prior to the planned date of surgery)
  - Confirm the need for graft material and volume
  - Identify the arthrodesis site(s) / index joint(s)

6.1.3 Day of Surgery

Once eligibility is confirmed the subject can be randomized, but the subject will not be notified of randomization result until after the surgery.

The following assessments/activities will be performed on the day of surgery:

- Verify subject meets eligibility criteria
- Record date and time of hospital admission
- Record medical history and comorbidities since screening
- Record vital signs
- Identify the arthrodesis site(s) / index joint(s)
- Collect urine sample for pregnancy test from female subjects of childbearing potential (within 24 hours prior to procedure)
- Record volume of blood loss and blood use during surgery
- Record the number and type of screws and screw systems used during surgery
- Record operation start and end time (incision to closure)
- Measure and record the volume of AMPLEX implanted per joint and identify the joint; and record the amount remaining after surgery. For ABG, record the volume harvested for treatment, implanted per joint, identify the joint, and record the amount remaining after surgery.
- Perform specific intraoperative data collection
- Record any protocol deviations
- Record all concomitant medications including (anesthesia) taken since the screening visit
- Record any AEs experienced from time of screening

PK Assessment:

- A Pharmacokinetic (PK) assessment will be conducted in a sub-set of subjects to assess the amount of B2A in blood (plasma) after surgery, on Days 1, 2, 4, 7, and 15, and will include a baseline, pre-procedure evaluation. The sub-set of subjects will include up to

approximately 30 AMPLEX subjects, allowing pharmacokinetic evaluation in at least 20 AMPLEX subjects. Both genders will be represented. Blood samples will be collected and processed to plasma for laboratory evaluation (plasma B2A concentration).

6.1.4 Surgical procedure

In addition to the below text, further detail on surgical procedure can be found in the Surgical Manual.

The operative site will be prepared and draped for surgery using standard technique. The arthrodesis site will be prepared by decorticating any remaining arthritic cartilage down to subchondral bone. High speed mechanical instruments such as burrs are avoided to prevent excessive heat at the fusion site that may be detrimental to the biological processes required for fusion. The graft material should be packed in the joint space to minimize the chance of extrusion. Stable fixation of joint in the appropriate position is achieved using 1 to 3 internal fixation screws with or without supplemental fixation. Wound closure is performed using standard technique. A dressing is applied and the ankle and hindfoot are immobilized with a cast, splint or boot.

Internal Fixation:

Screws will be used for internal fixation in order to standardize the hardware. All fusion constructs should be comprised of at least one but not more than 3 screws. Supplemental pins and staples may be used. Supplemental screws and plates external to the fusion site(s) are also allowed. The manufacturers of the screws provide Instructions for Use and Surgical Technique for their respective products. These documents must be consulted for guidance on the use of instruments for surgical preparation, sizing of screws, and placement of the screws.

Preparation of Graft Material:

Graft material will be prepared during surgery using either autogenous bone or the AMPLEX material assigned through randomization. Graft materials are to be placed ONLY within the joint space.

- *AMPLEX, Investigational Treatment.* AMPLEX should be prepared following the IFU accompanying the kit. If the subject is assigned to receive AMPLEX, the lyophilized B2A powder will be reconstituted in sterile WFI and mixed with the granules at the time of surgery as per the IFU. Once reconstituted and mixed with granules, implant-ready AMPLEX must be used within four hours.
- *Autogenous Bone Graft, Control Treatment.* The harvested bone (calcaneus, proximal tibia, distal tibia, iliac crest, etc.) will be cleaned of soft tissue and morselized. The volume of ABG harvested for treatment should be measured using a syringe.

- The aggregate volume of AMPLEX or ABG utilized in index joints will be at the discretion of the surgeon, provided the joint space(s) can be adequately filled with graft material according to the following parameters:
    - Single hindfoot joint fusion: up to 5 cm^3
    - Double or triple hindfoot fusion: each individual joint up to 5 cm^3, but overall, not more than 10 cm^3 for the full complement of joints
    - Ankle fusion: up to 10 cm^3

6.1.5 Post-Operative Care

While in the hospital, subjects should be encouraged to mobilize out of bed by the first post-operative day. Physical therapy for ambulation and activities of daily living should also be provided per standard of care. The following will be performed prior to subject's release from the hospital or within 1 week following the procedure:

- Collect A/P, lateral and oblique X-rays of the hindfoot/ankle after implant

Hospital discharge will occur in accordance with the institutions' standard of care. Discharge instructions will include prescriptions for pain management. Sites should provide standard-of-care prophylaxis for thromboembolic disease and this may include ASA up to 325 mg bid. With the exception of ASA up to 325 mg bid for either cardiovascular protection and/or DVT prophylaxis, subjects will be instructed to avoid non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids for the first 6 weeks following surgery. Subjects will be advised that the use of NSAIDs or systemic steroid therapy (not including topical steroid therapy) may interfere with bone healing. This also applies to limited use of NSAIDs for headache, dysmenorrhea, etc. Electromagnetic, ultrasound or osteobiologic treatments stimulating bone growth are not allowed. Subjects will be instructed to remain non weight-bearing for six (6) weeks, then allowed to progressively increase weight-bearing. During the progressively increased weight-bearing timeframe, a removable cast/splint or boot is worn, which is subsequently weaned after full weight-bearing is achieved. It is recommended that all subjects are directed to participate in a post-operative rehabilitation program consistent with the guidelines provided in Table 2. Subjects will be advised against the use of tobacco products for at least six (6) months after surgery. Tobacco products will be defined as all tobacco products (cigarettes [including e-cigarettes], cigars, and chewing tobacco) and will include gum or patches that contain nicotine. Subjects will be advised that nicotine may increase the chances of wound infection, pseudarthrosis (nonunion) and other complications.

Table 2 Post-operative Rehabilitation Guidance

Phase	Average Time Post-surgery	Immobilization	Examples of phase appropriate activities
Phase 1	0-2 weeks	• Rigid immobilization (e.g., cast)	• Gentle A/PROM of uninvolved joints (e.g., toes, knee, hip) • Limb elevation • Crutch/ambulatory aide instruction for strict NWB
Phase 2	2-6 weeks	• Rigid immobilization (e.g., cast, walking boot)	• Continued NWB instruction
Phase 3	6-12 weeks	• Rigid or flexible immobilization (e.g., walking boot, ankle brace)	• Progressive WB to tolerance
Phase 4	12-24 weeks	• Flexible immobilization as needed (e.g., ankle brace)	• Physical Therapy rehabilitation program

6.1.6 Follow-up Visit at 2 Weeks

The visit window is ± 3 days.

- Physical assessment of hindfoot/ankle, including vital signs
- Collect two blood samples for: 1) non-fasting chemistry and 2) hematology. Additional details for the collection and handling of blood samples are provided in the SRM
- Subject-based Assessment:
  - If subjects are in the ABG group, ask subjects to rate their graft site pain on the VAS
- Record adverse events
- Record concomitant medications

6.1.7 Follow-up Visit at 6 Weeks

The visit window is ± 14 days.

- Physical assessment of hindfoot/ankle, including vital signs
- Collect three blood samples for: 1) non-fasting chemistry, 2) hematology and 3) immunogenicity testing for B2A antibodies. Additional details for the collection and handling of blood samples are provided in the SRM
- Subject-based Assessment:
  - If subjects are in the ABG group, ask subjects to rate their graft site pain on the VAS

- Collect A/P, lateral and oblique X-rays of the hindfoot/ankle
- Record adverse events
- Record concomitant medications

6.1.8 Follow-up Visit at 12 Weeks

The visit window is ± 14 days.

- Physical assessment of hindfoot/ankle, including vital signs
- Collect three blood samples for: 1) non-fasting chemistry, 2) hematology and 3) immunogenicity testing for B2A antibodies. Additional details for the collection and handling of blood samples are provided in the SRM
- If immune testing is positive, the subject will be reevaluated at each subsequent follow-up visit until the response is resolved or to the end of the study
- Collect A/P, lateral and oblique X-rays of the hindfoot/ankle
- Perform a CT scan of the hindfoot/ankle
- Subject-based Assessment:
    - Review the instructions for and ask the subject to complete the FAAM-ADL Questionnaire and weight-bearing pain VAS
    - If subjects are in the ABG group, ask subjects to rate their graft site pain on the VAS
- Record adverse events
- Record concomitant medications

6.1.9 Follow-up Visit at 24 Weeks

The visit window is ± 30 days:

- Physical assessment of hindfoot/ankle, including vital signs
- Collect A/P, lateral and oblique X-rays of the hindfoot/ankle
- Perform a CT scan of the hindfoot/ankle
- Subject-based Assessment:
    - Review the instructions for and ask the subject to complete the FAAM-ADL Questionnaire and weight-bearing pain VAS
    - If subjects are in the ABG group, ask subjects to rate their graft site pain on the VAS
    - Review the instructions for and ask the subject to complete the SF-12 Questionnaire
- Record adverse events
- Record concomitant medications

6.1.10 Follow-up Visit at 52 Weeks

The visit window is ± 30 days:

- Physical assessment of hindfoot/ankle, including vital signs
- Collect A/P, lateral and oblique X-rays of the hindfoot/ankle
- Perform a CT scan of the hindfoot/ankle
- Subject-based Assessment:
    - Review the instructions for and ask the subject to complete the FAAM-ADL Questionnaire and weight-bearing pain VAS
    - If subjects are in the ABG group, ask subjects to rate their graft site pain on the VAS
    - Review the instructions for and ask the subject to complete the SF-12 Questionnaire
- Record adverse events
- Record concomitant medications

6.1.11 Follow-up Visit at 78 Weeks

The visit window is ± 30 days:

- Physical assessment of hindfoot/ankle, including vital signs
- Collect A/P, lateral and oblique X-rays of the hindfoot/ankle
- Record adverse events
- Record concomitant medications

6.2 Trial Flow Chart

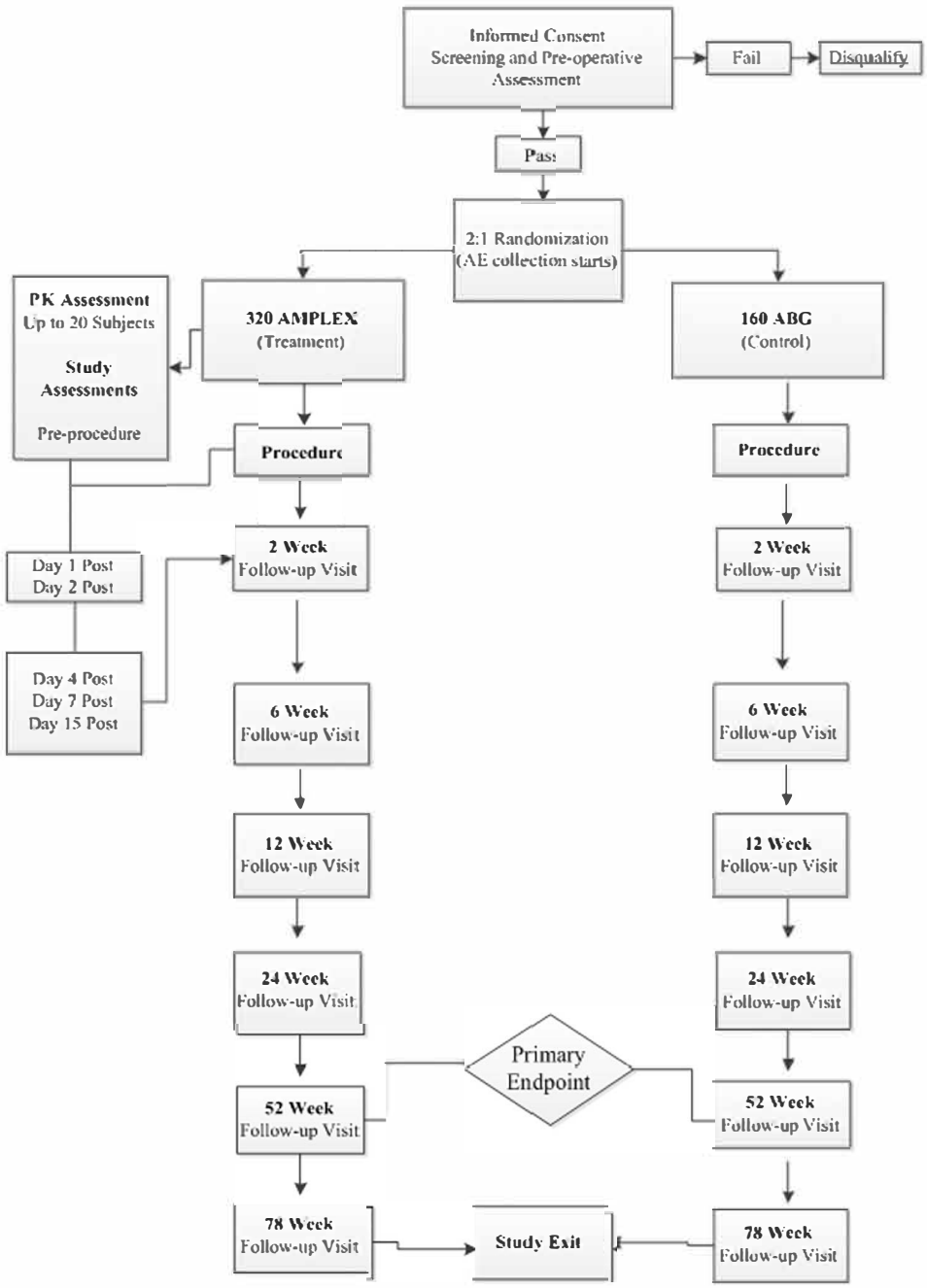

Figure 2 Trial Flow Chart

7 TRIAL ASSESSMENTS

7.1 Schedule of Assessments

Table 3 Schedule of Assessments

	Screening	Treatment	Follow-up					
Visit number	**V1**	**V2 Procedure**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**
Weeks	**-12**	**--**	**2**	**6**	**12**	**24**	**52**	**78**
Days	**Days -84 to -1**	**Day 1**	**Day 15 (+/- 3)**	**Day 43 (+/- 14)**	**Day 85 (+/- 14)**	**Day 169 (+/- 30)**	**Day 365 (+/- 30)**	**Day 547 (+/- 30)**
Informed consent	X							
Medical History/ comorbidities	X	X						
Supplemental graft requirement confirmation	X							
Eligibility criteria verification	X	X						
Physical assessment of foot/hindfoot, vital signs	X	X	X	X	X	X	X	X
Pregnancy test [1] (if applicable)	X	X						
Standard Unrinalysis [2]	X							
Clin. labs: chemistry and hematology [3]	X		X	X	X			
Immunological Testing for HBV, HCV and HIV	X							
Serum for B2A Ab testing [4]	X			X	X			
Identification of target arthrodesis site	X	X						
Subject randomization [5]		X						
Arthrodesis procedure		X						
Specific intraoperative data collection [6]		X						
Graft material volumes		X						
A/P, lateral and oblique X-rays of hindfoot/ankle	X†	X [7]		X	X	X	X	X
Foot and ankle CT scan					X	X	X	
FAAM-ADL	X				X	X	X	
Weight bearing pain at fusion site VAS	X				X	X	X	
Graft Harvest site pain VAS			X	X	X	X	X	
SF-12	X					X	X	
Adverse event evaluation [8]		X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X

† At the screening/pre-operative visit, A/P, oblique and lateral X-rays will be collected (historical X-rays taken up to 24 weeks prior to the planned date of surgery will also be accepted).
[1] Pregnancy test may be performed within 24 hours of the procedure
[2] If positive for blood, leukocytes, or nitrite, microscopic unrinalysis will be performed.
[3] HbA1c is to be performed at screening for all subjects
[4] B2A Antibody testing may continue past the 12 week follow-up visit if there is a positive test at 12 weeks.

[5] The subject will be randomized as close to the time of surgery as possible, with the recommendation that the randomization be performed on the day of the surgical procedure.
[6] See Section 6.1.4 referencing the Surgical Manual.
[7] Perform immediately following surgery or within 1 week following the procedure.
[8] Collected from time of informed consent. Post-treatment outcomes that are evaluated as efficacy endpoints, such as pain on weight-bearing, harvest site pain, etc. will not be reported as AEs.

Table 4 Schedule of Assessments for PK Sampling

	Screening	Treatment	Follow-up								
Visit number	V1	V2 Procedure	V3*				V4	V5	V6	V7	V8
Weeks	-12	--	2				6	12	24	52	78
Days	Days -84 to -1	Day 1	Day 2	Day 4	Day 7	Day 15	Day 43 (+/- 14)	Day 85 (+/- 14)	Day 169 (+/- 30)	Day 365 (+/- 30)	Day 547 (+/- 30)
PK assessment [1]		X	X	X	X	X					

[1] A sub-set of up to 20 evaluable AMPLEX subjects will have a PK assessment. An additional sample of blood will be collected at pre-procedure and after surgery on Days 1, 2, 4, 7, and 15.
* Visit 3 will also consist of Days 2, 4 and 7, for which there will be an **option for blood to be collected at home by a mobile laboratory unit.**

7.2 Assessments Related to Endpoints

7.2.1 Radiographic Assessments

The collection and assessment of radiographic information will follow a pre-defined imaging core laboratory protocol. The radiographic assessments (X-ray and CT) will be read by a central core imaging laboratory. The assessments will be made by independent board-certified radiologists. The reviewers will be blinded to treatment arm and will not have access to clinical outcomes data when conducting the assessments.

More specifically, radiographic assessments of osseous bridging will be performed by two independent radiographic reviewers (the "primary reviewers") blinded to each other's assessments. A third independent reviewer (the "adjudicator") will resolve disagreements between the primary reviewers. Each reviewer will be a US-based, board-certified, licensed and practicing radiologist with subspecialty training in musculoskeletal radiology.

7.2.1.1 X-rays

At the screening/pre-operative visit, A/P, lateral and oblique X-rays will be collected (historical X-rays taken up to 24 weeks prior to the planned date of surgery will also be accepted). These pre-operative X-rays are the baseline for subsequent safety evaluation. After surgery A/P, oblique and lateral X-rays will be collected at the following visits: Day of Procedure (e.g., after implant or within 1 week following surgery), and 12, 24, 52 and 78 weeks post-surgery. The core imaging laboratory will provide qualitative (safety) assessments of screw loosening and radiolucencies around the screws, (new) fractures, subsidence, device migration, radiographic nonunion, osteolysis and/or heterotopic ossification in the area surrounding the implant site. A radiographic nonunion is

defined on x-ray as radiographic evidence of nonunion (as defined in the REP) and the absence of radiographic progression of healing bone (as defined in the REP). The assessment will be conducted at Weeks 52 and 78.

7.2.1.2 Computerized Tomography (CT) and fusion success

CTs will be collected at 12, 24, and 52 weeks after surgery. Radiographic CT fusion success will be determined based on evaluation of CT slices in sagittal or coronal reconstructions. A joint will be considered successfully fused if there is evidence of bridging bone over ≥50% of the joint. If a subject undergoes fusion at more than one site, each fusion site will be assessed independently. A subject will be considered fused if all fusion sites (full complement of joints) independently have evidence of bridging bone over at least 50% of the joint in the absence of secondary surgical or nonsurgical interventions intended to promote fusion. By definition, immediately after surgery there is 0% bridging bone in the target joint. The progression of fusion over time will be assessed in each subject by monitoring the change in fusion status from the previous visit.

7.2.2 Subject self-assessments

7.2.2.1 FAAM-ADL Questionnaire

The Foot and Ankle Ability Measure (FAAM) is a subject self-assessment questionnaire comprised of the separately scored 21-item Activities of Daily Living ADL (FAAM-ADL) and 8-item sports subscales.[45] Each item is scored on a 5-point Likert scale anchored by 4 (no difficulty at all) and 0 (unable to do), with higher scores representing a higher levels of function.

In consideration of its target arthrodesis population, this study will utilize the FAAM-ADL sub-scale as a measure of functional improvement in the composite endpoint. The FAAM-ADL questionnaire (included in Appendix 2) will be utilized at screening and at 12, 24 and 52 weeks post-surgery. The questionnaire and its instructions for use will be provided in the SRM. Prior to administering the FAAM-ADL, subjects will be instructed on how to complete the questionnaire.

7.2.2.2 Weight-bearing Pain VAS

Weight-bearing pain at fusion site will be assessed using a VAS. Subjects will mark the location on a 100-millimeter line corresponding to the amount of pain they experienced with 0 mm being "no pain" and 100 mm being "the worst pain imaginable". The weight-bearing pain VAS will be completed at screening and at 12, 24 and 52 weeks post procedure. The assessment and its instructions for use will be provided in the SRM.

7.2.2.3 SF-12 Questionnaire

A validated SF-12 patient questionnaire will be completed at screening and at 24 and 52 weeks post-surgery. The SF-12 Health Survey includes 12 questions from the SF-36 Health Survey. These include: 2 questions concerning physical functioning; 2 questions on role limitations because of physical health problems; 1 question on bodily pain; 1 question on general health perceptions; 1 question on vitality (energy/fatigue); 1 question on social functioning; 2 questions on role limitations because of emotional problems; and 2 questions on general mental health (psychological

distress and psychological well-being). Scoring of individual items is identical to the SF-36 Health Survey. Scoring algorithms are then applied to produce the physical component summary and mental health component summary scores. The survey and its instructions for use will be provided in the SRM.

7.2.2.4 Graft Harvest Site Pain

Since AMPLEX subjects will not undergo graft harvest, this is a patient reported outcome that is applicable to ABG subjects only. Subjects in the ABG group will be asked to assess the pain associated with their graft site. ABG subjects will assess the pain using a VAS. Subjects will mark the location on a 100-millimeter line corresponding to the amount of pain they experienced with 0 mm being "no pain" and 100 mm being "the worst pain imaginable". This questionnaire will be completed at 2, 6, 12, 24 and 52 weeks after surgery. The assessment and its instructions for use will be provided in the SRM.

7.3 Other Assessments

7.3.1 Concomitant Medications

At all study visits, subjects will be instructed to report any medications used to treat them over the course of the study.

7.3.2 Vital Signs

Vital signs will be performed at all study visits. On the day of Treatment, vital signs must be performed prior to surgery. Weight, height and BMI will be performed at screening (Visit 1).

7.3.3 Clinical Laboratory Testing

Routine clinical laboratory tests (hematology and chemistry, including AST, ALT, ALP, GGT, bilirubin and hemaglobin A1c levels), will be performed at screening (Visit 1) and follow-up through 12 weeks. All female subjects of childbearing potential will have urine pregnancy tests performed at the screening (Visit 1) and within 24 hours of the procedure (Visit 2). At the discretion of the Investigator, additional blood samples may be taken for safety reasons to analyze other clinical laboratory endpoints. All blood samples will be analyzed by a central laboratory. Full details regarding sample collection, processing and shipping will be provided in the SRM. The lab results/reports will be provided to the site. If a laboratory result is abnormal, the Investigator will assess if it is clinically significant (CS) or not clinically significant (NCS). Clinically significant laboratory abnormalities are defined as abnormal results requiring treatment or medical intervention and should be recorded as adverse events. The severity of a clinically significant laboratory finding should be recorded as described; however, abnormal laboratory observations classified as NCS do not require an adverse event to be filed.

7.3.3.1 Standard Urinalysis

Diptstick urinalysis tests will be performed at screening (Visit 1), to assess blood, leukocytes, pH, specific gravity, nitrite, protein, glucose and urobilinogen. If dipstick urinalysis results are positive for blood, leukocytes or nitrite, microscopic urinalaysis will be performed.

7.3.3.2 Immunological Testing for HBV, HCV and HIV

Serological testing for HBV, HCV and HIV will be performed at screening (Visit 1). Negative results are required for study admission.

7.3.4 Antibody Monitoring

The presence of anti-B2A antibodies will be evaluated using a tiered approach consistent with FDA guidance. This evaluation consists of screening and confirming for B2A-specific antibodies with use of a ligand binding immunoassay. Following confirmation of the "positive" screening result an antibody titer will be determined. Subsequently, in confirmed ani-B2A antibody positive samples the BMP-2 cross-neutralization potential will be determined by a cell-based assay. Blood for immunogenicity testing will be collected at pre-operative/ screening visit, at 6 weeks and at 12 weeks after surgery. For subjects testing positive for antibodies to B2A, additional blood samples will be obtained at each subsequent follow-up visit and analyzed until antibody titers return to baseline or until the end of the study. Samples will be analyzed at a GLP-compliant laboratory under the responsibility of the Department of Bioanalysis, IPC, Ferring Pharmaceuticals A/S.

7.4 Human PK Assessment

A Pharmacokinetic (PK) assessment will be conducted in a sub-set of subjects to assess the amount of B2A in blood (plasma). Blood for assessment will be collected pre-procedure (baseline) and after surgery on Days 1, 2, 4, 7, and 15. Visit 3 will also consist of Days 2, 4 and 7, for which there will be an **option for blood to be collected at home by a mobile laboratory unit**. From the plasma concentration-time data of B2A, the following parameters will be estimated, if possible: AUC, AUCt, % AUC extrap, Cmax, Tmax, t½, lamda z, CL/F, Vz/F. The sub-set of subjects will include up to approximately 30 AMPLEX subjects, allowing pharmacokinetic evaluation in at least 20 AMPLEX subjects. Both genders will be represented. Subjects included in the PK sub-set will provide written informed consent prior to the fusion procedure.

8 ADVERSE EVENTS

8.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a subject participating in a clinical trial. It includes:

- Any unfavorable and unintended sign, symptom or disease temporally associated with the use of the investigational device or control material, whether or not considered to be caused by the investigational device or control material
- Adverse events commonly observed and adverse events anticipated based on the effect of the investigational device or control material
- Any laboratory abnormality, vital sign or finding from physical examination assessed as clinically significant by the Investigator
- Any accidental injuries, reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures

A Serious Adverse Event (SAE) is defined as any AE that:

- Results in death
- Is life threatening (the subject is at immediate risk of dying from the adverse experience)
- Results in subject hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse device effect when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

An unanticipated adverse device effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, graft material (either AMPLEX or ABG in the context of this protocol), if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a medical device that relates to the rights, safety, or welfare of subjects.

An anticipated adverse device effect is any adverse device experience, reported in this protocol, contained in a report of prior investigations, Informed Consent Form and, or general investigational plan.

A list of anticipated AEs is presented in Appendix 1.

Subsequent Secondary Surgical Interventions, which are surgical interventions occurring at the index fusion site(s) subsequent to the completion of the index procedure, will be evaluated and

presented separately from other adverse events. While secondary surgical interventions will not be classified as adverse events, the reasons for these procedures may be. An explanatory description will be provided as an adverse event narrative and will include:

- the reason for each subsequent secondary surgical intervention and
- the action taken
- the types and timing of these surgeries

The following are types of secondary surgical interventions at the index fusion site along with their definitions:

- **Revision.** A procedure that adjusts or in any way modifies or removes *part* of the original implant configuration, with or without replacement of a component. A revision may also include adjusting the position of the original configuration.
- **Removal.** A procedure where *all* of the original system configuration is removed with or without replacement due to, for example, mechanical failure of the graft material, pain, or infection.
- **Reoperation.** Any surgical procedure that does not include removal, modification, or addition of any components to the system (e.g., drainage of a hematoma at the surgical site).
- **Supplemental fixation.** A procedure in which additional instrumentation not under study in the protocol is implanted.

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

The Investigator must monitor the condition of the subject throughout the trial from the time of informed consent until the last visit.

The sources of adverse events include:

- The subject's response to questions about his/her health (a standard non-leading question such as "How have you been feeling since your last visit?" is asked at each visit)
- Symptoms spontaneously reported by the subject
- Investigations and examinations where the findings are assessed by the Investigator to be clinically significant changes or abnormalities
- Other information relating to the subject's health becoming known to the Investigator (e.g., hospitalization)

8.2.2 Recording of Adverse Events

All adverse events will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) (version effective at trial start).

During each clinical follow-up, the Investigator or Investigator designee will determine AE occurrences. Each adverse event is considered to be either anticipated or unanticipated as described above. The site is required to report all adverse events that occur during the trial. AEs will be collected from the time of informed consent until the final follow up.

Post-treatment outcomes that are evaluated as efficacy endpoints, such as pain on weight-bearing, harvest site pain, etc., will not be reported as AEs. Post-operative pain is, in general, anticipated, typically improves over time, and it will not be considered an AE. However, surgical site pain that is associated with a complication, or worsens over time, may be considered an AE.

Any abnormal laboratory test results or other safety assessments (e.g., vital signs measurements, etc.) considered to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs.

The sign and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Internal fixation medical devices (e.g., screws, plates, pins and staples) are being used in this study and are considered ancillary devices. Medical device events associated with these ancillary devices, including those resulting from screw loosening or malfunctions of the ancillary device, must be documented and reported as adverse events by the Investigator throughout the study.

8.2.3 Assessment of Adverse Events

AE Severity: All AEs will be assessed for severity (see table below). Note: the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 5 AE Severity Grading Scale

Severity Grade	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Moderate limitation in activity, minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required hospitalizations possible.

Device Related Adverse Event: Relationship to the graft material will be assigned *one* of the following:

- **Definitely**: Clear evidence event caused by graft material; strong temporal relationship and an alternative cause is unlikely.

- **Probably**: Reasonable probability event might be caused by graft material. The event has a temporal relationship to the study procedure(s), and follows a known pattern of response and an alternative cause seems unlikely.
- **Possibly**: Reasonable possibility event is caused by graft material. The event has a temporal relationship to the study procedure(s) and follows a known pattern of response, but a potential alternative cause may be present.
- **Unlikely**: Evidence that there may be other causes and the relationship to the graft material, although cannot be completely ruled out, is remote.
- **Unrelated**: Cause of the event is known and the event is in no way related to any aspect of the graft material.
- **Unknown:** Causality cannot be determined.

The causality of AEs will be determined by the Investigator, and the CEC will adjudicate it.

In addition to the graft material, the relationship to the following will also be determined for each AE, if possible:

- **Ancillary Device Adverse Event**: An adverse event which is determined to be a consequence of an ancillary device and is not specifically related to the use of graft material, but could be related to the placement of the graft material. An ancillary device is defined as an approved medical device used in conjunction with the graft material, and used during the study procedure (e.g., internal fixation screws, etc.)
- **Procedure-Related Adverse Event**: An adverse event which is determined to be a consequence of the arthrodesis or harvest procedure and is not specifically related to use of the graft material or ancillary devices, but could be related to the placement of the graft material or ancillary devices.

Every effort should be made to assess the causality of all events. If the causality cannot be determined, it should be classified as unknown. Events classified as "unknown" causality will be considered related for reporting purposes.

8.3 Pregnancy

If a pregnancy occurs, U.S. Pharmacovigilance at Ferring Pharmaceuticals must be informed. Contact details for the follow-up on the course and outcome of the pregnancy should be included. The mother and the fetus must be followed-up at least until the birth of the infant and one month after the birth of the infant. In general, the follow-up will include the course, duration and the outcome of the pregnancy as well as neonatal health. If a pregnancy results in an abnormal outcome (birth defect/congenital anomaly) this must be reported as a serious adverse event to U.S. Pharmacovigilance at Ferring Pharmaceuticals using the Safety Report Form.

8.4 Collection, Recording and Reporting of Serious Adverse Events

SAE Reporting by the Investigator

All SAEs must be reported **immediately** to Ferring U.S. Pharmacovigilance as soon as it becomes known to the Investigator and not later than within 24 hours of their knowledge of the occurrence of an SAE.

The Investigator is responsible for submitting the completed SAE Report Form with the fullest possible details **within 3 calendar days** of his/her knowledge of the SAE to Ferring U.S. Pharmacovigilance using the contact details below.

U.S. Pharmacovigilance, Ferring Pharmaceuticals A/S
E-mail: Safety.MailboxUS@ferring.com
Fax: [redacted]

Completion of the Demographics, Adverse Event Log, Medical History Log and Concomitant Medication Log are mandatory for initial reports and for follow-up reports if any relevant changes have been made since the initial report. Data entries must have been made in the eCRF for Ferring Global Pharmacovigilance to access the information.

Additional information relevant to the SAE such as hospital records, results from investigations, (e.g., laboratory parameters that are not already uploaded in the eCRF), invasive procedures, scans and x-rays, and autopsy results can be faxed or scanned and e-mailed to Ferring Global Pharmacovigilance using the contact details in the section above. In any case this information must be supplied by the Investigator upon request from Ferring. On any copies provided, details such as subject's name, address, and hospital ID number should be concealed and instead subject number should be provided.

The Investigator will supply Ferring and the IRB/REB with any additional requested information such as results of post-mortem examinations and hospital records.

Expedited Reporting by Ferring

As per Regulations, Ferring will report all adverse events that are **unexpected** to the relevant regulatory authorities within the stipulated timelines.

8.5 Follow-up of Adverse Events and Serious Adverse Events

8.5.1 Follow-up of Adverse Events with Onset during the Trial

During the trial, the Investigator must follow-up on each adverse event until it is resolved or until the medical condition of the subject is stable.

After the subject's last visit, the Investigator must follow-up on any adverse event classified as serious or considered to have a reasonable possible causality to the graft material until it is resolved or until the medical condition of the subject is stable. All such relevant follow-up information must be reported to Ferring. If the event is a chronic condition, the Investigator and Ferring may agree that further follow-up is not required.

8.5.2 Collection of Serious Adverse Events with Onset after Last Trial Visit

If an Investigator becomes aware of an SAE after the subject's last visit, and he/she assesses the SAE to have a reasonable possible causality to the graft material, the case will have to be reported to Ferring, regardless how long after the end of the trial this takes place.

9 STATISTICAL METHODS

Details of the statistical methodology will be provided in a separate statistical analysis plan (SAP).

9.1 Determination of Sample Size

Assuming true success rates of the primary endpoint to be 60% for ABG and 62% for AMPLEX groups, 396 subjects are needed to maintain 85% power to demonstrate non-inferiority of AMPLEX to ABG with a non-inferiority margin of -12% at a type I error rate of 1-sided 5% in a 2:1 randomization (264 for AMPLEX and 132 for ABG). To account for approximately 15% lost to follow-up, a total of 480 subjects (320 for AMPLEX and 160 for ABG) will be randomized.

In this calculation, the true success rate for AMPLEX is assumed to be slightly higher than that for ABG because of the potential benefit for AMPLEX on the absence of significant graft harvest site pain component. The assumption on the true success rate for ABG is made based on the clinical endpoint results in DiGiovanni et al. (2013) and the Augment SSED (2015). These data indicate relatively high success rates for each component at Week 52, and the success rate as a composite endpoint is estimated as approximately 60% under the independence assumption among components.

In the determination of the non-inferiority margin, retaining at least 80% of the assumed success rate in ABG is considered clinically meaningful, because it is inherently linked with substantial benefit of eliminating risks associated with ABG. Therefore, the non-inferiority margin is set to -12%.

In addition, the CT radiographic fusion success rate at 52 weeks for ABG is assumed to be 70% to 75% based on 24 and 36 weeks data available in FDA Orthopaedic and Rehabilitation Devices Division (2011). Assuming that the true CT radiographic fusion success rate for AMPLEX is the same as for ABG, the power to demonstrate the non-inferiority in the CT radiographic fusion success as an independent test with 396 subjects is 79% to 83% at 1-sided 5% significance level using the non-inferiority margin of -12%.

9.2 Subject Disposition

All subjects screened and randomized will be accounted for. All post-randomization discontinuations will be summarized by time of, and reason for, discontinuation. The number of subjects screened and not randomized will be presented.

9.3 Protocol Deviations

The final definition of protocol violations will be determined prior to the database lock. The number and percentage of subjects with important protocol deviations will be summarized.

9.4 Analysis Sets

9.4.1 Modified Intention-to-Treat (mITT) Analysis Dataset

The mITT analysis set will include all randomized subjects who have an attempted fusion of the index joint(s). If a subject becomes ineligible or withdraws prior to the initiation of surgery, the subject will not be included in the mITT analysis set. Once the surgery is initiated, all subjects will be included in the mITT analysis set.

9.4.2 Per Protocol (PP) Dataset

The PP analysis set will consist of all randomized subjects that: [1] complete the fusion procedure and receive either AMPLEX or ABG as assigned, [2] meet critical study eligibility criteria, and [3] have no significant protocol deviations.

9.4.3 Safety Dataset

The safety analysis set comprises all treated subjects and will be analyzed according to the actual treatment received.

9.5 Trial Population

9.5.1 Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics and medical history will be presented for the mITT, PP and safety analysis sets by treatment group. In addition, summary of demographic and baseline characteristics will be presented by trial site.

9.5.2 Medical History, Concomitant Medication and Other Safety Evaluations

Medical history will be coded by system organ class (SOC) and preferred term (PT) using the most current version of the MedDRA and summarized by SOC, PT, and treatment group for the mITT and Safety analysis sets. Prior and concomitant medications will be coded by the Anatomical Therapeutic Chemical (ATC) classification system and preferred drug name using the World Health Organization Drug Dictionary (WHO-Drug). Prior and concomitant drug usage will be summarized by ATC classification 1st level, ATC classification 2nd level and treatment group for subjects in the mITT and Safety analysis sets.

9.6 Endpoint Assessments

9.6.1 General Considerations

All efficacy analyses will be conducted for the mITT population. The primary and key secondary efficacy endpoints will be analyzed by a fixed-sequence procedure according to the following order to maintain the overall Type 1 error rate to a one-sided 5% for non-inferiority and a one-sided 2.5% for superiority testings.

1. Non-inferiority of AMPLEX to ABG in the primary efficacy endpoint

2. Non-inferiority of AMPLEX to ABG in the key secondary efficacy endpoint

3. Superiority of AMPLEX to ABG in the key secondary efficacy endpoint

4. Superiority of AMPLEX to ABG in the primary efficacy endpoint

Testing procedure will begin with the non-inferiority in the primary efficacy endpoint, and each test will be conducted without adjustment of multiplicity as long as all preceding tests are significant. All other secondary endpoints will be presented with the point estimate of the treatment group difference and the corresponding 2-sided 90% confidence interval.

9.6.2 Primary Endpoint

The primary efficacy endpoint will be the proportion of subjects who meet all of the following criteria for the SPC at 52 weeks:

- Improvement in pain on weight-bearing at fusion site (≥ 20 mm reduction from baseline on 100 mm VAS)
- Absence of significant graft harvest site pain (< 20 mm on 100 mm VAS)
- Improvement in Foot and Ankle Ability Measure Activities of Daily Living subscale (FAAM-ADL) (≥ 8 points improvement from baseline)
- Absence of device related or procedure related SAEs (up to Week 52)
- Absence of secondary surgical or nonsurgical interventions intended to promote fusion (up to Week 52)

Non-inferiority of AMPLEX to ABG will be claimed if the lower bound of the 2-sided 90% CI for the difference of the proportions (AMPLEX minus ABG) is greater than -12.0%. The superiority will be claimed if the lower limit of the 2-sided 95% CI is greater than zero. The CI will be constructed with the normal approximation to the binomial.

The primary efficacy analysis will be based on the mITT analysis set. A sensitivity analysis will be conducted for the PP analysis set. In the analysis on the mITT analysis set, subjects who do not receive the assigned treatment will be analyzed as randomized.

For the primary analysis, the last observation carried forward (LOCF) approach will be used for subjects with missing SPC endpoint at 52 weeks. If there is no SPC endpoint assessment prior to 52 weeks, the subject will be considered not meeting the criteria.

The primary endpoint will also be analyzed for the subgroups defined by demographic characteristics, baseline comorbidities, rheumatoid arthritis, or surgical site. The treatment group comparisons after controlling each of these factors will be conducted by stratified analyses using the Mantel Haenszel method as sensitivity analyses

9.6.3 Key Secondary Endpoint

The key secondary efficacy endpoint will be the proportion of subjects who meet the following criteria for the CT radiographic fusion success at 52 weeks:

- Radiographic evidence of fusion by CT scan (≥ 50% bone bridging across the joint space for the full complement of joints in the absence of secondary surgical or nonsurgical interventions intended to promote fusion)

Non-inferiority and superiority will be assessed in a similar manner to the primary efficacy endpoint, and each test will be conducted according to the fixed-sequence procedure described in Section 9.6.1.

9.6.4 Secondary Endpoint(s)

The following secondary efficacy endpoints will be assessed without multiplicity adjustments.

- Proportion of subjects achieving CT radiographic fusion success at 12 and 24 weeks (in the absence of secondary surgical or nonsurgical interventions intended to promote fusion)
- Change from baseline in pain on weight-bearing at fusion site at 12, 24, and 52 weeks (≥20 mm reduction from baseline on 100 mm VAS)
- ABG harvest site pain at 2, 6, 12, 24 and 52 weeks (<20 mm on 100 mm VAS)
- Change from baseline in FAAM-ADL at 12, 24 and 52 weeks
- SPC at 12 and 24 weeks
- Change from baseline in Short Form-12 (SF-12) at 24 and 52 weeks

The difference of the proportions of subjects achieving CT radiographic fusion success between treatment groups will be estimated with the 2-sided 90% confidence interval at 12 and 24 weeks. Similarly, the difference of the proportions of subjects meeting all the criteria for SPC between treatment groups will also be estimated at 12 and 24 weeks.

The change from baseline in weight-bearing pain at fusion site at 12, 24 and 52 weeks will be analyzed by the repeated-measures ANCOVA. The proportion of subjects achieving ≥20 mm reduction from baseline in weight-bearing pain at fusion site will also be summarized by treatment group at each visit.

The change from baseline in FAAM-ADL at 12, 24 and 52 weeks will be analyzed by a repeated-measures analysis of covariance (ANCOVA) model that includes treatment, time, treatment-by-time interaction, baseline score, and other relevant factors or covariates on the observed data. In addition, the proportion of subjects achieving ≥ 8 points improvement from baseline in FAAM-ADL will be summarized by treatment group at each visit.

The ABG harvest site pain at 2, 6, 12, 24 and 52 weeks will be summarized for the ABG group. The proportion of subjects with < 20 mm in ABG harvest site pain will also be summarized at each visit.

The change from baseline in SF-12 scores at 24 and 52 weeks will be analyzed by the repeated measures ANCOVA.

9.7 Safety

9.7.1 General Considerations

Safety parameters will be evaluated for the safety analysis data set.

9.7.2 Adverse Events

A treatment emergent adverse event (TEAE) will be an AE that occurs at the start of surgery and thereafter. An AE overview summary table will be prepared for the safety analysis set. It will display the number and percentage of subjects reporting an AE and the number of events reported for each treatment group. The following categories will be displayed:

- Unanticipated Adverse Device Effects
- SAEs
- Device related SAEs
- Procedure related SAEs
- Device related AEs
- Procedure related AEs
- Any TEAEs

Number and percentage of subjects reporting the following types of TEAEs will be summarized by MedDRA SOC (alphabetically) and PT (in decreasing frequency of occurrence):

- Unanticipated Adverse Device Effects
- SAEs
- Device related SAEs
- Procedure related SAEs
- Device related AEs
- Procedure related AEs
- Any TEAEs

9.7.3 Other Safety Variables

Descriptive statistics of subsidence, device migration, nonunion, osteolysis and/or heterotopic ossification in the area surrounding the implant site by radiographic assessment, clinical laboratory testing and antibody monitoring will be presented for the safety analysis set by treatment group.

Number and percentage of subjects reporting the following events will be summarized:

- Any secondary surgical interventions including revisions, removals, reoperations, or supplemental fixations
- Secondary surgical intervention related to the graft material including revisions, removals, reoperations, or supplemental fixations

9.8 Pharmacokinetic Assessment

The PK analysis will be performed by Department of Experimental Medicine, Ferring Pharmaceuticals A/S. The PK parameters will be calculated by non-compartmental analysis (NCA) using the software WinNonlin®Phoenix v. 6.4 (Pharsight Corporation, US). Plasma concentration values below LLOQ and missing values (e.g. no blood sample collected or no value obtained at analysis) will be excluded from the NCA and the number of observations adjusted accordingly. No formal analysis of "outliers" is planned.

PK parameters will be estimated based on measurements Pre procedure (baseline) to the last day of assessment Day 15 after fusion procedure. From the plasma concentration-time data of B2A, the following parameters will be estimated, if possible: AUC, AUCt, % AUC extrap, Cmax, Tmax, t½, lamda z, CL/F, Vz/F.

Actual sampling time points relative to dosing will be used for the NCA and on the individual plots of plasma concentration versus time. Values below LLOQ will be represented as LLOQ/2 in the plots.

PK parameters will be presented with number of measurements, number of missing data, mean, standard deviation, median, minimum, maximum, geometric mean, and coefficient of variation (CV [%]) on geometric mean (for AUC and Cmax). For tmax the geometric mean and the CV (%) will be omitted.

9.9 Handling of Missing Data

For the primary and key secondary analyses, the imputation method of LOCF will be used in subjects with an unknown outcome.

Sensitivity analyses of missing data will be performed by utilizing the following imputation methods:

1) "missing-equals-failure"

2) multiple imputation methods

3) a tipping point analysis will be performed for the primary and key secondary efficacy endpoints which will allow assessment of sensitivity without need for postulating any missing data mechanism. For this analysis, all possible combinations of missing data from the two arms will be considered, and the point at which significance is no longer achieved will be identified.

The planned sensitivity analyses for the primary and key secondary endpoints will be described in further detail in the Statistical Analysis Plan (SAP).

All data collected on safety or adverse events will be reported to the extent it is available, regardless of the active/withdrawn status of participants.

9.10 Pooling of Site Data

The primary analysis will be based on the pooled results. However, the homogeneity of study outcomes across study centers will be examined. The primary justification for pooling is that study centers will be following the same protocol, using the same device system, and following the same Instructions for Use/Surgical Manual. Additionally, frequent contact and monitoring of the centers will be performed to ensure that all study centers are evaluating participants and recording study results in a reliable and reproducible manner. It is not anticipated that any individual study center will dominate the study results. Therefore, it is considered that these procedures will ensure that the data from these study centers can be combined and analyzed.

To evaluate differences among centers in the study, a summary of important baseline variables, such as demographics, medical history and baseline clinical variables, will be presented by center. Additionally, variables related to procedures will also be summarized by center.

Poolability across study centers will be tested for the primary endpoint. Details of the method will be specified in the SAP.

It is also noted that the evaluation of center effect will consider OUS (outside U.S.) versus U.S.-based centers. Thus, another analysis of the center effect will consider the comparison between the results for these two geographical regions.

Further explanation on poolability analyses will be described in the SAP.

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data – ICH Definition

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents - ICH Definition

Source documents are defined as original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Trial-specific Source Data Requirements – Ferring

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

10.2 eCRF

An eCRF system provided by an independent third-party contract research organization (CRO) will be used for data capture. The system is validated and access at all levels to the system is granted/revoked following Ferring and vendor procedures, in accordance with regulatory and system requirements.

Development of the primary database for the study will be performed by the Sponsor or designee. The Sponsor or designee will also be responsible for the verification, validation and quality control of the database and confirming the overall integrity of the data.

Federal Regulations and Good Clinical Practice (GCP) Guidelines require that Investigators maintain information in the study patient's medical records that corroborate data collected on the eCRFs. In order to comply with these regulatory requirements, the following information should be maintained:

- Medical history/physical condition of the study patient before involvement in the study sufficient to verify protocol entry criteria
- Dated and signed notes on the day of entry into the study including the study Investigator, study name, patient number assigned and a statement that consent was obtained
- Dated and signed notes from each study patient visit with reference to the CRFs for further information, if appropriate (for specific results of procedures and exams)
- Information related to adverse events
- Study patient's condition upon completion of or withdrawal from the study
- Discharge summaries/procedure reports

10.3 Investigator Records

Investigators will maintain complete, accurate and current study records. All records shall, at a minimum, be retained for a period of time equivalent to the design and expected life of the device, but in no case less than 2 years from the date of release for commercial distribution by the manufacturer. Investigator records shall include the following materials:

- ***Correspondence***: Documentation of all verbal and written correspondence with FDA, Sponsor, the Clinical Monitor, the CEC, and other Investigators regarding this clinical study or any patient enrolled therein.
- ***Subject Records***: Signed informed consent forms, copies of all completed CRFs and supporting documents (laboratory reports, reports of diagnostic tests, medical records, etc.) and records of exposure of each subject to the device. Informed consent must comply with FDA regulations (21 CFR, part 50).
- ***Protocol***: A current copy of the CIP including IFU of the AMPLEX System and blank CRFs.
- ***Institutional Review Board (IRB)/Research Ethics Board (REB) Information***: All information pertaining to IRB/REB review and approval of this clinical study including a copy of the IRB/REB letter approving the clinical study, a blank informed consent form approved by the IRB/REB, and certification from the IRB/REB Chairman that the IRB/REB complies with FDA regulations (21CFR, Part 56)/regulatory body regulations, and that the IRB/REB approved the clinical study protocol based on the Report of Prior Investigations.
- ***Investigator Agreements***: Copies of signed Investigator, Co-Investigator and Sub-Investigator Agreements with accompanying curriculum vitae.
- ***Other***: Any other records that may be required by applicable state or federal laws.

10.4 Investigator Reports

The Investigator will prepare and submit the following reports:

- ***MDR***: Medical Device Reporting of all events related to the device or device malfunctions.
- ***Withdrawal of IRB Approval***: Withdrawal of approval shall be reported to the Sponsor or designee within five working days. The Investigator will provide a written report of the reason(s) approval was withdrawn.
- ***Progress Reports***: The Investigator will submit progress reports to the Sponsor or designee in the form of completed CRFs. The same forms will be used at all investigative centers for the recording of data on the findings of follow-up evaluations and complications. In addition, the Investigator may be asked to submit progress reports to the Sponsor or designee and the reviewing IRB that include the number of study subjects, a summary of follow-up data and complications and a general description the study progress.
- ***Final Report***: The Investigator shall submit a final report within three months of termination or completion of the study or that Investigator's participation in the study, to the Sponsor or designee and the IRB/REB.
- ***Other Reports***: Upon the request of Regulatory Agency/FDA, the reviewing IRB/REB, or the Sponsor or designee, the Investigator will provide accurate and timely information about any aspect of the clinical study.
- ***Emergency Protocol Deviations***: The Investigator shall notify the Sponsor or designee and the reviewing IRB/REB of any deviation from the study protocol intended to protect the life or physical well-being of a patient in an emergency. Such notice shall be given as soon as possible.,

10.5 Data Management

A data management plan will be created under the responsibility of the Global Biometrics Department of Ferring Pharmaceuticals A/S. The data management plan will be issued before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation.

The data management plan will describe captured methods, who is authorized to enter the data, decisions about ownership of data, source data storage, which data will be transferred (including timing of transfers), the origin and destination of the data and who will have access to the data at all times.

10.6 Provision of Additional Information

On request, the Investigator will provide Ferring with additional data relating to the trial, duly anonymized and protected in accordance with applicable requirements.

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to ensure adherence to the protocol, International Conference of Harmonization-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of eCRF entries compared to source data, verification of drug accountability and compliance to safety reporting instructions.

The Investigator will permit the monitor direct access to all source data, including electronic medical records, and/or documents in order to facilitate data verification. The Investigator will co-operate with the monitor to ensure that any discrepancies that may be identified are resolved. The Investigator is expected to be able to meet the monitor during these visits.

11.2 Audit and Inspection

The Investigator will make all the trial-related source data and records available at any time to quality assurance auditor(s) mandated by Ferring, or to domestic/foreign regulatory inspectors or representatives from IRBs/REBs who may audit/inspect the trial.

The main purposes of an audit or inspection are to assess compliance with the trial protocol and the principles of ICH-GCP including the Declaration of Helsinki and all other relevant regulations.

The subjects must be informed by the Investigator and in the Informed Consent Documents that authorized Ferring representatives and representatives from regulatory authorities and IRBs/REBs may wish to inspect their medical records. During audits/inspections the auditors/inspectors may copy relevant parts of the medical records. No personal identification apart from the screening/randomization number will appear on these copies.

The Investigator should notify Ferring without any delay of any inspection by a regulatory authority or IRB/REB.

11.3 Confidentiality of Subject Data

The Investigator will ensure that the confidentiality of the subjects' data will be preserved. In the eCRF or any other documents submitted to Ferring, the subjects will not be identified by their names, but by an identification system, which consists of an assigned number in the trial. Documents that are not for submission to Ferring, e.g. the confidential subject identification code and the signed Informed Consent Documents, will be maintained by the Investigator in strict confidence.

12 CHANGES IN THE CONDUCT OF THE TRIAL

12.1 Protocol Amendments

Any change to this protocol will be documented in a protocol amendment, issued by Ferring, and agreed upon by the Investigator and Ferring prior to its implementation. Amendments may be submitted for consideration to the approving IRB(s)/REB(s) and Regulatory Authorities, in accordance with local regulations. Changes to the protocol to eliminate immediate hazard(s) to trial subjects may be implemented prior to IRB(s)/REB(s) approval/favorable opinion.

12.2 Deviations from the Protocol

If deviations from the protocol occur, the Investigator must inform the monitor, and the implications of the deviation must be reviewed and discussed. Any deviation must be documented, either as an answer to a query in the eCRF, in a protocol deviation report or a combination of both. A log of protocol deviation reports will be maintained by Ferring. Protocol deviation reports and supporting documentation must be kept in the Investigator's File and the Trial Master File.

Investigators must report protocol deviations to the Sponsor or designee on a routine basis (e.g., in accordance with interim on-site monitoring activities and/or ongoing remote correspondence). Any protocol deviations that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances must be reported to the Sponsor or designee and to IRB/REB within 24 hours, if required by IRB/REB or national regulations. The Sponsor or designee should document unreported protocol deviations that are identified during monitoring visits.

12.3 Premature Trial Termination

Both the Investigator (with regard to his/her participation) and Ferring reserve the right to terminate the trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the two parties. In terminating the trial, Ferring and the Investigator will ensure that adequate consideration is given to the protection of the best interests of the subjects. Regulatory authorities and IRBs/REBs will be informed.

In addition, Ferring reserves the right to terminate the participation of individual trial sites. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter subjects at an acceptable rate.

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a clinical trial report prepared by Ferring or its designee and submitted for comments and signature to the signatory Investigator(s).

13.2 Confidentiality and Ownership of Trial Data

Any confidential information relating to the investigational device or the trial, including any data and results from the trial will be the exclusive property of Ferring. The Investigator and any other persons involved in the trial will protect the confidentiality of this proprietary information belonging to Ferring.

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

At the end of the trial, one or more manuscripts for joint publication may be prepared in collaboration between the Investigator(s) offered authorship and Ferring. In a multi-site trial based on the collaboration of many sites, any publication of results must acknowledge all sites. Results from multi-site trials must be reported in entirety in a responsible and coherent manner and results from subsets should not be published in advance or without clear reference to the primary publication of the entire trial.

Authorship is granted based on the International Committee of Medical Journal Editors (ICMJE) criteria (see current official version: http/www.ICMJE.org). The total number of authors is based on the guideline from the relevant journal or congress. In the event of any disagreement in the content of a publication, both the Investigator's and Ferring's opinion will be fairly and sufficiently represented in the publication.

Any external CRO or laboratory involved in the conduct of this trial has no publication rights regarding this trial.

If the Investigator wishes to independently publish/present any results from the trial, the draft manuscript/presentation must be submitted in writing to Ferring for comment prior to submission. Comments will be given within four weeks from receipt of the draft manuscript. This statement does not give Ferring any editorial rights over the content of a publication, other than to restrict the disclosure of Ferring's intellectual property. If the matter considered for publication is deemed patentable by Ferring, scientific publication will not be allowed until after a filed patent application is published. Under such conditions the publication will be modified or delayed at the Investigator's discretion, to allow sufficient time for Ferring to seek patent protection of the invention.

13.3.2 Public Disclosure Policy

ICMJE member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public, clinical trials registry. Thus, it is the responsibility of Ferring to register the trial in an appropriate public registry, e.g. www.clinicaltrials.gov which is a website maintained by the National Library of Medicine (NLM) at the U.S. National Institutes of Health (NIH).

14 ETHICAL AND REGULATORY ASPECTS

14.1 Institutional Review Board (IRB) or Research Ethics Board (REB)

An IRB/REB will review the protocol and any amendments and advertisements used for recruitment. The IRB/REB will review the Subject Information Sheet and the Informed Consent Form, their updates (if any), and any written materials given to the subjects. A list of all IRBs/REBs to which the protocol has been submitted and the name of the committee chairmen will be included in the Clinical Trial Report.

14.2 Regulatory Authority

The regulatory permission to perform the trial will be obtained in accordance with applicable regulatory requirements. All ethical and regulatory approvals must be available before a subject is exposed to any trial-related procedure, including screening tests for eligibility.

14.3 End-of-Trial and End-of-Trial Notification

The Sponsor may terminate the study at any time. If the study is terminated prior to the completion of expected enrollment for any reason, all participating centers will be notified within five working days. All subjects already enrolled will continue to be followed for the planned course of study described in this protocol. The study shall be terminated following the final follow-up visit of the last enrolled patient.

The Sponsor reserves the right to terminate study site participation and remove appropriate study materials at any time. Specific instances that may precipitate such termination include but are not limited to the following:

- Failure to meet minimum patient enrollment requirements
- Failure to comply with protocol specified procedures and documentation
- Failure to comply with GCP

The site Investigator may also discontinue study participation with suitable written notice to the Sponsor.

14.4 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, in compliance with the approved protocol, ICH-GCP and applicable regulatory requirements.

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB/REB. Any amendments to the protocol or consent materials must also be approved before they are placed into use.

14.5 Subject Information and Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/ administering study product. Consent forms will be IRB/REB-approved and the subject will be asked to read and review the document.

Upon reviewing the document, the Investigator will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any procedures being done specifically for the study. The subject should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate, unless study timeframes do not allow for such discussions. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.5.1 Subject Unable to Read or Write

Informed consent shall be obtained through a supervised oral process if a subject or legally authorized representative is unable to read or write. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject or his/her legally authorized representative and, whenever possible, either party shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained and that informed consent was freely given.

14.5.2 Emergency Consent

For clinical investigations involving emergency treatments, when prior informed consent of the subject is not possible because of the subject's medical condition, the informed consent of the subject's legally authorized representative, if present, shall be requested. When it is not possible to obtain prior informed consent from the subject, and the subject's legally authorized representative is not available, the subject may still be enrolled if a specific process has been described in the protocol.

Arrangements shall be made to inform the subject or legally authorized representative, as soon as possible, about the subject's inclusion in the clinical investigation, and about all aspects of the clinical investigation.

The subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The principal Investigator may enroll a subject without obtaining the informed consent of the subject or his/her legally authorized representative only when the following conditions are fulfilled:

- the prospective subject fulfills the emergency conditions and is obviously in a life-threatening situation;
- no sufficient clinical benefits are anticipated from the currently available treatment;
- there is a fair possibility that the life-threatening risk to the prospective subject can be avoided if the investigational device is used;
- anticipated risks are outweighed by the potential benefits of applying the investigational device;
- the legally authorized representative cannot be promptly reached and informed.

14.5.3 New Information

If new information becomes available that can significantly affect a subject's future health and medical care, then that information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

14.6 Subject Information Card

The subject will be provided with a Subject Information Card bearing the following information:

- That he/she is participating in a clinical trial (Trial Code: 000226).
- That he/she is treated with (AMPLEX or ABG).
- The name and phone number of the Investigator.
- Name and address of Ferring (if required by local regulations).

The subject will be asked to return the Subject Information Card at the last trial visit, if applicable.

14.7 Compliance Reference Documents

This clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, International Standard Organization (ISO 14155:2011) and any regional or national regulations.

The clinical investigation shall not begin until the required approval/favorable opinion from the IRB/REB or regulatory authority has been obtained, if appropriate.

Any additional requirements imposed by the IRB/REB or regulatory authority shall be followed.

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

The responsibilities of Ferring, the monitor and the Investigator are defined in the ICH-GCP consolidated guideline, and applicable regulatory requirements in the country where the trial takes place. The Investigator is responsible for adhering to the ICH-GCP responsibilities of investigators, for dispensing the investigational device in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

15.2 Liabilities and Insurance

In case of any damage or injury occurring to a subject in association with the investigational device or the participation in the trial, Ferring has contracted an insurance which covers the liability of Ferring, the Investigator and other persons involved in the trial in compliance with the laws in the countries involved.

16 ARCHIVING

16.1 Investigator File

The Investigator is responsible for maintaining all the records, which enable the conduct of the trial at the site to be fully understood, in compliance with ICH-GCP. The trial documentation including all the relevant correspondence should be kept by the Investigator in accordance with investigative site and local regulatory requirement. All records shall, at a minimum, be retained for a period of time equivalent to the design and expected life of the device, but in no case less than 2 years from the date of release for commercial distribution by the manufacturer.

The Investigator is responsible for the completion and maintenance of the confidential subject identification code which provides the sole link between named subject source records and anonymous eCRF data for Ferring.

No trial site document may be destroyed without prior written agreement between the Investigator and Ferring. Should the Investigator elect to assign the trial documents to another party, or move them to another location, Ferring must be notified. If the Investigator retires and the documents can no longer be archived by the site, Ferring can arrange having the Investigator File archived at an external archive.

16.2 Trial Master File

Ferring will archive the Trial Master File in accordance with ICH-GCP and applicable regulatory requirements.

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18 APPENDICES

Appendix 1 Anticipated Adverse Events

Safety assessments involving AEs and SAEs are critical in the clinical assessment of new medical devices. Clinical trials evaluating medical devices often involve surgical or other procedures. As a result, AEs and SAEs can result from the medical device, the procedure itself, or the underlying medical condition. All AEs and SAEs will be reported regardless of cause. Nevertheless, since some AEs and SAEs impact on the primary efficacy assessment, Device-relatedness will be determined by the Investigator and adjudicated by the CEC. However, the relatedness of a number of AEs and SAEs are known. This table is provided as a guidance in assessing the better-known complications of arthrodesis surgery.

Adverse events associated with any surgical procedure could include:

Likely:

- pain (not reported as an AE if related to graft site or harvest site)
- swelling
- adverse reaction to anesthesia including nausea, confusion, vomiting and elevations in liver enzymes

Less Likely:

- soft tissue injury (swelling, warm to touch and/or pain to affected area)
- surgical site wound infection (drainage or pus at surgical site)
- cellulitis (inflammation of the soft tissue, especially below the skin characterized by fever, swelling, redness and pain)
- failure of the tissue to heal properly (wound breakdown or opening)
- other wound problem (fluid pocket formation)
- other infection (fever, aches and/or pain)
- hemorrhage (severe bleeding)
- nerve damage (weakness, tingling, and or numbness)
- muscular damage
- swelling, pain and/or redness at affected area
- arrhythmia (abnormal heart rhythm)

Rare but serious:

- anesthesia complication (drug allergy, difficulty breathing, cardiac (heart) or systemic effect that could be life threatening)
- heart attack
- stroke
- pulmonary (lung) complications
    - pneumonia, (lung inflammation caused by infection)
    - atelectasis (shortness of breath caused by partial collapse of the lung)
    - respiratory distress (shortness of breath or respiratory failure)
    - pulmonary edema (excess water in the lung)
- pulmonary embolus (clogging of lung blood vessels by a blood clot)
- need for blood transfusion (risk of disease transmission)

- bad reaction to blood transfusion (fever, itching, heart failure or systemic illness)
- septicemia (life-threatening infection in the blood)
- seizures/convulsions
- changes in mental status
- death

Adverse events associated with foot/ankle fusion surgery include:

Likely:
- pain (evaluated as an efficacy assessment, not reported as an AE)
- swelling

Less likely:
- nerve injury (numbness sensation, tingling of affected area, decreased strength)
- adjacent joint degeneration (degeneration of the joint(s) next to the fusion at a later time requiring surgery)
- lack of pre-operative pain/symptoms reduction (signs and symptoms that were present before surgery remain the same after surgery)
- failure to achieve desired or any foot/ankle fusion (incomplete fusion of the bone)
- heavy surgical or post-surgical bleeding
- deep vein thrombosis (swelling or pain in the legs from a blood clot)
- paraesthesia (sensation of pricking, tingling and/or creeping on the skin)
- muscle and/or ligament injury

Rare but serious:
- fracture (bone breaks) of the tibia (leg), or bones of the foot
- osteolysis (resorption and/or dissolution of bone tissue)

Adverse events associated with foot/ankle instrumentation include:

Likely:
- pain and discomfort associated with implanted instrumentation (only of it can be differentiated from graft site pain)

Less Likely:
- misplaced, wrong sizing, loosened, broken or migrated implants (screws)
- implant displacement or migration (change of position)
- wear debris (accumulation of fragments)

Rare but serious:
- foreign body reaction to the implant (fever, swelling, and or discomfort)
- local or systemic allergic reaction (fever, aches and/or pain)
- damage to local structures

Adverse events associated with the study product include:

- Allergic reaction (local or systemic response)
- Ectopic bone growth (bone forming outside of normal bone growth areas)
- Abnormal cell growth (growth of tissue or cells beyond the norm)
- Negative effects on pregnancy or fetus
- Immune response (bodily response against foreign material)
- Significant increase in liver enzyme measures

Adverse events associated with harvesting autologous bone graft include:

- pain at the graft harvest site (evaluated as an efficacy assessment, not reported as an AE)
- swelling
- fracture at the graft harvest site
- soft tissue injury (swelling, warm to touch and/or pain to affected area)
- harvest site wound infection (drainage or pus at surgical site)
- cellulitis (inflammation of the soft tissue, especially below the skin characterized by fever, swelling, redness and pain)
- failure of the tissue to heal properly (wound breakdown or opening)
- other wound problem (fluid pocket formation)
- other infection (fever, aches and/or pain)
- hemorrhage (severe bleeding)
- nerve damage (weakness, tingling, and or numbness)
- muscular damage
- phlebitis thromboembolus (swelling, pain and/or redness at affected area)

Appendix 2 Foot and Ankle Ability Measure Activities of Daily Living (FAAM-ADL) Questionnaire