Axogen, Corporation.

Avance® Nerve Graft

PROTOCOL

A Multicenter, Prospective, *R*andomized, Subject and *E*valuator Blinded *C*omparative Study of Nerve Cuffs and Avance® Nerve Graft Evaluating Recovery *O*utcomes for the Repair of *N*erve Discontinuities (RECON)

Protocol No. ANG-CP-007

CONFIDENTIAL – PROPRIETARY INFORMATION

Development Phase:	Pivotal
Sponsor:	Axogen, Corporation 13631 Progress Blvd – Suite 400 Alachua, FL 32615
Sponsor Representative:	[redacted]
Lead Clinical Investigators:	L. Scott Levin, MD Philadelphia, PA Jonathan Isaacs, MD Richmond, VA
Immediately Reportable Adverse Event:	Clinical Safety [redacted]
Version: Issue Date:	4.0 12 May 2021

This clinical investigation will be performed to compliance with the protocol, the FDA Good Clinical Practices including 21CRF part 312, 601, 50, 56, ICH E6, and local applicable regulatory requirements. This document is a confidential communication of Axogen, Corporation. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein shall be published or disclosed without prior written approval, except that this document may be disclosed to the appropriate Institutional Review Boards under the condition that they keep it confidential.

[redacted]

Title of Study: A Multicenter, Prospective, *R*andomized, Subject and *E*valuator Blinded *C*omparative Study of Nerve Cuffs and Avance® Nerve Graft Evaluating Recovery *O*utcomes for the Repair of *N*erve Discontinuities (RECON)
Estimated Number of Study Centers and Countries: Up to 25 Centers in the US, Canada and Europe
Study Type: Pivotal
Study Design: Prospective, Subject and Evaluator Blinded, Randomized, Comparative Study
Objective: The primary objective of this study is to evaluate the difference in functional recovery outcomes between the study groups.
Study Population: Male and female adult subjects that have sustained injury to at least one nerve, distal to the superficial palmar arch and proximal to the distal interphalangeal joint, that after resection results in a nerve gap between 5 mm and 25 mm, inclusive.
Test Product: Avance® Nerve Graft
Control: Nerve Cuff [redacted] a Type I bovine collagen nerve cuff)
Number of Subjects per Treatment Group: Enroll an adequate number of subjects to obtain 88 subjects for evaluation.
Duration of Study: Up to 54 months including 12 months of follow-up on each subject.
Inclusion Criteria: 1. Subjects 18 to 65 years of age, inclusive; 2. Require primary or secondary nerve injury repair with nerve cuff [redacted] a Type 1 bovine collagen nerve cuff) or Avance® Nerve Graft in at least 1 digital nerve; 3. One of injury to nerve must be resectable; 4. Nerve gaps following resection, between 5 and 25 mm, inclusive; 5. Undergo tension free end to end nerve to nerve coaptation on both the proximal and distal portion of the nerve gap in the Avance® Nerve Graft Group or nerve entubulation in the Nerve Cuff group; 6. Have an uninjured contralateral or adjacent digit that is suitable to serve as a referenced digit for baseline functional assessments; 7. Be willing and able to comply with all aspects of the treatment and evaluation schedule over a 12-month duration; and 8. Sign and date an IRB-approved written informed consent prior to initiation of any study procedures.

[redacted]

Exclusion Criteria:

1. Estimated distance of regeneration of >150 mm (distance from proximal injury site to tip of target digit);
2. Injuries distal to the distal interphalangeal joint;
3. Extensive soft tissue injury which will impair recovery assessment;
4. Incomplete nerve transections;
5. Injury requiring replantation of target digit;
6. Injuries to the affected nerve proximal to the superficial palmar arch;
7. Nerve injuries >24 weeks post initial injury;
8. End to side nerve repair;
9. Injuries with vascular damage resulting in inadequate perfusion despite repair;
10. Subjects with Type 1 Diabetes Mellitus or Type 2 Diabetes Mellitus requiring regular insulin therapy;
11. Subjects who are undergoing or expected to undergo treatment with chemotherapy, radiation therapy, or other known treatment which affects the growth of neural and/or vascular system;
12. Use of bovine collagen-based nerve conduit in a subject with known or suspected bovine sensitivity;
13. History of neuropathy, diabetic neuropathy or any other known neuropathy;
14. Currently enrolled in another investigational study;
15. Expected use of medication during the study that is known to impact nerve regeneration or to cause peripheral neuropathy;
16. History of chronic ischemic condition of the upper extremity; and
17. Any subject who at the discretion of the Investigator is not suitable for inclusion in the study.

Conduct of Study: Randomized, prospective, subject and evaluator blinded, multi-center study. The study will be composed of seven (7) scheduled visits. See Appendix 2: Schedule of Assessments for details.

Criteria for Evaluation:

Primary Safety Endpoint

Adverse events associated with the qualifying nerve repair.

Primary Effectiveness Endpoint

Recovery of static two-point discrimination (s2PD) in the target digit.

Secondary Effectiveness Endpoints

Response rate for recovery for s2PD at Month 12,

[redacted]

Reduction in pain as measured with the VAS pain assessment

Percent recovery to pre-injury baseline in s2PD,

Time to recovery of s2PD

[redacted]

[redacted]

Medical Research Council Classification of Sensory Recovery (MRCC),

[redacted]

Statistical Methods:

The study is a prospective, randomized, comparator trial to assess the non-inferiority and superiority of Avance® Nerve Graft to nerve cuffs [redacted]. All summaries of categorical data will be presented in frequencies and percentages. All summaries of continuous data will be presented by the number of non-missing values, mean, standard deviation, standard error, median, minimum, maximum, and coefficient of variation. [redacted]

Sample Size:

The study was planned to enroll at least 150 subjects at 20 sites. Following a pre-planned blinded interim analysis, the sample size was increased to a maximum of 220 subjects at up to 25 sites.

[redacted]

Table of Contents

1 Introduction

Avance® Nerve Graft is a decellularized, predegenerated and sterilized extracellular matrix (ECM) processed from donated human peripheral nerve tissue (see Figure 1-1). The structure is the ECM of native peripheral nerve and is comprised of bundles of small diameter endoneurial tubes (as shown in Figure 1-2). The tissue is processed to remove cellular and non-cellular factors such as Schwann cells, fat, blood, axonal debris and chondroitin sulfate proteoglycans (CSPG), while preserving the three-dimensional scaffold, vascular structure, basal lamina laminin, fibronectin, and glycosmainoglycans.

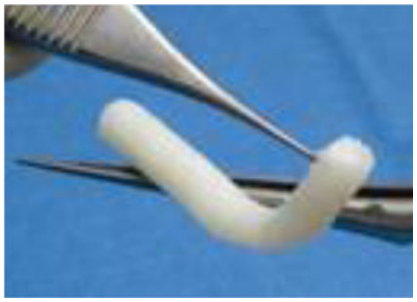


Figure 1-1
Avance® Nerve Graft

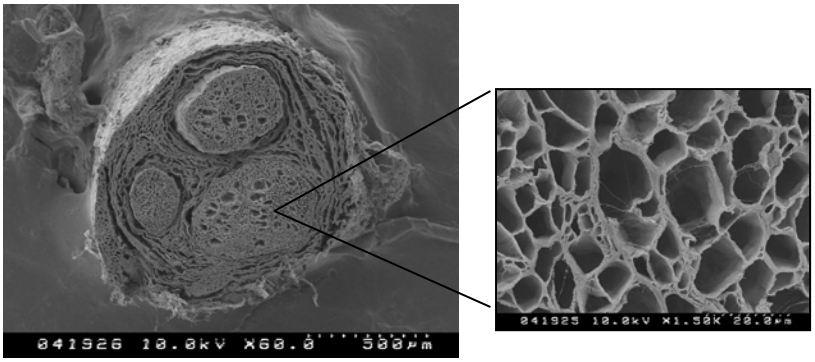


Figure 1-2
Scanning Electron Micrographs (SEMs) of the Avance® Nerve Graft showing the general overall tubular structure (scale bar=429um) and a close up view of the multiple empty tubes within the structure (scale bar=20um).

Avance® Nerve Graft is intended to reconstruct and repair peripheral nerve discontinues; and support axonal regeneration of peripheral nerves following transection injury. Processing results in a flexible, pliable, open multi-tubular ECM structure that can be sutured in place and allows for a tension free approximation of the proximal and distal nerve stumps (see Figure 1-2). The graft revascularizes and remodels into the patients' own tissue while supporting axonal growth across the nerve discontinuity. The resulting axonal growth can lead to functional recovery of the target organ. Furthermore, because Avance® Nerve Graft is decellularized, it does not require immunosuppressive therapy, which had previously limited the clinical use of cellular nerve allografts [1-4].

Currently, repair options for peripheral nerve discontinuities, when direct tension-free gap closure is not possible, include the nerve autograft and nerve cuff. While the use of the nerve autograft is considered the historical standard for gap repair, it in itself presents challenges to the surgeon and patient including: additional surgery and the risks associated with it, donor site morbidity and limited tissue availability (e.g. during a large traumatic nerve injury), as well as, increased operative time and cost associated with tissue harvest. The nerve cuff (Medical Device Product Code JXI) was made available in the 1990's as an alternative to sacrificing healthy nerve. While the nerve cuff has been used as an alternative nerve repair option, its mono-tubular structure and rigidity limit its use for repairs with branching nerves or across joints in the digits where early mobilization was prescribed due to concomitant tendon repairs. The flexible, pliable, multi-tubular structure of the Avance® Nerve Graft overcomes these limitations to provide the surgeon with an additional treatment option.

This study will evaluate the difference in functional recovery outcomes between the study groups to assess the non-inferiority and superiority of the Avance® Nerve Graft to nerve cuffs [redacted] a Type I Bovine Collagen nerve cuff).

1.1 Background

Peripheral Nerve Discontinuities

In normal nerve anatomy, nerve cell bodies are located in or near the spinal cord. The nerve processes or fibers (called axons) extend from the cell bodies and travel down little tubes (endoneurial tubes or basal lamina) in the nerve trunks and in the peripheral nerves, until they make contact with the appropriate end organ, such as muscle or skin. A signal generated in the brain travels down the spinal cord, into the axons, then to the muscle where it is converted into a muscle contraction, which results in arm motion. After a nerve is transected, many of the nerve cell bodies in and around the spinal column die just from the devastating shock of the injury. All nerve fibers in the distal (or downstream) nerve stump, that are now separated from their cell bodies, die and are quickly broken down by the body in a process called Wallerian Degeneration. Almost immediately after a nerve transection, all sensory and motor function directed by that injured nerve is lost. These types of injuries can severely impact patients in many different ways. For example, a nerve laceration in the hand may result in loss of movement or sensation in the fingers. In prostate cancer, the necessary removal of the prostate and associated cavernous nerves can result in erectile dysfunction and/or incontinence and injuries to the facial nerve can result in the patient losing the ability to smile.

Transected axons almost immediately start the regeneration process by sending out exploratory branches, however, these branches can only find their way into the distal nerve stump if an adequate surgical repair has been performed. Many nerve lacerations can be primarily repaired by suturing the cut ends together. Other times, either due to nerve tissue loss or nerve end retraction, a bridging material is required to connect the two ends [1]. This bridging material must be able to support regenerating axons. Recovery is not possible if the nerve is left unrepaired or if the method or material used to reconstruct the nerve discontinuities fails to support axonal regeneration across the nerve discontinuity [1,5,6].

Adequate repair of the nerve discontinuity is not the sole factor in ensuring the return of function. Patient demographics, general health of the patient, age of injury, location of injury, mechanism of injury, extent of trauma to surrounding and target tissue, patient compliance with rehabilitation regimen, and brain plasticity, all play a role in the clinical outcome.

Current Treatment Options

As stated previously, when possible, a direct tension free nerve repair is the ideal repair method. When an insurmountable gap exists, the separated nerve ends must be bridged using a biological or artificial material [1, 2, 7]. Currently, there are several "bridging" options including autograft nerve, Avance® Nerve Graft, and nerve cuffs (tubes). Unfortunately, use of autograft nerve tissue requires a secondary surgical procedure, which increases anesthesia time and facility cost, and sacrifices a healthy functioning nerve. This not only leads to functional (usually sensory) loss and scarring, but can also result in painful neuroma formation or other complications such as infection [1, 2, 5, 8-10]. The paucity of "expendable" nerves within the human body results in a limited supply of autograft and may necessitate size mismatching between donor and native nerve.

Spurred by many of the disadvantages of nerve autograft, nerve cuffs, first introduced in the 1990's, have seen a steady increase in popularity and, currently, multiple nerve cuffs are available for commercial use. Hollow tubes made from collagen or synthetic materials are designed to entubulate the proximal and distal ends of the transected nerve. A fibrin clot forms between the two nerve ends and is contained within the nerve tube. Axons can regenerate within this fibrin clot and cross the gap to the distal nerve stump. Single lumen nerve cuffs, however, have a limited effective length and undesirable handling characteristics, which limits their clinical application and acceptance.

Modern usage of viable, cellular nerve allograft was developed by Susan Mackinnon, M.D., in the 1990s. The results of her work were published in 2001 and detailed the outcomes of seven patients [4]. While the results of this study showed promise, cellular nerve allografting as a strategy for nerve reconstruction is hampered by the need for donor matched tissue and prolonged immunosuppression. Cellular nerve allograft remains commercially unavailable.

A more recent addition to the armamentarium of the nerve surgeon, processed acellular nerve allograft, does not require the immunosuppressive therapies associated with cellular nerve allografts. Avance® Nerve Graft was introduced as a 361 Tissue for Transplantation in 2007 and was the first commercially available decellularized nerve allograft product. Since that release date, Axogen has distributed over 7,000 grafts. Avance® Nerve Graft has been utilized in the reconstruction of traumatic and iatrogenic peripheral nerve transection injuries in the upper and lower extremities, head and neck, chest and pelvis. Mechanisms of injury have included, but are not limited to, laceration, blunt trauma, amputation, avulsion, gunshot wound, shrapnel, improvised explosive product (IED) blast trauma, neuroma resection, chemical burns, and oncologic resection.

Clinical Outcomes with Nerve Cuffs

Currently, there are very few controlled outcomes studies that compare the different peripheral nerve repair options [11]. Inherent challenges associated with this type of data collection include the heterogeneous nature of traumatic injuries, of which include varying degrees of nerve damage and concomitant injuries [12]. Conclusive comparative clinical efficacy evaluations require standardized, homogeneous samples [13].

Nerve cuffs, are regulated as class II medical devices under 510(k) exemption and are defined in the code of federal regulations (CFR) at 21 §CFR 882.5275 as "a tubular silicone rubber sheath used to encase a nerve for aid in repairing the nerve (e.g., to prevent in growth of scar tissue) and for capping the end of the nerve to prevent the formation of neuroma (tumors)". Since they are regulated as

predicate medical devices, well-controlled prospective clinical studies on their safety and efficacy have been limited.

Weber et al [14]. published the largest prospective, randomized, controlled study in peripheral nerve repairs. This report, which focused on a digital nerve injury model, has been widely accepted by the surgical community as the landmark study for the use of nerve cuffs in the reconstruction of nerve discontinuities. Table 1.1-1, represents a list of individual and composite data of the available scientific literature of reported outcomes from the use of nerve cuffs for discontinuities of the digital nerves in the hand. Static two point discrimination (s2PD) and MRCC were the most common assessments conducted to measure efficacy of the test articles. Success was defined as either recovery of s2PD (15mm or less) or an improved MRCC score to S3 or greater. The repair model (sensory nerve distal to the wrist) utilized in these studies has been shown to provide reproducible results for recovery of function following the repair of a peripheral nerve discontinuity.

Table 1.1-1: Reported Outcomes from Studies of Nerve Cuffs in the Hand

Study	N	Repair Model	Defined Success	Relevant Outcome Measure
Mackinnon and Dellon. 1990 Clinical Nerve Reconstruction with Bioabsorbable Poly-glycolic Acid Tube[15]	15	Sensory Nerve Repair in the Hand	Measurable recovery of 2-PD	40% Excellent, 33% Good, and 27% Poor recovery was noted. Average Two-Point Discrimination (2-PD) Moving: 3.3 mm Static: 4.6 mm
Weber et al. 2000 A Randomized Prospective Study of Poly-glycolic Acid Conduits for Digital Nerve Reconstruction in Humans[14]	98	Sensory Nerve Repair in the Hand	Measurable recovery of 2-PD	86% of subjects demonstrated return of 2 point discrimination in the direct repair and autograft group Average Two-Point Discrimination (2-PD) Moving: 7.0 mm Static: 9.3 mm 74% of subjects demonstrated return of 2 point discrimination in the PGA Nerve Cuff group Average Two-Point Discrimination Moving: 6.9 mm Static: 10 3 mm
Bertleff et al. 2005 A Prospective Clinical Evaluation of Biodegradable NeuroLac Nerve Guides for Sensory Nerve Repair in the Hand[16]	34	Sensory Nerve Repair in the Hand	Comparable level of recovery of 2-PD	Two-Point Discrimination was comparable between study groups. Reported level was less than 15 mm at 12 months.
Bushnell et al. 2008 Early Clinical Experience With Collagen Nerve Tubes in Digital Nerve Repair[17]	9	Sensory Nerve Repair in the Hand	2-PD good (S2+, S3) or excellent (S3+, S4)	Two-Point Discrimination results were good or excellent in 8 out of 9 of patients (88.9%)
Lohmeyer JA, et al. 2009 The Clinical Use of Artificial Nerve Conduits for Digital Nerve Repair: A Prospective Cohort Study and Literature Review[18]	12	Sensory Nerve Repair in the Hand	Recovery of 2-PD	Four out of twelve patients showed excellent sensibility with static Two-Point Discrimination of 7 mm (S4). 5 patients achieved good sensibility (static 2-PD<15 mm, S3+), 1 poor (s2PD>15 mm, S2), and 2 no sensibility (S0)

The repair model utilized in these studies has successfully demonstrated the ability to assess the efficacy of a nerve repair treatment option. The model is an accurate representation for nerve

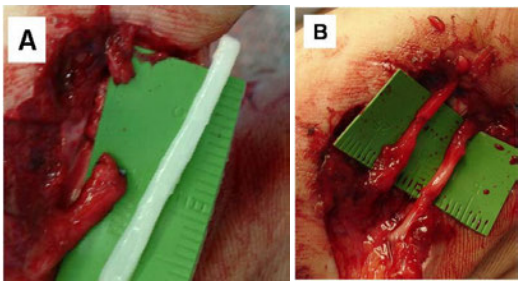
segmental defects, in that in order for function recovery to occur, the repair treatment must allow for regenerating axons to cross the discontinuity and enter the distal nerve sheath. The endpoint measures are well defined and can consistently be measured from subject to subject. Also, the endpoints allow for treatment efficacy to be reviewed within 12 months from repair, given that nerves regenerate at a rate of 1-2 mm per day. Additionally, the frequency of digital nerve injuries is such that it allows for enrollment of comparable injuries within a reasonable time period. Other repair models may report varying degrees of function recovery while utilizing different outcome assessments, as not all nerve types have homogenous outcomes, for instance, the repair of a mixed nerve will yield both sensory and motor outcomes.

1.2 Product Description

Avance® Nerve Graft is a decellularized, cleansed, and sterilized extracellular matrix from donated human peripheral nerve. The cleansing process preserves the inherent and relevant structural characteristics of the tissue.

Avance® Nerve Graft is intended to be used to repair nerve discontinuities anywhere in the body at lengths of up to 70mm. It has a flexible, pliable, multi-tubular ECM structure (See Figures 1-1, and 1-2) and handles similarly to nerve autograft allowing for versatile utilization including repairs across joints and shallow would beds; a limitation seen with the use of nerve cuffs[14, 15, 18]. These advantages provide the surgeon with a clinically beneficial off-the-shelf nerve graft option that avoids the disadvantages of autograft harvest or nerve cuff limitations.

Avance® Nerve Graft is provided frozen and sterile. After thawing the graft, implantation should be completed using the same tensionless surgical technique used when implanting a nerve autograft. The graft is positioned within the nerve gap and coapted to the proximal and distal stumps of the host nerve. See Figure 1.2-1.



Images Courtesy of Mayo Clinic Foundation

Figure 1.2-1
In-situ placement of the Avance® Nerve Graft. A. Surgeon will trim the graft to length dependent upon discontinuity. B. Avance® Nerve Graft after implantation for two individual nerve injuries.

1.3 Comparator Product Description

Regulated as Class II medical devices via FDA 510k clearance, absorbable nerve cuffs are marketed under numerous brand names (NeuroTube®, NeuroLac®, NeuraGen®, NeuroMatrix™, NeuroFlex™). Nerve cuffs, which are constructed from absorbable or non-absorbable polymers or processed

collagen, are molded or extruded to form a hollow tube structure that encases the proximal and distal ends of the injured nerve. For the purpose of this clinical study, [redacted] a Type I bovine collagen nerve cuff, will be utilized as the control treatment. Implantation is to be done according to the manufacturer's instructions (Appendix 4.0).

1.4 Risk Analysis

Inherent risks of any surgical procedure include: infection, blood loss, and anesthesia-associated complications. Complications specific to nerve reconstruction include pain, decreased or increased sensitivity, and impaired motor or sensory function. As with all peripheral nerve surgeries, there is a risk that the nerve may fail to regenerate.

Hypersensitivity, allergic reactions, or other adverse immune responses have not been seen in preclinical studies or reported clinically with the use of Avance® Nerve Graft. Because Avance® Nerve Graft is composed of proteins such as collagen and laminin; the potential may exist for such reactions. All adverse outcomes potentially attributed to Avance® Nerve Graft are to be promptly reported to Axogen, Inc, in accordance with state and federal regulations.

Avance® Nerve Graft is processed human nerve tissue. As with all donated human tissue products the risk for transmission of communicable disease does exist. Robust donor screening and selection is completed as required by FDA and is in accordance with American Association of Tissue Banks (AATB), state, and federal guidelines. Processing controls and terminal sterilization with gamma irradiation greatly reduce but cannot totally eliminate the risk of disease transmission. As disease-screening methods are limited, there is the potential for certain diseases to not be detected. The following complications of tissue transplantation may occur:

- Transmission of diseases of unknown etiology;
- Transmission of known infectious agents including, but not limited to viruses, bacteria, and fungi.

The processing of Avance® Nerve Graft was developed with a robust safety and efficacy profile to include extensive preclinical testing, established manufacturing controls, and documented previous human clinical experience.

Risks associated with the use of [redacted] include adverse events related to the implantation of a foreign body and reactions associated with the xenogeneic protein that is used to construct the nerve cuff. The implantation of a foreign body (such as a nerve cuff) in a non-sterile environment may increase the risk of infection. Inflammation or surgical site reaction has been observed with the use of nerve cuffs and can occasionally be severe enough to cause extrusion of the cuff through the skin. Additionally, use of [redacted] is contraindicated in individuals at risk of localized reaction or anaphylaxis due to known or suspected sensitivity to bovine proteins.

1.4.1 Preclinical Testing for Avance® Nerve Graft

Comprehensive in vitro and in vivo biocompatibility evaluations provide support that Avance® Nerve Graft is safe for use in humans. Additionally, in vivo testing utilizing well established and validated animal models has demonstrated efficacy in its intended use to reconstruct and repair peripheral nerve discontinues; and support axonal regeneration of peripheral nerves following transection injury.

Effective regeneration in this model has been well characterized by both Susan Mackinnon, MD at Washington University, St. Louis, MO and David Muir, PhD at the University Of Florida Department Of Neuroscience, Gainesville, FL. Both designed and conducted preclinical efficacy studies and are recognized as leaders in peripheral nerve research (summarized in Table 1.4.1-1).

Avance® Nerve Graft has been subjected to well established and accepted test panels for preclinical product safety evaluation and has been found to be a non-toxic, non-reactive, non-sensitizing, non-pyrogenic, non-mutagenic, and non-irritant.

Table 1.4.1-1: *In vivo* Preclinical Efficacy Study Summary

Study Description	Results
Reconstruction of Rat Sciatic Nerve Discontinuity with Avance® Processed Allografts or Nerve Grafts[19]	Avance® processed allografts effectively supported regeneration of axons across the 10 mm nerve discontinuity and compared favorably to isograft. Functional recovery results correlated with histological results. Processed allografts supported robust axon regeneration across the injury that was not statistically different from isograft. Nerve regeneration after reconstruction of a 10 mm sciatic nerve injury with Avance® processed grafts is comparable to that after standard nerve graft repair in its intended use and function as a conduit for axon regeneration across a gap.
Reconstruction of Rat Sciatic Nerve Discontinuity by Avance® Processed Allografts, Collagen Nerve Cuffs, or Nerve Grafts[20]	Avance® processed allografts effectively supported regeneration across the nerve injury in both 14 and 28 mm long defects. Based on total fiber counts at midgraft and distal to 14 mm grafts taken 6 weeks after repair, isograft performed better than processed allografts, which performed better than collagen nerve cuffs. At 12 weeks after repair, there were no measurable differences in fiber count or wet muscle mass ratios between groups. Fiber counts, fiber quality and electrical stimulation data following repair with 28 mm grafts demonstrated that isograft performed better than processed allografts, which performed better than collagen nerve cuffs. Wet muscle mass, extensor postural thrust testing, and walking track analysis demonstrated that nerves repaired with processed allografts functioned as well as and were not statistically different than those repaired with the NeuraGen® Nerve Guide.
Evaluation of the Effect of Nerve Graft Tissue Source on Graft Effectiveness in a Rat Tibial Nerve Injury Model[21]	Regardless of nerve type source (i.e. motor, sensory or mixed nerve), Avance processed allografts effectively supported regeneration of axons across a 5 mm tibial nerve discontinuity in a rat. Processed allografts support reproducible axon regeneration across the graft into the distal nerve based on both total and myelinated axon counts.

1.4.2 Manufacturing Controls

Axogen has established procedures for tissue recovery, relevant donor medical record review and release to processing criteria that meet FDA requirements as defined in 21 CFR §1271, state regulations, and AATB standards. Furthermore, Axogen utilizes validated processes for the handling of raw material components, environmental control, decellularization, and terminal

sterilization of the peripheral nerve allograft. In addition to ongoing monitoring activities for product conformity to specifications and sterility, product storage, shelf life and stability have been validated in accordance with applicable industry standards.

1.4.3 Previous Clinical Experience

1.4.3.1 General Use

Avance® Nerve Graft is a commercially available product that has been and continues to be marketed as a HCT/P tissue product in accordance with 21 CFR §1271 regulations since July 2007. Since that release date, Axogen has distributed over 7,000 grafts. Utilization of Avance® Nerve Graft has allowed for the reconstruction of traumatic and iatrogenic peripheral nerve transection injuries in the upper and lower extremities, head and neck, chest and pelvis. Injuries have included, but are not limited to, laceration, blunt trauma, amputation, avulsion, gunshot wound, shrapnel, improvised explosive product (IED) blast trauma, neuroma resection, chemical burns, oncologic resection such as facial nerve reconstruction following resection of parotid gland tumor, reconstruction of neurovascular bundle following radical prostatectomy, and reinnervation of breast reconstructions following mastectomy.

1.4.3.2 Published Clinical Studies

In 2009, Mayo Clinic published their results regarding the performance of Avance® Nerve Graft [3]. This investigator initiated study reported on segmental nerve defects in the hand and digits. Functional recovery was evaluated by blinded hand therapist using moving (m2PD) and static (s2PD) two point discrimination tests. All subjects recovered near normal two-point discrimination. Avance® Nerve Graft was demonstrated to be safe and effective with no reported signs of infection, rejection, or graft extrusion.

Ducic et al reported on outcomes from 54 discreet nerve repairs that were treated with various repair techniques [22] .The authors found that Avance® Nerve Graft returned functional improvements similar to those of other test groups. No safety concerns were discussed.

Shanti and Ziccardi reported on a single uncontrolled case of Avance® Nerve Graft for reconstruction of the Inferior Alveolar Nerve in the face [23]. Recovery of function was documented. No safety concerns were discussed.

The investigators from the Axogen sponsored RANGER® registry have independently reported on their experiences with the Avance® Nerve Graft in two separate peer-reviewed publications.
Brooks et al reported on 132 individual nerve injuries [24]. Twelve sites with 25 surgeons contributed data to this registry database. Data was analyzed to determine the safety and functional outcomes from the use of Avance® Nerve Graft. Sufficient data for efficacy analysis was reported in 76 injuries (49 sensory, 18 mixed, and 9 motor nerves). Subgroup analysis demonstrated consistency, with no significant differences with regard to recovery outcomes between the groups ($P>0.05$ Fisher's Exact Test). No implant related adverse experiences were reported. These outcomes were found to compare favorably to the established historical controls from the literature for nerve autograft and nerve cuffs. This work was expanded by Cho et al who reported on their finding from a subgroup analysis on outcomes, specifically for upper extremity nerve repairs with outcomes data from the RANGER® registry database [25]. In this analysis an upper extremity specific population was identified within the RANGER® database presenting with 71 nerves

repaired with Avance® Nerve Graft. Subgroup analysis demonstrated meaningful levels of recovery in sensory, mixed and motor nerve repairs with graft lengths between 5 and 50 mm. No implant related adverse experiences were reported. The authors state that the outcomes reported for Avance® Nerve Graft compare favorably to the established historical controls from the literature for nerve autograft and nerve cuffs.

2 Study Objectives

2.1 Primary Objective

The primary objective of the study is to evaluate the safety and efficacy of Avance® Nerve Graft for non-inferiority and if met, superiority, of static two-point discrimination at twelve months as compared to nerve cuffs [redacted]

Data collected from this study will be used to support a regulatory submission for a Biological License Application for Avance® Nerve Graft in accordance with 21 CFR §601.2.

2.2 Secondary Objectives

The secondary objectives of this study are to [redacted] compare functional recovery outcomes and rates; time to recovery; degree of recovery over time; [redacted] for each treatment group.

3 Study Design

3.1 Description of Design

This is a multicenter, prospective, randomized, controlled, evaluator and subject blinded study in subjects requiring nerve reconstruction in the hand distal to the superficial palmar arch. Published outcomes studies evaluating nerve cuffs validate the outcomes model of using sensory nerve repairs distal to the wrist to assess peripheral nerve discontinuity reconstruction.

By reducing variability, the digital nerve model can more clearly evaluate the regeneration of axons from the proximal nerve stump, across the reconstructed segmental nerve defect, into the distal nerve sheath, and finally to the sensory organelle end targets. The endpoint measures are well defined and can be consistently measured from subject to subject. This model overcomes the challenges that other models present with regard to varying degrees of recovery across the outcome assessments, i.e. mixed nerves have heterogeneous outcomes of both sensory and motor measures. Additionally, [redacted]

Up to 220 subjects in up to 25 sites at a target site enrollment range of 8-14 subjects may be enrolled to control for site effects while maintaining [redacted]% attrition. Digital nerve gap ranging from 5 to 25 mm in length, inclusive, will be randomized in this study. The injury with the longest qualifying nerve gap will serve as the target injury for stratification into the appropriate randomization group and subsequent data analysis. Subjects meeting the inclusion and exclusion criteria will be centrally randomized in a 1:1 ratio, following stratification [redacted], to receive either Avance® Nerve

[redacted]

Graft or [redacted]. Subjects requiring more than one repair should have all qualifying repairs made with the assigned treatment for the subject.

This study will consist of a screening visit, an operative visit, and 5 post-operative follow-up visits at 1, 3, 6, 9, and 12 months. This study will be conducted in accordance with the FDA, ICH/GCP requirements and regional IRB Regulations (21 CFR Parts 50 and 56, respectively).

3.2 Study Treatment

3.2.1 Identification of Products

3.2.1.1 Study Product

Description: Avance® Nerve Graft is processed allograft tissue intended for bridging nerve discontinuities. Avance® Nerve Graft is a decellularized and cleansed extracellular matrix from donated human peripheral nerve. The cleaning process preserves the inherent and relevant structural characteristics of the tissue. It is supplied sterile, in a variety of lengths and diameters. It is for single patient use only. Approximate graft lengths and diameters are listed on the package label. Avance® nerve Graft is coapted between the proximal and distal ends of a transected nerve. Regenerating axons can grow through the allograft scaffold, into the patient's distal nerve tissue and on toward the target muscle or skin.

Regulatory Classification: Avance® Nerve Graft is a human tissue for transplantation. It is processed and distributed in accordance with FDA requirements for Human Cellular and Tissue-based Products (HCT/P) (21 CFR Part 1271), State regulations and the guidelines of the AATB. This graft is to be dispensed only by or on the order of a licensed physician. See Appendix 3 for Instructions for Use.

3.2.1.2 Control Product

Description: [redacted], a Type I bovine collagen nerve cuff, will serve as the control in this study. These nerve cuffs are composed of purified bovine Type I collagen, sourced from bovine tendon. It is supplied sterile, in a variety of lengths and diameters. It is for single patient use only. Tube lengths and internal diameters are listed on the package label. The transected nerve ends are placed inside the internal diameter of the tube (entubulation) and serve as a containment area for the milieu of fluids that seep from the severed ends.

Regulatory Classification: Regulated as Class II medical devices via FDA 510(k) clearance. Nerve cuffs are manufactured to form a hollow tube construct to entubulate the injured nerve stumps. See Appendix 4 for Instructions for Use.

3.3 Study Population

Adult male and female subjects that have sustained an injury to at least one nerve, distal to the superficial palmar arch and proximal to the distal interphalangeal joint, which after resection results in a nerve gap between 5 mm and 25 mm, inclusive.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Written informed consent will be obtained from all subjects before any study related procedures are performed. Investigators may discuss the availability of the study and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research. The investigator(s) has both ethical and legal responsibility to ensure that each subject under consideration for enrollment is given a full explanation of the study. This shall be documented on a written Informed Consent Form (ICF), which shall be approved by the same Institutional Review Board/Independent Ethics Committee (IRB/IEC) responsible for approval of this protocol. Each ICF shall include the elements required by Food and Drug Administration (FDA) regulations in 21 (CFR) Part 50 and International Committee on Harmonization (ICH) Good Clinical Practice (GCP) and must adhere to the ethical principles that have their origin in the Declaration of Helsinki. The investigator agrees to obtain approval from the sponsor of any written ICF used in the study, preferably prior to submission to the IRB/IEC.

Once the appropriate, essential study information has been provided to the subject, fully explained by the investigator (or qualified designee) and it is agreed that the subject understands the implications of participating, the IRB/IEC –approved written informed consent form shall be signed and dated by all applicable parties in accordance to what is required by the IRB/IEC. The subject will be given a copy of the signed informed consent form and the original will be kept on file by the investigator. Explanation of study and the signing of the informed consent shall occur prior to the subject's participation in the trial.

3.4.2 Inclusion Criteria

To be considered for enrollment, subjects must meet the following inclusion criteria:

Table 3.4.2-1: Inclusion Criteria	
1.	Subjects 18 to 65 years of age, inclusive;
2.	Require primary or secondary nerve injury repair with [redacted], a bovine Type 1 collagen nerve cuff or Avance® Nerve Graft in at least 1 digital nerve;
3.	Zone of injury to nerve must be resectable;
4.	Nerve gaps following resection, between 5 and 25 mm, inclusive;
5.	Undergo tension free end to end nerve to nerve graft coaptation on both the proximal and distal portion of the nerve gap in the Avance® Nerve Graft Group or nerve entubulation in the Nerve Cuff group;
6.	Have an uninjured contralateral or adjacent digit that is suitable to serve as a referenced digit for baseline functional assessments;
7.	Be willing and able to comply with all aspects of the treatment and evaluation schedule over a 12 month duration; and
8.	Sign and date an IRB-approved written informed consent prior to initiation of any study procedures.

3.4.3 Exclusion Criteria

To be included in the study, the following criteria must not occur:

Table 3.4.3-1 Exclusion Criteria
1. Estimated distance of regeneration of >150 mm (distance from proximal injury site to tip of target digit);
2. Injuries distal to the distal interphalangeal joint;
3. Extensive soft tissue injury which will impair recovery assessment;
4. Incomplete nerve transections;
5. Injury requiring replantation of target digit
6. Injuries to the affected nerve proximal to the superficial palmar arch;
7. Nerve injuries >24 weeks post initial injury;
8. End to side nerve repair;
9. Injuries with vascular damage resulting in inadequate perfusion despite repair;
10. Subjects with Type 1 Diabetes Mellitus or Type 2 Diabetes Mellitus requiring regular insulin therapy;
11. Subjects who are undergoing or expected to undergo treatment with chemotherapy, radiation therapy, or other known treatment affects the growth of neural and/or vascular system;
12. Use of bovine collagen based nerve conduit in a subject with known or suspected bovine sensitivity;
13. History of neuropathy, diabetic or any other known neuropathy;
14. Currently enrolled in another investigational interventional study;
15. Expected use of medication during the study that is known to impact nerve regeneration or to cause peripheral neuropathy;
16. History of chronic ischemic condition of the upper extremity; and
17. Any subject who at the discretion of the Investigator is not suitable for inclusion in the study.

3.4.4 Enrollment in Study

3.4.4.1 Subject Screening and Numbering

After the subject has signed an IRB-approved informed consent form, they will be assigned a unique screening number. At each site, the screening numbers will start with S001. Subjects who meet the inclusion and exclusion criteria will be eligible for the study. Randomization will occur intra-operatively. A randomization number will be assigned to identify the enrolled subject.

3.4.4.2 Subject Withdrawal or Discontinuation

If a subject discontinues from the study, the reason given must be recorded in source documentation and the eCRF. If the subject is withdrawn due to an adverse event, the adverse event must be indicated as the reason for withdrawal. All subjects have the right to withdraw at any point during the treatment without prejudice. The investigator can also discontinue a subject's participation at any time if medically necessary.

The sponsor should be notified promptly when a subject is withdrawn or if the trial is stopped at a clinical site. For subjects that withdraw early (Early Termination), all efforts should be made to collect End of Study data points prior to final withdraw.

[redacted]

[redacted]

3.5 Endpoints

3.5.1 Primary Effectiveness Endpoint

Static Two Point Discrimination (s2PD): This sensory assessment measures nerve innervation density (the number of nerve ending present in the area tested) by determining the subject's ability to discern the functional difference between one and two points at set distance. It relates to subjects ability to determine not only that they can feel but also "what" they are feeling. The reliability of this tool had been established in Aberg et al. 2007 [26] as well as throughout the literature [27-30].

Measurement of s2PD will be completed using a standardized two point discriminator disk, a commercially available assessment tool widely adopted as standard of care among clinicians and hand therapists for sensory function evaluation. It consists of two plastic disks, each containing a series of metal rods, spaced at set intervals ranging from 2mm to 15mm apart. A standardized testing procedure will be used to collect measurements in the radial and ulnar autonomous zones of the affected digit, as well as, in an uninjured contralateral or adjacent digit.

3.5.2 Primary Safety Endpoint

Adverse events associated with the nerve repair.

3.5.3 Secondary Endpoints

3.5.3.1 Response Rate for Recovery of s2PD at Month 12

The number and response rate of subjects who recover s2PD in the target repair at Month 12 (i.e., s2PD of 16) will be summarized by repair method and analyzed for differences.

3.5.3.2 [redacted]

[redacted]

[redacted]

3.5.3.3 The Visual Analog or Analogue Scale (VAS) for Pain [31]

The VAS pain scale is designed in such a way that it allows a study subject to rate their pain using a scale with minimum constraints. Subjects will rate their current pain level by creating a mark on a 10 centimeter (100mm) line and the distance measured from 0mm to the mark will correspond to the amount of pain they are currently experiencing. The open line gives the subject the greatest freedom to choose their pain's exact intensity. VAS data are recorded as the number of millimeters from the left of the line with the range 0-100, with 0mm representing no pain, and 100mm representing the most pain.

3.5.3.4 Percent Recovery to Pre-Injury Baseline

All sensory assessments (s2PD, m2PD and Semmes Weinstein Monofilaments) will be completed on the uninjured contralateral or on an adjacent digit at each follow-up visit. The percent difference in the measured sensation of the repaired nerve as compared to the contralateral digit will be recorded at each visit.

3.5.3.5 Time to Recovery of s2PD

The differences in the number of months from the first instance of S3+ recovery until the subject has obtained S4 recovery will be assessed.

3.5.4 Tertiary Endpoints

3.5.4.1 [redacted]

[redacted]

3.5.4.2 [redacted]

[redacted]

3.5.4.5 MRCC Classification of Sensory Recovery

First developed in 1954 by the British Medical Research Counsel and later modified by Mackinnon and Dellon in 1988 to include 2-point discrimination[5], this scale serves to determine the level of sensory function of a target area in the hand (see Table 3.5.4.5-1). The number and percentage of subjects meeting each functional recovery classification for the target repair (MRCC Rating for Recovery of Sensory Function) will be presented by repair type and study visit.

Table 3.5.4.5-1: MRCC Classification for Recovery of Sensory Function

Rating	Medical Research Council Classification of Sensory Recovery as modified by Mackinnon
S0	Absence of sensibility in the autonomous area
S1	Recovery of deep cutaneous pain sensibility within the autonomous area of the nerve
S2	Return of some degree of superficial cutaneous pain and tactile sensibility within the autonomous area of the nerve
S3	Return of superficial cutaneous pain and tactile sensibility throughout the autonomous area, with disappearance of any previous over response
S3+	Return of sensibility as in S3; in addition, there is some recovery of 2-point discrimination within the autonomous area (7-15 mm)
S4	Complete recovery (2-point discrimination, 2-6 mm)

[redacted]

[redacted]

3.6 Measures to Minimize/Avoid Bias

Multiple measures will be put in place to minimize and avoid bias within the study. The following will be implemented:

- All investigators selected for participation must have completed a hand and/or microsurgical fellowship.
- Investigators will have prior experience with each product.
- For those investigators who have not implanted either of the products within the 12 months prior to the initiation of the study at the center, a bioskills lab will be conducted to re-familiarize the investigator with the handling, utilization and placement of each test article.
- Commercially available product will be utilized for both treatment groups.
- The target digit, as well as any additional repairs in the same hand will be followed in all subjects
- Standardization of sensory assessments at each follow-up visit.
- All evaluators completing follow-up sensory assessments will be trained to standardized sensory test procedures.
- Standardized evaluation tools [redacted] will be provided to each study center.
- Randomization at the time of surgery, intra-operatively.
- Subjects will be stratified by [redacted] then randomly assigned in a 1:1 fashion to a treatment group.
- Subjects and data evaluators will be blinded to the assigned treatment group.
- Evaluators will be blinded to subject outcome data [redacted].

3.6.1 Blinding

While blinding the surgeon to treatment is not possible, blinding the subject and the evaluator is possible and all efforts should be taken to preserve this blind. Randomization will be used to

assign the subject to a study group intra-operatively therefore the subject will be blinded to their treatment assignment. Direct verbal or written communication regarding treatment identification beyond what is required at the institution for the recording of the surgical procedures should be avoided. The assessments for the efficacy endpoints will be conducted by a qualified evaluator who had been blinded to the subject's study group assignment.

3.7 Randomization

Subjects will be centrally randomized by interactive response system to either Avance® Nerve Graft or using blocked supplies in a ratio of 1:1 after stratification

Only subjects meeting all inclusion and exclusion criteria should be randomized.

Each stratification group will have its own unique randomization series. It is anticipated that of the subjects will be enrolled into Group A and of the subjects will be enrolled into Group B. The randomization will occur intra-operatively, (see Figure 3.7-1).

Figure 3.7-1 Randomization Schema

3.7.1 Qualifying Injury/Repair and Assignment of Primary Target Repair

A qualified repair is defined as a repaired nerve injury in a randomized subject that meets inclusion and exclusion criteria. Subjects may have a single qualifying repair or multiple qualifying repairs. The qualifying repair with the longest gap length and will serve as the Primary Target Repair for primary endpoint assessments. If multiple injuries are of the same "longest qualifying" gap length then the investigator will assign one of the repairs as the target repair.

Examples for unilateral nerve injuries are as follows:

1. Radial digital nerve injury in the ring finger with 6 mm gap and uninjured ulnar nerve in same digit:
    a. Has a qualifying injury, the radial digital nerve injury in the ring finger.
    b.
    c. This injury will serve as the Primary Target Repair.

2. Common digital nerve injury in the palm with a gap of 24 mm:
    a. Has a qualifying injury, the common digital nerve in the palm.
    b.
    c. This injury will serve as the Primary Target Repair and all affected autonomous zones for the common digital nerve injury should be assessed for sensation.

If a subject presents with multiple nerve injuries, each repair that meets inclusion/exclusion criteria and can be individually assessed for return of sensation, may be tracked as part of the

[redacted]. The subject is then randomized and all qualifying nerve injuries should be reconstructed with the same assigned treatment. Nerve injuries that do not qualify for the study should also be documented, followed and reported upon for covariate analysis.

1. A subject that presents with a radial digital nerve injury in the ring finger resulting in a 15 mm gap and an ulnar digital nerve injury in the ring finger resulting in an 11 mm gap:
    a. Has two qualifying injuries, one radial and one ulnar in the ring finger.
    b. The radial digital nerve injury is the repair with the longest gap length, and thus is identified as the target repair
    c. [redacted]
    d. Both nerves should be repaired with the assigned treatment.
    e. The ring finger radial nerve injury (15 mm gap) serves as the Primary Target Repair.

2. A subject that presents with an ulnar digital nerve injury in the index finger resulting in a 4 mm gap and an ulnar digital nerve injury in the smaller finger resulting in an 11 mm gap:
    a. Has one qualifying injury, the small finger. The gap length in the index finger is outside of the protocol criteria and would not qualify for the study.
    b. [redacted]
    c. Should have the ulnar digital nerve injury to the small finger reconstructed with assigned repair and the index finger injury reconstructed as deemed appropriate by the investigator.
    d. Should have assessments done on both injuries, even though only the small finger injury qualifies for study treatment.
    e. The ulnar digit nerve to the small finger (11 mm gap) serves as the Primary Target Repair.

Note: While follow up assessments will be completed for all repaired nerves, injuries that are outside of the protocol criteria (i.e. 2 mm gap and the 28 mm gap) should be treated at the surgeon's discretion. Whether repairing one or multiple nerves with Avance® Nerve Graft or [redacted], the method of repair for non-qualifying injuries should be determined prior to randomization of that subject.

3.8 Study Procedures

Pre-op preparation and injury site dissection will be based on investigator preference and in accordance with their institution's standard of care. [redacted] should be performed prior to randomization and after debridement of injured nerve. Subjects will be stratified [redacted] and then randomized in a 1:1 fashion. Implantation of Avance® Nerve Graft or [redacted] should be conducted in accordance with each product's instructions for use. Subjects are considered enrolled into the study after successful implantation of the assigned treatment group. Photographs of the surgical site and surgical implant should be taken if possible. Wound closure and immobilization will be based on the institutions' standard of care. Subjects will be followed for a total of 12 months post enrollment into study. Standardized procedures will be used to conduct assessments at each visit. Sensory Assessments include: s2PD, [redacted],

MRCC Assessment. The uninjured contralateral or adjacent digit of each subject will serve as the internal control for determining return of function as it relates to pre-injury baseline. Study assessment time points are summarized in Appendix 2. Subjective measures i.e. patient questionnaires should be assessed prior to objective measures.

3.8.1 Visit 1: Pre-Operative Screening, Day-0 [redacted]

Once informed consent has been obtained, the subject will be assigned a screening number and the following pre-operative assessments will be performed at this visit:

- Inclusion criteria
- Exclusion criteria
- Relevant medical history
- Demographics
- Concomitant treatments

The following post injury baseline assessments should occur [redacted]

- Sensory Assessments to affected digit(s)
- Sensory Assessments of contralateral or adjacent digit
- Pain assessment with Visual Analog Scale (VAS)
- [redacted]

3.8.2 Visit 2: Operative Day, Day-0*

The following will be collected during the Operative Day:

- Inclusion criteria
- Exclusion criteria
- Nerve Injury History: including description of nerve injury and location
- Randomization
- Operative Information: description of nerve repair(s), location, and implantation information – see sequence below
- [redacted]
- Adverse events

*Note: In some instances, Visit 1 and Visit 2 could occur on the same day.

The following sequence of steps will take place intraoperatively:

- Identify injured nerve(s)
- Determine type of nerve repair needed, i.e. direct tensionless suture or other technique
- Measure gap length(s) with the affected digit(s) in full extension
- Measure distance from proximal nerve stump(s) to tip of the finger
- Identify the Target Repair (longest qualifying nerve injury)
- Randomize subject to treatment if protocol criteria is met
- Choose the appropriate product from stock and complete investigational/control product labeling

- Repair nerve in accordance to product IFU
- Record product code (Avance® Nerve Graft or [redacted]), size, length, and quantity of product used
- [redacted]

3.8.3 Visit 3-6: Post-Operative Visit, Month 1, 3, 6 [redacted], and 9 [redacted]

The following will be collected during each post-operative visit:

- Sensory Assessments to target digit(s)
- Sensory Assessments to contralateral or adjacent digit
- Pain assessment with Visual Analog Scale (VAS)
- [redacted]
- Adverse events

3.8.4 Visit 7: End of Study/Early Termination Visit, Month 12 [redacted]

The following will be collected during each post-operative visit:

- Sensory Assessments to target digit(s)
- Sensory Assessments to contralateral or adjacent digit
- Pain assessment with Visual Analog Scale (VAS)
- [redacted]
- Adverse events

3.9 [redacted]

[redacted]

3.10 [redacted]

[redacted]

[redacted]

3.11 Subject/Study Discontinuation

3.11.1 Screen Failures

A screening failure is defined as subject from whom informed consent is obtained, but, Inclusion/Exclusion criteria is not met, or subject was unable to be randomized, or the subject withdrew consent prior to surgical intervention.

3.11.2 Subject Discontinuation

Subjects may end their participation in the study at any time for any reason(s). The reason for discontinuation must be documented. For any subject who provides written informed consent but is deemed ineligible during the screening process, the reason should be recorded by the investigator in the subject-screening log.

Early termination will be defined as any post-randomization study termination prior to completion of the [redacted]. Subjects that terminate early will not be replaced. Reasons for early termination will be tabulated by center as well as by the study overall. Subjects that undergo baseline assessments and are randomized into the study, however, do not undergo any further procedures, will not be replaced.

Subjects that have not completed the study, are unable to be contacted, and the reason for participation discontinuation is unknown, will be considered "lost to follow-up." The site will make multiple attempts to contact the patient by either telephone, certified mail or by an alternative method when it is deemed appropriate. Sites will conduct due diligence to have subjects return for all study visits, regardless of whether previous visits have been missed, and will continue attempts to contact the patient until all efforts have been exhausted to have the subject return for the final visit. Alternative contact methods may be used when approved by the sponsor and in accordance with respective IRB policies or requirements, as needed. Subjects will not be considered lost to follow-up until missing the final visit.

3.11.3 Discontinuation of the Study

Conditions that may warrant termination of the clinical study include, but are not limited to, the following:

- Discovery of an unexpected, serious, or unacceptable risk to subjects; or,

- Decision by the sponsor to suspend or discontinue testing, evaluation, or development of the study product.

Conditions that may warrant termination of the clinical study at a particular investigative site include, but are not limited to, the following:

- The investigative site fails to comply with all applicable regulations;
- Deliberate submission of false information from the site to Axogen, Corporation., their designee, or regulatory authorities;
- Inadequate adherence to protocol requirements; or
- Inadequate enrollment.

In the event of a discontinuation of the study at an investigative site, the principal investigator will return all study materials including study documentation and CRFs to the sponsor, provide a written statement explaining the reason for termination, and notify the appropriate Institutional Review Board/Ethics Committee.

4 Adverse Events

4.1 Procedures for Eliciting Reports and Reporting of Adverse Events

The primary safety endpoint is intended to evaluate adverse events associated with the surgical repair of the injured nerve and is not intended to evaluate the adverse events of the trauma that precipitated the injury. Both the Avance® Nerve Graft and the [redacted] are commercially available products and are restricted to the implantation at the nerve injury site. The effect of each product is localized to the area of the nerve discontinuity only. Therefore, the intent is not to capture all adverse events that may occur in a subject throughout the follow-up period but only events directly relating to the study product and/or surgical intervention. Given the nature of traumatic hand injuries, in-depth medical management approach will be required for a majority of the subjects enrolled in the clinical study. Assessment of adverse events may be limited, to some degree, to those adverse events that are related directly to the injured hand, however, to prevent under reporting of potentially associated adverse events, the following may be collected:

Adverse events associated with the affected hand, may include but is not limited to:

- bleeding;
- infection in the affected hand;
- painful scar at the nerve reconstruction site;
- extrusion on nerve repair product;
- delayed wound healing;
- allergic reaction;
- hypersensitivity at or distal to the repair site;
- anaphylaxis;
- communicable diseases;
- any change in medical or overall health condition that results in the withdrawal of the subject from the study;

- any adverse event meeting the criteria for Serious Adverse Event; and/or any other event that in the opinion of an investigator warrants collection.

Concurrent illnesses that are present at or before study product implantation, which manifest with the same severity, frequency, or duration, subsequent to study product implantation, need not be recorded as AEs. Similarly, signs or symptoms related to a pre-existing disease need not be recorded as AEs. However, incidents where there is an increase in severity or duration of the concurrent illness or pre-existing disease that meet the above criteria must be reported.

Adverse events should be reported by the investigator or qualified designee in accordance with 21CRF part 312.32 and Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies.

4.2 Adverse Event Specific Definitions

Associated with the use of the drug. There is a reasonable possibility that the experience may have been caused by the drug.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience. Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected adverse drug experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

4.3 Review of safety information

The sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the agency by the sponsor.

4.4 Adverse Event

An AE is any untoward event experienced by a subject (whether or not considered product-related by the principal investigator or sponsor), or any event that has changed adversely in nature, severity, or frequency. An untoward AE or any event that has changed adversely in nature, severity, or frequency during the course of study product administration is considered to be a treatment-emergent adverse event.

An AE can be, but is not limited to, subjective symptoms experienced by a subject, or objective findings that may or may not include subjective symptoms. Examples of objective findings are clinically significant laboratory abnormalities. All AEs that occur during or after study product implantation/device insertion must be recorded in the subject's medical record (progress notes) and then transcribed onto the CRF. The investigator's assessment of the AE's relationship to the study product is unrelated to its characterization as an AE. For example, an anomaly that the investigator judges to be unrelated to the investigational/control product may nonetheless be identified as an AE. A serious adverse event (SAE) is an AE that causes death, is life threatening, is permanently disabling, or requires (or prolongs) hospitalization or interventional surgery.

4.4.1 List of Anticipated Adverse Event

Consistent with the subject's informed consent form and the risk analysis section of this protocol, the following adverse events are anticipated and may potentially occur during the subject's participation in this investigation:

- mild incisional redness;
- tenderness of surgical area;
- mild edema of surgical area;
- decreased pain at surgical area;
- numbness

These adverse events are considered expected and are not required to be recorded on the Adverse Events eCRF unless they increase in severity.

4.4.2 Severity of Adverse Events

Adverse events will be graded for severity and noted in the description of the event. The NCI (NIH)-developed Common Terminology Criteria for Adverse Events (NCI_CTCAE), Version 4.0, will be used. In addition, any AE associated with subject termination from the study must be reported to the sponsor or sponsor-approved designee within 7 days of knowledge. If the AE is a SAE, then the reporting requirements listed in section 4.5.2 will apply.

4.4.3 Relationship to Study Product

The principal investigator or designee will document his/her opinion on the relationship of the adverse event to the study product or control product for all adverse events, using the criteria outlined in Table 4.4.3-1.

Table 4.4.3-1 Relationship of Adverse Events to Study Product

Relationship	**Description**
Unrelated	An AE that is clearly and uncontrovertibly due to extraneous causes (disease, environment, etc.) and does not meet the criteria for study product relationship listed under possible or probable.
Possible	An AE may be considered as possibly related if: 1) it cannot be reasonably explained by the subject's clinical state by environmental or toxic factors; or 2) it follows a reasonable temporal sequence from administration of study product; or, 3) it follows a known pattern of response to the study product.
Probable	An AE considered, with a high degree of certainty, to be related to the study product. An AE may be considered probably related to study product if: 1) it cannot be reasonably explained by the known characteristics of the subject's clinical state or by environmental or toxic factors; 2) it follows a reasonable temporal sequence from administration of study product; 3) it follows a known pattern of response to study product; 4) it disappears or decreases upon removal.
Definitely Related	An AE that is clearly and uncontrovertibly due to study product.

4.4.4 Follow-up of Adverse Events

Subjects who present with unresolved or new adverse events at the final scheduled visit will be followed by the principal investigator:

- until the adverse event has resolved; or
- until the subject is lost to follow-up; or
- until the adverse event is stabilized or deemed a permanent disease or condition.

"Resolution" of an AE occurs when the subject has returned to his/her baseline state of health or when the principal investigator does not expect any further improvement or worsening of the AE. On the last clinical study day, the principal investigator will instruct the subject to report any subsequent adverse event that the subject or the subject's physician believes might reasonably be caused by, or probably caused by, the study product. The principal investigator will continue to report any significant follow-up information to the sponsor or authorized designee. All SAEs that occur up to 30 days following the subject's last study assessment must be reported immediately to the medical monitor.

4.5 Serious Adverse Event

4.5.1 Definition of Serious Adverse Event

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening – a "life-threatening" event is present when the subject is, in the opinion of the principal investigator, at immediate risk of death from the event as it occurs. Note that this definition does not include an event that, had it occurred in a more serious form, might have caused death;
- Requires in-patient hospitalization or prolongation of existing hospitalization – hospitalization for elective treatment of pre-existing condition that did not worsen during the clinical investigation is not considered an adverse event. Hospitalization or nursing home admission for the purpose of caregiver respite is not considered an adverse event. Complications that occur during hospitalization are adverse events, and if a complication prolongs hospitalization, the event is considered serious;
- Results in a persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions); or
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious events when, based upon medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

4.5.2 Reporting Serious Adverse Events

This protocol will follow the standard level of SAE reporting. Thus, it is necessary to report all SAEs following any exposure to study that:

- Result in death, regardless of relationship to study product;
- Result in persistent or significant disabilities or incapacities, regardless of relationship to study product;

- Are an adverse reaction, definitely, probably, or possibly related to study product, that requires or prolongs existing hospitalization, or requires intervention to prevent significant/permanent disability or death; or

- Are life threatening, including all Grade 4 adverse reactions that are definitely, probably, or possibly related to study product.

All SAEs must be reported immediately to sponsor or approved sponsor designee, followed by the completion of the SAE CRF. The sponsor or authorized designee, in turn, will promptly notify the medical monitor. The SAE report and CRF should contain all adverse event information available at time of event onset. As updates become available, the SAE report and CRF should be updated appropriately until event is resolved.

The sites will relay all SAE information to the sponsor or authorized designee within 24 hours of receipt. The SAE form will collect data surrounding the event, e.g., the nature of the symptom(s), time of onset in relation to placement of study product, and whether or not treatment with study product was interrupted or discontinued. The principal investigator's assessment on the probable cause of the event will also be included.

Subjects experiencing a SAE or emergency situation should be examined by a physician as soon as possible. The physician in attendance should do whatever is medically necessary for the safety and well-being of the subject. The subject will remain under observation for as long as medically indicated in the opinion of the principal investigator and/or attending physician. The SAE will be followed until resolved or until medically stabilized. The principal investigator or designee will notify the sponsor (and the IRB/Ethics Committee and appropriate regulatory body, if necessary) within 24 hours of event onset.

4.5.3 Relationship to Product and Study Procedure

The principal investigator will document his/her opinion on the relationship of the adverse event to the study product or control product and to the study procedure for all SAEs. The investigator should follow the same criteria outlined above when determining product- or procedure-relatedness.

4.6 IND Safety Reports

4.6.1 Written reports

The sponsor shall notify FDA and all participating investigators in a written IND safety report of:

- Any adverse experience associated with the use of the drug that is both serious and unexpected; or

- Any findings from tests in laboratory animals that suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information. Each written notification may be

submitted either on an FDA Form 3500A or in a narrative format (foreign events may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form; reports from animal or epidemiological studies shall be submitted in a narrative format) and shall bear prominent identification of its contents, i.e., "IND Safety Report." Each written notification to FDA shall be transmitted to the FDA product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. If FDA determines that additional data is needed, the agency may require further data to be submitted.

In each written IND safety report, the sponsor shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previous, similar reports.

4.6.2 Telephone and facsimile transmission safety reports

The sponsor shall also notify FDA by telephone, by facsimile transmission, or by electronic Common Technical Document (eCTD) transmission of any unexpected fatal or life-threatening experience associated with the use of the product as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information. Each telephone call or facsimile transmission to FDA shall be transmitted to the FDA to the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND.

4.6.3 Follow up

Follow up information to a safety report shall be submitted as soon as the relevant information is available. If the results of a sponsor's investigation show that an adverse experience was initially determined to be not reportable according to the applicable regulations, but is later deemed reportable, the sponsor shall report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made. Results of a sponsor's investigation of other safety information shall be submitted, as appropriate, in an information amendment or annual report.

5 Statistical Considerations

Descriptive statistical methods will be used to summarize the data from this study, with hypothesis testing performed for the primary and other selected efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of events (n), mean, median, standard deviation (SD), standard error, minimum, maximum, and coefficient of variation (CV) for continuous data and frequencies and percentages for categorical data. The term "repair type" refers to randomized treatment assignment of either [redacted] or Avance® Nerve Graft. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by repair type, subject number, and then by date within each subject number.

Unless specified otherwise, all statistical testing will be two-sided and will be performed using an overall significance (alpha) level of 0.05.

All statistical analyses will be conducted with the SAS® System, version 9.1.3 or higher.

5.1 Data Collection Methods

The data will be recorded on an approved Case Report Form (CRF). The CRF for this study may be either a paper CRF, or at Axogen's discretion, the data collection methods may be an electronic CRF. All documentation supporting the CRF data, such as laboratory or hospital records, must be readily available to verify entries in the CRF.

Documents (including laboratory reports, hospital records subsequent to SAEs, etc.) electronically transmitted should be de-identified and contain no patient identification information with the exception of a subject's assigned study ID. This will help to ensure subject confidentiality.

5.2 Statistical Analysis Plans

A statistical analysis plan (SAP) will be created and approved prior to completion of enrollment. This document will provide a more technical and detailed description of the proposed data analyses and statistical methods.

5.3 Hypotheses Tested

Test of non-inferiority and superiority of Avance® Nerve Graft to nerve cuffs with respect to static 2 point discrimination (s2PD) will be conducted using closed testing procedures. [redacted]

[redacted]

5.4 Sample Size Estimates

The study was planned to enroll at least 150 subjects at 20 sites. Following a pre-planned blinded interim analysis, the sample size was increased to a maximum of 220 subjects at up to 25 sites. [redacted]

[redacted]

5.5 Analysis Populations

The population defined for analysis will include the intent-to-treat (ITT), safety population, and the per protocol (PP) population. Additional analysis populations may be defined to evaluate study results. Any additional analysis populations will be defined in the statistical analysis plan (SAP).

Intent-To-Treat Population: The ITT population will include all subjects who were randomized. Subjects will be analyzed in the repair group to which they were randomized. The ITT population will be used for analyses of accountability, demographics, efficacy (superiority testing), and the calculation of the 95% confidence interval about the mean s2PD in the Avance® Nerve Graft group for the testing of the null hypothesis H_{01B}

Safety Population: The safety population will include all subjects who underwent a nerve repair. Subjects will be analyzed according to the repair received. This population will be used for all safety analyses.

Per Protocol Population: The PP population will include all subjects in the ITT population who have no major protocol violations and completed at a minimum of 6 months follow-up. This population will be the primary analysis population for the test of non-inferiority using the difference between repair types.

5.6 Planned Analyses

[redacted]

A final analysis is planned after the last subject completes or discontinues the study, and the resulting clinical database has been cleaned, quality checked, and locked.

5.7 General Issues for Statistical Analysis

5.7.1 Multiple Comparisons and Multiplicity

[redacted] As the tests of non-inferiority and superiority are being performed in a closed testing procedure and there will be no adjustment for multiple secondary endpoints, a step-down procedure will be utilized in the assessment of the secondary efficacy endpoints:

- Response rate for recovery for s2PD at Month 12,
- [redacted]
- Reduction in pain as measured with the VAS pain assessment,
- Percent recovery to pre-injury baseline in s2PD,
- Time to recovery of s2PD.

For this procedure, the hypotheses will be tested sequentially based on the specified ordering. Statistical testing will continue at the =0.05 level until a p-value greater than 0.05 is observed.

5.7.2 Covariates

All primary and secondary efficacy analyses will be adjusted according to [redacted] stratification and analyzed as a continuous variable. These analyses may be stratified further to identify other important factors which may impact nerve recovery such as [redacted]

5.7.3 Planned Subgroups

[redacted]

5.7.4 Missing Data

Every effort will be made to obtain the required data at each scheduled evaluation from all subjects who have been randomized. In assessing the primary efficacy endpoint, a repeated measures mixed model will be utilized on all observed data. [redacted]

5.7.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics including age, sex, race, type of traumatic injury sustained, nerves that are injured, assessment of functional loss due to injury, sensory assessments, [redacted] for each subject will be summarized descriptively by repair type.

5.8 Efficacy Analyses

5.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the s2PD in the target repair at 12 months. Differences between the two repair types will be assessed using the LS Mean differences from a repeated measures ANCOVA model with fixed effects of repair type, gap length, and visit, and a random effect for subject. A ninety-five percent (95%) confidence interval will be constructed about the LS Mean difference. This CI will be utilized to first assess non-inferiority and then if the criteria is met, superiority. The 95% confidence interval about the LS Mean of the Avance® Nerve Graft group will also be constructed from the same ANCOVA model, but utilizing the ITT population. Summary statistics for other time points will be provided by repair type and study visit. Graphical presentations of these data will be provided.

5.8.2 Secondary Efficacy Endpoints

All secondary endpoints will be summarized using descriptive statistics by repair type and by study day/time, if appropriate.

The number and response rate of subjects who recover s2PD in the target repair at Month 12 (i.e., s2PD of 16) will be summarized by repair type. Differences between the repair types will be assessed using a logistic regression analysis with effects for repair type and [redacted].

The percent recovery to baseline in s2PD in the target repair will be summarized for each repair type and study visit. A test of superiority of the Avance® Nerve Graft to the nerve cuff will be assessed using the LS Mean differences from a repeated measures ANCOVA model with fixed effects for [redacted]. Analysis for all other continuous endpoints [redacted], VAS pain assessment, and percent recovery to baseline will be conducted in a similar manner.

Time to recovery of s2PD is defined as the number of months from the initiation of S3+ recovery until a subject has S4 recovery in the target repair. [redacted].

5.8.3 [redacted]

[redacted]

[redacted]

The number and percentage of subjects meeting each functional recovery classification for the target repair (MRCC Rating for Recovery of Sensory Function) will be presented by repair type and study visit.

[redacted]

5.9 Safety Analyses

The safety endpoints will compare the nature and incidence of AEs between treatment groups. The safety objective is to show that there is no clinically significant difference of product-related adverse events between Avance® Nerve Graft and nerve cuff study arms. Specifically, AEs will be analyzed as a group and any change in the incidence rate of the listed AEs post treatment will be noted. AE nomenclature will be standardized according to the Medical Dictionary for Medical Activities (MedDRA)-preferred term and system organ classification. The occurrence of the treatment-emergent AEs (TEAEs) will be summarized by repair type using MedDRA preferred terms, system organ classifications, and severity. All AEs will be listed for individual subjects and summarized by verbatim and preferred terms. Separate summaries of treatment-emergent SAEs and AEs related to repair type will be generated.

Any event reported on the eCRF that occurs on or after the repair will be defined as treatment-emergent. Additionally, it is assumed that an AE, which was reported to have started on Day 0 without an associated onset time, may have occurred after the repair. Hence, AEs occurring on Day 0 with no defined onset time will also be considered treatment-emergent.

Subject disposition will be presented for all subjects. The number of subjects who completed the study and discontinued from the study will be provided. The reasons for early discontinuation will also be presented.

5.10 Study Success

Study success is defined as demonstrating the static two-point discrimination of Avance® Nerve Graft is non-inferior or superior to the static two-point discrimination outcome of nerve cuffs following 12 months post implantation. In addition, there should be no clinically significant difference of product related adverse events rates following implantation of Avance® Nerve Graft compared to nerve cuffs.

6 Study Product Management

6.1 Packaging and Labeling

Commercially available product will be used for both treatment groups, however each site will be provided quality controlled serialized investigational product and control product labeling. Once subject has been randomized the appropriate investigational product labeling will be affixed to product packaging and returned to CRO for documentation and label accountability. Refer to the Study Operations Manual for labeling procedures.

6.2 Handling, Storage, and Disposal

Per product specifications as defined in the Instructions for Use.

7 Records Management

Questions or interpretations of the protocol or CRFs must be referred to the sponsor or its representatives.

7.1 Data Collection

During each subject's visit, the investigator or designee should document all significant observations. Information from the source documents will be promptly transcribed to into the electronic data capture system (EDC) via electronic case report forms.

Any changes in information in the study progress notes or other source documents will be initialed and dated on the day the change is made, by a site study staff member authorized to make the change. Changes will be made by striking a single line through erroneous data, and clearly entering the correct data. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change on the source document and updated accordingly in the EDC system.

7.2 Source Documents

Source documents are defined as the result of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the investigators and made available for direct inspection by authorized persons.

All source documents from this study will be maintained by the study center and made available for inspection by authorized persons. The original signed Informed Consent Form for each subject shall be filed with a patient's clinical record at the site and a copy shall be given to the subject and/or legally authorized representative.

7.3 File Management at the Study Site

It is the responsibility of the investigator to ensure that the site files are maintained in accordance with Section 8 of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) and FDA regulations.

7.4 Records Retention at the Study Site

Essential documents should be retained until at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the investigational product. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the sponsor. It's the responsibility of the sponsor to inform the principal investigator that the essential documents no longer need to be retained.

8 Quality Control and Quality Assurance

8.1 Data Management Considerations

Data Management will be overseen by an independent CRO contracted and qualified by the sponsor. All data points in the study will be held to a global Data Management Plan. Original study logs will remain secured at the clinical site and a copy will be transmitted to the data manager. Paper copies received by the data manager will be scanned and electronically saved as a Portable Document Format (pdf). The scanned copy will be compared to the paper copy to assure all pages are accounted for and quality meets expectations.

Data will be entered in to the EDC by the site coordinator or other qualified site personnel. Quality control checks will be established for each data management procedure in order to ensure accuracy and to preserve the integrity of the data. Onsite data monitoring visits will be conducted by certified Clinical Research Associates (CRA) employed by the study's CRO. Visits will be conducted according to an established procedure and occur according to a predetermined schedule for the entire length of the study.

8.2 Monitoring

The sponsor or their authorized designee will conduct routine monitoring visits to ensure the safe and ethical conduct of the study. This will include routine data monitoring of the study's critical variables that are defined in the data management plan and clinical monitoring plan. As part of a concerted effort to fulfill the requirements of the protocol, the sponsor or designee may visit the center during the study in addition to maintaining frequent telephone and written communication.

8.3 Auditing

The sponsor's Quality Assurance Unit or authorized designee may conduct audits at the study site(s). Audits will include, but are not limited to, product supply, presence of required documents, the informed consent process, and comparison of case report forms with source documents. The investigator agrees to participate with audits conducted at a reasonable time and in a reasonable manner.

Regulatory authorities may also audit the investigator during or after the study. The investigator should contact the sponsor immediately if this occurs, and must fully cooperate with the regulatory bodies during the conduct of the study audit.

9 Ethics and Responsibility

This study must be conducted in compliance with the protocol, FDA regulations, the ICH GCP Guidelines, and all other applicable regulatory requirements.

The study protocol and the written informed consent form must be submitted to the IRB/IEC identified with the responsibility to approve research for the study site. Written approval must come from the IRB/IEC Chairman or Secretary, either as a letter or as a copy of the appropriate sections of the IRB/IEC meeting minutes where the review of the study protocol and associated informed consent form were discussed and approved. The investigator will not participate in the decision. If the investigator is an IRB/IEC member, the written approval must indicate such non-participation.

The investigator will submit study status reports to the IRB/IEC no less frequently than annually (when applicable). The investigator must notify the IRB/IEC in writing of the interruption and/or completion of the study. The investigator must promptly report to the IRB/IEC all changes in research (protocol amendments), and will not make such changes without IRB/IEC approval except when necessary to eliminate apparent immediate hazards to human subjects. In these cases, the IRB/IEC must be notified with 5 working days of the change. The investigator will promptly report to the IRB/IEC all unanticipated problems involving risks to subjects or others. The investigator must maintain accurate and complete records of all correspondence written to and received from the IRB/IEC and must agree to share all such documents and reports with the sponsor.

10 Clinical Study Report

Upon completion of the study, the data management group biostatisticians will generate the Tables, Forms, and Listings for the Lead Investigators and sponsor to review. Once verified and approved, the Tables, Forms, and Listings will be finalized. Based on this study data, a study report will be drafted. This report will be provided to the collaborative investigators for review and comment. The sponsor will then finalize and distribute the study report to the appropriate parties.

11 Confidentiality

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without first written permission from Axogen. However, authorized regulatory officials and Axogen personnel (or their representatives) will be allowed full access to inspect and copy study records. All study materials collected shall be used solely in accordance with this protocol, unless first agreed to in writing by Axogen.

Subjects will be identified only by initials and unique subject numbers in CRFs. Their full names may, however, be made known to a regulatory agency or other authorized officials if necessary.

12 Regulatory Considerations

12.1 Amendments

The investigator will not make any changes to this protocol without prior written consent from the sponsor and subsequent approval by the IRB/IEC. Any permanent change to the protocol, whether an overall change or a change for specific study center(s), must be handled as a protocol amendment. Any amendment to the protocol identified as necessary and occurring during active study conduct, will be fully discussed by the investigator(s) and the sponsor prior to any protocol updates. If agreement is reached regarding the need for an amendment, the sponsor will be responsible for updating the protocol. The written amendment must be submitted to the chairman of the IRB/IEC designated with this responsibility. Except for 'administrative amendments' investigators must await IRB/IEC approval of protocol amendments before implementing the changes(s). Administrative amendments are defined as having no effect on the safety of the research subjects, scope of the investigation, or quality of the trial. However, a protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, and the IRB/IEC notified within five working days. Axogen will submit all official protocol amendments to the FDA or other regulatory agencies.

When, in the judgment of the chairman of the IRB/IEC, the investigators and/or the sponsor, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject, the currently approved written informed consent form will require similar modification. In such cases, repeat informed consent will be obtained from all subjects enrolled in the study before continued participation.

12.2 Protocol Deviations

This study is intended to be conducted as described in this protocol. In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the sponsor at the earliest possible time by telephone. This will allow for an early, joint decision regarding the subject's continuation in the study. This decision will be documented by the investigator and the sponsor, and reviewed by the monitor.

12.3 Sponsor and Investigator Responsibilities

The sponsor and participating investigators shall be responsible for the conduct of this clinical study as specified in 21CRF part 312 Subpart D. This clinical investigation will be performed in compliance with the protocol, Clinical Study Agreement, the FDA Good Clinical Practices including 21CRF part 312, 601, 50, 56, ICH E6, and local applicable regulatory requirements.

13 References

1. Lundborg, G., A *25-yr perspective of peripheral nerve surgery: evolving neuroscientific concepts and clinical significance.* Journal of Hand Surgery [Am], 2000. **25**: p. 391-414.

2. Dvali, L. and S. Mackinnon, *Nerve repair, grafting, and nerve transfers*. Clinics in Plastic Surgery, 2003. **30**: p. 203-221.

3. Karabekmez, F.E., A. Duymaz, and S.L. Moran, *Early Clinical Outcomes with the use of Decellularized Nerve Allograft for Repair of Sensory Defects Within the Hand*. Hand (NY), 2009. **4**(3): p. 245-9

4. Mackinnon, S.E., et al., *Clinical outcomes following nerve allograft transplantation.* Plastic and Reconstructive Surgery, 2001. **107**: p. 1419-1429.

5. Mackinnon, S.E. and A.L. Dellon, *Results of Nerve Repair and Grafting, in Surgery of Peripheral Nerve.* 1988, Thieme Medical: New York.

6. Millesi, H., *Nerve Grafting.*Clin Plast Surg, 1984. **11**: p. 105-113.

7. Noble, J., et al., *Analysis of Upper and Lower Extremity Peripheral Nerve Injuries in a Population of Recipients with Multiple Injuries.* The Journal of Trauma, 1998. **45**: p. 116-122.

8. FF, I.J., J.P. Nicolai, and M.F. Meek, *Sural nerve donor-site morbidity: thirty-four years of follow-up*. Ann Plast Surg, 2006. **57**(4): p. 391-5.

9. Frykman, G. and K. Gramyk, Results of nerve grafting, in *Operative nerve repair and reconstruction*, R. Gelberman, Editor. 1991, JB Lippincott: Philadelphia.

10. Meek, M.F., J.H Coert, and P.H. Robinson, *Poor results after nerve grafting in the upper extremity: Quo vadis?* Microsurgery, 2005. **25**(5): p. 396-402.

11. Campbell, W.W., *Evaluation and management of peripheral nerve injury*. Clinical Neurophysiology, 2008. **119** p. 1951-1965.

12. Birch, R., G. Bonney, and C.B. Wynn Parry, *Surgical disorders of the peripheral nerves*. 1998, Churchill Livingstone, Edinburgh.

13. Friedman, L., C. Furberg, and D. DeMets, *Fundamentals of clinical trials*. 3rd ed. 1999.

14. Weber, R.A., et al., *A Randomized Prospective Study of PGA Conduits for Digital Nerve Reconstruction in Humans*. Plast Recon Surgery, 2000. **106**: p. 1036-1045.

15. Mackinnon, S.E.a.D., A.L., *Clinical nerve reconstruction with a bioabsorbablepolyglycolic acid tube.*Plast Recon Surgery, 1990. **85**(3): p. 419-424.

16. Bertleff, M.J., M.F. Meek, and J.P. Nicolai, *A prospective clinical evaluation of bioabsorbableneurolac nerve guides for sensory nerve repair in the hand*. J Hand Surg Am, 2005. **30**(3): p. 513-8.

17. Bushnell, B.D., et al., *Early clinical experience with collagen nerve tubes in digital nerve repair.* J Hand Surg Am, 2008. Sep. **33**(7): p. 1081-7.

18. Lohmeyer, J.A., et al., *The clinical use of artificial nerve conduits for digital nerve repair: a perspective cohort study and literature review*. J Reconstr Microsurg, 2009. Jan. **25**(1): p. 55-61.

19. Graham, J.B., et al., *A chrondroitinase-treated, decellularized nerve allograft compares favorably to the cellular isograft in rat peripheral nerve repair*. Journal of Neurodegeneration and Regeneration, 2009. **2**(1): p. 19-29.

20. Whitlock, E.L., et al., *Processed allografts and type I collagen conduits for repair of peripheral nerve gaps.* Muscle Nerve, 2009. **39**(6): p. 787-99.

21. Neubauer, D., J.B. Graham, and D. Muir, *Nerve grafts with various sensory and motor fiber compositions are equally effective for the repair of a mixed nerve defect*. Experimental Neurology, 2010. **223**: p. 203-206.

22. Ducic, Ivica, Rose Fu, and Matthew L Iorio. *Innovative Treatment of Peripheral Nerve Injuries: Combined Reconstructive Concepts.* Ann Plast Surg 68.2 (February, 2012): 180-7.

23. Shanti RM, Ziccardi VB. *Use of decellularized nerve allograft for inferior alveolar nerve reconstruction: a case report.* J Oral Maxillofac Surg. 2011 Feb;69(2):550-3.

24. Brooks D, Weber RV, Chao JD, et al. *Processed nerve allografts for peripheral nerve reconstruction: a multicenter study of utilization and outcomes in sensory, mixed, and motor nerve reconstructions.* Microsurgery, 2012;32:1-14.

25. Cho, M. S., B. D. Rinker, R. V. Weber, J. D. Chao, J. V. Ingari, D. Brooks and G. M. Buncke, *Functional outcome following nerve repair in the upper extremity using processed nerve allograft*. J Hand Surg Am (2012). 37(11): 2340-2349.

26. Aberg, M., et al., *Considerations in evaluating new treatment alternatives following peripheral nerve injuries: a perspective clinical study of methods used to investigate sensory, motor and functional recovery.* Plast Reconstr Aesthet Surg, 2007. **60**(2): p. 103-13.

27. Mackinnon, S.E. and A.L. Dellon, *Surgery of the Peripheral Nerve.* 1st ed. 1988, New York: Thieme Medical.

28. Dellon, A.L., et al., *Reliability of two-point discrimination measurements.* J Hand Surg Am, 1987 Sep. **12**(5.1): p. 693-6.

29. Crosby, P.M., et al., *Comparison of two-point discrimination testing devices.* Micro Surg., 1989. **10**: p. 134-137.

30. Stone, J.H., *Sensibility,* In *Clinical Assessment Recommendations,* 2nd ed. 1992, Chicago: American Association of Hand Therapists.

31. Aitken, R.C.B. *Measurement of feelings using visual analogue scales.* In *Proceedings of the Royal society of Medicine*. 1969: Visual Analogue Scales (VAS).

32. Beaton, D.E., W.J., Katz, J.N., *Development of the QuickDASH: Comparison of three item-reduction approaches.* Journal of Bone & Joint Surgery, 2005. **87**(5): p. 1038-1046.

33. Aleid C.J. Ruijs, J.-B.J., H.A.M. Daanen, S.E.R. Hovius, *Cold Intolerance of the Hand Measured By the CISS Questionnaire in a Normative Study Population.* J Hand Surg Eur 2006. **31**(5): p. 533-536.

34. Oud, T., et al., *Sensory re-education after nerve injury of the upper limb: a systematic review.* Clin Rehabil, 2007. **21**(6): p. 483-94.

35. Daniele, H.R. and L. Agued, *Early compensatory sensory re-education*. J Reconstr Microsurg, 2003. **19**(2): p. 107-10; discussion 11-2.

36. Rinker, B. and J.Y. Liau, *A prospective randomized study comparing woven polyglycolic acid and autogenous vein conduits for reconstruction of digital nerve gaps.* J Hand Surg Am. **36**(5): p. 546-7.

37. Altissimi, M., G.B. Mancini, and A. Azzara, *Results of primary digital nerve repair*. J Hand Surg Br, 1994. **19**(2): p. 255-7.

38. Al-Ghazal, S.K., et al., *Results of clinical assessment after primary digital nerve repair.* J Hand Surg Br, 1994. **19**(2): p. 255-7.

14 Appendix 1 – Investigator Agreement

Agreement Signatures

I have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal, and scientific information necessary to conduct this study. I will personally conduct this study as described herein and in Axogen's Clinical Trial Agreement.

I will provide copies of the protocol to all study staff who will participate in the study as part of my study team. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the conduct and requirements of the study. I am aware that this protocol must be approved by the IRB governing the research conducted at my Institution. I agree to adhere strictly to the protocol (unless amended, at which time I agree to adhere strictly to the protocol as amended). I understand that this IRB-approved protocol will be submitted to the Food and Drug Administration by Axogen. I agree that clinical data entered on case report forms by me and my staff will be utilized by Axogen in various ways, including but not limited to, submission of data to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow Axogen monitors and auditors (or their designees) full access to all medical records at the research facility for subjects screened or enrolled in the study.

I agree to provide all subjects with informed consent forms, as required by local and federal regulatory bodies as well as in accordance with ICH regulations. I agree to report to Axogen any adverse experiences in accordance with the terms of Axogen (or designee's) Clinical Trial Agreement and FDA regulations, 21 CFP 312.64. I further agree to provide all required information regarding financial certification or disclosure to Axogen for all investigators and sub-investigators in accordance with the terms of FDA regulation 21 CFR 54.

I assure that my participation in this clinical study will be conducted according to all requirements of this protocol, the FDA Good Clinical Practices including the Investigational New Drug regulation (IND) and other GCP regulations, and local regulatory requirements.

_____		_____
Printed Name Principal Investigator	Date	Signature Principal Investigator

15 Appendix 2 : Schedule of Assessments

Assessments	Visit 1[1] Screening [redacted]	Visit 2[1] Operative Day 0	Visit 3 Month 1 [redacted]	Visit 4 Month 3 [redacted]	Visit 5 Month 6 [redacted]	Visit 6 Month 9 [redacted]	Visit 7 Month 12 [redacted]
Informed Consent	X						
Inclusion/Exclusion Criteria	X	X					
Relevant Medical History	X						
Demographics	X						
Traumatic Injury History		X					
Operative Information		X					
Randomization		X					
Sensory Assessments [2]	X[3]		X	X	X	X	X
Pain Assessments – VAS	X[3]		X	X	X	X	X
[redacted]		[redacted]					
[redacted]		[redacted]					
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Events		X	X	X	X	X	X

1. Screening and Operative Day 0 assessments may be performed on the same day.
2. Sensory Assessments should include:
   a. Static 2-Point Discrimination [redacted]
   c. MRCC Rating for Recovery of Sensory Function.
3. [redacted]
5. [redacted]

16 Appendix 3 - Instructions for Use: Avance® Nerve Graft (LB-211)

Instructions for Use

Customer Care
Direct Dial: 888-AxoGen1 (888.296.4361)
International: 386.462.6800
CustomerCare@AxoGenInc.com

DESCRIPTION

Avance® Nerve Graft is processed nerve allograft intended for bridging nerve discontinuities to support axon regeneration. It is decellularized and cleansed extracellular matrix from donated human peripheral nerve. The cleansing process preserves the inherent microtubular structure of the native nerve extracellular matrix, while clearing the cells, cellular debris and certain proteins such as chondroitin sulfate proteoglycans (CSPG).

Avance® Nerve Graft is implanted and connects the proximal and distal ends of a transected nerve. The processed nerve allograft serves as a scaffold allowing regenerating axons to grow into the patient's distal nerve tissue toward the target muscle or skin.

Avance® Nerve Graft offers structural characteristics and handling similar to nerve autograft; pliability of soft tissue, an intact epineurium to suture the nerve graft in place, and intact endoneurial tubes for the axons to grow through.

Avance® Nerve Graft is supplied sterile in a variety of lengths and diameters to allow the surgeon to match the size of the injured nerve and provide a tensionless repair of the defect. It is for single patient use only. Approximate graft lengths and diameters are listed on the package label.

REGULATORY CLASSIFICATION

Avance® Nerve Graft is processed and distributed in accordance with US FDA requirements for Human Cellular and Tissue-based Products (HCT/P) under 21 CFR Part 1271 regulations, US State regulations and the guidelines of the American Association of Tissue Banks (AATB). Additionally, international regulations are followed as appropriate.

Avance® Nerve Graft is to be dispensed only by or on the order of a licensed physician.

INDICATIONS FOR USE

Avance® Nerve Graft is processed nerve allograft (human) intended for the surgical repair of peripheral nerve discontinuities to support regeneration across the defect.

CONTRAINDICATIONS

Avance® Nerve Graft is contraindicated for use in any patient in whom soft tissue implants are contraindicated. This includes any pathology that would limit the blood supply and compromise healing or evidence of a current infection.

WARNINGS

Careful donor screening, laboratory testing, tissue processing, and gamma irradiation have been utilized to minimize the risks of transmission of relevant communicable diseases to the patient. As with any processed human donor tissue, Avance® Nerve Graft cannot be guaranteed to be free of all pathogens.

Do not reuse or re-sterilize Avance® Nerve Graft and do not refreeze the graft once it has been thawed.

DONOR RECOVERY AND SCREENING

After consent for donation is obtained, surgical recovery of the peripheral nerve tissue is performed in an aseptic manner by appropriately licensed US tissue banks. Donor eligibility is carefully evaluated as required by the US FDA and US State regulations. Additionally, donor eligibility is determined in accordance with AATB standards and appropriate international regulations. Tissue donors are evaluated for high risk behaviors and relevant communicable diseases. Evaluation includes a review of the donor medical and social history, a physical assessment of the donor at time of tissue recovery, a review of an autopsy (if performed), serology testing, tissue recovery microbiology, and cause of death.

Each donor is tested and shown to be **negative or nonreactive** for the following:

- Human Immunodeficiency Virus (HIV) Type 1 Antibody
- Human Immunodeficiency Virus (HIV) Type 2 Antibody
- Hepatitis C Virus (HCV) Antibody
- Hepatitis B Virus (HBV) Surface Antigen
- Hepatitis B Virus (HBV) Core Antibody (total)
- Syphilis Rapid Plasma Reagin or Treponemal Specific Assay
- Human Immunodeficiency Virus (HIV) Nucleic Acid Test (NAT)
- Hepatitis C Virus (HCV) Nucleic Acid Test (NAT)

Additional testing may be performed, as required by local authorities in international markets, and may include the following:

- Hepatitis B Virus (HBV) Nucleic Acid Test (NAT)
- Human T-Cell Lymphotropic Virus (HTLV) Type I Antibody
- Human T-Cell Lymphotropic Virus (HTLV) Type II Antibody

All testing is performed by a laboratory certified to perform such testing on human specimens under the US Clinical Laboratory Improvement Amendments of 1988. The testing is conducted using test kits approved by the US FDA for testing cadaveric specimens where available.

The Medical Director of AxoGen (US state licensed) has determined that the tissue is suitable for transplantation in humans. Records of all testing and medical releases are maintained by AxoGen.

PROCESSING

Avance® Nerve Graft is processed in controlled environments using Good Tissue Practice (GTP) methods designed to prevent contamination and cross contamination of the tissue. Processing involves the use of proprietary physiological buffers, enzyme and surfactants and the processed tissue may contain traces of these processing agents. The cleansing process preserves the inherent microtubular structure of the native nerve extracellular matrix while clearing the cells, cellular debris and certain

proteins such as chondroitin sulfate proteoglycans (CSPG). After completion of processing, Avance® Nerve Graft is sized, packaged and sterilized using gamma irradiation in accordance with ISO 11137[1] guidelines.

Avance® Nerve Graft has been tested in accordance with ISO 10993[2] standards. The test results demonstrated that the processed nerve allograft is biocompatible.

The processed nerve allograft tissue will naturally vary in color from white, off-white, pink, pale pink, and yellow to pale yellow. Occasional dark spots or localized discoloration is a normal occurrence.

HOW SUPPLIED

Avance® Nerve Graft is placed into a plastic tray and then inserted into chevron pouches. Each chevron pouch is heat-sealed to provide a sterile barrier and each pouch has a chevron seal. The outer chevron pouch is foil to provide a moisture barrier. Approximate graft lengths and diameters are listed on the package label. Avance® Nerve Graft is irradiated and supplied frozen. Contents of the foil package are sterile unless the package is opened or damaged.

TRANSPORT AND STORAGE

Avance® Nerve Graft is shipped frozen on dry ice via validated shipping containers. Upon arrival, the product should be removed from the shipping container and placed in a freezer at or below -40°C (-40°F). Expiration date is three (3) years from date of packaging provided that the Avance® Nerve Graft has been stored at temperatures at or below -40°C (-40°F). ***See product label for expiration date.***

Temporary storage conditions

Temporary storage of Avance® Nerve Graft at -20°C to -40°C (-4°F to -40°F) is limited to six (6) months total, and grafts stored at this temperature range must then be transferred to -40°C (-40°F) or colder freezer, used or discarded.

It is the responsibility of the health care institution to track the expiration date of the Avance® Nerve Graft and ensure that the product is stored properly.

WARNING

If the outer foil chevron pouch and/or inner Tyvek® chevron pouch is compromised (shows evidence of being torn or opened in any manner), **DO NOT USE** the Avance® Nerve Graft and notify AxoGen Customer Care immediately.

INSTRUCTIONS FOR USE

1. Follow standard operating procedures for exposure and mobilization of the injured peripheral nerve.
2. Determine the injured nerve diameter in millimeters (mm) using a suitable measuring instrument.

3. Select Avance® Nerve Graft(s) of comparable diameter to match the native nerve and of sufficient length to ensure a tension free repair.
4. To prepare the Avance® Nerve Graft,
   a. Remove the foil chevron pouch containing Avance® Nerve Graft, Instructions for Use, patient record labels and Tissue Utilization Report (TUR) from the package.
   b. Compare the distinct lot number on the foil chevron pouch with the lot number on the package. If the numbers do not match, **DO NOT USE** the product and notify AxoGen Customer Care immediately.
   c. Using standard aseptic technique, peel open the outer foil chevron pouch and pass the inner Tyvek® chevron pouch to the sterile field for further handling.
   d. Open the Tyvek® chevron pouch and remove the plastic tray.
   e. Open the plastic tray and fill the pre-molded thawing reservoir with room temperature sterile saline or sterile Lactated Ringer's Solution (LRS). Do not heat the graft or add heated saline or LRS to the graft.
   f. Allow Avance® Nerve Graft to thaw completely before use which will take approximately 5 – 10 minutes. Once thawed, Avance® Nerve Graft is soft and pliable throughout. Avance® Nerve Graft must be either implanted or discarded within 12 hours. **NEVER IMPLANT A PARTIALLY OR FULLY FROZEN PRODUCT.**
5. Handle Avance® Nerve Graft by outer most epineurium and avoid crimping or crushing the graft.
6. Implant Avance® Nerve Graft using the same tensionless surgical technique used when implanting a nerve autograft. Either end of the processed nerve allograft can be coapted to the proximal stump of the host nerve.
7. Destroy any thawed allograft tissue not used in the surgical procedure in accordance with local, state and federal or country regulations for disposal of human tissue.
8. Complete and send the Tissue Utilization Report (TUR) back to AxoGen.

TISSUE UTILIZATION REPORT (TUR)

Each Avance® Nerve Graft package contains a Tissue Utilization Report (TUR). **In accordance with US FDA, US Joint Commission and international requirements, a TUR should be completed for each Avance® Nerve Graft used in the procedure and returned to AxoGen or other representative as described on the TUR.**

Record the distinct HCT/P identification code in hospital or facility records and in the patient's file. Complete all information on the card, affix ONE (1) peel-off label of each Avance® Nerve Graft used, seal and return to AxoGen or other representative as described on the TUR.

It is the responsibility of the health care institution to maintain recipient records for the purpose of tracking tissue post-implantation. The Tissue Utilization Report is **NOT** intended to be a substitute for a facility's internal tissue transplantation tracking system.

POTENTIAL COMPLICATIONS

The following adverse events are anticipated and may potentially occur during treatment:

- mild incisional redness;
- tenderness of surgical area;
- mild edema of surgical area;
- controllable pain at surgical area;
- decreased sensation; and,
- numbness

These adverse events are considered expected and are not required to be recorded unless they increase in severity.

Inherent risks of any surgical procedure include, infection, blood loss, and anesthesia associated complications. Complications specific to nerve reconstruction include pain, decreased or increased sensitivity, and impaired motor or sensory function. As with all peripheral nerve surgery, there is a risk of failure of the nerve to regenerate.

Hypersensitivity, allergic reactions, or other adverse immune responses have not been observed in preclinical studies or reported clinically with the use of Avance® Nerve Graft. Because Avance® Nerve Graft is composed of proteins such as collagen and laminin, the potential may exist for such reactions.

Avance® Nerve Graft is processed human nerve tissue. As with all donated human tissue products the risk for transmission of communicable disease does exist. Robust donor screening and selection criteria, completed as required by the FDA and in accordance with AATB, state, and federal guidelines, processing controls, and terminal sterilization with gamma irradiation greatly reduce but cannot totally eliminate this risk. As disease screening methods are limited, certain diseases may not be detected. The following complications of tissue transplantation may occur:

-Transmission of diseases of unknown etiology;

-Transmission of known infectious agents including, but not limited to viruses, bacteria, and fungi.

DISPOSAL

Dispose of Avance® Nerve Graft in accordance with local, state and federal or country regulations for disposal of human tissue.

REFERENCES

1. ISO 11137:2006 Sterilization of health care products — Radiation guidelines
2. ISO 10993:2003 Biological evaluation of medical devices

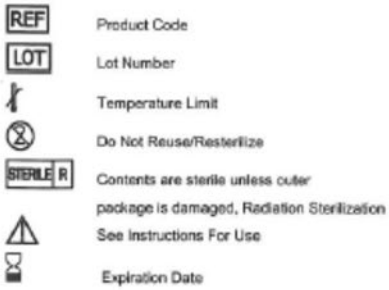
INQUIRIES

For additional information, to place an order, or to report errors, accidents or adverse reactions, contact:

If in the US: AxoGen Customer Care
Phone: 888.AxoGen1 (888.296.4361)
Email: CustomerCare@AxoGenInc.com

Customers outside of US: Contact the AxoGen authorized distributor servicing your facility, email AxoGen Customer Care or contact AxoGen directly in the US at (386) 462.6800.

Symbols used on Product Packaging



This product, its manufacture and use is covered by one or more of U.S. Patent No. 6,972,168, U.S. Patent No. 7,402,319, U.S. Patent No. 7,732,200, Japanese Patent No. 4749667, Europe Patent No. EP1425390 and other patents pending

Canada CTO Registration #100065

Avance® Nerve Graft is processed in the United States by:

AxoGen

13631 Progress Blvd., Suite 400
Alachua, FL 32615
www.AxoGenInc.com

Avance® Nerve Graft is a registered trademark of AxoGen.
Tyvek® is a registered trademark of E.I. DuPont De Nemours & Co.

LB-211 R05

[redacted]

[redacted]