Axogen Corporation

Axoguard® Nerve Cap

PROTOCOL

A Multicenter, Prospective, Randomized and Subject Blinded Comparative Study of Axoguard® Nerve Cap and Neurectomy for the Treatment of Symptomatic Neuroma and Prevention of Recurrent End-Neuroma Pain

Protocol No. CAP-CP-001

CONFIDENTIAL – PROPRIETARY INFORMATION

Development Phase:	Pilot Cross-over to Comparative Parallel Group
Sponsor:	Axogen Corporation 13631 Progress Blvd – Suite 400 Alachua, FL 32615
Sponsor Representative:	[redacted]
Immediately Reportable Adverse Event:	Clinical Safety [redacted]
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Title of Study: A Multicenter, Prospective, Randomized, Subject Blinded Comparative Study of Axoguard® Nerve Cap and Neurectomy for the Treatment of Symptomatic Neuroma and Prevention of Recurrent End-Neuroma Pain
Estimated Number of Study Centers and Countries: Up to 20 Centers in the US
Study Type: Pilot to Comparative Parallel Group
Study Design: Randomized, controlled, prospective, subject blinded, multi-center, pilot to comparative parallel group study
Objective: The primary objective of the pilot phase of this study is to evaluate the difference in pain scores from baseline at 12 weeks; The primary objective of the comparative phase is the differences in pain assessments between the study groups at 12 months. The secondary objectives of this study are to compare degree of recovery over time (reduction in pain); quality of life and economic data for each treatment group over a 12-month period.
Study Population: Adult male and female subjects with symptomatic neuroma in the foot or ankle to at least one nerve where the nerve cannot be repaired to a distal nerve end
Test Product: Axoguard® Nerve Cap
Control: Neurectomy
Number of Subjects per Treatment Group: Enroll approximately 15 evaluable subjects in the pilot study. Enroll approximately 86 additional subjects for the randomized comparative study.
Duration of Study: Up to 13 months including screening period.
Inclusion Criteria: **Potential Subjects must:** 1. Be able and willing to provide documented informed consent prior to the conduct of any study procedures; 2. Be an adult male or non-pregnant female ≥ 18 years of age; 3. Report baseline pain scores of ≥65mm on a 100mm Visual Analog Scale (VAS) at screening; 4. Have a documented diagnosis of symptomatic neuroma of at least one interdigital nerve in the foot which cannot be repaired to a distal nerve end; 5. Must have the of the following: • Pain with at least 3 of the following characteristics: burning, sharp, shooting, electric, parasthesias, numbness, cold intolerance; • Symptoms in a defined neural anatomic distribution • History of nerve injury or suspected nerve injury Must have at least 1: • Positive response to local anesthetic injection • US or MRI confirmation of neuroma 6. Be candidates indicated for surgery to address a symptomatic neuroma; 7. Have sufficient healthy soft tissue available to adequately cover the Axoguard® Nerve Cap;

8. In the surgeon's opinion, be likely to achieve complete resection of the symptomatic neuroma and be able to undergo implantation with the Axoguard® Nerve Cap or complete the neurotomy procedure in the control group;
9. Be willing and able to comply with all aspects of the treatment and evaluation schedule over a 12-month duration.

Exclusion Criteria:

Potential subjects must not:

1. Have undergone surgical treatment of pain from symptomatic neuroma in the target nerve(s)on three or more occasions;
2. Have biomechanical pathology and associated pain (such as plantar fasciitis, bursitis, sesamoid bone pain, tendinitis, etc);
3. Have a life expectancy of less than 12 months;
4. Have a history of or planned radiotherapy in the area of the end-neuroma;
5. be contraindicated for soft tissue implants.; this includes but is not limited to any pathology that would limit the blood supply; compromise healing or indicate the presence of a local infection;
6. Have a history of chronic ischemic conditions of the extremity;
7. Have a diagnosis of type 1 Diabetes Mellitus; or uncontrolled Type 2 Diabetes Mellitus (at the discretion of the investigator);
8. Have a history of diabetic neuropathy;
9. Be undergoing or expected to undergo treatment with chemotherapy, radiation therapy, or other known treatment which affects the growth of neural and/or vascular system;
10. Be immunosuppressed, immunocompromised or have planned immunosuppressive therapy within 12 months following the study procedure;
11. Have a History of congenital neuropathy or compressive neuropathy affecting the target limb;
12. Have a history of prior surgical management of more proximal compressive neuropathies or spinal conditions (e.g. spinal stenosis) not related to the symptomatic neuroma that affect the target limb;
13. Currently use or likely need to use medication during the study known to impact nerve regeneration or to cause peripheral neuropathy;
14. be pregnant or plan to become pregnant during the duration of the study;
15. Be or have been enrolled in another interventional study within 30 days prior to consenting;
16. Have a known allergy to anesthetic agents;
17. Have a known sensitivity to porcine derived materials; or
18. Be, in the opinion of the Investigator, unsuitable for inclusion in the study.

Conduct of Study: Randomized, controlled, prospective, subject blinded, multi-center comparative parallel group study. The study will be composed of eight (8) scheduled visits. See Appendix B: Schedule of Assessments for details.

Criteria for Evaluation:

Safety Endpoints

Primary Safety Endpoints:

1. Serious Adverse Events (SAEs) at 3 months
2. Adverse Events (AEs) or Unanticipated Adverse Device Effects (UADEs) at 3 months

Secondary Safety Endpoints:

1. SAEs, AEs and/or UADEs at 6, 9 and 12 months

Efficacy Endpoints

Primary Efficacy Endpoints:

1. Change in VAS score at 3 months compared to baseline (pilot study)
2. Change in VAS score at 12 months compared to baseline (comparative study)

Secondary Efficacy Endpoints:

1. Change in VAS score at 1, 3, 6, 9 and 12 months compared to baseline
2. Change in PROMIS score at 1, 3, 6, 9 and 12 months compared to baseline
3. Change Foot Health Status Questionnaire (FHSQ) score at 1, 3, 6, 9 and 12 months compared to baseline
4. Change in Quantity and class of pain medication use at 1, 3, 6, 9 and 12 months compared to baseline
5. Rate of recurrence of symptomatic neuroma

[redacted]

Statistical Methods:

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. Mann-Whitney U tests will be used to compare baseline data to ensure poolability across centers.

Sample Size and Analysis of Data:

The study is a randomized, controlled, prospective, subject blinded, multi-center study to evaluate the safety and performance of Axoguard® Nerve Cap for the treatment of symptomatic neuroma as compared to neurectomy. Tests of non-inferiority and superiority will be conducted in the comparative phase. Sample sizes for both pilot (15 subjects) and comparative (86 subjects) study phases were based on similar injury-type studies published and referenced in the protocol. As a point of reference, outcomes will also be compared to historical controls of subjects undergoing neurectomy.

[redacted]

[redacted]

[redacted]

[redacted]

Table of Contents

ACRONYMS:

AE:	Adverse Effects / Events
CRA:	Clinical Research Associate
CRF(S):	Case Report Forms
CTA:	Clinical Trial Agreement
ICH:	International Conference on Harmonization
IRB:	Institutional Review Board
EOS:	End of Study
EOT:	End of Treatment
EU:	European Union
FDA:	Food and Drug Administration
FHSQ:	Foot Health Status Questionnaire
GCPs:	Good Clinical Practices
IDE:	Investigational Device Exemption
ISO:	International Standards Organization
PROMIS®:	Patient Reported Outcome Measurement Information System
SAE:	Serious Adverse Event
UADE:	Unanticipated Adverse Device Effect
VAS:	Visual Analogue Scale
WIRB:	Western Institutional Review Board (central IRB)

1. INTRODUCTION

1.1 Background

A neuroma is formed when a peripheral nerve's continuity is substantially disrupted or injured. Nerve trauma types include cut nerves as in amputations or autograft sites, crushed nerves in carpal tunnel syndrome, or stretched nerves from high velocity accidents. When a disrupted nerve cannot be repaired, Schwann cells, attempting to restore axonal continuity, proliferate ahead of the injury site. This process creates a path through which axons grow in a disorganized fashion. In severe tissue damage the regenerating axons cannot reach their target tissue, and instead form a tangled bulbous mass which causes pain when stimulated.[2,3]

There is no currently accepted technique that has been clinically shown to prevent or mitigate neuroma formation. With more than 700,000 peripheral nerve injuries that require surgery every year and a rapidly increasing number of diabetes-related limb amputations, the number of patients suffering from debilitating neuroma pain is significant and increasing.[4] Painful neuroma following amputation is a disabling condition for which treatments are not usually satisfactory.[5]

Currently available treatment options after limb amputation or an unrepaired transected nerve injury incompletely address pain-inducing neuroma formation.[6] Treatments include both surgical methods to remove neuromas or limit neuroma pain with pharmacological therapies directed at pain management. Attempts to treat symptomatic neuroma formation have been met with limited success, which is reflected by the recorded use of over 150 physical and chemical treatment methods, none of which have been uniformly successful.[7,8,9]

[redacted]

VAS pain scores have consistently been the measure of choice for assessing treatment interventions for pain, but the minimum clinically significant difference has typically been reported as a reduction between 14 – 20 mm .[11, 12]

Pharmacological methods may employ antidepressants, anticonvulsants, agonists, opioids, and lidocaine. Unfortunately, although pharmacological therapy may lead to transient relief, amputees often experience considerable side effects and reduced benefit over time, not to mention the possibility of abuse and dependency.[13] Multiple clinical and non-clinical studies have demonstrated that neuroma pain is best controlled by the use of opioid medications, as it is refractory to other first-line neuropathic pain medications.[14,15] For some amputees suffering from neuroma pain, the improvement in function offered by effective pain control is worth the trade-off of moderate to severe side effects including the risk of hyperalgesia.[14] However, chronic use of opioid analgesics is associated with an increased risk of dependence and abuse.[16] Local treatment options, such as cauterization and steroid, phenol, and alcohol injections are merely a temporary solution as repeated injections are required.[6] Thus, a better approach to long-term relief may be surgical methods designed to prevent neuromas and eliminate or reduce symptomatic neuroma pain.

This study is to evaluate the safety and performance of the Axoguard Nerve Cap for surgical nerve amputation in the treatment of symptomatic neuroma compared to neurectomy. By providing a new treatment option to surgeons, the vision is for patients to benefit from reduced pain, improved rehabilitation outcomes, reduced dependence on opioids, and overall better quality of life. We predict that the partition design of the Axoguard Nerve Cap will cushion the axons within the nerve end and protect them from external stimulation and prevent painful neuroma formation post implant.

1.2 Product Description

Axoguard® Nerve Cap is a surgical implant that is a tubular device with one open end, one sealed end (cap) and internal channels designed to provide protection for a peripheral nerve end or stump where repair is unattainable or not desired. The device isolates the nerve stump from the surrounding soft tissue bed by pulling the nerve into the tube and suturing the nerve within the cap. The end of cap has a suturable tab to allow the surgeon to suture the device to surrounding tissue. See Figure 1.2-1 for Image of Axoguard® Nerve Cap, and figure 1.2-2 for Image of placement of Axoguard® Nerve Cap.

Axoguard® Nerve Cap is an extracellular matrix (ECM) that is fully remodeled during the healing process. When hydrated, Axoguard® Nerve Cap is easy to handle, soft, pliable, nonfriable and porous. Axoguard® Nerve Cap is flexible and pliable to accommodate movement of the joints and surrounding soft tissues and has sufficient mechanical strength to hold appropriately sized non-absorbable suture.

Processed porcine ECM is readily and available proven to be safe and effective in a wide range of clinical applications.[17, 18]

Axoguard® Nerve Cap is provided sterile, for single use only, and in a variety of sizes to meet clinical needs. The device is supplied in a plastic tray within a sterile pouch. The pouch is heat-sealed to provide a sterile barrier and has a chevron seal. Contents of the package are guaranteed sterile unless the package is opened or damaged. Axoguard® Nerve Cap and packaging does not contain natural rubber latex.[19] To assure patient safety, the small intestine submucosa (SIS) material undergoes a thorough disinfection, decellularization, and viral inactivation process. As a final step in the process, all SIS products are sterilized by validated sterilization methods.[20]

Porcine ECM processed by Cook Biotech is decelluarized and elicits an immune response that is predominately Th-2-like, promoting remodeling of soft tissues rather than eliciting an acute rejection response.[21]

Axoguard® Nerve Cap should be stored in a clean, dry location between 10 – 30°C/50 – 86°F. The device should be used prior to the "Use By" date specified on the package. The "Use By" date is in the form Year-Month-Day.[19]

Regulatory Classification: Axoguard® Nerve Cap is a class II device which obtained 510(k) clearance (K163446).[24]

Figure 1.2-1: Image of Axoguard® Nerve Cap

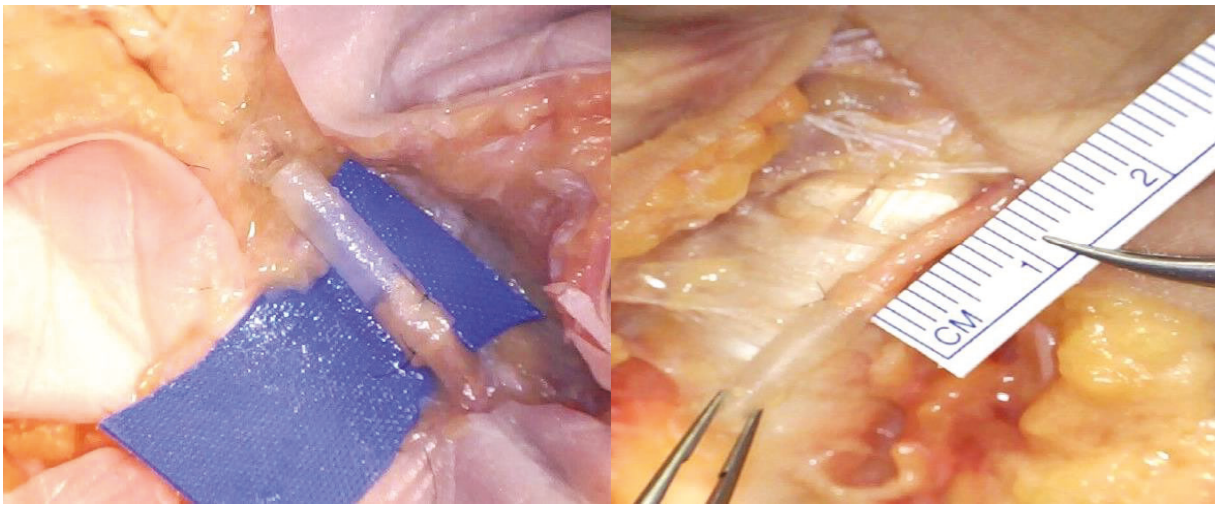


Figure 1.2-2: Diagram placement of the Axoguard® Nerve Cap

1.3 Risk Analysis

Axoguard® Nerve Cap is contraindicated for use in any patient for 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. Axoguard® Nerve Cap is derived from a porcine small intestinal submucosa (also called SIS) and should not be used for patients with known sensitivity to porcine derived materials.[19]

If any of the following conditions occur and cannot be resolved, careful removal of the device should be considered:

- Infection;
- Allergic reaction; and/or
- Acute or chronic inflammation (initial application of surgical graft materials may be associated with transient, mild, localized inflammation).

As with any surgical procedure, complications can occur such as pain, infection, decreased or increased nerve sensitivity, and complications associated with the use of anesthesia.

Additional complications that may be associated with these types of procedures may potentially occur after implantation. These complications may be expected and are not required to be recorded unless they increase in severity:

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

The following precautions should be taken into consideration prior to implanting the Axoguard® Nerve Cap:[19]

Adverse events associated with the use of Axoguard® Nerve Cap may include but are not limited to:

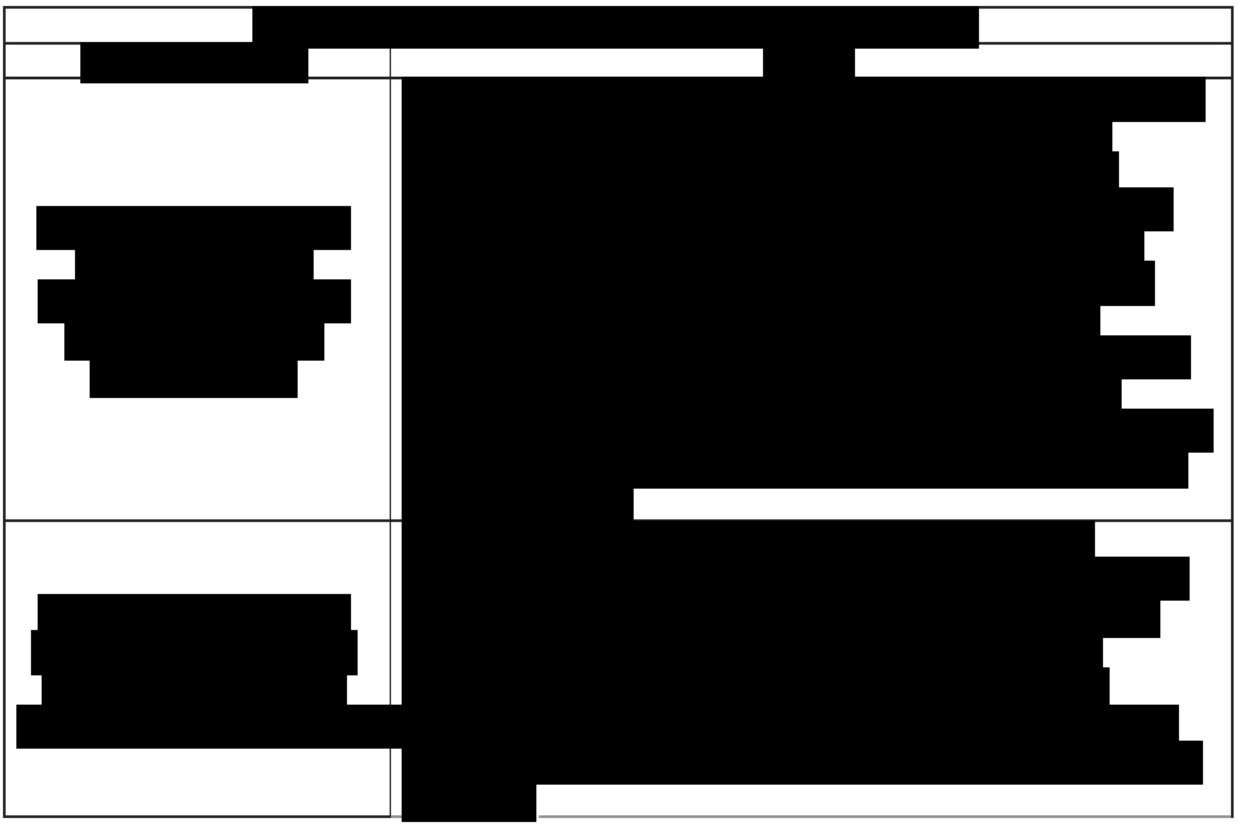
- Failure to reduce symptomatic neuroma pain
- Transitory local irritation
- Infection
- Allergy
- Delayed wound healing; and/or
- Protrusion

1.3.1 Preclinical Testing for Axoguard® Nerve Cap

Comprehensive in vitro and in vivo biocompatibility evaluations provide support that Axoguard® Nerve Cap 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

discontinuities; and support axonal regeneration of peripheral nerves following traumatic or oncologic nerve amputations.

Additionally, in vivo testing utilizing well established and validated animal models has demonstrated efficacy in reduced behavioral pain responses and increased optical density of the regenerating nerve stump resulting in the reduced likelihood of symptomatic neuroma formation and related pain following traumatic or oncologic nerve amputation.[22, 23]



1.3.2 Manufacturing Controls

Axoguard® Nerve Cap is manufactured in accordance with current good manufacturing practices (cGMPs) for medical devices. The biomaterial undergoes a thorough disinfection, decellularization, and viral inactivation process. As a final step in the process, the biomaterial is sterilized via validated sterilization methods and then is vacuum pressed prior to packaging. To confirm biocompatibility, the material is tested by accredited, independent laboratories, using testing methods based on international standards and FDA guidance.

Axoguard® Nerve Cap has been sterilized using an established ethylene oxide (EO) cycle that has been validated to a sterility assurance level (SAL) of 10^{-6} in conformance with ISO standards.[24]

1.3.3 Previous Clinical Experience

General Use

To date, there has been no published clinical data collected for the use of Axoguard® Nerve Cap. This pilot study will serve to provide early feasibility data on patient reported outcomes for the treatment of symptomatic neuroma. The SIS material used in the design of the Axoguard® Nerve Cap is the same used in the design of the Axoguard® Nerve Protector and the Axoguard® Nerve Connector (K132660 and K162741 respectively), and are commercially available products for peripheral nerve repair.

1.3.4 Published Clinical Studies

As noted above, to date there has been no published clinical data collected for the use of Axoguard® Nerve Cap. [redacted]

The use of SIS source material provides an environment for supporting natural tissue repair and without limiting vascularity throughout the implant.[26, 27].

Axoguard® Nerve Connector:
In previous clinic studies the Axoguard® Nerve Connector demonstrated promising benefits over direct repair in alleviating tension through the nerve's full range of motion and at the nerve site; while allowing vascular channels to remain open.[28]

Axoguard® Nerve Protector:
In previous clinic studies the SIS material used in nerve repair with the Axoguard® Nerve Connector demonstrated promising benefits over repair with reconstituted collagen implant by preserving the extracellular matrix to support the natural healing process, retaining non-collagenous components that support host tissue response, and in providing an environment for natural tissue repair.[26,29,30,31,32]

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary efficacy objective of the pilot phase of this study is to evaluate the difference in pain scores from baseline at 3 months for subjects receiving Axoguard® Nerve Cap; The primary efficacy objective of the comparative phase is the difference in pain assessments at 12 months between the two study groups (Axoguard® Nerve Cap vs standard neurectomy).

The aim is to see a reduction in pain caused by symptomatic neuroma, improved quality of life, reduction in the use of or strength of pain medication used to treat neuroma pain, and a reduction in recurrence of symptomatic neuroma within 3 months.

2.2 Secondary Objectives

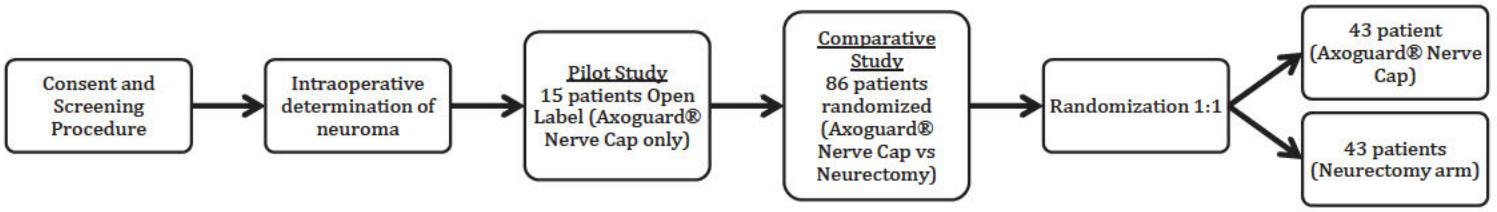
The secondary objectives of this study are to compare degree of recovery over time (reduction in pain); quality of life data; [redacted]

3. STUDY DESIGN

3.1 Description of Design

This is a multicenter, prospective, randomized, controlled, subject blinded comparative parallel group study in patients presenting with symptomatic neuroma (verified by diagnostic block or imaging (US or MRI confirmation) with a baseline pain level of ≥65 mm on a 100 mm Visual Analog Scale (VAS) during screening. Fifteen (15) pilot subjects will receive the Axoguard® Nerve Cap in the pilot phase of the study. In the comparative phase of the study, approximately 86 adult subjects meeting inclusion/exclusion criteria will be centrally randomized in a 1:1 ratio to receive either Axoguard® Nerve Cap or neurectomy. This study design overview is found in Figure 3.1. This study is intended to collect post-operative data as well as physician experience surveys on the clinical use of Axoguard® Nerve Cap to evaluate its safety and performance as compared to subjects receiving neurectomy.

Figure 3.1. Study Design



This study will consist of a total of 8 visits [redacted] This study will be conducted in accordance with the FDA regulations21 CFR Parts 50 and 56 and current cGCP requirements as described in the ISO 14155:2011 standards, applicable IRB regulations.

3.2 Study Treatment - Identification of Products

3.2.1 Study Product

Description: Axoguard® Nerve Cap is a surgical implant that is a tubular device with one open end, one sealed end (cap) and internal channels designed to provide protection for a peripheral nerve end or stump where repair is unattainable or not desired. The device isolates the nerve stump from the surrounding soft tissue bed by pulling the nerve into the tube and suturing the nerve within the cap. The end of cap has a suturable tab to allow the surgeon to suture the device to surrounding tissue.

Axoguard® Nerve Cap is provided sterile, for single use only, and offered in a variety of sizes to allow the surgeon to choose the appropriate size to address the injured tissue. Multiple patient labels with product code, lot number and expiration date are provided for subject records.

Federal (U.S.A.) law only allows Axoguard® Nerve Cap to only be sold under or by the order of a physician. This product is intended for use by trained medical professionals only.

3.2.2 Control

Description: Standard surgical treatment with neurectomy.

Neurectomy is a surgical treatment for symptomatic neuroma. It entails neuroma excision with high transection of the nerve. The goal is to relocate the nerve stump proximally into an area more protected by muscle and soft tissue, where it is less likely to become irritated and symptomatic.[33]

3.3 Study Population

Adult male and female subjects (age ≥ 18 years old) with symptomatic neuroma in the foot or ankle to at least one nerve where the nerve cannot be repaired to a distal nerve end.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Authorized written informed consent (witnessed, where required by law or regulation) 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 prior to obtaining consent. However, informed consent must be obtained and documented on a written IRB approved consent form prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research. The site 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 current Good Clinical Practices (GCP) as described in the ISO 14155:2011 standard; 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, 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 all associated risks with participating on the study, 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 site 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

Potential Subjects must:

1. Be able and willing to provide documented informed consent prior to the conduct of any study procedures;
2. Be an adult male or non-pregnant female ≥ 18 years of age;
3. Report baseline pain scores of ≥65mm on a 100mm Visual Analog Scale (VAS) at screening;
4. Have a documented diagnosis of symptomatic neuroma of at least one interdigital nerve in the foot which cannot be repaired to a distal nerve end;
5. Must have the following:
   - Pain with at least 3 of the following characteristics: burning, sharp, shooting, electric, parasthesias, numbness, cold intolerance;
   - Symptoms in a defined neural anatomic distribution
   - History of nerve injury or suspected nerve injury

     Must have at least 1:
   - Positive response to local anesthetic injection
   - US or MRI confirmation of neuroma
6. Be candidates indicated for surgery to address a symptomatic neuroma;
7. Have sufficient healthy soft tissue available to adequately cover the Axoguard® Nerve Cap;
8. In the surgeon's opinion, be likely to achieve complete resection of the symptomatic neuroma and be able to undergo implantation with the Axoguard® Nerve Cap or complete the neurotomy procedure in the control group;
9. Be willing and able to comply with all aspects of the treatment and evaluation schedule over a 12-month duration.

3.4.3 Exclusion Criteria

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

Table 3.4.3-1 Exclusion Criteria

Potential subjects must not:

1. Have undergone surgical treatment of pain from symptomatic neuroma in the target nerve(s)on three or more occasions;
2. Have biomechanical pathology and associated pain (such as plantar fasciitis, bursitis, sesamoid bone pain, tendinitis, etc);
3. Have a life expectancy of less than 12 months;
4. Have a history of or planned radiotherapy in the area of the end-neuroma;
5. be contraindicated for soft tissue implants.; this includes but is not limited to any pathology that would limit the blood supply; compromise healing or indicate the presence of a local infection;
6. Have a history of chronic ischemic conditions of the extremity;
7. Have a diagnosis of type 1 Diabetes Mellitus; or uncontrolled Type 2 Diabetes Mellitus (at the discretion of the investigator);
8. Have a history of diabetic neuropathy;
9. Be undergoing or expected to undergo treatment with chemotherapy, radiation therapy, or other known treatment which affects the growth of neural and/or vascular system;
10. Be immunosuppressed, immunocompromised or have planned immunosuppressive therapy within 12 months following the study procedure;
11. Have a History of congenital neuropathy or compressive neuropathy affecting the target limb;
12. Have a history of prior surgical management of more proximal compressive neuropathies or spinal conditions (e.g. spinal stenosis) not related to the symptomatic neuroma that affect the target limb;
13. Currently use or likely need to use medication during the study known to impact nerve regeneration or to cause peripheral neuropathy;
14. be pregnant or plan to become pregnant during the duration of the study;
15. Be or have been enrolled in another interventional study within 30 days prior to consenting;
16. Have a known allergy to anesthetic agents;
17. Have a known sensitivity to porcine derived materials; or
18. Be, in the opinion of the Investigator, unsuitable for inclusion in the study.

3.4.4 Enrollment in Study

3.4.4.1 Treatment of Multiple Neuromas

In instances where subjects have multiple neuromas in the foot/ankle, the surgeon must identify the target nerve for inclusion in this study, and agree to treat all additional neuromas as per the randomization assignment. Additionally, if subjects are diagnosed with bilateral neuromas (whether interdigital or elsewhere in the foot/ankle) each limb and all affected nerves must follow the same randomization assignment. Please note, for instances of bilateral neuromas, surgical treatment for each foot may be completed at the same time, but no later than 270 days after subject randomization.

For instances when surgical intervention cannot be completed for the contralateral foot by day 270, further surgical intervention is to occur after the subject has completed the study, or study participation must discontinue.

3.4.4.2 Subject Screening and Numbering

After the subject has signed an IRB-approved informed consent form, he/she 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. In the comparative phase, randomization will occur intra-operatively, and a randomization number will be assigned to identify the enrolled subject.

3.4.4.3 Subject Withdrawal or Discontinuation

If a subject discontinues early from the study, the reason should be recorded in source documentation and the CRF. If the subject is withdrawn due to an adverse event, the adverse event should be indicated as the reason for withdrawal. All subjects have the right to withdraw at any point during the study without prejudice. The Investigator (in consultation with the sponsor) can discontinue a subject's participation at their discretion at any time if medically necessary or in the case of non-compliance with the study protocol at.

The investigator shall promptly notify the sponsor 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 discontinuation.

3.4.4.4 Subject Replacement

Once a subject is randomized, they may not be replaced.

3.5 Study Endpoints

3.5.1 Safety Endpoints

Primary Safety Endpoint

1. The rate of occurrence of Serious Adverse Events (SAEs) at 3 months
2. The rate of occurrence of Adverse Experiences (AEs) or Unanticipated Adverse Device Effects at 3 months

Secondary Safety Endpoints

1. The rate of occurrence of SAEs, AEs and/or UADEs at 6, 9 and 12 months

3.5.2 Efficacy Endpoints

Primary Efficacy Endpoints

1. The change in VAS score at 3 months compared to baseline (pilot phase)
2. The change in VAS score at 12 months compared to baseline (comparative phase)

Secondary Efficacy Endpoints

1. The change in VAS score at 1, 3, 6, 9 and 12 months compared to baseline
2. The change in PROMIS® score at 1, 3, 6, 9 and 12 months compared to baseline
3. The change in FHSQ score at 1, 3, 6, 9 and 12 months compared to baseline
4. Changes in pain medication use at 1, 3, 6, 9 and 12 months compared to baseline
5. Rate of recurrence of symptomatic neuroma within 12 months

3.6 Assessments, Questionnaires, Surveys, Diaries

3.6.1 Pain Assessments – VAS and PROMIS®

Pain Assessments (VAS and PROMIS®) will be completed by the subject at the screening visit and all six (6) follow-up visits after the Daily Pain Diary review. Pain assessments may also be done on the operative day (but prior to nerve block or surgical intervention) if the nerve block is planned to occur at this time.

The Visual Analog Scale (VAS) is a pain scale designed in such a way that it allows a study subject to rate their pain with minimum constraints.[34] Subjects will rate their current pain level by creating a mark on a 10 centimeter (100 millimeter) line. The distance measured from 0 millimeter to the patient's mark corresponds to the amount of pain the subject is 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 0 millimeter representing no pain, and 100 millimeters representing the most pain.

PROMIS® is a set of person-centered measures that evaluate and monitor physical, mental, and social health in adults and children. Measures are applicable to the general population and to those with

chronic conditions. For this study, PROMIS® measures will be used to monitor a subject's physical health/pain.

3.6.2 Quality of Life Questionnaires (FHSQ

Quality of Life Questionnaires (FHSQ [redacted] will be completed by the subject at visits 1, 4, 5, 6, 7, and 8.

3.6.2.1 Foot Health Status Questionnaire (FHSQ)

The FHSQ was developed to help better measure responsiveness in overall foot health status in 4 areas (foot function, foot health, footwear and foot pain).[35] The FHSQ's 4 scale have shown to be better predictors of foot responsiveness than other index rating scores.[36] The FHSQ bank of 19 questions demonstrate a high degree of content, criteria, construct validity and retest reliability and have been used as an outcome measure in clinical trials for a range of foot disorders.[37]

[redacted]

3.6.5 Concomitant Medication Log and Daily Pain Medication Diary (Quantity and Class)

Concomitant Medication logs and Daily Pain Medications Diaries (quantity and class of pain medication treatments) being prescribed/administered by the subject will be collected. A Daily Pain Medication Diary will be provided to each subject to take home and complete or subjects will be sent reminders to complete their daily pain diaries via ePRO for those subjects that enroll in ePRO. Daily Pain Medication diaries will be completed by the study subjects each day and will be reviewed at all six (6) follow-up visits. The subject will present the Daily Pain Medication Diary at each study visit for review by the site team, and a new diary will be dispensed to the subject at each visit. The collected medication diary will be filed in the subject chart for record of the study visit and for CRF completion/review. The site team will also capture any non-pain concomitant medications the subject is taking at each study visit.

[redacted]

[redacted]

3.6.8 Daily Pain Diary

A daily pain diary will be provided to each subject at the Screening visit (visit 1), and a new diary will be dispensed to the subject at Visits 2 through 7 to track incidence, frequency and severity of pain (using a 10-point scale) on a daily basis. Similar to the pain medication diaries, subjects will complete the daily pain diary either on paper or through the ePRO module of the EDC. The diary will be reviewed and collected at each study visit (by the site team with the subject) prior to completing the scheduled pain assessments (VAS/PROMIS®).

3.7 Measures to Minimize/Avoid Bias

The following control measures will be put in place to minimize and/or avoid bias within the study.

- All Investigators selected for participation must have completed a foot and/or microsurgical fellowship.
- Investigators will have prior experience performing neurectomy procedures in the foot or ankle, and will either have prior experience implanting the Axoguard® Nerve Cap or will receive in-service training to ensure correct and consistent technique.
- For those Investigators who have not implanted the product within the 12 months prior to the initiation of the study; a training in-service and/or bioskills lab will be performed to re-familiarize the Investigator with the handling, utilization and placement of each test product.
- Standardized evaluation tools [redacted] will be provided to each study center.
- During the comparative phase, 1:1 randomization will occur at the time of surgery.
- Subjects will be blinded to the assigned treatment group until they complete the study.

3.7.1 Blinding

While blinding the surgeon to treatment is not possible, blinding the subject 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 ensuring the subject is blinded to their treatment assignment. Direct verbal or written communication regarding treatment identification beyond what is required at the institution for documentation/recording the details of the surgical procedure should be avoided. Safety assessments should be performed by a qualified medical professional.

3.8 Randomization (comparative phase only)

In the pilot phase, the initial 15 subjects in will be assigned to open label treatment with Axoguard® Nerve Cap. In the subsequent comparative phase, subjects will be centrally randomized using an Interactive Web Response System (IWRS), OpenClinica, to undergo either neurectomy or implantation of the Axoguard® Nerve Cap in a ratio of 1:1. Only subjects meeting all inclusion and exclusion criteria shall be randomized.

3.9 Study Procedures

After written informed consent is obtained, a pre-operative screening visit (visit 1) will be conducted to assess eligibility for the study. At the Operative Visit (visit 2), pre-operative preparation, debridement

[redacted]

and mobilization of the nerve stump will be per performed in accordance with the Investigator's/Institution's standards-of-care. After interoperative confirmation of eligibility is determined, randomization will occur. For patients randomized to receive Axoguard® Nerve Cap, the investigator will determine nerve diameter and select an appropriately sized Axoguard® Nerve Cap to fit the nerve stump, accounting for post-operative swelling and sufficient to allow easy insertion of the nerve stump into the device. Entubulation should be conducted in accordance with the product instructions for use (see IFU appendix C). Photographs of the surgical site, neuroma prior to resection and post-treatment (i.e. surgical implant or resected end) should be taken, if possible. Wound closure and immobilization will occur based on the institution's standard of care. Subjects will be followed for a total of 12 months post-operatively. Standardized assessments will occur at each visit. Study assessment time points are summarized below and in the Schedule of Assessments (see Appendix B).

3.9.1 Visit 1: Pre-Operative Screening [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 the Pre-Operative Screening visit

1. Assess Inclusion/Exclusion criteria
2. Obtain relevant vital signs (height / weight)
3. Identify relevant medical history
4. Demographics
5. Assess for Neuroma
6. Pain Assessments (VAS, PROMIS®) prior to nerve block
7. Pain Assessment (VAS) post nerve block (if applicable)
8. Quality of Life Questionnaires (FHSQ [redacted]
9. Concomitant Medication review and Daily Pain Medication Diary issuance (treatments including quantity and class of pain medications, dispense and review with subject)
10. Dispense Daily Pain Diary (review instructions with subject)
11. For subjects with multiple neuromas, additional Neuroma Information must be captured for each neuroma treated.

3.9.2 Visit 2: Operative Day, Day 0 [redacted]

The following will be collected during the Operative Day:

1. Verify Inclusion/Exclusion criteria
2. Obtain Vital signs
3. Document Operative Information: description of nerve injury presentation and location, and implantation information – see sequence below[19]
4. Randomization (comparative study only)
5. Pain Assessments (VAS, PROMIS®) prior to nerve block, if not performed during screening
6. Pain Assessment (VAS) post nerve block, if not performed during screening
[redacted]
8. Concomitant Medication review and Daily Pain Medication Diary review (treatments including quantity, quality and class of pain medications, review with subject and re-educate if needed)
9. Daily Pain Dairy (review with subject prior to Pain Assessments, re-educate if needed)
10. Adverse Events review

[redacted]

[redacted]

The following sequence of steps will take place intraoperatively for the Nerve Cap group:[19]

1. After debridement and mobilization of the nerve stump, determine the nerve diameter in millimeters (mm).
2. Select an Axoguard® Nerve Cap to fit the nerve stump, accounting for post-operative swelling and to allow easy insertion of the nerve stump into the device. If there is no Axoguard® Nerve Cap that matches the diameter of the nerve stump, select the device that is one size larger.
3. Hemostasis of the proximal nerve stump must be achieved prior to beginning the entubulation procedure. If a tourniquet is used, release the tourniquet and achieve hemostasis before entubulating.
4. Open the outer carton and remove the chevron pouch. Using standard aseptic technique, open the pouch and pass the inner tray into the sterile field for further handling.
5. Open the tray and fill the pre-molded reservoir with room temperature sterile saline or sterile Lactated Ringer's solution. Allow the Axoguard® Nerve Cap to hydrate for at least 10 seconds or until the desired handling characteristics are achieved, but not more than 20 minutes. NOTE: Small diameter Axoguard® Nerve Caps may need to be hydrated by flushing the lumen of the cap with solution. Care should be taken to avoid puncturing the Axoguard® Nerve Cap during this process.
6. Transfer the Axoguard® Nerve Cap from the reservoir and entubulate approximately 3-5 mm of the nerve stump into the Nerve Cap. Entubulate the stump by passing the suture (non-absorbable) through the wall of the tube from outside to inside at least 2 mm from the edge. Then pass the suture transversely through the epineurium of the nerve stump at a distance of at least 1 mm from the cut nerve face. Reverse the suture and pass it through the wall of the Axoguard® Nerve Cap by pulling the suture so that the nerve stump is drawn into the cap. Ensure that the nerve stump face is linearly aligned within the cap. To reduce the potential risk for misalignment, avoid abutting the nerve stump up to or inserting past the internal partition.
7. Tie suture securely being careful not to generate excess tension at the suture site. If desired, add sutures to secure the device to the nerve stump.
8. The lumen of the Axoguard® Nerve Cap may be gently filled/flushed with sterile saline or Lactated Ringer's solution. Ensure the nerve stump is not expelled from the tube while irrigating the lumen.
9. Once the Axoguard® Nerve Cap is securely sutured onto the nerve stump, the distal tab of the Nerve Cap may be sutured to a plane of surrounding soft tissue if desired (e.g., muscle or fascia). Tie the suture so that it is secure but avoid generating tension on the nerve when securing.
10. Prior to surgical site closure, visually confirm final alignment of the nerve within the cap.
11. Close the surgical site as required by your institutional practices or professional judgement concerning patient care.
12. Discard any unused portions of the Axoguard® Nerve Cap according to institutional guidelines for biological waste.

3.9.3 Visit 3: Post Operative Visit, Day 14/Week 2 [redacted]

Visit 3 (Week 2) is a safety visit and the following will be performed.

1. Obtain relevant vital signs (height / weight)
2. Post-Operative Care
3. Wound Assessment (safety check - remove sutures, wound check, etc.)
4. Pain Assessments (VAS, PROMIS®)
5. Concomitant Medication review and Daily Pain Medication Diary review (treatments including quantity and class of pain medications, review with subject and re-educate if needed, dispense new diary)
6. Daily Pain Diary (review with subject, re-educate if needed, dispense new diary)
7. Adverse events review

[redacted]

3.9.4 Visits 4: Months 1 [redacted]

The following will be performed at Visits 4:

1. Obtain relevant vital signs (height / weight)
2. Wound Assessment
3. Pain Assessments (VAS, PROMIS®)
4. Quality of Life Questionnaires (FHSQ [redacted]
6. Concomitant Medication review and Daily Pain Medication Diary review (treatments including quantity and class of pain medications, review with subject and re-educate if needed, dispense new diary)
7. Daily Pain Diary (review with subject, re-educate if needed)
8. Adverse Events review

[redacted]

3.9.5 Visits 5-7: Months 3, 6, 9 [redacted]

The following will be performed at Visits 5 through 7:

1. Obtain relevant vital signs (height / weight)
2. Pain Assessments (VAS, PROMIS®)
3. Quality of Life Questionnaires (FHSQ [redacted]
5. Concomitant Medication review and Daily Pain Medication Diary review (treatments including quantity and class of pain medications, review with subject and re-educate if needed, dispense new diary)
6. Daily Pain Diary (review with subject, re-educate if needed)
7. Adverse Events review

[redacted]

3.9.6 Visit 8: End of Study/Early Termination Visit, Month 12 [redacted]

The following will be performed at Visit 8/End of Study/Early Termination:

1. Obtain relevant vital signs (height / weight)
2. Wound Assessment
3. Pain Assessments (VAS, PROMIS®)
4. Quality of Life Questionnaires (FHSQ [redacted]

[redacted]

6. Concomitant Medication review and Daily Pain Medication Diary review (treatments including quantity and class of pain medications, review with subject)
7. Daily Pain Diary (review with subject)
8. Adverse Events review

[redacted]

3.10 Subject/Study Discontinuation

3.10.1 Screen Failures

A screen failure is defined as subject from whom informed consent is obtained, but

- Inclusion/Exclusion criteria are not met, or
- Subject was unable to be randomized, or
- Subject withdrew consent prior to randomization/surgical intervention.

3.10.2 Subject Discontinuation

Subjects may end their participation in the study at any time for any reason(s). The reason for discontinuation should be documented.

Early termination will be defined as any post-randomization study termination prior to completion of the Month 12 assessment. 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 have not completed the study and who are unable to be contacted or for whom the reason for discontinuation is unknown will be considered "lost to follow-up". The site will make three attempts to contact the subject by either telephone, certified mail or by an alternative method. The site may continue to try to achieve appropriate follow-up until the 12 month follow-up visit [redacted]. Because these follow-ups typically only require the collection of pain assessments, Quality of Life assessments, Daily Pain Medication Diary, and Daily Pain Diary, the assessments may be captured via phone or returned to the site electronically or by mail.

3.10.3 Termination 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 an 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, Corp., 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 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 Adverse Event Definitions

An adverse event (AE) is defined as any untoward event (including abnormal lab findings) experienced by a subject (*whether or not considered product-related by the Investigator or Sponsor*) after the patient consents to participate in the trial. All AEs that occur during or after study product implantation/device insertion must be recorded in the subject's medical record and reported on the adverse event CRF.

4.2 List of Anticipated Adverse Events

Consistent with the subject's informed consent form and the risk analysis section of this protocol, the following adverse events are known 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; and/or
- numbness

4.3 Severity of Adverse Events

Adverse events will be graded for severity and noted in the description of the event using the NCI (NIH)-developed Common Terminology Criteria for Adverse Events (NCI_CTCAE), Version 5.0. In addition, any AE associated with subject termination from the study must be reported according to IRB requirements. The following severity grades (1-5) shown below in table 4-1 will be used in assessing adverse events using the CTCAE V5.0 as a guiding reference:

Table 4.3–1: Severity of Adverse Events

Grade	Description
Grade 1 (Mild)	Asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated

Grade 2 (Moderate)	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3 (Severe)	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4 (Life Threatening)	Life-threatening consequences; urgent intervention indicated
Grade 5 (Death)	Death related to AE

4.4 Relationship to Study Product or Control Procedure

The Investigator will assess the relationship of each adverse event to the study product and study procedure. using the criteria outlined in Table 4.4-1.

Table 4.4–1: Relationship of Adverse Events to Study Product or Control Procedure

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 device 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 or by environmental or toxic factors; or 2) it follows a reasonable temporal sequence from administration of study device; or, 3) it follows a known pattern of response to the study device.
Probable	An AE considered, with a high degree of certainty, to be related to the study device. An AE may be considered probably related to study device if: 1) it cannot be reasonably explained by the known characteristics of the subject's clinical state or by environmental or toxic factors; and at least one of the following is true: 2) it follows a reasonable temporal sequence from administration of study device; 3) it follows a known pattern of response to study device; 4) it disappears or decreases upon removal
Definitely Related	An AE that is clearly and uncontrovertibly due to study device.

4.5 Adverse Event Reporting Procedures

The Investigator is responsible for recording and reporting all Adverse Events observed or reported during the study, regardless of their relationship to the study product or their clinical significance. Subjects will be instructed to contact the site Investigator at any time if symptoms develop. The adverse event reporting window will begin at the time the subject signs the informed consent form and will continue throughout the study and up to 30 days following the End of Study visit. The Investigator is required to completely document all adverse events in detail in the subject's medical record (source documents) and report the event on the Adverse event CRF. Whenever possible, the AE will be

recorded using standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions.

Concurrent illnesses that are present at or before study device administration, which manifest with the same severity, frequency, or duration subsequent to study device administration, need not be recorded as AEs. Similarly, signs or symptoms related to a pre-existing disease (prior to patient consenting) need not be recorded as AEs and will be recorded in the medical history CRF. However, medical history events that increase in severity or duration must be reported on the AE CRF.

Each AE must be promptly recorded and sufficiently documented by the Investigator or a qualified designee, even if the AE is assessed by the Investigator as unrelated to therapy with study device. The Investigator or qualified designee should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms. Each AE must also be described by date and time of onset, date and time of cessation, frequency (intermittent or continuous), the action taken (change in study device, concomitant medication, etc.), and outcome. In addition, the site Investigator must evaluate all AEs with respect to their severity and relationship to the study device according to the definitions given in the above tables 4-1 and 4-2.

4.6 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that occurs per the following definition:[39]

- Results in death;
- Is immediately life threatening – In the opinion of the site Investigator, the participant was at substantial risk of dying at the time of the event, or use or continued use of the device might have resulted in the death of the subject;
- Requires in-patient hospitalization or prolongation of existing hospitalization.Complications that occur during hospitalization are adverse events, and if a complication prolongs hospitalization, the event is considered serious. Emergency room visits that do not result in overnight hospital admissions should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage);
- Results in disability or Permanent Damage - substantial disruption of a person's ability to conduct normal life functions, i.e., resulted in a significant, persistent or permanent change, impairment, damage or disruption in body function/structure, physical activities and/or quality of life;
- Results in a Congenital Anomaly/Birth Defect - suspect that exposure to the device prior to conception or during pregnancy may have resulted in an adverse outcome in the child; or
- Requires Intervention to Prevent Permanent Impairment or Damage – medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of the device.
- Other Serious (Important Medical Events) - when the event does not fit the other outcomes, but the event may jeopardize the subject and may require medical or surgical intervention

(treatment) to prevent one of the other outcomes. Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

4.6.1 Reporting Serious Adverse Events

All SAEs must be reported immediately to the Sponsor or designee (within 24 hours of awareness)Serious Adverse Event forms should be submitted to:

Ivica Ducic, MD PhD
Axogen, Corp.
Medical Affairs
13631 Progress Blvd; Suite 400
Alachua, FL 32615
[redacted]

The site Investigator or designee may also be required to notify the IRB/Ethics Committee and appropriate regulatory body, as required per IRB/Ethics Committee guidelines. The SAE report and CRF should contain all adverse event information available at the time of event onset. As updates become available, the SAE report and CRF should be updated appropriately until the event is resolved including whether or not the event is required to be reported to the local/central IRB (based on local/central IRB reporting guidelines). 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 site Investigator's assessment on the probable cause of the event will also be included.

Subjects experiencing a SAE or medical emergency 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 Investigator and/or attending physician. The SAE will be followed until resolved or until medically stabilized.

4.7 Unanticipated Adverse Device Effects (UADE)

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

4.7.1 Reporting of Unanticipated Adverse Device Effects (UADE)

The Investigator should report any unanticipated adverse device effects to the Sponsor and the IRB as soon as possible, but no less than 10 working days after the site Investigator first learns of the UADE. The Sponsor must immediately conduct an evaluation of the UADE and determine whether the UADE presents an unreasonable risk to the subject. If an unreasonable risk is concluded, the Sponsor shall terminate all or part of the investigation as soon as possible but no later that 5 working days after the Sponsor make the determination and no later than 15 working days after the Sponsor first learns of the effect.

4.8 Follow-up of Adverse Events

All adverse events ongoing at the final study visit will be followed by the site 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 site Investigator does not expect any further improvement or worsening of the AE. On the last clinical study day, the 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 site Investigator will continue to report any significant follow-up information to the Sponsor or designee.

All SAEs that occur up to 30 days following the subject's last study assessment must be reported immediately to the medical monitor.

4.9 Review of Safety Information

The Sponsor shall promptly review all information relevant to the safety of the study device 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.

5. STATISTICAL CONSIDERATIONS

Descriptive statistical methods will be used to summarize the data from this study. 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. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted by 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 investigative site source documentation supporting the CRF data, such as laboratory or hospital records, physician dictations, nurse notes, any study-related subject logs, subject diaries and/or completed questionnaires must be readily available to verify entries in the CRF.

Any investigative site source document (including laboratory reports, hospital records, etc. subsequent to SAEs, etc.) electronically transmitted are to be de-identified and contain no subject 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 the beginning of subject 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 Axoguard® Nerve Cap compared to neurectomy with respect to VAS (visual analog scale) pain score will be conducted using closed testing procedures. [redacted]

[redacted]

5.4 Sample Size Estimates

A total of 101 subjects at up to 10 sites may be enrolled to control for site effects [redacted].

For the pilot study, 15 evaluable subjects will first be selected to receive the open label Axoguard® Nerve Cap. [redacted]

For the comparative study, 86 evaluable subjects will then be selected for enrollment. [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.

5.5.1 Intent-To-Treat Population

The ITT population will include all subjects who were randomized, received the study device or underwent neurectomy, and completed at least one post-baseline assessment of efficacy. Subjects will be analyzed in the 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 VAS change in the Axoguard® Nerve Cap group for the testing of the null hypothesis H_{0B}.

5.5.2 Safety Population

The safety population will include all subjects who had the study device inserted. This population will be used for all safety analyses.

5.5.3 Per Protocol Population

The Per Protocol population will include all subjects in the ITT population who have no major protocol violations [redacted] 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. The pilot phase data will be included along with the comparative phase data in the final data analyses.

5.7 General Issues for Statistical Analysis

5.7.1 Multiple Comparisons and Multiplicity

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. Mann-Whitney U tests will be used to compare baseline data to ensure poolability across centers.

As the final data analysis is to be conducted using blinded group data, no adjustment for type I error is necessary for analysis. As the tests of non-inferiority and superiority are being performed in a closed testing procedure, there will be no adjustment for multiple secondary endpoints; a step-down procedure will be utilized in the assessment of the secondary efficacy endpoints:

1. VAS score at 1, 3, 6, 9 and 12 months compared to baseline
2. PROMIS® score at 1, 3, 6, 9 and 12 months compared to baseline
3. FHSQ score at 1, 3, 6, 9 and 12 months compared to baseline
4. Quantity, quality and class of pain medication use at 1, 3, 6, 9 and 12 months compared to baseline

   Quantity class of pain medication used for end-neuroma pain

Rate of recurrence of symptomatic neuroma

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

These analyses may be stratified to identify other important factors which may impact nerve recovery such as ag [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, pain assessments, concomitant treatments, quality of life assessments will be summarized descriptively.

5.8 Efficacy Analyses

5.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint for both the pilot and comparative studies will be the change of VAS score at 3 months compared to baseline for subjects in both the Axoguard® Nerve Cap study arm and the neurectomy control arm.

5.8.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for the comparative study are VAS, PROMIS® and FHSQ scores at months 1, 3, 6, 9 and 12 compared to baseline; and quantity and class of pain medication use at months 1, 3, 6, 9, and 12 months compared to baseline for subjects assigned to the Axoguard® Nerve Cap. The secondary efficacy endpoints for the comparative study are VAS, PROMIS® and FHSQ scores at months 1, 3, 6, 9 and 12 compared to baseline; and quantity, quality and class of pain medication use at months 1, 3, 6, 9, and 12 months compared to baseline for subjects in both the Axoguard® Nerve Cap study arm and the historical control neurectomy study arm.

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

[redacted]

[redacted]

5.8.3 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[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 Axoguard® Nerve Cap and neurectomy 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 CRF that occurs on or after the treatment 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 treatment. 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 reduction in pain by VAS score with the treatment of Axoguard® Nerve Cap is superior to the reduction in VAS score for neurectomy group [redacted] In addition, there should be no clinically significant difference of product related adverse events rates following implantation of Axoguard® Nerve Cap compared to neurectomy.

6. STUDY PRODUCT MANAGEMENT

6.1 Packaging and Labeling

Commercially available product will be used.

6.2 Handling, Storage, and Disposal

Per product specifications as defined in the Instructions for Use (see Appendix C).

7. RECORDS MANAGEMENT

7.1 Data Collection

During each subject's visit, the Investigator or designee shall document all significant observations. Information from the source documents will be promptly transcribed to either a paper case report form (CRF) document or an electronic data capture system (EDC) via electronic CRFs.

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 study personnel 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 site 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 subject's clinical record at the site and a copy shall be given to the subject and/or legally authorized representative. All Daily Pain Diaries and Concomitant and Pain Medication Diaries will be collected from the site by the sponsor representative or designee and may be included in the final data analysis.

7.3 File Management at the Study Site

It is the responsibility of the site Investigator to ensure that the site files are adequately and accurately maintained in accordance with Section 8 of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) FDA regulations and ISO 14155:2011.

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. Study sites must obtain approval from the study sponsor prior to discarding any study records.

8. QUALITY CONTROL AND QUALITY ASSURANCES

8.1 Data Management Considerations

Data analysis will be overseen by the Sponsor's Data Management Team. All data associated with this study will be held to a 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 Management Team 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 is maintained.

Quality control checks will be established for each data procedure to ensure accuracy and to preserve the integrity of the data. Onsite interim monitoring visits will be conducted by the Sponsor's Clinical Research Associate (CRA).

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 a contact log to include telephone and written communications.

8.3 Auditing

The Sponsor or Regulatory representatives 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, logs/forms, training and qualifications. The site Investigator agrees to participate with audits conducted.

Regulatory authorities may audit the site Investigator or clinical site. The site Investigator should contact the Sponsor of any such audits, whether the audit is related to the study, immediately upon notification 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, ICH and GCP Guidelines, ISO 14155:2011 and all other applicable regulatory requirements.

The study protocol and the written informed consent form must receive a favorable review and/or approval from the governing IRB/IEC with the responsibility to approve research for the study site. The site Investigator will not participate in the approval process of a clinical study he/she is conducting. If the site Investigator is an IRB/IEC member, the written approval must indicate such non-participation.

The site Investigator will submit study status reports to the IRB/IEC in accordance with local IRB/IEC requirements. The site Investigator must notify the IRB/IEC in writing of the interruption and/or completion of the study. The site 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 site Investigator will promptly report to the IRB/IEC all unanticipated problems involving risks to subjects or others. The site 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

a final clinical study report will be prepared at the completion of the study. This report will be provided to the collaborative site Investigators.

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 written permission from Axogen, Corp. However, authorized regulatory officials and Axogen, Corp. 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, Corp.

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 required. Under the Health Insurance Portability and Accountability Act (HIPAA), Axogen, Corp. is committed to upholding the security and privacy provisions for protected health information (PHI) of the Act (1996) and the additional obligations introduced by the HIPAA Omnibus Final Rule (2013).

12. REGULATORY CONSIDERATIONS

12.1 Amendments

The site Investigator will not make any changes to this protocol without prior written consent from the Sponsor and subsequent approval by the IRB/IEC. Any 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 site 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' site 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.

When, in the judgment of the chairman of the IRB/IEC, the site 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, re-consenting will be obtained from each enrolled subject at the onset of their next scheduled study visit.

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 site Investigator or designee must notify the sponsor as soon as possible. This will allow for an early, joint decision regarding the subject's continuation in the study. This decision will be documented by the site Investigator and the Sponsor and be reviewed by the study monitor.

12.3 Sponsor and Site Investigator Responsibilities

The Sponsor and participating site Investigators shall be responsible for the conduct of this clinical study in compliance with the study protocol, FDA 21 CFR parts 50, and 56, ICH/GCP guidelines (ICH E6), ISO 14155:2011, and applicable local regulatory requirements and study specific trial agreements. All site Investigators will agree to comply with the protocol and these responsibilities by signing the Investigator Agreement in Appendix A.

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APPENDIX A: INVESTIGATOR AGREEMENT

Agreement Signatures

I have read and understand the protocol 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 Corporation'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 agree to allow Axogen, Corp. 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, Corp. any adverse events in accordance with the terms of Axogen, Corp. (or designee's) Clinical Trial Agreement (CTA). I further agree to provide all required information regarding financial certification or disclosure to Axogen, Corp. for all site Investigators and site 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 (GCPs) and other GCP regulations (including ISO 14155:2011), and local regulatory requirements.

Printed Name Principal Investigator	Date	Signature Principal Investigator	Date

APPENDIX B: SCHEDULE OF ASSESSMENTS

Assessments	Visit 1 Screening [redacted] Pre-operative	Visit 2 Operative Day 0 Operative	Visit 3 Week 2 Day 14 [redacted] Post-Op	Visit 4 Week 4 Month 1 Day 30 [redacted] Assessment	Visit 5 Week 12 Month 3 Day 90 [redacted] Assessment	Visit 6 Month 6 Day 180 [redacted] Assessment	Visit 7 Month 9 Day 270 [redacted] Assessment	Visit 8 Month 12 Day 360 [redacted] EOS/ET
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Relevant Medical History	X							
Demographics	X							
Neuroma Information	X							
Relevant Vital Signs[1]	X	X	X	X	X	X	X	X
Operative Information		X						
Randomization[2]		X						
Post-operative Care			X					
[redacted]		[redacted]						
Wound Assessment			X	X				X
Pain Assessments[3]	X	X	X	X	X	X	X	X
Quality of Life Questionnaires[4]	X			X	X	X	X	X
[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daily Pain Medication Diary and Concomitant Medication Log [5]	X	X	X	X	X	X	X	X
Daily Pain Diary	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] Vital signs to include weight, Height will only be recorded one time at visit 1
[2] Comparative study only
[3] Pain Assessments: VAS and PROMIS® (for V2 Operative Day 0, VAS and PROMIS® performed prior to nerve block, and VAS performed again post nerve block – ONLY if nerve block is performed during screening visit).
[4] Quality of Life Questionnaires include: FHSQ[redacted]
[5] Daily Pain Medication Diary (including quantity, quality and class of pain medications) related to the nerve injury should be collected during Screening and Operative day and any changes/additions should be collected during the study.

APPENDIX C: INSTRUCTIONS FOR USE Axoguard® Nerve Cap (LB-580 R04)

Document Number: LB-0580 Title: AxoGuard Nerve Cap Instructions for Use Revision: 04 Vault: Label and Literature-rel

AxoGuard® NerveCap

Instructions for Use

Carefully read all instructions prior to use. Observe all warnings and precautions noted throughout these instructions. Failure to do so may result in complications.

AxoGen.
Customer Care: 888.AxoGen1 (888.296.4361)
International: 1.386.462.6800
CustomerCare@AxoGenInc.com

DESCRIPTION

The AxoGuard® Nerve Cap is a surgical implant that is a tubular device with one open end, one sealed end (cap) and internal channels designed to provide protection for a peripheral nerve end or stump where repair is unattainable or not desired. The device isolates the nerve stump from the surrounding soft tissue bed by pulling the nerve into the tube and suturing the nerve within the cap. The end of the cap has a suturable tab to allow the surgeon to suture the device to surrounding tissue.

AxoGuard® Nerve Cap is an extracellular matrix (ECM) and is fully remodeled during the healing process. When hydrated, AxoGuard® Nerve Cap is easy to handle, soft, pliable, nonfriable and porous. AxoGuard® Nerve Cap is flexible and pliable to accommodate movement of the joints and surrounding soft tissues and has sufficient mechanical strength to hold appropriately sized non-absorbable suture. AxoGuard® Nerve Cap is provided sterile, for single use only, and in a variety of sizes to meet clinical needs.

INDICATIONS FOR USE

AxoGuard® Nerve Cap is indicated to protect a peripheral nerve end and to separate the nerve from surrounding environment to reduce the development of symptomatic or painful neuroma.

RX Only

CAUTION: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician. This product is intended for use by trained medical professionals.

CONTRAINDICATIONS

AxoGuard® Nerve Cap is derived from a porcine source and should not be used for patients with known sensitivity to porcine derived materials. AxoGuard® Nerve Cap is contraindicated for use in any patient for 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.

AxoGuard® Nerve Cap should not be implanted directly under the skin.

NOTE: This device is not intended for use in vascular applications.

PRECAUTIONS

- This device is designed for single use only. **Do not re-sterilize the device.**
- Discard all open and unused portions of the device.
- Device is sterile provided the package is dry, unopened and undamaged. Do not use device if the package seal is damaged or open.
- Discard device if mishandling has caused possible damage or contamination, or if the device is past its expiration date.
- Device should be hydrated prior to suturing.
- Avoid crushing, crimping, kinking or other damage due to application of surgical instruments such as forceps, needle holders and scissors during handling of the device.
- Avoid tension on the nerve end.
- Ensure sufficient healthy soft tissue is available to cover the AxoGuard® Nerve Cap in order to avoid protrusion or wound dehiscence.

POTENTIAL COMPLICATIONS

As with any surgical procedure, complications can occur such as pain, infection, decreased or increased nerve sensitivity, and complications associated with use of aesthesia.

If any of the following conditions occur and cannot be resolved, careful removal of the device should be considered:

- Infection
- Allergic reaction
- Acute or chronic inflammation (initial application of surgical graft materials may be associated with transient, mild, localized inflammation).

ADVERSE EVENTS

Adverse events associated with the use of AxoGuard® Nerve Cap may include but are not limited to:

- Failure to reduce symptomatic neuroma pain:
- Transitory local irritation;
- Infection;
- Allergy;
- Delayed wound healing;
- Protrusion.

STORAGE

AxoGuard® Nerve Cap should be stored in a clean, dry location between 10 – 30°C/50 – 86°F. Use the device prior to the "Use By" date specified on the package. The "Use By" date is in the form Year-Month-Day.

STERILIZATION

AxoGuard® Nerve Cap has been sterilized with ethylene oxide (EO).

HOW SUPPLIED

AxoGuard® Nerve Cap is supplied in a plastic tray within a sterile pouch. The pouch is heat-sealed to provide a sterile barrier and has a peelable seal. Contents of the package are guaranteed sterile unless the package is opened or damaged. AxoGuard® Nerve Cap and packaging does not contain natural rubber latex.

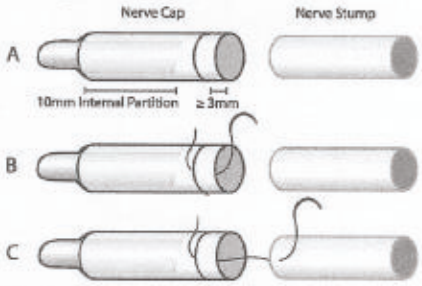
Do not use if the peel pouch appears to be open or damaged. Multiple Patient labels with product code, lot number and expiration date are provided for patient records. A Product Feedback Form is also provided and can be returned back to AxoGen as indicated on the card.

Suggested Instructions for Use (General Procedure). These recommended Instructions for Use are designed to serve as a general procedure. They are not intended to supersede the institutional protocols or professional judgement concerning patient care.

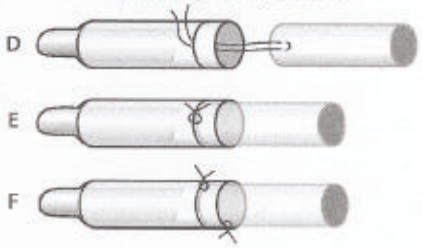
NOTE: Always handle AxoGuard® Nerve Cap using aseptic technique. Minimize contact with latex gloves. Do not trim the tab of the AxoGuard® Nerve Cap prior to implantation.

Document Number: LB-0580 Title: AxoGuard Nerve Cap Instructions for Use Revision: 04 Vault: Label and Literature-rel

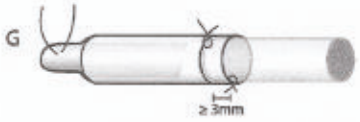
1. After debridement and mobilization of the nerve stump, determine the nerve diameter in millimeters (mm).
2. Select an AxoGuard® Nerve Cap to fit the nerve stump, accounting for post-operative swelling and to allow easy insertion of the nerve stump into the device. If there is no AxoGuard® Nerve Cap that matches the diameter of the nerve stump, select the device that is one size larger.
3. Hemostasis of the proximal nerve stump must be achieved prior to beginning the entubulation procedure. If a tourniquet is used, release the tourniquet and achieve hemostasis before entubulating.
4. Open the outer carton and remove the chevron pouch. Using standard aseptic technique, open the pouch and pass the inner tray into the sterile field for further handling.
5. Open the tray and fill the pre-molded reservoir with room temperature sterile saline or sterile Lactated Ringer's solution. Allow the AxoGuard® Nerve Cap to hydrate for at least 10 seconds or until the desired handling characteristics are achieved, but not more than 20 minutes. NOTE: Small diameter AxoGuard® Nerve Caps may need to be hydrated by flushing the lumen of the cap with solution. Care should be taken to avoid puncturing the AxoGuard® Nerve Cap during this process.
6. Transfer the AxoGuard® Nerve Cap from the reservoir and entubulate approximately 3-5 mm of the nerve stump into the Nerve Cap. Prior to final placement and suturing of the nerve stump, assess the need to trim the AxoGuard® Nerve Cap. If trimming is desired, ensure that adequate length is maintained so that the nerve does not abut against the internal partition. Entubulate the stump by passing the suture (non-absorbable) through the wall of the tube from outside to inside at least 2 mm from the edge. Then pass the suture transversely through the epineurium of the nerve stump at a distance of at least 1 mm from the cut nerve face. Reverse the suture and pass it through the wall of the AxoGuard® Nerve Cap by pulling the suture so that the nerve stump is drawn into the cap. Ensure that the nerve stump face is linearly aligned within the cap. To reduce the potential risk for misalignment, avoid abutting the nerve stump up to or inserting past the internal partition. **See Figure 1 A, B and C.**



7. Tie suture securely being careful not to generate excess tension at the suture site. If desired, add additional sutures to secure the device to the nerve stump. **See Figure 1 D, E and F.**



8. The lumen of the AxoGuard® Nerve Cap may be gently filled/flushed with sterile saline or Lactated Ringer's solution. Ensure the nerve stump is not expelled from the tube while irrigating the lumen.
9. Once the AxoGuard® Nerve Cap is securely sutured onto the nerve stump, the distal tab of the Nerve Cap may be sutured to a plane of surrounding soft tissue if desired (e.g., muscle or fascia). Tie the suture so that it is secure, but avoid generating tension on the nerve when securing. **See Figure 1 G.**



10. Prior to surgical site closure, visually confirm final alignment of the nerve within the cap.
11. Close the surgical site as required by your institutional practices or professional judgement concerning patient care.
12. Discard any unused portions of the AxoGuard® Nerve Cap according to institutional guidelines for biological waste.

INQUIRIES

For additional information, to place an order, or to report errors, accidents or adverse reactions, contact:
AxoGen Customer Care: 888.Axogen1 (888.296.4361), or
Email: CustomerCare@AxoGenInc.com

RETURNED GOODS POLICY:

Authorization from AxoGen Customer Care must be obtained prior to returning product to AxoGen Corporation. Sterile product must be returned in unopened, undamaged cartons and packaged to prevent damage.

SYMBOLS USED ON LABELING

STERILE EO	Sterilized using ethylene oxide		Manufacturer
	Temperature limit	MR	MR Safe
	Attention, see instructions for use	Rx	Prescription only
	Do not reuse		Made in the USA
	Use by date		

Manufactured for:

AxoGen.

AxoGen Corporation
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