AWARD NUMBER: W81XWH-19-1-0487

TITLE:

Tolerability and Feasibility Pilot Clinical Study of a Large-Diameter Nerve Cap for Protecting and Preserving Terminated Nerve Ends

PRINCIPAL INVESTIGATOR: Ivica Ducic, MD, PhD

CONTRACTING ORGANIZATION: AxoGen Inc.

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Fort Detrick, Maryland 21702-5012

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1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
October 2023	Annual	30SEPT22 - 29SEPT23

4. TITLE AND SUBTITLE

Tolerability and Feasibility Pilot Clinical Study of a Large-Diameter Nerve Cap for Protecting and Preserving Terminated Nerve Ends

5a. CONTRACT NUMBER
W81XWH-19-1-0487

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER:

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

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12. DISTRIBUTION / AVAILABILITY STATEMENT

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The primary objective of this study is to evaluate Axoguard Nerve Cap in large diameter sizes (5mm - 7mm) for protecting and preserving terminated large diameter nerve endings after limb trauma or amputation when immediate attention to the nerve injuries is not possible. The secondary objective of this study is to demonstrate proof-of-concept that large diameter nerve caps can prevent or reduce the formation of symptomatic neuromas in large diameter nerve endings after trauma or amputation when immediate attention to the nerve injuries is not possible.

Study Aims:

1. Demonstrate safety of the Axoguard Nerve Cap from implantation through 15-months; (Safety Endpoint)

2. Demonstrate the role of Axoguard Nerve Cap in protecting and preserving terminated nerve endings after limb trauma or amputation when immediate attention to these injuries is not possible by providing easier dissection and access to terminated nerve endings to optimize subsequent reconstructive procedures, if performed. (Primary End Point)

3. Demonstrate reduction or mitigation of nerve pain and its effect on limb function (as measured by BAM-ULA and/or Timed Up & Go and/or 10-meter walk test) associated with segmental nerve loss (Secondary End Point)

4. Determine recruitment feasibility and protocol refinement opportunities for next phase clinical studies of this new treatment.

15. SUBJECT TERMS
Symptomatic neuroma; amputation; Axoguard Nerve Cap®

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRDC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	UU	13	**19b. TELEPHONE NUMBER** *(include area code)*
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1. INTRODUCTION:

The primary objective of this study is to evaluate Axoguard Nerve Cap® in large diameter sizes (5mm - 7mm) for protecting and preserving terminated large diameter nerve endings after limb trauma or amputation when immediate attention to the nerve injuries is not possible. The secondary objective of this study is to demonstrate proof-of-concept that large diameter nerve caps can prevent or reduce the formation of symptomatic neuromas in large diameter nerve endings after trauma or amputation when immediate attention to the nerve injuries is not possible.

2. KEYWORDS:

Amputation; symptomatic neuroma; Axoguard Nerve Cap®

3. ACCOMPLISHMENTS:

What were the major goals of the project?

1. Study start-up: protocol finalization; IRB submission, review and approval; study database preparation: build database, validate database, complete eCRF completion guidelines; 100% completed.
2. Study initiation, subject recruitment, enrollment and follow- up, and study conduct (monitoring activities): Both sites (TTUHSC and MGH) are open to enrollment and screening of eligible subjects based in the inclusion/exclusion criteria are ongoing. Original target for completion: June 2022; Updated target: July 2025
3. Study Close-out: database preparations, QC audit, database lock, finalize tables and listings, Clinical study report: Original target: September 2022; Updated target: October 2025.

What was accomplished under these goals?

Study activities were significantly delayed due to the impact of the COVID-19 pandemic. Despite these delays, a number of study development activities were completed. Key accomplishments this period include: Subject enrollment, ongoing monitoring activities, subject safety monitoring, protocol amendment and obtained WCG-IRB (sIRB of record), OHRO and sub-site IRB approval, database updates and personnel training.

1. Study Start-up: 100% complete

2. Study Initiation, subject enrollment, and study conduct:
    a. Subject enrollment: First subject enrolled on 14Mar2023, and fourth subject enrolled on 28Sep2023. (25% complete)
    b. Periodic site monitoring visits: First routine monitoring visit on 04Apr2023 (20% complete).

3. Protocol amendment (version 4.0):
    a. WCG-IRB (sIRB of record) approval was obtained on 07Jul2023.
    b. OHRO approval was obtained on 26Jul2023.
    c. Electronic Data Capture (EDC) system updates implemented.
    d. Source document case report forms completed.
    e. Site personnel training completed.

4. Study Close-out, Clinical Study Report (CSR) preparation review and finalization:
    a. Database preparations (0% complete)
    b. QC audit (0% complete)
    c. Database lock (0% complete)
    d. Finalize tables and listings (0% complete)
    e. Clinical Study Report (CSR) preparation, review, and finalization (0% complete)

What opportunities for training and professional development has the project provided?

Nothing to Report.

How were the results disseminated to communities of interest?

Nothing to Report.

1. Continue efforts for subject recruitment, subject enrollment and study conduct including subject follow-up and monitoring activities:
    a. Continue to capture follow-up visits according to protocol schedule of assessments.
    b. Conduct periodic site monitoring visits according to clinical monitoring plan.

4. **IMPACT:**

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report.

What was the impact on other disciplines?

Nothing to Report.

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS:

1. Potential subjects have not been meeting the Inclusion/Exclusion criteria.

2. The protocol is seeking to enroll young, healthy individuals having an amputation which limits enrollment. Increasing the age range would potentially increase chances of enrolment.

3. Relatively young, healthy individuals receiving amputations are not likely to choose to participate in a study that delays a TMR procedure. Treatment of amputees has changed since the creation of this protocol and amputees are now likely to receive TMR at the time of amputation or shortly thereafter rather than 6-12 months post amputation.

Actual or anticipated problems or delays and actions or plans to resolve them

Study start-up and initiation activities were significantly delayed due to the impact of the COVID-19 pandemic.

1. Potential subjects have not been meeting the Inclusion/Exclusion criteria of protocol version 3.0; hence sites have encountered enrollment challenges. The protocol was amended to version 4.0 to revise the I/E criteria and facilitate enrollment.
2. Protocol version 3.0 was seeking to enroll young, healthy individuals having an amputation which limits enrollment. The protocol amendment to version 4.0 increases the age range to ≥18 to ≤80 would potentially increase chances of enrolment.
3. Relatively young, healthy individuals receiving amputations are not likely to choose to participate in a study that delays a TMR procedure. Treatment of amputees has changed since the creation of this protocol and amputees are now likely to receive TMR at the time of amputation or shortly thereafter rather than 6-12 months post amputation. The protocol amendment to version 4.0 includes Regenerative Peripheral Nerve Interface (RPNI) as an option for secondary surgery (in addition to TMR) and inclusion of those with previous amputation that will be undergoing surgery to address terminated nerve ends to increase the rate of enrollment.
4. The list of prohibited medications and pregnancy criterion on version 3.0 was removed as that limited subject enrollment. The investigators provided guidance on this change to help increase enrollment.
5. Version 3.0 was limited to MRI as an imaging modality and the protocol amendment to version 4.0 has included CT scan as an alternative to those who have contraindications to MRI.

Changes that had a significant impact on expenditures

1. Expenditures in this reporting period were significantly less than anticipated due to related delays in study start-up and subject enrollment.
2. Due to challenges in enrolling subjects meeting I/E criteria, expenditures are significantly impacted.
3. Due to the significant delay in subject enrollment, no cost extension application was submitted and approved.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report.

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

  Journal publications.

  Nothing to Report.

Books or other non-periodical, one-time publications.

Nothing to Report.

Other publications, conference papers and presentations.

Nothing to Report.

- **Website(s) or other Internet site(s)**

Nothing to Report.

- **Technologies or techniques**

Nothing to Report.

- **Inventions, patent applications, and/or licenses**

Nothing to Report.

- **Other Products**

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Ray A. Rivera BSMT, MD*
Project Role:	*Clinical Trials Administrator*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*5*
Contribution to Project:	*Dr. Rivera performed overall study management ensuring adherence to study protocol. Conducted ongoing monitoring activities and personnel training.*
Name:	*Hiral Patel*
Project Role:	*Data Manager*
Researcher Identifier (e.g. ORCID ID):	*N/A*
person month worked:	*1.2*
Contribution to Project:	*Ms. Patel managed data management functions, EDC programming and User Acceptance Testing. Finalize database and release to production environment.*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

Premier Histology Lab
PO Box 18592
Boulder, CO 80308

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *N/A*

QUAD CHARTS:

Tolerability and Feasibility Pilot Clinical Study of a Large Diameter Nerve Caps for Protecting and Preserving Terminated Nerve Ends

W81XWH-18-PRORP-CTRA Log No: OR180222

PI: Ivan Ducic, MD **Org:** Axogen Corp. **Award Amount:** $ 1,211,638

Study/Product Aim(s)

- Detect safety and complications of AxoGuard® Nerve Cap during implant through post-op follow-up;
- Demonstrate the role of AxoGuard® Nerve Cap in protecting and preserving terminated nerve endings after limb trauma or amputation when immediate attention of these injuries is not possible and provides for easier dissection and access to terminated nerve endings to optimize subsequent reconstructive procedures.
- Demonstrate reduction or mitigation of nerve pain associated with segmental nerve loss prior to TMR procedure.
- Determine recruitment feasibility and protocol refinement requirements for next phase clinical studies of this new treatment.

Approach

Pilot study on tolerability and feasibility of the use of large (5-7mm) diameter, FDA cleared (510k K163446) AxoGuard® Nerve Cap in terminated nerves in candidates for targeted muscle reinnervation (TMR) undergoing TMR as a planned secondary procedure. The intent is to protect and preserve the maximum length of the nerve and provide for easier dissection in order to optimize the TMR procedure and provide proof of concept that large diameter nerve caps can prevent or reduce the formationof neuroma in terminated nerve ends.

Goals

- ❑ Milestone 1: Project planning, administrative activities, protocol submission, IRB review and approval, database preparation, study start-up
  - ❑ Original Target: Month 1-6 (March 2020)
  - ❑ Complete
- ❑ Milestone 2: Study initiation, subject enrollment and study conduct (Subjects enrolled, surgery performed, follow-up completed and study monitoring activities)
  - ❑ Original Target: Month 7-33 (June 2022)
  - ❑ Updated Target: July 2025
- ❑ Milestone 3: study Close-out and Clinical study report completed
  - ❑ Original Target: Month 34-36 (September 2022)
  - ❑ Updated Target: October 2025

Timeline and Cost

Activities	2019	2020	2021	2022	2023	2024	2025
Start-up Activities							
OHRO & sIRB Approval							
Subject Enrollment							
Subject Follow-up Period							
Data Analysis/Site Close out							
Clinical Study Report							
Estimated Budget ($K)	$20	$250	$100	$150	$350	$400	$350

Milestones/Accomplishments

- ❑ Milestone 1: Study Start-up: Protocol Finalization/IRB Preparations/Vendor Identification; Clinical Plan/Data Management Activities
  - ❑ Percent complete/Updated Target: 100% (April 2022); delayed due to Covid-19impact
- ❑ Milestone 2: Study Initiation: HRPO/IRB approvals/Contract Finalization/Clinical Site Training; First subject enrolled
  - ❑ Percent complete/Updated Target: 35% (July 2025); delayed due to Covid-19 impact
- ❑ Milestone 3: Study Close-out and Clinical Study Report
  - ❑ Percent complete/Updated Target: 0% (October 2025)
- ❑ Budget Expenditures to date:
  - ❑ Projected Expenditure: $570K
  - ❑ Actual Expenditure: $484K

Axogen Corporation Updated: 10/26/2023

9. APPENDICES: *N/A*