**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 Corporation, Alachua, FL

**REPORT DATE:** October 2022

**TYPE OF REPORT:** Annual

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

# REPORT DOCUMENTATION PAGE

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| 1. REPORT DATE | 2. REPORT TYPE | 3. DATES COVERED |
|---|---|---|
| October 2022 | Annual | 30Sep2021-29Sep2022 |

**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**
W81XWH-18-PRORP-CTRA

**5c. PROGRAM ELEMENT NUMBER: N/A**

**6. AUTHOR(S)**

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**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**
WS00215119

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

Axogen Corporation
13631 Progress Blvd, Ste. 400
Alachua, FL 32615

**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)**

**11. SPONSOR/MONITOR'S NUMBER(S)**

**12. DISTRIBUTION / AVAILABILITY STATEMENT**

Approved for Public Release, Distribution Unlimited

**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** | Unclassified | 13 | **19b. TELEPHONE NUMBER** *(include area code)* |
| Unclassified | Unclassified | Unclassified | | | |

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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 in Q2 2022.
2. Study initiation, subject enrollment and follow- up, and study conduct (monitoring activities): First site (TTU) was initiated in Q2 2022; second site (MGH) was initiated in Q3 2022. Both sites 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 2024
3. Study Close-out: database preparations, QC audit, database lock, finalize tables and listings, Clinical study report: Original target: September 2022; Updated target: September 2024.

**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: WCG-IRB (sIRB of record), HRPO and sub-site IRB approval, site initiation activities and personnel training

1. Study Start-up: 100% complete

2. Study Initiation, subject enrollment and study conduct:
    a. Initiate first site: Delayed due to COVID-19 (100% complete – March 2022)
    b. Initiate second site: Delayed due to COVID-19 (100% complete – April 2022)
    c. Subject enrollment: Delayed due to COVID-19 (0% complete)
    d. Periodic site monitoring visits: Delayed due to COVID-19 (0% complete).

3. 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.

*Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.*

1. Subject enrollment and study conduct including subject follow-up and monitoring activities:
    a. Initiate subject enrollment and follow-up visits
    b. Begin periodic site monitoring visits

***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.

*If there is nothing significant to report during this reporting period, state "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. Study start-up activities (specifically finalization of the study protocol, related documents, study database, IRB submissions, and CTA negotiations) were significantly delayed by over one year due to COVID-19 closures, travel restrictions, and personnel availability. We were aggressively pursuing these activities as COVID-19 restrictions began to lift.

2. Study initiation activities including IRB and HRPO approvals, site initiations, and enrollment activities were significantly delayed due to COVID-19 closures. The sIRB designation was delayed due to long processing times of sub-site reliance agreements. We have obtained approval from WCG-IRB, sIRB of record in December 2021 and HRPO approval for the study in February 2022.

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

4. 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.

5. 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.

**Changes that had a significant impact on expenditures**

1. Expenditures in this reporting period were significantly less than anticipated due to COVID-19 pandemic related delays in study start-up. These costs will be pushed into the next reporting period.
2. Due to challenges in enrolling subjects meeting I/E criteria, expenditures are significantly impacted.

**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 start-up and preparation activities for the project under Major Task Milestone 1* |
| *Funding Support:* | *N/A* |

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

A key Axogen personnel, Kyle Icke, PhD replaced John Reviere.

**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 2024
- ❑ Milestone 3: study Close-out and Clinical study report completed
  - ❑ Original Target: Month 34-36 (September 2022)
  - ❑ Updated Target: October 2024

**Timeline and Cost**

| Activities | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|---|---|
| Start-up Activities | | | | | | |
| HRPO and IRB approval | | | | | | |
| Subject Enrollment | | | | | | |
| Subject Follow-up Period | | | | | | |
| Data Analysis/Site close out | | | | | | |
| Clinical Study Report | | | | | | |
| **Estimated Budget ($K)** | $20 | $250 | $100 | $200 | $350 | $200 |

**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 2024); delayed due to Covid-19 impact
- ❑ Milestone 3: Study Close-out and Clinical Study Report
  - ❑ Percent complete/Updated Target: 0% (October 2024)
- ❑ Budget Expenditures to date:
  - ❑ Projected Expenditure: $570K
  - ❑ Actual Expenditure: $484K

Axogen Corporation Updated: 09/30/2022

## *9.* APPENDICES: *N/A*