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

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

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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
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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?

. Study start-up: protocol finalization; IRB submission, review and approval; study database preparation: build database, validate database, review and finalize SAP, complete eCRF completion guidelines; Study operations' preparations: finalize case report forms, finalized operations and training manual - to be completed by February 3, 2021

a. Investigator's meeting – not planned due to COVID-19 travel restrictions

. Study initiation, subject enrollment and study conduct: First site initiated by February 3, 2021; second site initiated by March 31, 2021. Subject enrollment will take place following site initiation and screening of eligible subjects based in the inclusion/exclusion criteria. Study conduct; periodic site monitoring visits, last patient/last visit (LPLV) will take place until ~June 1, 2023.

. Study Close-out: database preparations, QC audit, database lock, finalize tables and listings will take place until July 6, 2023

. Clinical Study report preparation, review and finalization will take place ~ August 9, 2023.

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: Protocol development | alignment with coordinating investigators, protocol finalization, sub-award and Clinical Trial Agreement negotiation, preparations for HRPO and sub-site IRB submissions, development of draft Case Report Forms, development of operational documents including clinical monitoring plan, and initiation of the study database build.

1. Study Start-up:
    - **a.** Study protocol finalization (100% complete)
    - b. IRB submission: HRPO and sub-site IRB submissions in development (25% complete)
    - c. Study database build initiated and pending eCRF finalization (80% complete); database validation (0% complete); Data Management Plan development and CRF completion guidelines (0% complete); Case Report Forms (eCRFs) drafted and undergoing final revisions (80% complete)
    - d. Investigator meeting postponed due to COVID-19 travel and gathering restrictions. Plans for a virtual investigator meeting are underway pending HRPO approval. (0% complete)
    - **e.** Execute sub-award clinical trial agreements: Site 1 CTA routing for signatures; site 2 CTA in final negotiations. (50% complete)

2. Study Initiation, subject enrollment and study conduct:
    - a. Initiate first site: Delayed due to COVID-19 (0% complete – targeted for completion by February 3, 2021)
    - b. Initiate second site: Delayed due to COVID-19 (0% complete – targeted for completion by March 31, 2021)
    - 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:
    - a. Database preparations (0% complete)
    - b. QC audit (0% complete)
    - c. Database lock (0% complete)
    - d. Finalize tables and listings (0% complete)

4. 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.

What do you plan to do during the next reporting period to accomplish the goals?

1. Study Start-up:
    a. IRB submission: HRPO and sub-site IRB submissions (December 2020)
    b. Study database build and eCRF finalization; database validation; Data Management Plan development and CRF completion guidelines; Case Report Forms (eCRFs) finalization (January 2021)
    c. Virtual Investigator meeting (due to COVID-19 travel and gathering restrictions) (February 2021)
    d. Execute sub-award clinical trial agreements (December 2020)

2. Study Initiation, subject enrollment and study conduct:
    a. Initiate first site: (February 2021)
    b. Initiate second site: (March 2021)
    c. Initiate subject enrollment (March 2021)
    d. Begin periodic site monitoring visits (March 2021)

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. The original project narrative defines the eligible subject age range from ≥ 18 to ≤ 35 years of age. We propose increasing the eligible age range to include patients ≥ 18 to ≤ 50 years in effort to improve patient catchment and timely enrollment of the study. This change is not expected to introduce any increased risk to participants, nor is it expected to adversely impact or significantly change the aims of the study. Additionally, the study investigators believe the proposed range increase remains representative of the ages expected within the military population.

2. In the original project proposal, Investigator Dr. Ian Valerio was listed as being affiliated with Ohio State University (OSU). Dr. Valerio has since left OSU to accept a position at Massachusetts General Hospital (MGH). He intends to continue his participation in the study at this new institution. MGH has also agreed to his participation and we do not anticipate this change will impact the previously agreed upon subaward budget amounts.

3. In addition, Dr. Valerio has requested to add a sub-investigator, Dr. Kyle Eberlin, to the MGH study team. This change will not impact the previously agreed upon subaward budget amounts.

4. The original project proposal included the use of an open source electronic data capture system (OpenClinica Community Edition - EDC) for data management. We have since learned that the open source version has limited capabilities necessary to support more complex eCRF structures and electronic validation procedures, and we have subsequently upgraded to the commercial 21CRF11 compliant version (OpenClinica enterprise edition | OC4 stack 11) which requires a monthly maintenance and operational fee. This fee will be invoiced towards the grant as 'Other Direct costs' with supporting documentation of EDC fees.

5. The original project proposal listed Florence Beck as the Clinical Research Manager. We have since experienced a personnel change beginning August 2020. John B. Reviere has now been assigned as the Clinical Research Manager. This change does not impact the previously approved grant award total.

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 approximately 6-months due to COVID-19 closures, travel restrictions, and personnel availability. We are aggressively pursuing these activities as COVID-19 restrictions begin to lift.

2. Study initiation activities including IRB approvals, site initiations, and enrollment activities were significantly delayed by approximately 6-months due to COVID-19 closures, travel restrictions, and personnel availability. We are aggressively pursuing these activities in parallel with review/approval by HRPO and sub-site IRBs. Additionally, we have proposed the previously reported changes in eligible subject age to increase enrollment catchment, which will provide the added benefit of reducing overall enrollment time to accommodate some of these delays.

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. The original project proposal included the use of an open source electronic data capture system (OpenClinica Community Edition - EDC) for data management. We have since learned that the open source version has limited capabilities necessary to support more complex eCRF structures and electronic validation procedures, and we have subsequently upgraded to the commercial 21CRF11 compliant version (OpenClinica enterprise edition | OC4 stack 11) which requires a monthly maintenance and operational fee. This fee will be invoiced towards the grant as 'Other Direct costs' with supporting documentation of EDC fees.

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

Significant changes in use or care of human subjects

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?

Nothing to Report.

What other organizations were involved as partners?

Nothing to Report.

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 formation of neuroma in terminated nerve ends.

Photo showing the 510(k) cleared AxoGuard® Nerve Cap

Accomplishments: TBD

Timeline and Cost

Activities	19	20	21	22	23
Start-up Activities					
HRPO and IRB approval					
Subject Enrollment					
Subject Follow-up Period					
Data Analysis/Site close out					
Clinical Study Report					
Estimated Budget ($K)	$150	350	$350	$350	$200

Updated: 10/21/2020

Goals/Milestones

CY19 Goal –Study Start -up

☐Protocol Finalization/IRB preparations/Vendor Identification

☐Clinical Plan/ Data Management Activities

CY20 Goals – Study Initiation

☐HRPO/IRB approvals/Contract Finalization/Clinical Site Training

CY21 Goal – Ongoing Enrollment

☐First Subject Enrolled/ Data Monitoring Activities

Last Subject Enrolled

CY22 Goal – Study Completion and Closeout

☐Completion of Follow-up

☐Data analysis/ Site Close Out/ Write up Clinical Study Report

Comments/Challenges/Issues/Concerns

- TBD
- **Budget Expenditure to Date**
  Projected Expenditure: TBD
  Actual Expenditure: TBD

9. APPENDICES: *N/A*