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Award Number: W81XWH-14-2-0193

TITLE: Prevention of Bone Loss after Acute SCI by Zoledronic Acid: Durability, Effect on Bone Strength, and Use of Biomarkers to Guide Therapy

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REPORT DATE: Dec 2019

TYPE OF REPORT: Final

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

DISTRIBUTION STATEMENT:

☑ Approved for public release; distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
Dec 2019	Final	30 Sep 2014-29 Sep 2019

4. Title

Prevention of Bone Loss after Acute SCI by Zoledronic Acid:

Durability, Effect on Bone Strength, and Use of Biomarkers to Guide Therapy

5a. CONTRACT NUMBER
W81XWH-14-2-0193

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Thomas J. Schnitzer, MD, PhD

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Northwestern University, 633 Clark St.,

Evanston,IL 60208-0001

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
US Army Medical Research and
Materiel Command
Fort Detrick, MD 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

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

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Rapid bone loss is a universal accompaniment of acute spinal cord injury (SCI) and leads to severe loss of bone mass and bone strength with a marked increased risk of fracture. This 24 month double-blind, randomized, placebo-controlled study evaluates in 60 participants the efficacy (bone mass and bone strength) and safety of zoledronic acid administered early after acute SCI to prevent bone loss, the duration of its effects and the value of using biomarkers to guide therapy. Data collection (bone imaging and biomarkers) occurs at baseline and after 3, 6 and 12 months during the first year; participants are re-randomized after 12 months with subsequent data collection at 18 and 24 months. Currently, all regulatory requirements for the study have been completed. All sixty (60) participants have been randomized and treated. No unexpected safety events have occurred. Data collection is on-going.

15. SUBJECT TERMS
Spinal cord injury, bone mass, bone strength, osteoporosis, zoledronic acid

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	11	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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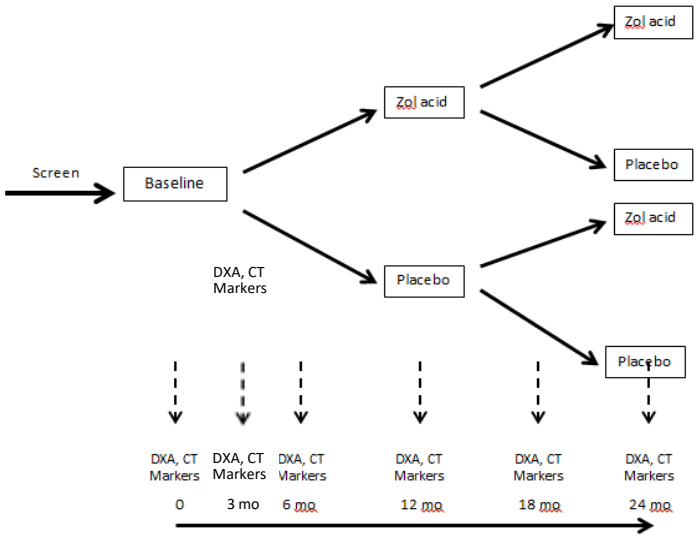
1. **INTRODUCTION:** Rapid bone loss is a universal accompaniment of acute spinal cord injury (SCI) and leads to severe loss of bone mass and bone strength with a marked increased risk of fracture. The study proposed is a 2 year, randomized, double-blind placebo-controlled study of zoledronic acid to evaluate its efficacy and safety for the prevention of bone loss and maintenance of bone strength in individuals with recent onset SCI (see diagram below). At the end of the first year of the study, each treatment groups will be re-randomized to either zoledronic acid or placebo to evaluate the durability of response to zoledronic acid and the utility of serum bone markers to guide therapeutic decision making. DXA imaging, CT imaging and bone markers will be obtained at baseline, 3 months, 6 months, 12 months, 18 months and 24 months.



2. **KEYWORDS:** spinal cord injury, bone mass, bone strength, osteoporosis, zoledronic acid.

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

Specific Aim 1: Determine Timing and Frequency of Administration of Zoledronic Acid for Maximum Effect

Major Task 1: Regulatory Approval
Milestone Achieved: HRPO Approval (Goal - Month 2) – 100% complete

Major Task 2: Prepare Study Documents and Materials
Milestone Achieved: Study materials completed, ready for use (Goal - Month 2) – 100% complete

Major Task 3: Enroll and Treat Participants
Milestone Achieved: All participants enrolled (Goal - Month 20) – 100% complete
Milestone Achieved: Last participant visit (Original goal - Month 44; Modified Goal – Month 66) – 65% of participants completed month 24 visit; 83% of participants have had their last visit including those who discontinued or withdrew.

Major Task 4: Data Completion and Analysis
Milestone Achieved:
Complete data analysis (Original goal - Month 48; Modified Goal – Month 72) - 30% complete

Specific Aim 2: Evaluate Use of Serum Bone Biomarkers to Guide Therapeutic Decisions

Major Task 1: Obtain results of serum levels of bone biomarkers
Milestone Achieved:
Results of all bone biomarkers available (Original goal - Month 45; Modified Goal – Month 67) - 0% complete; biomarkers are being collected and stored and will be assayed in one batch after last participant's final visit.

Major Task 2: Analyze data with regard to BMD changes
Milestone Achieved:
Data analysis completed (Original goal - Month 48; Modified Goal – Month 72) **-** 0% complete
To be completed after last participant's final visit and the database lock.

Specific Aim 3: Quantify changes in torsional and compressive strength at the distal femur and proximal tibia

Major Task 1: Application of refined FE model
Milestone Achieved:
Data obtained and entered (Original goal – Month 45-48; Modified Goal – Month 67-70) - 30% complete

- **What was accomplished under these goals?**

All objectives outlined in the Statement of Work to be completed during the fifth year have been completed or are on-going. All regulatory approvals have been maintained. Screening and enrollment of participants (Specific Aim 1, Major Task 3) was completed in February 2018. All 60 participants (100% of original goal) have been enrolled and treated. Thirty-nine participants (65%) have completed the final Month 24 follow up visit, 10 participants (17%) are currently still active in the study and 11 participants (18%) have discontinued (withdrawn consent or are lost to follow-up). Data are being obtained and entered into the study database, and study materials are being collected and maintained for future assay (biomarkers; part of Specific Aim 2, Major Task 1) or for image analysis (CT bone scans; part of Specific Aim 3, Major Task 1). As the investigators remain blinded to allocation of treatment assignment, it is not possible to know efficacy results until the end of the study. Safety is being continually monitored by collection of adverse events. The medical monitor continues to review all AEs and study procedures at the regularly held data safety monitoring committee meetings. No safety concerns have been identified and no changes in the study proposed. The next safety monitoring committee meeting will take place after the last participant's final visit and the blind has been broken.

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

  There have been 3 post-doctoral fellows who have participated in this project and for whom this project has provided valuable training and professional development. Additionally, this project has provided the PI the opportunity to attend professional meetings (American Society of Bone and Mineral Research) to discuss data with others in the field.

- **How were the results disseminated to communities of interest?**

  Portions of the data collected have been utilized for an abstract presented at last year's American Society of Bone and Mineral Research meeting and published in Osteoporosis International. Additionally, information regarding bone health in patients with spinal cord injury is presented to patient groups at Shirley Ryan AbilityLab once every 3 months in a lecture.

- **What do you plan to do during the next reporting period to accomplish the goals?**
  During the next reporting period, we plan to finish data collection as outlined in the protocol. This includes collecting and storing biospecimens and sending the remaining CT data to the University of Calgary for analysis. After the last participant's final study visit, all biospecimens will be sent out for bone markers analysis. The remaining participants' data collected at this site will be entered into the REDCap database. The database will then be cleaned and locked. Once all data is clean, the blind will be broken and data analysis will commence. A final data safety monitoring committee meeting will take place. Participants will be notified of their treatment group allocation along with results of the data analysis, if available. Analyzed data will be summarized in a manuscript and submitted to a relevant journal for publication.

4. **IMPACT:**

- **What was the impact on the development of the principal discipline(s) of the project?**
  The results of this study are not available as yet. As noted above, some of the baseline data have been incorporated into an abstract presented at this discipline's primary professional meeting, the American Society of Bone and Mineral Research meeting, in 2018.

- **What was the impact on other disciplines?**
  The results of this study are not available as yet.

- **What was the impact on technology transfer?**
  Nothing to report.

- **What was the impact on society beyond science and technology?**
  Nothing to report.

5. **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**

Nothing to report.

- **Actual or anticipated problems or delays and actions or plans to resolve them**
  Nothing to report.

- **Changes that had a significant impact on expenditures**
  There were 2 significant delays in the project that have been previously documented. The first was due to time taken to get regulatory approvals in place. The second was due to the fact that the hospital where we recruit subjects moved into a new building and suspended all research activities for several months. Based on these delays, we have reduced the effort of various research staff throughout these periods. Additionally, as recruitment was somewhat slower than had been forecast, we were able to manage data collection and participants' involvement with fewer resources, allowing us to have funds remaining to allow full data collection of all 60 participants, which was the prespecified enrollment target. We have already been granted a 12 month no cost extension for this closing year. As we anticipated, we will need an additional 12 months to complete the project in its entirety. The last participant's visit is scheduled for February, 2020, so data collection can only be completed at that time. We still need to send biospecimens for analysis, clean and lock the database, undertake analyses and then submit publications. We therefore requested a second extension without additional funds (reply not yet received).

- **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.**
  Not applicable.

- **Significant changes in use of biohazards and/or select agents**
  Not applicable.

6. **PRODUCTS:**

- **Publications, conference papers, and presentations**
  Haider I, Lobos S, Simonian N, Schnitzer TJ, Edwards WB. Bone Fragility after Spinal Cord Injury: Reductions in Stiffness and Bone Mineral at the Distal Femur and Proximal Tibia as a Function of Time. Poster Presentation at the American Society for Bone and Mineral Research Annual Meeting, Montreal, Canada, September 28-October 1, 2018.

- **Journal publications**
  Haider I, Lobos S, Simonian N, Schnitzer TJ, Edwards WB (2018). Bone Fragility after Spinal Cord Injury: Reductions in Stiffness and Bone Mineral at the Distal Femur and Proximal Tibia as a Function of Time. *Osteoporosis International, 29(12):2703-2715*. doi:10.1007/s00198-018-4733-0.

- **Books or other non-periodical, one-time publications. 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:	***Thomas J. Schnitzer, MD, PhD***
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*3*
Contribution to Project:	*Dr. Schnitzer has been providing oversight of regulatory and recruitment activities for this project.*
Funding Support:	*No change*
Name:	***Narina Simonian, BS, CCRC***
Project Role:	*Lead Study Coordinator*
Researcher Identifier (e.g. ORCID ID):	*n/a*
Nearest person month worked:	*5*
Contribution to Project:	*Mrs. Simonian has been maintaining regulatory approvals and performing study visits.*
Funding Support:	*No change*
Name:	***W. Brent Edwards, PhD***
Project Role:	*Principal Investigator (University of Calgary)*
Researcher Identifier (e.g. ORCID ID):	*n/a*

Nearest person month worked:	*3*
Contribution to Project:	*Dr. Edwards is responsible for CT data analysis.*
Funding Support:	*No change*
Name:	***Frances Leung, MPH, MD***
Project Role:	*Post-Doctoral Fellow*
Researcher Identifier (e.g. ORCID ID):	*n/a*
Nearest person month worked:	*5*
Contribution to Project:	*Dr. Leung has helped with scheduling visits, data management and data entry.*
Funding Support:	*No change*
Name:	***Ifaz Haider, PhD***
Project Role:	*Post-Doctoral Fellow (University of Calgary)*
Researcher Identifier (e.g. ORCID ID):	*n/a*
Nearest person month worked:	*4*
Contribution to Project:	*Dr. Haider assists with CT data analysis.*
Funding Support:	*No change*

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  The PI has obtained funding as a co-investigator in the project noted below:

  P50 DA044121-01A1 Apkarian (PI) 09/01/2018-06/30/2023
  NIH/NIDA
  Center for Chronic Pain and Drug Abuse
  The goal of the Northwestern University Center for Chronic Pain and Drug Abuse is to address two critical challenges regarding chronic pain and its treatment: 1) Unravel the interaction between development of chronic pain, and opiate analgesia and opiate addiction; and 2) pursue molecular and circuit targets underlying the maladaptive plasticity that controls the interaction between chronic pain and opiate exposure, to discover potential novel minimally-addictive or non-addictive therapies for chronic pain.
  Role: Co-Investigator

- **What other organizations were involved as partners?** *:*

Organization Name: University of Calgary

- **Location of Organization:** Calgary, Alberta, Canada
- **Partner's contribution to the project:**
- **In-kind support**: salary support, Dr. Edwards

- **Collaboration**: partner's staff work with project staff on the project

Organization Name: Shirley Ryan AbilityLab (previously known as Rehabilitation Institute of Chicago (RIC))

- **Location of Organization:** Chicago, IL, USA
- **Partner's contribution to the project**
- **In-kind support**: none
- **Facilities:** project staff use the partner's facilities for project activities; participants are recruited from this facility
- **Collaboration:** partner's staff work with project staff on the project
-

8. **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS:**

  Not applicable.

- **QUAD CHARTS:**

  Attached.

9. **APPENDICES:**

   None

Prevention of Bone Loss after Acute SCI by Zoledronic Acid: Durability, Effect on Bone Strength and Use of Biomarkers to Guide Therapy

Proposal Log Number SC130125; Award # W81XWH-14-2-0193; HRPO Log A-18350

PI: Dr. Thomas J. Schnitzer **Org:** Northwestern University Feinberg School of Medicine **Award Amount: $2,011,846**

Study/Product Aims

- Define timing and frequency of administration of zoledronic acid that will result in optimal prevention of bone loss after acute SCI.
- Evaluate the use of serum markers of bone metabolism to guide therapeutic decisions of timing and need for retreatment with zoledronic acid after acute SCI.
- Evaluate effects of zoledronic acid in mitigating loss of bone strength that occurs after acute SCI.

Approach

This is a 2 year, randomized, double-blind placebo-controlled study. Subjects will be randomized at baseline and again at 12 months to receive either zoledronic acid or placebo each time. Subject will be followed for 24 months with repeat DXA scans, CT scans, and serum bone markers.

IRB approval received at all sites. Enrollment is complete, with all 60 subjects randomized. Thirty-nine subjects have completed the final study visit and 10 remain active.

Timeline and Cost

Activities / CY	14	15	16	17	18	19	20
Study Start-Up Activities							
Participant Enrollment							
Data Collection and Entry							
Data Analysis							
Estimated Budget ($K)	**$138K**	**$541K**	**$503K**	**$465K**	**$365K**	**$0K**	**$0K**

completed | original projection | current projection

Updated: 15 October 2019

Goals/Milestones

CY14 Goals – Begin study start-up; Regulatory approval at all sites
CY15 Goals – Complete start-up, Begin recruitment and enrollment
CY16 Goals – Continue recruitment and enrollment
CY17 Goals – Complete subject enrollment (56/60 completed)
CY18 Goals – Enrollment completed (60/60); continue data collection
CY19 Goals - Continue data collection
CY20 Goals – Complete data collection; data analysis; final study report

Comments/Challenges/Issues/Concerns

Delayed HRPO approval, hospital move delayed projected timelines
Enrollment is 100% complete.
Under budget to allow for longer recruitment period and follow-up

Budget

Budget Expenditure to Date:
Projected Expenditure: $2,011,846
Actual Expenditure: $1,611,491 (includes encumbered subcontracts)