

AWARD NUMBER: **W81XWH-19-2-0029**

TITLE: Sustained Delivery of Simvastatin to Augment Meniscal Healing: Is Regenerative Healing Possible?

PRINCIPAL INVESTIGATOR: **Brian Grawe, MD**

CONTRACTING ORGANIZATION: **University of Cincinnati**

REPORT DATE: **OCTOBER 2023**

TYPE OF REPORT: **Annual Report**

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

DISTRIBUTION STATEMENT: **Approved for Public Release;
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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE OCTOBER 2023		2. REPORT TYPE Annual		3. DATES COVERED 30SEPT2022 - 29SEPT2023	
4. TITLE AND SUBTITLE: Sustained Delivery of Simvastatin to Augment Meniscal Healing: Is Regenerative Healing Possible?				5a. CONTRACT NUMBER W81XWH-19-2-0029	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Brian Grawe MD E-Mail:grawebn@uc.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Cincinnati Sponsored Research Services University Hall, Suite 530 51 Goodman Dr. PO Box 210222				8. PERFORMING ORGANIZATION REPORT NUMBER	
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 REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The aim of this clinical trial is to evaluate the safety and effectiveness of an injection containing simvastatin hydroxy acid (AM3101) in supporting meniscal repair. The goal is to decrease the occurrence of non-healing complications and associated morbidities following unsuccessful meniscal repair. This prospective, randomized, controlled, double-blinded, multi-center study plans to enroll a total of 74 subjects. To date four subjects have been enrolled and randomized.					
15. SUBJECT TERMS NONE LISTED					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
U	U	U	UU	10	19b. TELEPHONE NUMBER (include area code)

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INTRODUCTION

The aim of this clinical trial is to evaluate the safety and effectiveness of an injection containing simvastatin hydroxy acid (AM3101) in supporting meniscal repair. The goal is to decrease the occurrence of non-healing complications and associated morbidities following unsuccessful meniscal repair. This prospective, randomized, controlled, double-blinded, multi-center study plans to enroll a total of 74 subjects.

Participants will be divided into two groups:

Group 1: Consisting of 37 subjects treated with meniscal repair along with a 2 ml injection of 0.9% sodium chloride as a placebo.

Group 2: Comprising 37 subjects undergoing meniscal repair with an injection of AM3101 (1 mg/ml for 2 ml; total dosage of 2 mg).

The study is designed to span 12 months for each participant, encompassing screening, surgery, and follow-up evaluations at 6 weeks, 3 months, 6 months, and 12 months.

KEYWORDS

Meniscal repair, simvastatin hydroxy acid, healing, functional outcomes

ACCOMPLISHMENTS

Major Task 1: Regulatory and Compliance

On June 30, 2022, the U.S. Food and Drug Administration granted approval (IND 146131) for AM3101, a compound featuring simvastatin hydroxy acid ammonium salt. The University of Cincinnati Institutional Review Board (UC IRB) serves as the central IRB for this study and endorsed the UC site on September 7, 2022. The approval from the US Army Medical Research and Development Command Office of Human Research Protections (USAMRDC OHARO OHRO) for the UC site specifically was secured on February 7, 2023.

This study involves three participating sites:

- San Antonio Military Medical Center [Site PI: Andrew Sheean, MD]
- Oregon Health & Science University [Site PI: Jacqueline Brady, MD]
- Case Western Reserve University [Site PI: Jacob Calcei, MD]

Anticipated completion of UC IRB and USAMRDC OHARO OHRO approvals for all sites is targeted for November 2023.

Major Task 2: Coordinate Study Staff for Clinical Trials

A committed research coordinator is currently actively engaged in overseeing the study at the University of Cincinnati. Additionally, coordinators for the three other sites have been designated and will commence their involvement in the study upon receiving the necessary approvals.

Major Task 3: Participant Recruitment, Injection, Participant Patient Reported Outcomes

As of October 12, 2023, four subjects have been successfully enrolled, randomized, and undergone surgery. The initial participant has completed the 3-month visit, while the second participant has concluded the 6-week visit. To ensure a cautious approach, enrollment for the first five subjects across all sites undergoing active treatment is staggered by a minimum of 3 days. This deliberate spacing allows for the assessment of any potential significant toxicity.

Adverse event data collected during this phase will undergo careful scrutiny by the Data Safety Review Committee (DSRC) before proceeding to treat the subsequent subject. Furthermore, cumulative and unblinded safety data from the initial five subjects will be subject to review by the DSRC. This comprehensive evaluation, guided by pre-determined stopping/pausing rules, will inform the decision to continue enrollment, emphasizing the paramount importance of safety considerations.

Major Task 4: Data Analysis

Data analysis is scheduled to commence only after the completion of the one-year follow-up visit for all 74 subjects.

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?

Over the next 12 months, our objective is to secure approvals for all participating sites and successfully enroll and randomize 74 subjects into the study.

IMPACT

Nothing to Report.

CHANGES/PROBLEMS

According to FDA's clearance of the requested IND, only the Active Pharmaceutical Ingredient would be used without the hydrogel excipient as the test article in the present trial. Consequently, saline injection was demanded as the control group so that the required randomization of treatments (double blinded) can be met and performed. An amended study protocol was then submitted and approved by the UC IRB on September 7, 2022, followed by the approval of the Office of Human Research Protection on February 7, 2023.

In addition, over the past year, adjustments were made to the originally planned study sites outlined in the initial grant application. Here are the changes:

- 1) Initially, the Walter Reed Medical Center (WMRC) was intended to participate in the study under the guidance of site PI Jonathan F. Dickens, MD, LTC, USA. However, Dr. Dickens retired from the military in December 2021. Subsequently, in September 2022, Dr. Christopher Tucker took on the role of site PI for WMRC. However, due to budget constraints, it was decided, during the no-cost extension submitted in September 2023, that WMRC would not continue as a subsite for the study.
- 2) The San Antonio Military Medical Center was introduced into the study to incorporate military members and their families, expanding the scope of the research.
- 3) Case Western Reserve University was added as a study site with the aim of expediting the enrollment process, thereby reducing the time required to reach the target of 74 subjects in the upcoming year.

PRODUCTS

Nothing to Report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

University of Cincinnati

Name	Bran Grawe MD
Project Role	Principle Investigator
Researcher Identifier	0000-0002-3778-7260
Nearest person month worked	3
Contribution to Project	Dr. Grawe oversees consenting and recruiting patients. He oversees the execution of the inventions. Dr. Grawe also leads all reporting, compliance, data interpretation and study management responsibilities.
Funding Support	NA

Name	Chia-Ying Lin PhD
Project Role	Co-Investigator
Researcher Identifier	0000-0002-3170-0910
Nearest person month worked	1
Contribution to Project	Assisted in the filing of IND application, communication with FDA to ensure regulatory compliances required, and coordination of production for the compound used in the study.
Funding Support	NA

Name	Wei-Wen Hsu, PhD
Project Role	Statistician
Researcher Identifier	0000-0002-7822-0826

Nearest person month worked	<1
Contribution to Project	Designed randomization methods.
Funding Support	NA

Name	Kimberly Hasselfeld MS CCRP
Project Role	Primary Research Coordinator
Researcher Identifier	0000-0002-1659-6131
Nearest person month worked	1
Contribution to Project	She is responsible for logistics of the trial concerning patient recruitment, consenting, study management and subject monitoring.
Funding Support	NA

Name	Rebekah West
Project Role	Research Coordinator
Researcher Identifier	None
Nearest person month worked	1
Contribution to Project	She is involved in the consenting and collection/compilation of data. She assists in ensuring that follow-up appointments are made and met as well as critical time elements of the patient throughput is achieved.
Funding Support	NA

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.

SPECIAL REPORTING REQUIREMENTS

A QUAD CHART has been included as an Appendix.

Appendix – Quad Chart for end of Year 4

Sustained Delivery of Simvastatin to Augment Meniscal Healing: Is Regenerative Healing Possible?

Funding Opportunity Number: W81XWH-18-PRORP-CTRA

Pre-application OR180066



PI: **Brian M Grawe MD**

Org: University of Cincinnati College of Medicine

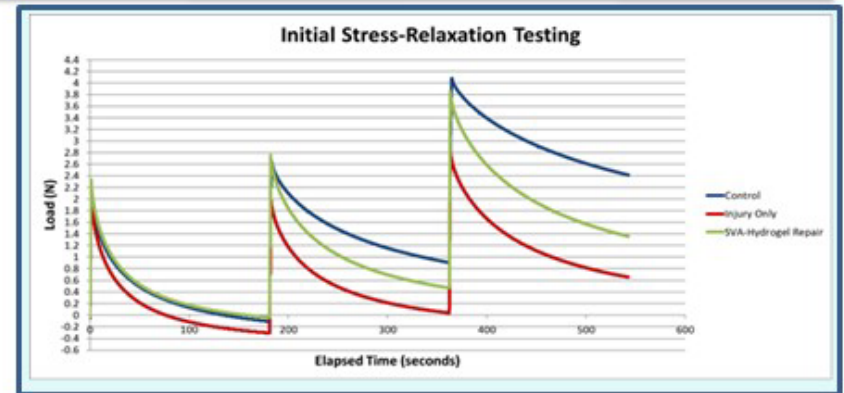
Award Amount: \$1,973,671.00

Study/Product Aim(s)

- Evaluate the integrity of repaired meniscal tissue following injection with simvastatin. The presence or absence of healing will help to assess the efficacy of simvastatin in stimulating new meniscal tissue growth in human subjects. Meniscal integrity will be assessed by MRI imaging studies over a 24-month period. A grading scale correlating signal intensity to the presence or absence of meniscal healing will be used.
- Report functional outcomes in patients receiving simvastatin injection following meniscal repair. Functional outcome measures are important for translating the biological evidence of meniscal tissue regeneration to the clinical evidence of the patient's functional restoration. Functional outcomes will be evaluated by physical exam (range of motion, muscle strength testing) and validated patient reported outcome measures.

Approach

The study will be prospective, randomized, and double blinded. It will consist of a total of 74 patients (determined by power analysis). The patients will be divided into 2 cohorts. One cohort will consist of 37 patients treated with meniscal repair and 2 ml 0.9% sodium chloride as a placebo, the second cohort will consist of 37 patients treated with meniscal repair and AM3101 (1 mg/ml for 2ml; total dosage of 2 mg).



Repaired meniscus treated by simvastatin-hydrogel compound in our preliminary animal model work was able to retain the viscoelastic properties. The results found the drug depot of simvastatin was capable of achieving functional tissue repair of meniscus.

Timeline and Cost

Activities (Year)	19	20	21	22	23	24
IND enabling and filing* (delayed due to COVID-19)		█				
Recruit Study Subjects					█	
Data Collection					█	
Data Statistical Analysis						█
Final Report Completed						█
Estimated Budget (\$K)		\$125	\$500	\$500	\$500	\$375

Updated: 03-Oct-2023

Goals/Milestones

CY23 Goal - Protocol implementation

Started enrolling subjects April 2023

CY23 Goal - Enrollment and data analysis

Enrolling subjects

Quality checks of data being captured and preliminary analysis

CY24 Goal - Enrollment completed

Data analysis

CY24 Goal - All subjects completing follow-up visits

CY24 Goal - Complete statistical analysis and dissemination of information.

Comments/Challenges/Issues/Concerns

- If subject recruitment is low, will look to advertise for subjects in the Greater Cincinnati area.

Budget Expenditure to Date is \$917,866.

Available Direct Balance is \$706,811.