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TITLE: Phase 3 Clinical Trials: D-Methionine to Reduce Noise-Induced Hearing Loss

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14. ABSTRACT Hearing loss can render a soldier less able to detect and identify the enemy, less able to understand commands, particularly in background noise typical on the battlefield, and may permanently reduce quality of life. Currently, no FDA approved pharmacological prevention exists for noise-induced hearing loss (NIHL). We have documented in animal studies that administration of D-methionine (D-met) can reduce or prevent NIHL. We now need to determine if it has similar efficacy in humans. This prospective study is a randomized, double-blind, placebo-controlled Phase 3 clinical trial of oral D-met to reduce noise-induced hearing loss (NIHL) and tinnitus. The goal of the study is to develop a safe, oral pharmacological agent to augment physical hearing protectors for noise exposures that exceed the protective capabilities of ear plugs and/or muffs. The study population is a cohort of Drill Sergeant (DS) instructor trainees during and 22 days after their 11 day weapons training. The primary objective of this study is to determine the efficacy of D-Met in preventing NIHL or reducing tinnitus secondary to a minimum of 500 rounds of M-16 weapons training occurring over an 11 day period.					
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INTRODUCTION:

The purpose of this Phase I clinical trial is to determine if an oral, orange flavored suspension of D-methionine can prevent noise-induced hearing loss (NIHL) and tinnitus in our troops.

Hypotheses:

Primary Hypothesis: Administration of oral D-methionine prior to and during weapons training will reduce or prevent permanent NIHL.

Secondary Hypothesis: Administration of oral D-methionine prior to and during weapons training will reduce or prevent noise-induced tinnitus.

Primary outcome to test the primary hypothesis: Pure tone air-conduction thresholds.

Primary outcome to test the secondary hypothesis: Tinnitus questionnaires.

Specific Aims:

1. To determine whether administering oral D-methionine (D-met) can prevent permanent NIHL after weapons training. This aim will be addressed by comparing the results of D-met versus placebo administration starting 3 days prior to, during the 11 day period of weapons training (Monday-Friday of week 1 and Monday-Thursday of week 2), and 4 days after for a total of 18 days. Pure tone hearing thresholds will be assessed before and 19-22 days after completion of weapons training (i.e., 15-18 days after the last day of study drug/placebo administration).
2. To determine whether administering oral D-met can prevent tinnitus after weapons training. This aim will be addressed by comparing the results of D-met versus placebo administration starting 3 days prior to, during the 11 day period of weapons training (Monday-Friday of week 1 and Monday-Thursday of week 2) and 4 days after for a total of 18 days. Tinnitus questionnaires will be assessed before and 19-22 days after completion of weapons training (i.e., 15-18 days after the last day of study drug/placebo administration).
3. To monitor for any potential side effects of D-met in human subjects. This aim will be accomplished by subject query on each day of drug administration with routing of any adverse event reports to study medical personnel, statisticians and to the Food and Drug Administration (FDA).

Primary Endpoints

- 1) Primary endpoint is to confirm safety and tolerability of up to 100 mg/kg daily given in divided doses 12 hours apart.
- 2) Primary efficacy endpoint is change from baseline in pure-tone threshold as measured by absolute change and frequency of significant noise-induced threshold shift (STS)...
- 3) Secondary efficacy endpoint is change from baseline scores for the tinnitus scales for both loudness and annoyance.

Study Design:

This prospective study is a randomized, double-blind, placebo-controlled Phase I clinical trial of oral D-met to reduce NIHL and tinnitus. The goal of the study is to develop a safe oral pharmacologic agent to augment physical hearing protectors for noise exposures that exceed the protective capabilities of ear plugs and/or muffs. The study population is a cohort of Drill Sergeant (DS) instructor trainees during and 21 days after their 11 days of weapons training. The primary objective of this study is to determine the efficacy of D-Met in preventing or reducing NIHL and tinnitus secondary to a minimum of 500 rounds of M-16 weapons training occurring over a 2 week period. A total of 600 Drill Sergeant Instructor Trainees will be enrolled in the study and randomized to study drug or placebo for a final study cohort of 504 subjects. Subjects will be recruited during the first week of training. Participation will consist of an on-site Screening visit followed by a Baseline visit (Study Visit 1), an, and an End of Study visit (Study Visit 3), for a total of 3 Study Visits for each subject. Compliance and adverse event checks will be performed daily throughout the drug administration period. Subjects will be prescreened to review inclusion/exclusion criteria and medical history. Baseline and final audiologic testing will include otoscopy, tympanometry, and pure-tone hearing threshold testing at .5, 1, 2, 3, 4, 6, 8 kHz bilaterally. Tinnitus will be measured using standardized tinnitus assessment questionnaires. Subjects will take either the oral study drug or flavor matched placebo twice per day for 18 days starting 3 days prior to the weapons training, during the weapons training period and for an additional 4 days. Data will be independently analyzed through the Yale Occupational and Environmental Medicine Program. Data will be analyzed to determine 1) if there is a significantly reduced change in hearing threshold in the average of both ears for the D-met group as compared to the placebo group at the tested audiometric frequencies, 2) to determine if there is a significantly lower rate of significant threshold shift (STS) according to the Defense Occupational Environmental Health Readiness System- Hearing Conservation (DOEHRSHC) in either ear for the D-met group as compared to the placebo group 3) to determine if there is a significant difference in reported level of tinnitus between the D-met and the placebo groups and 4) to detect, report and analyze any side effects. This study is a collaboration among Southern Illinois University School of Medicine, the U.S. Army, and Yale University. The study includes a regulatory consultant to ensure full compliance with all regulatory agencies, committees, and boards. It is hoped that this study will move us forward in preventing NIHL and tinnitus world-wide.

Relevance: This study will test the hypotheses that oral D-met can prevent or significantly reduce permanent NIHL and potentially tinnitus in US military troops during weapons training in a cohort of experienced soldiers.

BODY:

The original Statement of Work (SOW) outlined several tasks to be completed within the first year of the grant before data collection could begin. We have completed all appropriate documents for submission to the appropriate regulatory agencies for approval. In addition, the study drugs have been formulated, undergone stability testing and are

ready for shipment to the testing site. Once IRB approval is granted, all personnel are in place and the Manual of Operations is completed and approved, we will initiate recruitment and begin data collection. Due to significant delays experienced with this project, we are completing first year tasks in the second year of the granting period. Below are our original SOW tasks planned for the first year and the accomplishments made on each task to date:

SOW Task 1: First Quarter (Year 1): *To submit a complete Investigational New Drug (IND) Application to the FDA:*

We submitted three copies of 15 volumes (~300 pages per volume) of our IND application to the FDA on May 23, 2013. The FDA completed the 30-day safety review on our May 2012 IND submission and granted approval for the study to proceed. However, the FDA made strong recommendations to amend the clinical protocol to include clinical and pharmacology assessments. The FDA recommended including laboratory evaluations (hematology, blood chemistry, and urinalysis) on all study participants. The purpose of these recommendations were 1) to exclude participants with mild renal impairment until the PK assessment of D-met was better understood and 2) to explore a range of D-met doses in the subjects in order to characterize the dose-response relationship for efficacy and safety. However, on September 24, 2012, the Ft Jackson authorities denied our request to add these assessments to the protocol and recommended that we proceed with the study as originally approved by them (see attached letter in the appendices).

Due to the inability to include the additional FDA recommended assessments into the FT Jackson protocol to qualify the study as a phase 3 pivotal study, we have initiated discussions with CDR Royce Clifford, US Navy and the Hearing Center for Excellence (HCE) regarding the possibility of conducting a new phase 3 pivotal study with Marine recruits under her supervision at Camp Pendleton, California. We submitted a modified version of the Ft Jackson clinical protocol to her on March 22, 2013 including all FDA recommended assessments to be conducted with the Marine Corp Recruit Depot (MCRD) in a similar manner to previous clinical trials with N-acetylcysteine (NAC).

SOW Task 2: First Quarter (Year 1): *To submit a completed Institutional Review Board (IRB) application:*

An IRB Authorization Agreement (IAA) was sent from us to the DDEAMC IRB on May 17, 2012. We received and submitted the DoD Institutional Agreement for IRB Review (IAIR) to the DDEAMC on September 12, 2012 and the document was approved and executed on November 28, 2012.

We composed all study documents using DDEAMC IRB templates during the first quarter of this second grant year but encountered delays due to the reassignment of our study PI (CPT Callis) to a new site in June 2012. LTC Neil Page subsequently stepped in as PI during the second quarter and also assigned CPT Ludwig (On-site Supervising Audiologist) to serve as our POC. CPT Ludwig has been a significant asset to the project by helping facilitate the composition and submission of all IRB documents.

Although all DDEAMC IRB documents were prepared for submission in the second quarter of the second granting year, we were unable to make final revisions to the documents at that time as we were awaiting Ft Jackson's decision concerning the proposed FDA recommendations. However, on September 24, 2012, Ft Jackson denied our request for adding the FDA recommendations of blood analysis and urinalysis for the study participants to the study protocol. Therefore, during the third quarter, no additions were made to the original protocol and Dr. Jill Anderson traveled to Ft. Jackson on Oct.10-13, 2012 and uploaded all original IRB documents through the Army (AKO) IRBNet system with the approval of Principal Investigator, LTC Neil Page, Principal Investigator. CPT Rebecca Ludwig, Co-PI electronically submitted them to the DDEAMC IRB on October 17, 2012. Initial feedback from the DDEAMC IRB was obtained on October 25, 2012 asking for clarification on some content in the clinical protocol and minor changes to the Informed Consent Form. The minor changes to the ICF were made and clarification of content was submitted to the DDEAMC IRB on November 14, 2012. On November 27, 2012, the DDEAMC IRB made an additional request for a change in the proposed roster of the Data Safety Monitoring Committee outlined in the clinical protocol. This change in personnel was made and the clinical protocol was resubmitted to DDEAMC on December 3, 2012.

During the fourth quarter of the second year of the granting period, the study protocol and relevant study documents received a full board review from the Ft. Gordon IRB on February 14, 2013. The board notified us on March 20, 2013 that the protocol was "Tabled Without Action" due to the request for a few clarifications and/or modifications. The study team addressed each of the requested modifications and CPT Rebecca Ludwig resubmitted the protocol and accompanying study documents through the Army IRB website on March 11, 2103. The Ft. Gordon IRB reviewed our modifications on March 14, 2013 and again notified us that a few of the outstanding issues had not been completely resolved. We have again addressed these issues and plan to resubmit the updated protocol and study documents on April 2, 2013. We expect to receive full approval at the next board meeting scheduled for April 11, 2013.

SOW Task 3: First Quarter(Year 1) *To complete the Hiring of Study Staff and finalize corporate contracts*

(Year 1) SOW Task 3: *To complete the Hiring of Study Staff and finalize corporate contracts*

- a. Yale Occupational Environmental Medicine Program: The Subcontract for Yale has been finalized and is in force.
- b. Ft. Jackson: We have signed an agreement with the Geneva Foundation to hire on-site study personnel (two full-time study coordinators) through the Foundation. We are in the process of interviewing two prospective on-site study coordinators and plan to have the primary study coordinator on site by June 1, 2013.

- c. SIUSOM/; SIU Center for Clinical Research: All study personnel have been recruited, trained and are currently working on different aspects of the project.
- d. KP Pharmaceuticals: The study drug and placebo have been ready and available for shipping to the study site.
- e. Judi Weissinger, PhD: The contract for Dr. Weissinger, is finalized and in force.
- f. Colleen Le Prell, PhD: Dr. Le Prell's consulting contract has been re-budgeted to reflect her significant decrease in active participation in the project.

SOW Task 4: First Quarter(Year 1) *To complete study Site Visits*

- a. Dr. Campbell has traveled to the study site on two occasions to finalize the study protocol/logistics and met with site leadership/study personnel. The initial visit was made on **December 11-13, 2011**. Due to significant changes in personnel at Ft Jackson, a subsequent site visit was made on **October 3-5, 2012** to orient new personnel to the study protocol.
- b. An on-site visit and audit of KP Pharmaceuticals was made by Dr. Kathy Campbell in **May, 2012**.
- c. The study team, comprised of Dr. Campbell and Dr. Milbrandt, including Dr. Puczynski (SIU CCR Director), traveled to the study site on **August 7-8, 2012**. The study team met with key personnel representing most of the divisions which will be actively involved in study related activities including LTC Ludwig (Audiology), COL Mark Hidgon (Commander of MACH), and LTC Neil Page (PI and Chief of Clinical Services). The study team toured the facilities and was able to determine a new location at the DSS in which to install 2 new sound booths for study related audiological testing. The study team also met with MAJ Ochoa, the pharmacist from MACH, and worked out study drug related issues. The team also toured the DSS training center and met with the DSS Command and received updates/modifications on the DSS training schedule. The site visit proved successful in refining the study protocol and in establishing better interpersonal relations between the SIU and Ft Jackson study teams.
- d. Dr. Anderson, SIU study coordinator, traveled to the study site on **October 10-13, 2012** to upload study documents into the DDEAMC IRBNet since SIUSOM does not have access through Army Knowledge Online (AKO).
- e. **A site initiation visit will be scheduled as soon as IRB approval has been obtained and on-site study personnel have been recruited and are in place.**

SOW Task 5: Third Quarter: (Year 1): *To complete all necessary study documents.*

All original study documents were completed and electronically submitted through the DDEAMC IRBNet on October 17, 2012 by CPT Rebecca Ludwig. The initial full board review on February 14, 2013 yielded requests for minor changes to the study documents. All first round revisions were submitted on March 7, 2013. A Subsequent board review of our first round revisions yielded requests for a few additional changes. Second round revisions to the study documents are completed and will be resubmitted on April 2, 2013 for full board review. We are expecting full board approval at the next board review on April 11, 2013.

The Manual of Operations has been drafted but will not be finalized until the new on-site study personnel are in place. Once the onsite study personnel are in place and have gained familiarity with the FT Jackson facility and their standard operating procedures, we will be able to include the necessary details needed to finalize the Manual of Operations.

Our SIU study coordinator (Dr. Anderson) created all electronic data capture documents through the Yale REDCap system with final approval from the Yale University study statistician (Mr. Slade). These electronic documents were submitted to the Ft Gordon IRB for their approval. There were no requested amendments/changes to the documents from the IRB. The reference guide for the use of the REDCap system has not yet been completed but will be finalized along with the Manual of Operations once Ft Gordon IRB final approval has been obtained and the on-site study coordinators are in place.

SOW Task 6: *To recruit subjects for first pilot data.*

Subjects have not yet been recruited. Commencement of the study is contingent upon regulatory approvals.

SOW Task 7: *Send pilot data sent to Yale for data checking*

Commencement of the study has not yet occurred. Pilot data has not been collected.

SOW Task 8: *To continue enrollment and recruitment with new classes starting every 2-3 weeks*

Subject enrollment has not yet begun.

KEY RESEARCH ACCOMPLISHMENTS:

- Corporate contracts are in place
- All SIUSOM clinical trial personnel are hired, trained and completing assignments

- Study drug and placebo have been formulated, tested and are ready for shipment
- Initial on-site visits have been made
- We received FDA approval to proceed with the study
- The study team completed an on-site visit on August 7-8, 2012 to address unresolved study dilemmas and to garner greater interpersonal relations between SIU and Ft Jackson
- Ft Jackson Pharmacy has been recruited to assist with study drug management
- The CRADA/SOW was approved by Ft Jackson
- All second round IRB revisions have been made and will be submitted on April 2, 2013. We are expecting full approval from the board on April 11, 2013.
- All audiological equipment has been delivered, set-up and calibrated at Ft Jackson.
- All electronic data capture forms have been created. Trial runs will be conducted once the on-site study personnel are in place.
- All electronic data capture forms have been created and we are awaiting a trial run once the on-site study personnel are in place and instructed on the use of the system.

REPORTABLE OUTCOMES:

To date, there are no reportable outcomes as the clinical trial has not yet begun.

CONCLUSION:

Excellent progress has been made regarding the start-up issues during the second 12 months of the grant period. All contracts are signed and in force. We have received FDA approval to proceed with the study and we anticipate full IRB approval of the study protocol on April 11, 2013. Both study audiologists are on-site and familiar with the audiological equipment and we have interviewed excellent candidates who have the requisite qualifications to provide on-site study coordination support for this trial. We fully anticipate being prepared to enroll subjects during the first quarter of the third grant year.

Immediate Future Plans:

- We will honor any/all suggested changes made by the DDEAMC IRB and update the appropriate study documents to reflect the changes.
- We will complete a site initiation visit for the appropriate SIUSOM study team members before beginning data collection.
- Train all newly hired on site study personnel
- On-site personnel will complete the Manual of Operations
- Complete 'run through' with new on-site personnel of the REDCap data transfer system

- Have all remaining study supplies ordered and delivered to the study site (i.e. pregnancy tests)
- Recruit first group of Soldiers for pilot study
- First delivery of study drug to Ft Jackson from KP Pharmaceuticals
- Report all IRB protocol changes to the FDA
- We've identified three ombudsmen to date who've agreed to assist with this study during all subject recruitment sessions

Overall, we are very appreciative of the number of individuals in the US Army in research administration and at Ft. Jackson and at Yale, the University of Florida, KP Pharmaceuticals, SIUSOM legal (counsel), clinical trials and grants offices, and our consultants that have been willing to patiently work with us on performing the extra work required for this collaboration to successfully move forward. We are all fully committed to preventing noise-induced hearing loss and tinnitus in our troops. We are very grateful for this opportunity.

REFERENCES: N/A

APPENDICES:



REPLY TO
ATTENTION OF

MCXL-MH

DEPARTMENT OF THE ARMY
Headquarters, U.S. Army Medical Department Activity
4500 Stuart Street
Fort Jackson, South Carolina 29207-5720

24 Sep 2012

MEMORANDUM FOR Dr. Kathy Campbell, Southern Illinois University

SUBJECT: D-Methionine Clinical Drug Study at Ft. Jackson

1. We received your request to conduct the following additions or changes to the protocol for the upcoming D-Methionine Clinical Drug Study at Ft. Jackson:
 - a. Blood draws on each subject- pre, during, and post drug administration.
 - b. Urinalysis at same intervals.
 - c. An additional dosing level.
2. We have determined that any changes to the current study protocol will require complete resubmission through the chains of command involved in the study, including: TRADOC (Training & Doctrine Command, over Drill Sergeant School), MEDDAC (chain of command for Medical Company, over Ft. Jackson audiologists), Moncrief Army Community Hospital (sponsoring the study), and Ft. Jackson Post Command.
3. The resubmissions would significantly delay data collection, if they are approved at all.
4. The recommendation is to proceed with the study in its current version, which has been approved for data collection to begin with the next cycle of Drill Sergeant School, beginning January 2013.
5. The point of contact for this memorandum is CPT Rebecca S. Ludwig at 803-751-3153 or rebecca.ludwig@amedd.army.mil, the undersigned.

REBECCA S. LUDWIG, Au.D.
CPT, MS
Chief, Ft. Jackson Hearing Program