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Award Number: W81XWH-12-1-0487

TITLE: A PHASE II TRIAL ON THE EFFECT OF LOW-DOSE VERSUS HIGH-DOSE VITAMIN D SUPPLEMENTATION ON BONE MASS IN ADULTS WITH NF1

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REPORT DATE: Oct 21018

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Oct 2018	Annual	15 Sep 2017-14 Sep 2018

4. TITLE AND SUBTITLE:
A Phase II Trial on the Effect of Low-dose versus High-dose Vitamin D Supplementation on Bone Mass in Adults with NF1

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W18XWH-12-1-0487

5c. PROGRAM ELEMENT NUMBER

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel 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

This is a study to determine the best dose of vitamin D to supplement adults with neurofibromatosis type 1 (NF1) who have a vitamin D insufficiency. Usually, skin exposure to ultraviolet radiation is ample for adequate levels of vitamin D. However, for those who need supplementation, the usual dose is 600 IU of vitamin D_3 orally per day. Individuals with NF1 have lower 25-hydroxy vitamin D levels than the unaffected population, and they tend to have osteopenia (low bone mineral density), even at relatively young ages. Thus, this study will determine if higher daily doses of vitamin D_3 (4,000 IU) lead to preservation of bone mineral density in both men and women between 25 and 40 years of age who have NF1.

15. SUBJECT TERMS
NF1, vitamin D, osteopenia, adults, double-blind randomized trial

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

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1. INTRODUCTION:

Neurofibromatosis type 1 (NF1) is a multisystem disease, and many patients have skeletal manifestations that fall into three general categories: (1) characteristic focal lesions, (2) short stature, and (3) osteomalacia, osteoporosis, or low BMD (bone mineral density), which occurs in almost all affected individuals by age 50. Vitamin D therapy appears to have some benefit in treating osteoporosis in the general population, and administration of vitamin D in a dose that maintains the serum 25-hydroxy vitamin D level above 30 ng/mL significantly improves BMD in individuals with NF1. These observations led to the development of a phase II clinical trial to evaluate the effectiveness of vitamin D_3 dosing in NF1 patients. This study is designed to assess the efficacy of oral vitamin D_3 and calcium therapy to prevent abnormal loss of bone mass in adults with NF1. The clinical trial is a double-blind, dose comparison of efficacy of high-dose versus low-dose vitamin D_3 on preservation of bone density as measured by DXA scanning after 2 years of treatment. It compares 2 groups of adults with NF1 between 25 and 40 years of age with insufficient levels of serum 25-hydroxy vitamin D at study entry. Participants are randomized and one group will take 600 IU and the other will take 4,000 IU on a daily basis for 2 years. Participants and investigative teams are blinded to the vitamin D_3 dose. The primary outcome measure is bone mineral density at the spine and hip. Secondary patient reported outcome (PRO) measures include a quality of life questionnaire (SF-36), fracture history survey, and activity survey.

2. KEYWORDS:

25(OH)D = 25-hydroxy vitamin D
BMD = bone mineral density
CCTS = Center for Clinical & Translational Science at the University of Utah
Cholecalciferol=vitamin D3
CIN = University of Cincinnati enrollment center
CGRP = Clinical Genetics Research Program
DEXA = dual energy x-ray absorptiometry
Ddrops = formulation of cholecalciferol (vitamin D_3)
DXA = dual energy x-ray absorptiometry
FDA= Federal Drug Administration
HAM = University of Hamburg enrollment center
IRB = Institutional Review Board
NF1 = neurofibromatosis type 1
PCTO = Pediatric Clinical Trials Office at the University of Utah
PRO= Patient Reported Outcome
UBC = University of British Columbia enrollment center

3. OVERALL PROJECT SUMMARY (STATEMENT OF WORK)

Overall Objective: Determine best dose of cholecalciferol supplementation to optimize maintenance of bone mineral density in adults with neurofibromatosis type 1 (Funding: 9/30/2012 -09/29/2016; 48 months) – No cost extension granted through 9/29/2018,

pending for an additional 2 years.

I. Major Goal - Assemble a cohesive multi-center team for phase II clinical trial

Task I.1 (mo 0-2): compile subcontracts between UTA and the following sites UBC (University of British Columbia, Canada), CIN (University of Cincinnati, USA), HAM (University of Hamburg, Germany).

Subcontracts have been distributed by the University of Utah Office of Sponsored Projects. The University of Cincinnati has submitted invoices, and payout for October 1, 2014-September 30, 2015 was $58,000. It has requested carryover from year 2 to year 3, cognizant of the need hold funds for an extension of the study since it has been over 2 years in getting underway. The University of British Columbia has submitted invoices, and payout for October 1, 2014-September 30, 2015 was $26,877. The subcontract with University of Hamburg has been executed, and payment of $60,000 has been sent.

The European Union Clinical Trials group (EurodratCT) has not approved the study. After extensive discussions between the University of Hamburg and DDropsTM of Canada, the EurodratCT group did not accept the trial supplier of cholecalciferol. Attempts by the University of Hamburg to identify a local supplier that could provide 2 doses of cholecalciferol failed. Due to this impasse, the University of Hamburg is no longer a participating site for this study.

Task I.2 (mo 2): conduct an organizational face-to-face meeting between 4 PIs and data monitor

A face-to-face meeting will not occur. All study teams have agreed teleconference calls are sufficient.

Task I.3 (mo 2-3): assemble manual of operations and distribute to each site

A manual of operations was been amended in Feb 2016 and has been distributed to all sites. This was approved by the FDA.

Task I.4 (mo 1-2): establish lines of communication between PIs, coordinators, financial managers at each site

As part of the subcontracts appropriate financial managers have been identified at each of the 4 institutions. Email has been the primary line of communication. Monthly conference calls have been initiated in summer of 2015.

Task I.5 (mo 2): establish long-term contract with courier for shipment of samples, supplies, study drug

DDrops shipped the full supply of study drug (Vitamin D Drops) directly to University of Utah. Study drug was re-labeled and shipped to site investigational pharmacies at the University of Cincinnati and University of British Columbia using FedEX or UPS.

Task I.6 (mo 7-48): maintain regular monthly reports regarding enrollment, data collection, and safety issues

Enrollment was delayed until ----- A RedCap database has been constructed and reports developed for review by the Data and Safety Monitoring Board.

II. Major Goal - Enroll human subjects into a phase II clinical trial with vitamin D3 supplementation

Task II.1 (mo 0-5): establish IRB approvals at 4 sites and USAMRMC ORP HRPO review

Approval from the FDA to use the 4,000 IU dosing of cholecalciferol in the adult NF1 population was obtained in September of 2013. An annual report has been submitted to the FDA. The only significant change has been an alteration in the concentration of Ddrops. The manufacturer will provide a concentration of 300 IU/drop and a concentration of 2,000 IU per drop. Randomized participants will both take 2 drops per day instead of 1 drop per day.

IRB at the University of Utah approved the clinical trial application at the end of November, 2013. Minor amendments reflecting changes in the manual of operations and personnel changes have been submitted for continuing review, which was approved November 30, 2015. Continuing Review for 2016 is pending.

USAMRMC ORP HRPO approved a modified U of Utah IRB-approved protocol in February, 2014, and the continuing review in November 2014 and November 2015.

UBC ethics committee approval was established, and USAMRMC ORP HRPO approval was provided October 20, 2015. Additional continuing review approval in August 2016.

U of Cincinnati IRB protocol was approved by the local IRB and submitted to the USAMRMC ORP HRPO on May 5, 2015. Additional continuing review locally was obtained September 21, 2015 and August 27, 2016.

U of Hamburg protocol was not completed due to issues with supplier of study drug.

Task II.2 (mo 1): confirm oversight by an external safety monitor

The safety monitor is Dr. Richard Kanner from the Center for Clinical and Translational Sciences (CCTS) at the University of Utah serves as chair of a 3-member committee to oversee safety issues related to the study. They will meet face to face or by teleconference every 6 months to review recruitment and participant enrollment, monitor summarized data collection from the 3 sites as submitted to the DSMB, review adverse events, and monitor serum collection and disposition of samples.

Task II.3 (mo 4-23): recruit adults with NF1 to consider participation in clinical trial

Coordinators at each site have alerted their respective adult NF1 population of the upcoming trial. Enrollment has commenced at 3 sites have achieved institutional human subjects protection approval.

Task II.4 (mo 3): establish failsafe mechanism to determine pregnancy status prior to densitometry

The manual of operations specifies local coordinator oversight of urine pregnancy testing prior to the initial DXA scan and exit DXA scan. Coordinators will review of reproductive history with females throughout the study.

Task II.5 (mo 6-15): first enrollment period for 25(OH)D serum screening/vitamin D3 supplementation

ongoing, 6 patients were enrolled from Feb 2018 to Sept 2019

Task II.6 (mo 18-23): second enrollment period for 25(OH)D serum screening/vitamin D3 supplementation

ongoing

Task II.7 (mo 6-15; mo 18-23): verify enrollment with unique identifier by hard copy and electronic means

Not applicable.

Task II.8 (mo 5-48): maintain ongoing IRB approval

DoD HSPO approval is established for 3 sites. Approvals from the 2 subcontracted sites will be collated by the lead coordinator at the University of Utah. These will be forwarded to the DoD HSPO in a timely fashion.

Task II.9 (mo 12, 24, 36, 48): annual review by safety monitor and distributed to each IRB and USAMRMC

Per IRB stipulation, safety reviews of adverse events will take place every 6 months. Data including a spreadsheet of all adverse events will be compiled by the coordinator at the University of Utah and submitted to the safety monitoring committee for review. The FDA also will be appraised of adverse events, and a summary of the safety monitoring committee will be provided to the FDA as part of the annual report of cholecalciferol use in adults with NF1.

Task II.10 (mo 18-27; mo 30-35): data monitor safety assessment for loss of bone mineral density of >7% loss

Not applicable.

III. Major Goal - Obtain laboratory, bone density, and survey data on participants in the study

Task III.1 (mo 3-5): establish scheduling processes for each enrollment center

Scheduling processes have been established at the UTA site through CCTS facilities as an approved protocol. With IRB approval at UBC and CIN, scheduling processes have been established. HAM scheduling processes have not been approved as part of ethics review panel.

Task III.2 (mo 3-5): complete assessment of cross-calibration of DXA machines at 4 sites

DXA machines and scanning teams have been established at each of the 3 sites. Internal standardization of each machine is performed on a daily basis. There is a possibility that the same DXA machine will not be in use from the initial DXA to the exit DXA scan 2 years later. Each site will cross-calibrate machines so that data collected on one machine can be adjusted as part of this process.

Task III.3 (mo 2-5): assemble all data collection forms, blood collection kits, and CDs at each enrollment center

Clinical report forms (CRFs) with revisions have been included in IRB applications. HAM has translated the forms to German but did not submit for review due to lack of agreeable supplier for study drug. Blood collection kits have been identified. Electronic data collection processes are established.

Task III.4 (mo 3-5): establish and verify access to the study-specific, web-based, password-protected database

REDCAP is the study database. Access to database will be granted by Project Manager at the University of Utah for all sites. REDCAP requires a password.

Task III.5 (mo 4): develop mechanism to obtain blood samples for 25(OH) vitamin D screening (ARUP Lab)

Blood samples are sent every 3-4 months from outside sites to ARUP. All University of Utah labs are processed by ARUP.

Task III.6 (mo 6-15; mo 18-23): obtain serum 25(OH)D on 316 enrollees across 4 enrollment centers

As of 30 Sep 2018, 17 patients were screened. 3 patients didn't qualify due to normal viatamin d levels. 14 patients had completed day 1. 6 patients had completed 6 months.

Task III.7 (mo 5-7): document processes for timely notification of serum 25(OH)D results and randomization

N/A

Task III.8 (mo 6-15; mo 18-23): Randomize 226 participants to either 600 IU or 4,000 IU of daily vitamin D3

As of 30 Sep 2018 14 patients have been randomized.

Task III.9 (mo 6-15; mo 18-27; mo 30-39; mo 42-47): perform initial DXA scans, brief physical exam, and perform surveys on 226 participants at 3 time-points

As of 30 Sep 2018 14 patients have had a baseline DXA.

IV. Major Goal - Monitor data acquired throughout the study period

Task IV.1 (mo 3-5): establish confidential procedures for monthly data acquisition monitoring and reporting

Sites will be required to enter visit information into REDCAP. Project manager at the University of Utah will verify Vitamin D samples received in lab and entered in database.

Task IV.2 (mo 3-5): establish access for the data monitoring team to the study-specific database

CRFs have been provided to the medical monitoring team.

Task IV.3 (mo 6-48): verify quality of data acquisition with coordinators at each enrollment center

N/A

Task IV.4 (mo 18-21): perform interim analysis on a subset of enrollees at 1 year for change in BMD of hip

Unable to perform. DXA's at 1 yr was removed from protocol.

V. Major Goal - Provision of vitamin D3 and calcium supplementation

Task V.1 (mo 3-5): verify formulation of vitamin D3 in the form of Ddrops

Documentation has been provided by the manufacturer, Ddrops, on the formulation and distribution of batches of Ddrops to the University of Utah medical monitor team. The manufacturer has altered the concentrations of vitamin D3. Originally, it was to concoct concentrations of 600 IU per drop and 4,000 IU per drop. This has been modified to 300 IU per drop and 2,000 IU per drop. Thus, randomized participants will take 2 drops of

either low-dose or high-dose vitamin D3.

Task V.2 (mo 5): distribute Ddrops from dispensing site in Ontario Canada to the University of Utah

The total shipment of DDrops has been delivered to the University of Utah research pharmacy The HAM site failed to approve direct shipment from Ddrops,.

Task V.3 (mo 2-4): establish failsafe methodology to mask the bottle of Ddrops and provide unique identifier

The medical monitor office has established the plan to remove the Ddrops manufacturer label and replace with a label that enables the randomization team to allocate relabeled study drug upon receipt of notification of enrollment at each of the 4 sites. This entails having the designated vials (low-dose and high-dose) in storage at the respective site's research pharmacy only to be released to a randomized participant by the site clinical research coordinator. Affirmation that the unique identifier of the participant is linked to a unique identifier on the vial will be performed by the local site coordinator and the data monitoring team, under the direction of the medical monitor.

Task V.4 (mo 6-15; 18-23): randomize participants with a unique bottle number/communicate to site coordinator

Redcap is randomizing participants. Site coordinator then provides the unique bottle ID to pharmacy for dispensing.

Task V.5 (mo 6-47): implement methods to educate/monitor participants on aspects of vit D3 and calcium intake

A weekly diary has been IRB approved at the University of Utah, UBC, and CIN.

Task V.6 (mo 12-41): ensure resupply of Ddrops bottle corresponds to the initial bottle designation

DDrops shipped all drug at the same time. DDrops has a self-life of 4yrs.

Task V.7 (mo 6-48): monitor potential side effects of vit D3 supplementation

CRFs for adverse event reporting have been developed and included in the protocols submitted for IRB approval and the revised manual of operations.

VI. Major Goal - Establish a bio-repository of serum samples

Task VI.1 (mo 2-5): develop protocol to process samples at the CGRP freezer storage facility at the U of Utah

This protocol has been approved by the FDA (with amendment) and the U of Utah IRB. Retention of serum after completion of the study has been addressed in IRB protocols. These specimens will be destroyed, unless the participant has signed other IRB approved consent for retention of sample for other studies.

Task VI.2 (mo 6-47): ensure participant identifier corresponds to consent to store samples for future studies

N/A

Task VI.3 (mo 6-47): document acceptance of storage sample in the CGRP database and vit D3 study database

The process for storage of sample in the CGRP database has been established. Information for the vitD3 study database has been established in RedCap.

VII. Major Goal - Data analyses

Task VII.1 (mo 6-48): collect data on all enrollees both by hard copy forms and in the study-specific database

All enrolled participants are entered in RedCap. Project manager receives hard copies of ARUP results. DXA transmittal to occur later.

Task VII.2 (mo 6-48): validate data collection on a monthly basis by data monitor

Records are directly entered into RedCap by sites promptly after visits.

Task VII.3 (mo 7-48): verify accuracy of data collection by enrollment center coordinators

Project manager is reviewing data for completeness and outliers.

Task VII.4 (mo 47-48): perform comparison of low-dose vit D3 versus high-dose vit D3 on data collections

N/A

Subcontracts between U of Utah (UTA) and CIN, UBC, and HAM

Organization name: Cincinnati Children's Hospital Medical Center (CIN)
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4. KEY RESEARCH ACCOMPLISHMENTS – As of Sept 2018, 14 participants have been enrolled and completed day 1.

5. CONCLUSION:

At 3 of the 4 sites are active and enrolling participants. Due to logistical issues HAM will not be continuing as a site. Funds from HAM will be distributed to other sites for participant recruitment and additional participant visits needed.

Vitamin D was received from DDrops in Aug 2017. Vitamin D has been randomized and will be shipped. In mid-Nov 2017, DDrops notified us that one of the two lots had been determined to have decline in potency at at a greater than anticipated rate. DDrops monitors all lots on a monthly basis. All sites sent all DDrops back to the University of Utah at the end of Nov 2017. DDrops resent a new batch. New labels and drug assignment was completed and shipped to sites in Feb/Mar 2018. Screening and enrollment began in Feb/Mar at UTA and CIN, and in Sept at UBC. Enrollment is ongoing but early in the process.