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TITLE: A Phase II Trial on the Effect of Low-Dose versus High-Dose Vitamin D Supplementation on Bone Mass in Adults with Neurofibromatosis 1 (NF1)

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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

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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
UTA = University of Utah

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, Apr 2019, 2020, unable to submit for 2021 due to not received full award extension.

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, 2019 was $74,805.68*. The University of British Columbia has submitted invoices, and payout for October 1, 2014-September 30, 2019 was* $51,323*. 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.

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

Task II.1 (mo 0-24): Recruit adults with NF1 to consider participation in clinical trial
To date, 27 participants have been enrolled and treated with vitamin D3 supplementation.

Task II.2 (mo 1): Ensure pregnancy status prior to densitometry
Female participants of childbearing potential receive a urine pregnancy test prior to densitometry.

Task II.3 (mo 0-12): first enrollment period for 25(OH)D serum screening/vitamin D3 supplementation *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. ongoing, 27 patients were enrolled from Feb 2018 to Mar 2020*

Task II.4 (mo 12-24): second enrollment period for 25(OH)D serum screening/vitamin

D3 supplementation – Enrollment is still open. Due to COVID-19 enrollment was halted at all sites in March 2020. UTA and CIN re-opened for enrollment in Jun 2020. UBC remains closed.

A recruitment flyer was sent to the national patient support organizations to bolster recruitment and assess interest around the country. Potential participants were given a link to the survey monkey. The link opened on Oct 8, 2020. As of Dec 8, 2020 the survey results showed:

- 43 participants opened the survey
- 35 participants had NF1 and were possibly interested in the study
- 25 of 34 respondents were eligible based on gender and age
- 20 of the 25 patients are not taking Vitamin D or a multivitamin
- 19 of 20 eligible recruits would be willing to travel

This survey demonstrated that we could not achieve study enrollment goals.

Task II.5 (mo 6-15): Maintain ongoing IRB approval

Task II.6 (mo 18-23): Bi-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.

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

Task III.1 (mo 0-48): Assemble all data collection forms, blood collection kits, and CDs at each enrollment center

Sites are responsible for their own supplies. Samples have been sent to central lab per protocol.

Task III.2 (mo 0-24): Obtain serum 25(OH)D on 316 enrollees across 4 enrollment centers

As of Dec 2021, 34 patients have been screened. Six patients didn't qualify due to normal serum vitamin D levels. 27 participants have completed day 1/randomized; 26 participants were dispensed study drug. 10 participants have completed year 2. 17

participants have withdrawn or have been lost to follow up and will not complete year 2. 2 of the participants were unable to complete their final DXA due to the COVID-19 pandemic travel restrictions.

Task III.3 (after visits): document processes for timely notification of serum 25(OH)D results and randomization

Reports are sent to sites after completion of analysis at central lab via email.

Task III.4 (mo 0-24) : Randomize 226 participants to either 600 IU or 4,000 IU of daily vitamin D3

As of Dec 2021- 27 participants have been randomized.

Task III.5 (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 2 time-points

As of Dec 2021 – 10 participants have completed 2 DXA scans.

IV. Major Goal – Data Analyses

Task IV.1 (mo 3-5): Collect data on all enrollees both by hard copy forms and in the study-specific database

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 (monthly): Validate data collection on a monthly basis by data monitor

Project manager at the University of Utah has verified all Vitamin D samples received in lab and entered in database.

Task IV.3 (throughout study): Verify accuracy of data collection by enrollment center coordinators

Project manager at the University of Utah has verified Vitamin D samples received in lab and entered in database.

Task IV.4 (48 months) Perform comparison of low-dose vit D3 versus high-dose vit D3 on data collections - A review of the DXA results on the first 10 completed patients is pending.

Task IV.5 (48 Months): Perform all analyses according to specifications, share output and finding with all investigators- n/a

Task IV.6 (48 Months): Work with data core and dissemination of findings (abstracts, presentation, publications, DOD) - n/a

Task IV.7 (48 Months): *Milestone Achieved: Report results from data analyses* - n/a

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

Organization name: Cincinnati Children's Hospital Medical Center (CIN)
Organization address:
Tana Housh
Manager, Sponsored Projects 3333 Burnet Ave-MLC 7030
Cincinnati, OH 45229-3039
Investigators: Elizabeth Schorry, MD Collaborators: Heidi Kalkwarf, PhD

Organization name: University of British Columbia (UBC)
Organization address:
Dr. Martin Kirk
Director, Research Services 102-6190 Agronomy Rd. Vancouver, BC V6T 1Z3
Investigators: Jan M. Friedman, MD, PhD Collaborators: David Kendler, MD

4. KEY RESEARCH ACCOMPLISHMENTS – As of Dec 2021, 27 participants have been enrolled. 10 participants have completed 2 years on the study.

5. CONCLUSION:

Only 3 of the 4 anticipated sites became active and enrolled participants. Due to logistical issues HAM could not enroll as a site. Funds designated for HAM site were 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 shipped. In mid-Nov 2017, DDrops notified us that one of the 2 lots had been determined to have declined in potency 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 2018 at UTA and CIN, and in Sept 2018 at UBC.

We needed to recruit at least 163 participants, which was determined to require a recruitment effort throughout North America for 2 of the 3 sites to make up for lost enrollment from the MAN site, which was anticipated to enroll the highest number of participants. Flyers were made available to NF1 patients nationwide who were identified through the CTF (Children's Tumor Foundation) and NF Network. Of those who contacted Utah, we compiled a list to determine if we could recruit 163 participants. The survey was left open for 2 months. There were 43 responses and 20 participants eligible for enrollment. A request to the statistician on our DSMB was sent to review the DXA results of the 10 completed patients to determine the

observed mean difference in BMD loss between the groups to determine a revised enrollment goal, and if such enrollment could be achieved.

In May 2021 DEXA data from 10 patients was quickly reviewed. The last 2 participants were unable to travel to UBC for their final DEXA due to the COVID-19 pandemic travel restrictions in Canada. A decision was made to end the study based on futile enrollment determined from survey results and travel restrictions on travel to open sites.

The year 2021 was spent trying to obtain approval of our No Cost Extension needed to close out the study. Our NCE was approved on Mar 4, 2022. The CIN site PI, Elizabeth Schorry, MD, retired in 2021, and a replacement has not been identified to close out the study at the CIN site.