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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

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, and pending for 2020.

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 . The University of British Columbia has submitted invoices, and payout for October 1, 2014-September 30, 2019 was . The subcontract with University of Hamburg has been executed, and payment of 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 37 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

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 24Mar2020, 34 patients have been screened. 6 patients didn't qualify due to normal vitamin d levels. 27 patients have completed day 1/randomized, only 26 patients were dispensed study drug. 12 patients have completed year 1. 6 patients have been lost to follow up and will not complete year 2.

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 25 Mar 2020 - 37 patients 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 25 Mar 2020 - 26 patients have had a baseline DXA.

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 will verify 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 will verify Vitamin D samples received in lab and entered in database. Project manager is reviewing all data on an ongoing basis.

Task IV.4 (48 months) Perform comparison of low-dose vit D3 versus high-dose vit D3 on data collections - n/a

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
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Investigators: Elizabeth Schorry, MD Collaborators: Heidi Kalkwarf, PhD

Organization name: University of British Columbia (UBC)
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Investigators: Jan M. Friedman, MD, PhD Collaborators: David Kendler, MD

Organization name: University Medical Center Hamburg-Eppendorf (HAM) Organization address:
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Department of Finance University Medical Center Hamburg-Eppendorf
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Investigators: Victor F. Mautner, MD Collaborators: Said Farschtshi, MD

4. KEY RESEARCH ACCOMPLISHMENTS – As of Mar 2020, 26 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.

We need to recruit at least 163 participants, which will require a recruitment effort throughout North America. Flyers will be made available to NF patients identified through the CTF (Children's Tumor Foundation) and NF Network. Of those who contact Utah, we will compile a list to determine if we can recruit 163 participants. 6 Weeks after flyers have been mailed we will determine if we have made a concerted effortcan achieve sample size needed. If sample size can be achieved those who contact Utah will be referred to the closest study location. If a determination of futility is made, we will proceed with study closure due to lack of enrollment.