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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 study has not been fully implemented. Clinical trial regulatory processes have taken more time than anticipated in the Statement of Work. An IND from the FDA to use high-dose vitamin D in the NF1 (neurofibromatosis type 1) population has been obtained, as requested by the University of Utah IRB. There has been one amendment to the original FDA IND approval. The study was approved both by the University of Utah IRB and the DoD USAMRMC ORP HRPO. Ethics board approval from UBC has been approved by HRPO, and U of Cincinnati is under review. The University of Hamburg is working with the European Union Clinical Trials group (EurodratCT) to implement this study, and a document of agreement to perform a joint clinical trial with the University of Utah has been executed. The Clinical Trials office in Hamburg has reviewed the proposal and we have accommodated the custodianship of study drug, cholecalciferol, from the manufacturer in Canada directly to Germany. Reviews from the IRBs and EurodratCT have led to revision of the manual of operations, which is included in this report. We have instituted monthly conference calls, which has enabled us to finalize the manual of									
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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 D₃ dosing in NF1 patients. This study is designed to assess the efficacy of oral vitamin D₃ 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 D₃ 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 D₃ 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 D₃)

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 9/29/2017.

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 approved the study contingent on assurance that drug is shipped directly from the manufacturer to the University of Hamburg research pharmacy. No funds have been allocated to HAM.

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

A proposal with Marken, an international courier service, is in the process. Marken will be used for shipment of all laboratory samples.

DDrops will ship study drug (Vitamin D Drops) directly to University of Hamburg. All other shipments will come to the University of Utah for re-labeling and then be shipped to site investigational pharmacies using FedEx or UPS.

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

Enrollment has not begun. It is anticipated for Fall 2016 for U of BC, U of Cincinnati, and U of Utah to correspond to the seasonal basis of serum 25-OH vitamin D. Enrollment at U of Hamburg will begin upon human subjects research approval from DoD USAMRMC ORP HRPO.

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 is under revision as reflected in our updated manual of operations, and once translated to German will be submitted to its ethics committee. The CRFs have been translated into German and will be submitted for ethics review once the manual of operations is completed and final revision completed by the U of Utah medical monitor office.

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, and he will serve 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 4 sites as submitted to the Pediatric Clinical Trials Office (director, TBD), 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 will commence when all 4 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

Enrollment is pending arrival of DDrops (study medication) to University of Utah for relabeling and distribution to CIN and UBC.

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

To commence in Spring of 2017.

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

Amendments will be introduced to each of the sites as a final DoD HSPO approval is established for all 4 sites. Approvals from the 3 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 apprised 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 4 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 and will submit as part of ethics panel review. Blood collection kits have been identified. Electronic data collection processes are in transition.

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)

Pending final approval of contract with the shipping agency.

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

N/A

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

N/A

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

N/A

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

Task IV.1 (mo 3-5): establish 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

This has been initiated and is pending final negotiations between DDrops and the University of Utah. The research pharmacist at University of UTah is prepared to receive shipment for all anticipated enrollees, and have approved the shelf life of Ddrops so that storage on site is feasible. HAM has been approved to receive the shipment directly from Ddrops, contract pending.

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

N/A

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 and is pending for HAM.

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

DDrops will ship 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, but linkage of information for the vitD3 study database has not been established.

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

N/A – no enrollees as of yet.

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

N/A

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

N/A

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

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

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Investigators: Jan M. Friedman, MD, PhD Collaborators: David Kendler, MD

Organization name: University Medical Center Hamburg-Eppendorf (HAM)

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Investigators: Victor F. Mautner, MD Collaborators: Said Farschtshi, MD

4. KEY RESEARCH ACCOMPLISHMENTS – None to report

5. CONCLUSION: The implementation of this trial has been delayed for 3 main reasons. The initial assessment by the University of Utah IRB that supplementation of vitamin D required an FDA exemption led to an application that resulted in a denial of exemption, and requirement for an IND for the administration of high-dose (4,000 IU) of cholecalciferol to a selected population of NF1 patients. Approval of an IND through the FDA was obtained in September of 2013. This has been amended in March 2016 to reflect changes in the data collection and safety monitoring. After FDA approval, we could begin the IRB approval process at the University of Utah, which was completed in November of 2013 and reviewed and approved by the DoD HSPO in February of 2014. The next major hurdle has been regulatory compliance with the European Union Clinical Trials organization (EurodratCT) for implementation of a clinical trial through the University of Hamburg. We are working with EurodratCT to finalize our protocol, especially as it relates to the manufacture and transportation of study drug, cholecalciferol. The EurodratCT also required the establishment of a designated legal representative from the sponsoring agency, which was established as the University of Utah. We combined the designated legal representative language with the subcontract, which has been executed. We had anticipated working directly with the University of Hamburg, and the additional regulatory oversight by the EurodratCT was not foreseen in our original application. The administrative costs of this additional regulatory component are provided by the University of Hamburg. Of all 4 sites, HAM is anticipated to have the most adults with NF1 who are insufficient for 25(OH) vitamin D. Without its full participation, it would be nearly impossible to enroll a large enough sample size to achieve statistical significance. We are now poised to complete the ethics review in Germany to begin recruitment in Fall of 2016, and it is anticipated that UBC, CIN, and UTA will be ready to enroll in Fall 2016.

With input from our pediatric clinical trials office (PCTO), we have finalized the manual of operations to reflect the combined needs of all 4 sites and the medical monitoring team. The cost of using the PCTO under new leadership was above what was originally budgeted in the funded proposal, therefore after a teleconference call between the 4 sites we integrated the administrative component of this trial within the Clinical Genetics Research group with Carrie Bailey as the clinical trial manager and the University of Utah Center for Clinical and Translational Sciences.

It is recognized that delays in implementation of the trial will likely lead to cost overrun. Dr. Viskochil has sought no-cost extension approvals to enable funding to the subcontracted sites, and he applied for additional funding from the Childrens Tumor Foundation (CTF) as supplemental funding up to \$150,000 as a CTF-sponsored Clinical Trial Award. The full proposal was submitted in Sept 2016 for competitive review.

The electronic database harboring data entry from each of the 4 sites is being developed in REDCAP by Bernie LaSalle in the CCTS (Center for Clinical Translation Sciences).