Study Title: Safety, Efficacy, and Feasibility of High-dose Cholecalciferol in Pediatric Patients with Cystic Fibrosis

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1. Abstract

Children and adults with Cystic Fibrosis (CF) are at risk of developing a vitamin D deficiency or insufficiency, defined as a 25-hydroxyvitamin D (25OHD) serum blood level <30 ng/mL. Greater than 85% of people with CF have pancreatic insufficiency, which contributes to poor absorption of fat soluble vitamins and dietary fats. A 25OHD level greater than 30 ng/mL has been shown to provide improvements to markers of inflammation in adults with CF and is known to improve bone mineral density and prevent bone fractures in all populations, including CF. This study will assess the safety of a one-time high dose of cholecalciferol or vitamin D3 along with efficacy and feasibility of providing this therapy.

Children between the ages of 3 years and 18 years (inclusive), with a 25OHD level <30 ng/mL will be provided with a vitamin D3 supplement of 250,000 international units (IU) observed in our CF clinic. We hypothesize that this one-time, oral, high dose of vitamin D3 will safely and effectively raise the 25OHD level to above 30 ng/mL.

Safety will be monitored using a tiered safety protocol. Within the first tier, a serum calcium level and a serum phosphorus level will be measured at 1 week and 3 months following the dosage. This timing is appropriate as cholecalciferol has a half-life of 2-3 weeks and these timed levels would be at or near the middle of the 25-OHD range. A second tier safety evaluation will only be done if serum calcium levels or serum phosphorus levels are elevated. For this second tier, the participant will have a parathyroid hormone level measured (PTH) as well as a spot urine calcium to creatinine ratio.

Feasibility is to be measured using a 10-question phone survey 1 week following the dosage (see appendix A - attached). Efficacy will be measured by the 25OHD level itself; if 25OHD levels are found to be between 30-100 ng/mL over the course of the study, the dose will have demonstrated effectiveness in achieving the study's goal.

The purpose of this study is to show that 25OHD levels can be safely corrected with a one-time dose of vitamin D3 and be feasibly provided in the outpatient setting to children with CF.

2. Objectives (include all primary and secondary objectives)

Primary

1. Assess the safety of a single dose of oral vitamin D3 (250,000 IU) for the treatment of vitamin D insufficiency in pediatric cystic fibrosis patients.

Secondary

1. Assess the feasibility of undertaking a future large scale randomized controlled trial. Specifically, we will:
    (a) Assess the acceptability and timing of the selected outcome measures;
    (b) Obtain estimates needed to design a full-scale randomized trial design (if warranted), including: number of eligible participants, recruitment rate, retention rate, response rates to initial and follow up questionnaires.
2. Determine the efficacy of a single dose of oral vitamin D3 (250,000 IU) for the treatment of vitamin D insufficiency in pediatric cystic fibrosis

3. Background

Cystic Fibrosis is an inherited disease that primarily affects the lungs but also can affect the pancreas, liver and gastrointestinal tract. Subsequently, the bone health of individuals is also compromised due to complications arising from malnutrition, malabsorption, and repeated pulmonary exacerbations.

Greater than 85% of individuals with Cystic Fibrosis have pancreatic insufficiency, meaning that their pancreas does not produce digestive enzymes to chemically break down carbohydrates, fats, and proteins. It is known that a majority of digestion takes place in the duodenum of the small intestine where the digestive enzymes are secreted by the pancreas to the duodenum in preparation for the chyme that is released from the stomach. Without digestive enzymes, individuals with CF end up with large macronutrients passing through the small and large intestine undigested, unabsorbed and eventually excreted. Maldigestion and malabsorption results in steatorrhea or fatty stools. Therefore, individuals with CF are required to take porcinebased pancreatic replacement enzymes before each meal or snack to digest and absorb the carbohydrates, fats and proteins in their food.

In addition to having difficulty digesting and absorbing macronutrients, individuals with CF also have difficulty absorbing fat soluble vitamins such as vitamin A, vitamin D, vitamin E and vitamin K . Therefore, individuals with CF are prescribed higher maintenance dosages of these 4 micronutrients to ensure they have adequate absorption and do not become deficient. Individuals with CF require significantly more than the current recommendations vitamins, calories and protein. Recent literature has demonstrated that a substantial proportion of patients with CF are vitamin D insufficient and the current guidelines in treating their clinical insufficiency are not adequate (1).Adequate vitamin D status is defined and measured by a 25OHD level of greater than or equal to 30 ng/mL. Vitamin D insufficiency is defined as a 25OHD level of between 2029 ng/mL and vitamin D deficiency is defined as a 25OHD level of less than 20 ng/mL.

Adequate vitamin D levels have been frequently linked to improving bone mass in those with and without CF. Low levels of vitamin D (25OHD) make it difficult for the body to produce sufficient osteoclasts, which are found in growing bone (1). Lower than expected bone mass of the spine and whole body has been potentially linked to suboptimal levels of vitamin D in

pediatric patients with CF (2). In adult CF populations, sufficient levels of vitamin D have also been linked to reductions in inflammatory markers such as tumor necrosis factor and interleukin6 (3).

The Cystic Fibrosis foundation currently outlines step-wise treatment for vitamin D insufficiency as well as for vitamin D deficiency (4). A Cochrane review describing vitamin D supplementation in cystic fibrosis was published in 2012. The authors reported that none of the studies in the review had closely examined bone mineral density relationship, nutritional status, or growth related to vitamin D. Lung function at baseline was reported in one of the studies; however, no data was collected in any of the reviewed studies indicating proportions of respiratory exacerbations and none of the reviewed studies assessed quality of life (5). Therefore, there is still extensive research needing to be performed with regards to CF and vitamin D insufficiency.

Currently, our CF center at Johns Hopkins All Children's Hospital are seeking to improve the administration of vitamin D to our insufficient CF patients. We know that individuals with CF are burdened with multiple medications throughout the day. The current administration of vitamin D to our patients who have vitamin D insufficiency include a recommendation for the parent or caregiver to purchase vitamin D as cholecalciferol in the prescribed amount, at a local drug store, and to administer to the patient once daily with food and with enzymes (if applicable). After consistently providing this prescribed dose for 12 weeks, the patient is asked to have his/her 25OHD level re-drawn with a second venipuncture. Anecdotally we have discovered that parents and caregivers often do not obtain the prescribed amount of vitamin D by the next CF clinic visit 2-3 months later and will also delay the second episode of venipuncture due to anxiety surrounding this procedure.

When we analyzed our center specific data on vitamin D levels and treatment, we discovered that our current efforts reveal approximately 87% of our population have vitamin D levels within the past twelve months. Of those tested, 53 (40%) demonstrate levels between 30 ng/ml and 40 ng/ml and 43 (33%) below 30 ng/ml (insufficient), the remaining 27% had levels below 20 ng/mL (deficient). Current empirical and anecdotal data show a clear need for improvement in administration of vitamin D3 for the purpose of correcting vitamin D insufficiency and deficiency in this pediatric CF population.

As evidenced by our recent analysis, we continue to face challenges in our efforts to improve vitamin D abnormalities. Insurance companies rarely, if ever, cover vitamin supplements, putting the financial burden on parents. Adding additional medication to already expansive chronic therapy increases the burden of care for everyone involved. Repeating vitamin D level tests several times a year results in significant patient and family stress for those with needle aversion, including additional costs to insurance and other financial entities.

To address these challenges, we are exploring alternatives to our current treatment methods. These include increasing the daily maintenance dose of vitamin D3 across the board.

Alternatively, we are evaluating implementation of STOSS (single high-dose oral vitamin D3) therapy. Research has shown that a one-time high dosage of cholecalciferol (vitamin D3), increases 25OHD levels in the Cystic Fibrosis population as well as the non-CF population in both pediatric and adult individuals, without hypercalcemia and with reductions in parathyroid hormone (PTH) (6, 7, 8, 9). If successful, changing the current route of correcting vitamin D insufficiency via STOSS therapy would provide financial relief related to medication access and a decrease in burden of care.

Research has displayed that the human body's response to vitamin D3 is biphasic, meaning it responds rapidly to low vitamin D3 doses and responds much slower to a larger vitamin D3 dose. Heaney et al. found that the low doses of vitamin D3 had a half-life of 20-30 days, but a high dose, such as 100,000 IU vitamin D3 had a half-life of 50 days (10). The authors hypothesized that perhaps at this higher dosage the vitamin D3 is being stored in fat and other body tissues and then slowly released; whereas the daily low doses of vitamin D3 provide an immediate increase or response that can sometimes be reflected in the blood sample.

In children and adults without malabsorption disorders, the current recommended range of daily vitamin D intake ranges from 400 IU per day for children as recommended by the American Academy of Pediatrics (11). Whereas the Institute of Medicine or IOM recommends a range of 600 IU to 4000 IU per day based on the age of the child. The IOM committee did increase its "upper level intake". That dose is 4,000 IU/day for adults, 3,000 IU/day for kids aged 4-8, 2,500 IU/day for kids aged 1-3, 1,500 IU/day for infants aged 6-12 months, and 1,000 IU/day for infants aged 0-6 months. The Endocrine Society for Patients at risk for vitamin D deficiency recommend a daily requirement of 400 IU-1000 IU for children depending on age and their upper level intake is 2000-4000 IU per day depending on age as well (12, 13). However, these recommendations are not for children with absorption disorders such as Cystic Fibrosis.

According to the National Institutes of Health, 25-OHD levels which are consistently greater than 200 ng/mL are "potentially toxic" (13). The IOM committee found no conclusive evidence that increased vitamin D levels confer increased health benefits, challenging the concept that "more is better". However, this was meant to be applied to healthy populations. A review of literature conducted in 2013 displayed that intoxication from vitamin D supplementation was rare in the pediatric setting. This same review also found that hypervitaminosis was "usually asymptomatic" and errors in formulation of the vitamin, manufacturing or prescription of the vitamin resulted in intoxication (13).

Vitamin D toxicity or hypervitaminosis D is characterized by elevated serum calcium levels or hypercalcemia (14). Due to the hypercalcemia, acute symptoms of toxicity can include muscle weakness, confusion, vomiting, anorexia, polyuria and polydipsia. In addition, hypercalcemia can be chronic, and those symptoms of intoxication from hypervitaminosis D could include bone demineralization, pain, and nephrocalcinosis.

Therefore, we believe STOSS therapy will efficaciously, safely and feasibly increase vitamin D levels to above 30 ng/mL in our pediatric CF population. We hypothesize that STOSS therapy

administered once in clinic as witnessed by a designated clinician, will maintain 25OHD levels greater than or equal to 30 ng/mL without instances of hypercalcemia (7).

4. Study Procedures

The study is a phase 2 single arm study that will assess the safety, feasibility and efficacy of a high dose of vitamin D3 as cholecalciferol in Cystic Fibrosis pediatric patients with a 25OHD level <30 ng/mL. The members of the study team will enroll 30 participants who have consented and meet eligibility criteria, including a baseline 25OHD level <30 ng/mL which is measured annually, at a minimum, as a part of the current standard of care. All patients with CF, will be consented to participate upon having his/her annual lab work collected.

As patients present with a 25OHD level < 30 ng/mL they will be screened to see if they meet full eligibility criteria for enrollment. This will include a phosphorus level and spot urine calcium to creatinine ratio which will be collected at their CF visit (patients seen at the St. Petersburg office) or within 2 weeks prior to their visit if in Sarasota or Tampa. (See section 5 for complete inclusion/exclusion criteria). Screening will also consist of a urine pregnancy test to be completed the day of the administration of the high dose of vitamin D.

After a patient meets full eligibility criteria, they will be enrolled in the study and we will administer the 250,000 IU vitamin D3 at that visit. Upon administration, each participant will be provided with an oral, one-time dosage of vitamin D3 (cholecalciferol) in the form of capsules that will be swallowed; the capsule cannot be crushed or dissolved in anything in order to be administered.

Participants will be witnessed by a member of the study team to confirm 100% adherence. With this, they will also be provided with water and saltine crackers to take with the vitamin D by mouth. If the participant is on pancreatic enzymes, they will be required to take their prescribed snack dosage with this as outlined by their CF Physician. The participants will be notified to bring their own supply of pancreatic enzymes to this visit with them. If the participant forgets to bring pancreatic enzymes, enzymes will be provided to them at a dosage closest to the prescribed snack dosage.

If the participant has an episode of emesis upon taking the high dose of vitamin D3 at any time following the dose, the participant will not be provided or required to take any additional high dose of vitamin D3 for study purposes. They will continue to be followed in the study. They will also continue to take their previously prescribed standard CF vitamins as dictated by standards of care throughout the study; this information will be kept in a secure study database. Information on the participant's daily CF vitamin/mineral prescription, including total International Units of cholecalciferol they are receiving will be collected at each study visit. Additionally, information on the participant's pancreatic function, i.e.: pancreatic insufficiency or pancreatic sufficiency will be collected at baseline, among other demographic data.

As much as possible, we will try to have study visits coincide with clinic visits which usually occur every 3 months as a part of the current standard of care. A study calendar describing all study procedures is found at the end of this section.

The following safety measures have been reviewed and approved by two Johns Hopkins All Children's Hospital Endocrinologists: As additional measures of safety at 7 days to the next working business day of the administration of the 250,000 IU of vitamin D3, all participants will also have a serum calcium and serum phosphorus level measured. If any participant has a serum calcium above the upper limits of normal (ULN) for their age (appendix B), they will be contacted via telephone to be queried about symptoms of hypercalcemia such as muscle weakness, confusion, vomiting, anorexia, confusion, polyuria and polydipsia. If the patient has more than 1 symptom of hypercalcemia and an elevated serum calcium level, we will consider this an adverse event. During this communication, it will be decided if any type of treatment will be needed to remedy the complaint (see section on treatment of hypervitaminosis D from hypercalcemia).

If any participant has a serum calcium level greater than the ULN for age or a serum phosphorus level greater than the ULN for age, a second tier of safety measures will be taken. This will include measuring a PTH with reflex calcium level as soon as possible, within approximately 7 days (± 3 days) of the serum calcium or phosphorus lab draw. In addition, we will obtain a spot urine calcium to creatinine ratio. Calcium levels and/or phosphorus levels will be repeated every 2 weeks (±7 days) until normalized for age. If the spot urine calcium to creatinine ratio is > ULN for age (Appendix C) we will obtain an Endocrinology consult and if symptomatic be instructed to go to the Johns Hopkins All Children's Hospital for evaluation . The urine calcium to creatinine ratio will be repeated in 1 week (±3 days) and then monthly (±7 days) until normalized for age. Proposed treatment for hyperphosphatemia will involve increased fluids and restriction of phosphorus loaded foods. Proposed treatment for hypercalcemia, as reflected by a serum calcium level, is detailed in another section of this protocol.

To evaluate for feasibility, at 7 days to the next working business day after administration of the 250,000 IU administration of Vitamin D3, participants will be contacted by a member of the study team via phone to answer a 10-item questionnaire which is included as an appendix at the end of this protocol. This questionnaire is to assess feasibility of the 250,000 IU Vitamin D3.

Regardless of serum calcium level or other labs collected, if a participant does become ill after taking the high dose of vitamin D3 (e.g., muscle weakness, confusion, vomiting, anorexia, polyuria and polydipsia, etc.) they will be asked to call the CF office number, 727.767.3995. During this communication, it will be decided if any type of treatment will be needed to remedy the complaint (see section on treatment of hypervitaminosis D from hypercalcemia). If their serum calcium level was within normal limits for age, but they have symptoms of those found with hypercalcemia, it will be noted in our study findings but not classified as an adverse event.

At 12 weeks (± 30 days) from the initial study visit, participants will be required to have another 25OHD level measured via venipuncture as a part of standard of care. In addition, as a part of the

first tier of safety measures, a serum calcium and serum phosphorus level will be measured again. If either of these levels is elevated, a PTH level will be measured as soon as possible within approximately 14 days (± 3 days) of this serum calcium lab draw. If serum calcium level is above ULN a spot urine calcium to creatinine ratio will be ordered. At 26 weeks (± 30 days) and 52 weeks (± 30 days) the participants will have 25OHD levels measured again. No additional one-time high dosage of vitamin D3 will be prescribed or provided during the study period for any reason to any of the participants. No additional measures of safety, in the forms of serum calcium labs, serum phosphorus, or PTH will be measured.

Any participant with an elevated serum calcium level of anything above normal limits for age will be instructed to limit calcium containing foods in their diet, stop supplements with additional vitamin D and/or calcium. Since these participants will be called regarding their elevated serum calcium level to query about symptoms of hypercalcemia, we will be able to instruct them on this.

If at any time after the study intervention has started and the participant has a 25OHD level less than 30 ng/mL, they will be placed on the current standard CF Foundation step-wise guidelines for treatment appropriate for their low vitamin D level.

There will not be a placebo group, as the study design does not support this; providing a placebo is not ethical in this population for this condition.

If a patient does not complete the study for any reason, meaning they do not get each set of lab work completed, their results up to that point in time will still be used in the study but their duration of participation will be noted in the results section. Every effort will be made to contact patients who are lost to follow up to ascertain the reason for withdrawal.

Study Procedures		**Study Time-points**						
	Screening/ Eligibility	**Base-line**	***Week 1* +/- 3 day**	***Week 1 B:*** Week 1+/- 14 days***	**Week 12 +/- 30 days**	***Week 12 B:*** Week 12 +/- 42 days***	**Week 26 +/- 30 days**	**Week 52 +/- 30 days**
Informed Consent	X							
25OHD Lab	X				X		X	X
Screening / Eligibility Verification (including pregnancy test)	X							
Eligibility screening: Spot Urine Calcium to Creatinine Ratio	X							
Study Registration		X						
Medication Review*		X			X		X	X
STOSS Vitamin D3 Administration		X						
Serum Calcium Test & Hypercalcemia Monitoring			X	X	X	X		
Serum Phosphorus	X		X	X	X	X		
Parathyroid Hormone (PTH) Level (2^{nd} tier only)				X		X		
Spot Urine Calcium to Creatinine Ratio (2^{nd} tier only)				X		X		
Administration of Appendix A Questionnaire			X					
Adverse Event Assessment**		X	X	X	X	X	X	X

* *Medication review will consist of surveying the patient's current daily maintenance dosage for vitamin D as previously prescribed.*

** *AEs and SAEs are defined per 21CFR312.32. All adverse events will be monitored and processed from study start until 30 days after study product administration. All adverse events deemed related to known vitamin D supplementation risks and/or study procedures will be monitored for 12 months post drug administration.*

*** *2nd tier safety assessment using PTH will only be performed in the event serum calcium levels or serum phosphorus levels are elevated greater than the upper limit of normal for age. A spot urine calcium to creatinine ratio will be done.Repeat calcium and phosphorus will be provided every 2 weeks until normalized.*

5. Inclusion/Exclusion Criteria:

1. Exclusion Criteria:
    a. Any history of kidney disease, kidney stones, or on dialysis
    b. Any history of hypercalcemia above upper limits of normal for age within the last six months (see appendix B for normal calcium levels).
    c. Elevated serum phosphorus level at screening
    d. Elevated spot urine calcium to creatinine ratio at screening
    e. Abnormal serum creatinine level 2 times the upper limit of normal for age within the last 6 months
    f. History of unresolved, abnormal liver function (ALT or AST>4times upper limit of normal (ULN)) or any history of portal hypertension.
    g. Pregnant or breast feeding adolescent females; upon enrollment, will test urine sample for pregnancy in females 8 years and older
    h. Any history of parathyroid disorders
    i. Inability to swallow pills by mouth 2. Inclusion Criteria:
    a. Children with Cystic Fibrosis ≥36 months of age
    b. Serum/blood 25OHD level < 30 ng/mL
    c. Ability to provide valid informed consent to be a part of the study
    d. Negative urine pregnancy test upon enrollment

6. Drugs/ Substances/ Devices

This trial is being conducted under Investigational New Drug (IND) application # 128487 – IND Sponsor: Deanna Green, MD; all relevant FDA regulations will be followed.
Cholecalciferol (Vitamin D3) capsules from Biotechpharmacal will be used. Each capsule has 50,000 International Units of Vitamin D3. Each participant will be provided with 250,000 IU Vitamin D3 (5 capsules) regardless of age, sex or 25OHD level.

The dosage of 250,000 IU Vitamin D3 has been shown to be safe and effective in raising the 25OHD level in adult patients with CF and dosages higher than this have been shown to be safe and effective at raising 25OHD levels in pediatric patients as young as 36 months old with dosages of 100,000 IU Vitamin D3 in addition to pediatric patients 12 years old receiving 400,000 IU Vitamin D3 as a one-time dosage without any adverse events, including hypercalcemia.

The safety of high dose of Vitamin D3 has not been evaluated in pediatric CF patients in the U.S.

7. Off-Treatment and Off-Study Criteria

1. Off-Treatment Criteria: Any patient who requires high dose supplemental vitamin D prescribed outside the study.
2. Off-Study Criteria:
    a. Refusal of further study follow-up by patient or legal guardian

b. Lost to follow-up
c. Death
d. Completion of study requirements

8. Reporting Mechanisms

1. Study Registration
   a. All patients will be registered by the Research Coordinator. The following forms will be completed: Eligibility checklist, On-study form, and Concomitant information form.
2. Toxicity and /or Adverse Reactions
   a. All adverse events will be monitored and processed from study start until 30 days after study product administration.
   b. All adverse events deemed related to known vitamin D supplementation risks and/or study procedures will be monitored for 12 months post drug administration. Serious adverse events will be defined by the criteria specified in 21CFR312.32.
   c. All safety-related event meeting FDA's expedited or annual reporting requirements as stated in 21 CFR 312.32 and 21 CFR 312.33, respectively, will be reported to the FDA.
   d. All safety-related events meeting the IRB's reporting requirements will be submitted to the IRB.
3. Informed Consent
   a. All patients and/or their legal guardian must sign a document of informed consent consistent with local institutional and federal guidelines stating that they are aware of the investigational nature of this protocol and of the possible side effects of treatment. Further, patients must be informed that no efficacy of this therapy is guaranteed and that unforeseen toxicities may occur. Patients have the right to withdraw from this protocol at any time. No patient will be accepted for treatment without such a document signed by him or his legal guardian. Full confidentiality of patients and patient records will be provided according to institutional guidelines.
4. Clinical Trial Oversight and Monitoring
   a. This protocol will be monitored and evaluated in accordance with Johns Hopkins All Children's Hospital CTRO's quality assurance procedures.

9. Statistical Analysis

The primary safety endpoint will be serum calcium levels one-week after administration of the high dose of vitamin D3. Other variables related to safety include the frequency and severity of adverse events and early stopping rules.

Serious Adverse Experiences (SAE): An SAE is defined as any AE that results in any of the following outcomes:

- Death;

- Life-threatening adverse experience;
- In-patient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the participant or require intervention to prevent one of the outcomes listed.

For this study, important medical events that will be reported as an SAE per protocol also include:

If at any time >10% of the participants experience hypercalcemia, accrual will be held pending safety analysis and will be restarted only with the approval of the Data Safety Monitoring Board.
A hypercalcemia level with serum calcium measure of > 13.5 mg/dL requiring hospitalization and treatment.

The following additional demographic and clinical information will be collected at baseline for each participant: Age, gender, pancreatic status (pancreatic insufficiency or pancreatic sufficiency), brand of daily vitamin, prescribed dosage and amount of vitamin D3 in prescribed daily dosage. Qualitative data on the appropriateness of study materials and reasons for nonparticipation and attrition will also be collected to inform future improvement in study materials and recruitment and retention strategies.

Demographic and clinical characteristics of participants will be summarized using counts and percentages for categorical variables and mean and standard deviation or median and range for continuous variables. The mean and corresponding standard deviation of serum calcium level one-week after administration of the high dose of vitamin D3 as well as the proportion and 95% confidence interval of participants with elevated serum calcium levels for age will be calculated.

Feasibility and efficacy parameters including recruitment rate, retention, response percentages to initial and follow up questionnaires and proportion of participants with serum 25OHD level >30 ng/mL at the end of the study will be calculated with the corresponding
95% confidence intervals. All adverse events and study related adverse events will be summarized using counts and percentages.

The aim of the study is to determine safety and feasibility of a single high dose (250,000 IU) oral vitamin D3 for the treatment of vitamin D insufficiency/deficiency in pediatric cystic fibrosis patients. The study is therefore not powered to detect a difference in a clinically important endpoint. We intend to consecutively enroll 30 patients in the study. A sample size of 30 should be sufficient to determine the safety and feasibility and to also estimate the parameters needed to perform a definitive sample size and power estimation of a large-scale RCT if safety and feasibility are shown in the current study. An appropriate sample size and power calculation based on the parameters obtained in this study will be presented in a future large-scale RCT protocol.

Early Stopping Rules:

1. Participants who experience hypercalcemia as defined by a serum calcium greater than 13.5 mg/dL or with a spot urine calcium to creatinine ratio >2 times ULN will be allowed to stop the study and resume standard of care of treatment of their vitamin D insufficiency and will be required to receive treatment for their severe hypercalcemia (defined below in section 10 under "steps taken to minimize the risks").
2. Participants who experience a 25OHD level as defined by a level of >100 ng/mL will continue to be followed in the study and be monitored for hypercalcemia or hypercalciuria with the study protocol.

10. Risks:

Risks of the trial include:

a. Venipuncture risks at baseline, 1 week, 3 mo, 6 mo, & 12 mo;
b. Swallowing risks at baseline;
c. risk of hypervitaminosis D at 3 mo, 6 mo, & 12 mo;
d. risk of hypercalcemia at 1 week, 3 mo, 6 mo, & 12 mo;
e. risk of renal stones at 1 week, 3 mo, 6 mo, & 12 mo;
f. risk of continued vitamin D deficiency/insufficiency regardless of treatment throughout the study duration;
g. Other minor risks associated with the trial include upset stomach (nausea) and taking a vitamin supplement by mouth.

Steps taken to minimize the risks:

a. Standard precautions will be used with other venipuncture occurrences;
b. Patients will be monitored as they are administered their one-time, oral, high dose vitamin D in CF Clinic. They will be provided with water to take it with by mouth;
c. To minimize the risk of hypervitaminosis D and hypercalcemia, the participants are having their serum levels of 25OHD, calcium and phosphorus monitored in the study. Participants with an elevated serum calcium will be called and queried about symptoms of hypercalcemia as well as instructed to stop any calcium containing supplements, any vitamin D containing supplements, and to limit foods containing calcium from their diet.
d. In the event of hypervitaminosis D, hypercalcemia, and/or hyperphosphatemia, Dr. Green, study Principal Investigator, will be notified as soon as possible. She will evaluate the event and decide on the appropriate action for further testing and/ or referral. Subjects with calcium levels >ULN for age will require a spot urine calcium to creatinine ratio. Those with Grade 4 severity will require further intervention.
    1. Grade 1 severity: corrected serum calcium of >ULN – 11.5 mg/dL
    2. Grade 2 severity: corrected serum calcium of > 11.5 -12.5 mg/dL
    3. Grade 3 severity: corrected serum calcium >12.5- 13.5 mg/dL
    4. Grade 4 severity or severe hypercalcemia corrected serum calcium of >13.5 mg/dL. If subjects are found to have grade 4 severity or severe hypercalcemia, they will be treated as follows (16, 17):

a. Volume expansion with isotonic saline at an initial rate of 200 to 300 mL/hour that is then adjusted to maintain the urine output at 100 to 150 mL/hour
b. Administration of calcitonin (4 IU/kg) and repeat measurement of serum calcium in several hours.
   If a hypocalcemic response is noted, then the patient is calcitoninsensitive and the calcitonin can be repeated every 6 to 12 hours (4 to 8 IU/kg). We typically administer calcitonin (along with a bisphosphonate) in patients with calcium >14 mg/dL who are also symptomatic.
c. The concurrent administration of a bisphosphonate, such as zoledronic acid or pamidronate, per institutional guidelines.

Significant reduction in serum calcium levels should be seen within 12-48 hours of administration of saline plus calcitonin

During the study, we may obtain research data about the participant's health. If there are unexpected findings from our research that are important to their health and should be discussed with them and or their family, we will notify them.

Patient data will be stored for research purposes as a HIPAA defined limited data set in a secure, password protected web-based electronic data capture (EDC) system. Each patient will be assigned a unique Participant ID number in the EDC system. Access to the EDC system will be restricted to those users identified as part of the research study team and permission will be granted based on levels of access deemed necessary for their role. Data extractions as well as modifications or edits to data will be logged appropriately to adhere to audit trail requirements. No financial risks to participants have been identified.

11. Benefits

Previous studies of a high dose of vitamin D3, in adults with CF, have shown that they have a decrease in markers of inflammation, specifically interleukin and TNF. Studies have also shown that adequate vitamin D may help to maintain or improve lung function although this has not been proven. Adequate vitamin D is widely known to improve bone mineral density in children and adults, with and without CF. It is hoped that this study might provide additional information regarding the role of a high dose of vitamin D in relation to sustaining an appropriate serum 25OHD level for up to 12 months, safely and feasibly.

12. Costs

Labs:

Serum calcium levels measured at 1 week post administration of the high dose vitamin D3 and at the 3 month visit post administration of vitamin D3 will be covered by a grant. The cost of each serum calcium measurement will be billed as "research" and will cost approximately $62.64 for each draw.

Serum phosphorus will be measured at baseline, 1 week post administration of the high dose vitamin D3 and again at the 3 month visit along with serum calcium and 25OHD. The cost of serum phosphorus will be billed as "research" and is $31.42 per draw and will be covered by a grant provided by the ACH foundation.

Spot urine calcium to creatinine ratio levels will be done as a part of the screening process for this study as well as if a participant has a serum calcium level >ULN. The cost of one spot urine calcium to creatinine ratio is $73.52. This will cost approximately $2205.60 for the screening purpose of this test for 30 participants.

We will additionally budget the cost of three participants requiring this test as a measure of safety, as this will be 10% of our overall goal number of study participants. Once we have 10% of our study participants with hypercalcemia and requiring additional safety testing, the study will be held until the DSMB can review.. The cost of three participants requiring this test at week 1 and at month 3, will cost $441.12 ($73.52 per test).

The cost for the urine pregnancy tests will be about $1.98 per test or $49.63 per box of 25 tests. We do not expect to need more than 25 pregnancy tests since these will only be used for female participants greater than 8 years old.

25OHD level is a part of the standard of care for pediatric patients with Cystic Fibrosis and will be measured for "baseline" measures prior to enrollment in the study and upon annual exam. Therefore, the cost fits within the usual cost to the participant even if they weren't participating in the study. In addition, each time they are required to have it re-measured at 3 mo, 6 mo & 12 mo it will continue to be a part of the standard of care for assessing their vitamin D. There will be standard costs associated with it that the participant would be paying even if they weren't participating in this study.

Vitamins/Supplements:
Vitamin D3 water miscible form will be purchased via grant funds from BioTechPharmacal.com for $18.00 per 100 capsules of a water soluble and vegetarian vitamin D3 – 50,000 IU per capsule (18 cents per capsule or maximum cost per STOSS dosage of 250,000 IU is $0.90).

CF specific vitamins are currently prescribed to all patients upon diagnosis. Therefore, participants will already be prescribed these as a part of the standard of care for the nutritional management of pediatric patients with CF and pancreatic insufficiency. Patients who are pancreatic sufficient will be on a standard regular multivitamin with minerals as a part of the standard of care. Neither of these will accrue additional cost to our center or to the patient.

Other: Support Personnel
A research coordinator will act as a part of the research time. He/she will assist in approaching eligible patients to obtain consent for participation in this study, scheduling necessary lab work, conducting the 10-item questionnaire and inputting the necessary data into the Red Cap database

over the course of 12 months from the start of the study. This person's salary will be covered by a grant previously awarded to our CF Center and through CTRO funds.

Diana Hodge will work as the regulatory affairs and quality measures manager for this study.

Other: Data Safety Monitoring Board – DSMB
We will require 3 members for our DSMB, one of which will be the chair person. The first DSMB meeting will occur at 50% of participant enrollment, the second meeting when 50% of participants have had their 3-month evaluation (after the safety endpoints have been evaluated), the third meeting when 50% of participants have completed the study and the fourth meeting when all have completed study.

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Appendix A – Phone Survey 1 – week following dosage

NOTE: the following questions will be based on the previous week only and will be about how you usually feel or symptoms you otherwise usually have.

1) Over the last week, since you have taken the vitamin D3 of 250,000 IU have you:
   i) Experienced feeling an increased amount of nausea?
   (1) NO
   (2) YES ii) Experienced an increased frequency of emesis (vomiting)?
   (1) NO
   (2) YES iii) Experienced an increased amount of diarrhea?
   (1) NO
   (2) YES iv) Experienced any constipation?
   (1) NO
   (2) YES
   v) Experienced increased gas production, such as burping or passing gas?
   (1) NO
   (2) YES vi) Experienced an increased amount of abdominal pain/stomach aches?
   (1) NO
   (2) YES

2) Since taking the vitamin D3 last week, have you experienced an increase in heart burn or reflux? i) NO ii) YES

3) Did you find the one-time dose of vitamin D3 to be easy to take?
   i) NO
   ii) YES

4) Would this type of medication be something you would do next year if you had another low vitamin D level?
    i) NO
    ii) YES

5) Would you prefer taking a one-time dose of vitamin D to treat a low vitamin D level instead of taking a daily vitamin D supplement?
    i) NO
    ii) YES

Appendix B Normal Calcium Values for age (JHACH Laboratory reference values)

	Normal
0 Year 00M 00D F	7.5-11.3
0 Year 00M 00D M	7.5-11.4
0 Year 00M 08D F	8.4-11.9
0 Year 00M 08D M	8.6-11.7
0 Year 01M 00D F	8.0-11.1
0 Year 01M 00D M	8.5-11.3
0 Year 03M 00D F	7.7-11.5
0 Year 03M 00D M	8.3-11.4
0 Year 06M 00D F	7.8-11.1
0 Year 06M 00D M	7.7-11.0
1 Year 00M F or M	8.7-9.8
4 Year 00M F or M	8.8-10.1
10 Year 00M F or M	8.9-10.1
12 Year 00M F or M	8.8-10.6
14 Year 00M F or M	9.2-10.7
16 Year 00M F or M	8.9-10.7
20 Year 00M F or M	8.4-10.2

Appendix C Normal Urine Calcium:Creatinine Ratios for age (Harriet Lane Handbook Table 19-3)

	Normal
< 07 M F or M	0.86
7-18 M F or M	0.60
19 M -6 Y F or M	0.42
>6 Y F or M	0.22