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# HIGH DOSE CHOLECALCIFEROL SUPPLEMENTATION IN ADULTS WITH CYSTIC FIBROSIS

Running Title: HIGH DOSE CHOLECALCIFEROL SUPPLEMENTATION

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**Abstract**

Introduction:

Despite the availability of consensus guidelines for treatment of vitamin D deficiency, there is a lack of prospective trials examining alternative dosing strategies for adult patients with cystic fibrosis (CF) who do not meet therapeutic goals with standard regimens.

Objectives:

The primary objective of this study was to determine the efficacy of high-dose cholecalciferol supplementation in increasing serum vitamin D (25-OHD) levels in adult patients with CF.

Methods:

Patients were eligible for inclusion if they were ≥18 years old, had baseline 25-OHD levels less than 30 ng/mL, and were diagnosed with CF and pancreatic insufficiency. Patients were given a single dose of cholecalciferol 300,000 or 500,000 IU based on baseline 25-OHD levels. Response was defined by 25-OHD and ionized calcium levels at 3 months. At 6 months, responders received a second dose of the same strength, and non-responders were given a weekly supplement of cholecalciferol 50,000 IU in addition to cholecalciferol 500,000 IU. A second 25-OHD level was obtained at 9 months.

Results:

Of 46 patients enrolled, 32 patients (70%) completed the study. Baseline levels of 25-OHD significantly increased over time in the per-protocol population at 3 months and 9 months. A total of 16 patients (50%) were considered non-responders and required weekly supplementation.

Conclusion:

A protocol using high-dose cholecalciferol or high-dose plus weekly cholecalciferol is safe and effective in treating adult patients with CF and pancreatic insufficiency.

**Keywords:**

Cholecalciferol, Vitamin D, nutrition, cystic fibrosis, adults with CF

## Introduction

Malabsorption of fat and fat-soluble vitamins A, D, E, and K due to pancreatic insufficiency is a common extra-pulmonary complication of cystic fibrosis (CF). In 2016, more than 80% of patients with CF under the age of 40 were taking pancreatic enzyme replacement therapy (PERT).[1] Vitamin D deficiency an increasingly significant problem in this population because the median predicted survival age for patients with CF has improved to approximately 48 years.[1] Negative consequences of vitamin D deficiency include reduced peak bone mass, chronic bone pain, chest deformity, and increased risk of vertebral fractures.[2] In addition, studies have demonstrated possible positive effects of adequate vitamin D levels on lung inflammation, pulmonary function, and CF-related diabetes.[3-5]

Current standard of practice for vitamin D deficiency in patients with CF includes daily supplementation with cholecalciferol to maintain a goal serum 25-hydroxyvitamin D (25-OHD) concentration of 30 ng/mL or greater.[6-7] Because most patients with CF have pancreatic insufficiency and are not able to maintain this goal vitamin D level, large doses of supplemental vitamin D are required to overcome impaired absorption. The most recent consensus guidelines recommend a daily cholecalciferol dose of at least 800-2,000 IU. This may be accomplished with a CF multivitamin with high content of vitamins A, D, E, and K; however, patients often require additional cholecalciferol supplementation, further increasing pill burden. For patients who are still not within goal, recommendations are to increase the dose to as much as 10,000 IUs per day.[6] There is a lack of prospective trials examining alternative dosing strategies in adult patients with CF who do not meet goals of

therapy on standard regimens.

The efficacy of single, high-dose cholecalciferol (ie, stoss dosing) was evaluated in 38 children with CF.[8] Patients received a single oral dose of cholecalciferol 100,000 – 600,000 IUs followed by a recommended intake of 800 IUs vitamin D as maintenance therapy. Dosing was individualized based on 25-OHD and age. Patients older than 12 years received doses of 300,000 IU, 500,000 IU, or 600,000 IU based on 25-OHD levels of 20-30 ng/mL, 10-20 ng/mL and ≤10 ng/mL, respectively. Mean 25-OHD levels recorded at 1, 3, and 6 months were above the goal level of 30 ng/mL; however, at the 12-month time point, mean 25-OHD fell below goal to 25.9 ng/mL. No adverse effects of therapy were reported. The findings of this study showed safety and partial efficacy of stoss dosing in children with CF.[8]

The efficacy of stoss dosing in pediatric patients with CF is promising. However, stoss dosing has not been studied in adults with CF. The objective of the current study was to determine if two treatments with high-dose cholecalciferol would allow adult patients with CF to reach and maintain goal 25-OHD levels.

**Methods**

Study Design

This study was an open-label, prospective study, with patients serving as their own controls. The study design was reviewed and approved by the Indiana University-Purdue University Indianapolis (IUPUI) institutional review board (IRB), and the study began enrolling patients in October 2015. Patients received cholecalciferol doses based on baseline serum 25-OHD levels of 25-OHD 20-<30 ng/mL (300,000 IUs) or 25-OHD <20 ng/mL (500,000) (Figure 1). Dosing was based on the pediatric stoss dosing study[8], but simplified to include the two lower dosing options due to low anticipation of patients with 25-OHD ≤10 ng/mL. Patients

were not prescribed additional daily vitamin D supplementation, but they were instructed to continue taking their CF multivitamin. At 3 months, the 25-OHD concentration was repeated. If serum 25-OHD was less than 45 ng/mL, patients were eligible to receive a second dose of cholecalciferol at 6 months. The upper limit of 45 ng/mL was chosen because of the potential for toxicity with redosing when 25-OHD levels exceed 45 ng/mL, the upper limit of normal at our institution. The 25-OHD level was measured again after 9 months.

Calcium levels were also obtained as a safety endpoint at 3 months following original dose. Patients with calcium above normal laboratory limits (calcium >10.5 mg/dL or ionized calcium >5.4 mg/dL) would be ineligible to receive the dose of cholecalciferol at 6 months.

*Patient Selection*

Established patients of the Indiana University (IU) Health Adult Cystic Fibrosis Clinic were eligible for inclusion in this study if they were at least 18 years of age, diagnosed with CF and pancreatic insufficiency, and had a recorded baseline 25-OHD of <30 ng/mL in the last 5 months. Patients who were pregnant or who had undergone lung transplantation were excluded. A retrospective chart review was conducted to identify patients who had 25-OHD levels <30 ng/mL at each quarterly clinic visit or inpatient admission to the pulmonary service at IU Health University Hospital. Target enrollment was 40 patients based on power calculation assuming a 40% change from baseline based on the published stoss study results.[8] Baseline characteristics collected included age, gender, genotype (presence of F508del or G551 mutation), weight, height, body mass index (BMI), use of a CF transmembrane conductance regulator (CFTR) modulator, hospitalization status at enrollment, and baseline forced expiratory volume at 1 second (FEV1) percent predicted.

Patients were excluded from analysis if they withdrew from the study, entered hospice treatment, or received lung transplantation during the study period. Additionally, patients were considered lost to follow up and excluded from the analysis if a 25-OHD level was >90 days overdue.

*Description of Study Treatments*

Cholecalciferol was supplied as a 50,000 IU capsule, with dose of either 6 or 10 capsules depending on baseline 25-OHD. Patients were given a high-fat snack or dietary supplement and water to take with their dose. Patients were encouraged, but not required, to take PERT with the dose. Study personnel directly observed administration of each cholecalciferol dose.

Protocol Change

At interim analysis, the investigators identified a large variation in response to treatment. After reviewing the initial results, an interdisciplinary group made up of the clinic physician, nurse practitioner, dietician, and clinical pharmacists determined that a protocol change was needed. Two distinct treatment arms were formed: responders and non-responders. Responders were defined as patients with a ≥25% increase from baseline in 25-OHD or who met goal of ≥30 ng/mL. Treatment continued as planned at 6 months for responders. In non-responders, who were defined as patients with any decrease, increase of <25%, or a 3-month 25-OHD <20 ng/mL, a weekly dose of cholecalciferol 50,000 units was initiated immediately following determination of non-response (see Figure 2). While some participants had 25-OHD levels that were suboptimal (<30 ng/mL), the investigators chose not to initiate additional supplemental 25-OHD in patients who meet criteria as a responder

due to concerns for hypervitaminosis D, lack of prior experience with stoss dosing at 6-month intervals, and the large percent increases seen in some patients. The new protocol was reviewed and approved by the IRB in April 2016. All patients were re-consented and treated as directed by the updated protocol.

Statistical Analysis

The primary endpoint was change in 25-OHD over time per the updated protocol. Repeated measures ANOVA with Bonferroni correction was used to determine change in 25-OHD over time. Subgroup analysis for change in 25-OHD over time in responders and non-responders was not performed because of the small sample sizes for each group. Post-hoc logistic regression analysis identified factors associated with response, including age, gender, weight, BMI (and BMI <18 kg/$m^2$), FEV1 at baseline, CFTR modulator status, presence of F508del or G551 mutations, and hospitalization status at dose 1. Additionally, Fisher's exact test was used to test whether enrollment in spring/summer versus fall/winter impacted response or if there was seasonal variation in goal attainment at month 9. Statistical significance was defined as a p-value of <0.05 for all endpoints (SPSS v24, IBM, Armonk, NY).

**Results**

Of the 46 patients who were enrolled, 32 patients (70%) completed the study per protocol. Patients who completed the study were evenly distributed between male/female, were on average 25.7 years with FEV1 of 53%, and 94% had at least one copy of F508del (Table 1). Seven patients were taking CFTR modulators on enrollment, including ivacaftor (n=4) and ivacaftor/lumacaftor (n=3). Three patients initiated ivacaftor/lumacaftor within 1 month of the initial dose, and one patient who was taking ivacaftor before enrollment discontinued

the medication after the initial cholecalciferol dose. There were 14 patients excluded from analysis, with the majority being lost to follow up (n = 10). Other reasons for exclusion, in one patient each, were lung transplantation, hospice admission, physician withdrawal due to concern for severe intestinal malabsorption with history of multiple bowel resections for distal intestinal obstruction syndrome, and patient withdrawal of consent.

For patients completing the study protocol, 25-OHD levels significantly increased over time (Figure 3). The difference remained significant between baseline and months 3 and 9, respectively. By the end of the study, mean 25-OHD levels increased by 13.78 ng/mL over mean baseline levels. A total of 16 patients were considered non-responders and required additional weekly supplementation. No significant differences in baseline characteristics existed between responders vs non-responders (Table 2), with numerical differences noted in age (27 vs 24 years), gender distribution (44% vs 56% male), and hospitalization on enrollment (50% vs 38% hospitalized).All patients, including the non-responders, achieved levels above 20 ng/mL by month 9. At the end of the study, 18 patients (56%) had 25-OHD at goal of 30 ng/mL or above, with 9 patients from both the responder and non-responder groups reaching this target.

Season of enrollment did not affect response, with 40% of patients with baseline levels in spring/summer (n = 4 of 10) vs 55% in fall/winter (n = 12 of 22) classified as responders (p=0.7). Goal attainment was not significantly different in patients with 25-OHD levels drawn in spring/summer compared to the fall/winter seasons, with 55% and 43% of patients classified as responders with 3-month levels drawn in spring/summer (n=10 of 18) and fall/winter (n= 6 of 14), respectively (p=0.72). All calcium levels obtained were within or below normal limits, with mean serum calcium of 8.81 mg/dL and ionized calcium of 4.6 mg/dL. No adverse effects were reported during the study period. Logistic regression did

not identify factors that predicted response to treatment, including genotype or CFTR modulator status. All variables tested, including age, gender, weight, BMI, BMI <18 kg/$m^2$, FEV1 at baseline, CFTR modulator status, presence of F508del or G551 mutations, and hospitalization at dose 1 were not significant ($p>0.05$). Of note, all 4 patients taking ivacaftor did respond to treatment, while only 1 of the 3 patients taking ivacaftor/lumacaftor at baseline responded to treatment. Though these differences were not statistically significant, trials with larger number of patients may find increased response in those with residual function gating mutations on ivacaftor. After the initial cholecalciferol dose was given, 3 additional patients initiated ivacaftor/lumacaftor, all within one month of the initial dose. Two of these patients were non-responders at 3 months and one failed to meet criteria for response even at month 9, suggesting that Vitamin D deficiency may persist despite treatment with CFTR modulators. The percent of patients taking CFTR modulators who met goal at month 9 was 56%, which mirrors the larger study population. Other variables considered but found to have no difference included age, FEV1 percent predicted, hospitalization status, BMI <18 kg/$m^2$, and gender.

**Discussion**

This study demonstrated that a protocol of high-dose cholecalciferol or high-dose plus weekly cholecalciferol safely and effectively increases 25-OHD concentration to therapeutic levels. A majority of patients in the study were able to achieve goal 25-OHD levels of ≥30 ng/mL, with equal rates between the responders and non-responders at month 9. Responders did not require daily supplementation outside of their CF multivitamin and could benefit from both reduced pill burden and increased compliance, as the high-dose cholecalciferol therapy can be administered in the clinic or inpatient setting at a very low

cost. In a study estimating treatment burden on adult patients with CF, patients reported taking a median of 3 unique oral medications in addition to pancreatic enzymes, with a range of 0-7, and dosing often required multiple times a day.[9] Non-responders required an additional weekly 50,000 IU dose of cholecalciferol. It is possible that more frequent stoss doses could be used to obtain goal 25-OHD in these patients, but this strategy has not been studied to date.

Approximately 40% of adults with CF have severe lung disease and meet clinical criteria for osteoporosis. The need for adequate vitamin D dosing is evident.[10] The results of the present study are encouraging because earlier studies have demonstrated lack of response to alternative treatment regimens. One study examining Vitamin D supplementation in adults with CF found that <10% of patients treated with 50,000 IU cholecalciferol weekly for 8 weeks reached a 25-OHD of ≥30 ng/mL,[11] and the mean increase was only 0.3 ng/mL over baseline levels.[10] While the pediatric stoss dosing study demonstrated significant increases in 25-OHD at all time points, the mean 25-OHD levels achieved were below goal at month 12.[8] Given this finding, the study evaluated endpoints at 3 and 9 months to allow for dosing every 6 months with follow up levels at the standard of care schedule of quarterly clinic visits.

In this study, 50% were considered non-responders. This rate is much higher than other previously reported studies.[8,12] Though neither weight nor BMI predicted response in our post-hoc analysis, it is possible that the differing body composition of adults as compared to children could explain some differences in response. Genotype and CFTR modulator status also did not predict response. This study was not powered to detect differences in these variables, and larger studies may be needed to identify predictors.

The present study was conducted in Indianapolis, Indiana, United States, which has on average only 186 days of sunshine annually.[13] Though no direct comparison data are available, the potential for decreased exposure to sunlight when compared to other studied populations could impact absorption of vitamin D from the skin. Seasonal variations in 25-OHD level are known to occur, and patients were enrolled throughout the year to minimize potential bias; however, individual variations in sun exposure could confound results. There are limitations to the present study, including the unblinded design and single treatment center. The 30% attrition rate was largely due to patients being lost to follow up, defined as failure to return to clinic within 90 days. Compliance with weekly doses of cholecalciferol was not tracked. The protocol was used in a real-world setting, with many of the doses and levels obtained after desired time frame. Though overdue levels and doses may lead to lower 25-OHD levels, this aids in validity for a clinic setting in which patients frequently reschedule appointments or get off schedule for their quarterly visits due to hospitalization or illness. Additionally, there was a need for a protocol revision midway through the study. Though all patients were re-consented on the updated protocol, the study was not originally designed or powered for the dual-pathway approach. As patients frequently changed brand of CF multivitamin due to cost and availability, the amount of background therapy may have varied slightly during the study period (between 2,000 and 3,000 IU). We elected not to collect CF multivitamin brand(s) used during the study period for simplicity, but some changes in supplement may have impacted 25-OHD level. However, given that all patients were prescribed a CF multivitamin prior to study initiation, the impact of these variations are likely minimal.

While these limitations exist, the present study has encouraging results. Despite the large portion of patients with very low baseline 25-OHD levels, a level of ≥20 ng/mL was obtained for all participants. While wewere initially concerned about elevated 25-OHD levels, there were no levels at or above the laboratory standard upper limit of normal of 50 ng/mL. Calcium levels were also either below or within normal limits, and no adverse effects of therapy were reported. With the safety of this regimen established, future studies could be conducted to determine if more frequent stoss doses could be used in non-responders to maintain goal 25-OHD. Additionally, use in conjunction with new formulations of CF multivitamins with higher cholecalciferol content (up to 5,000 IU/dose) could help reduce need for further supplementation in some patients.

**Conclusion**

A protocol using high-dose cholecalciferol or high-dose plus weekly cholecalciferol is safe and effective in increasing 25-OHD levels in adult patients with CF and pancreatic insufficiency. This dosing strategy could help reduce pill burden for patients who respond to treatment, avoiding the need for daily supplementation with additional cholecalciferol.

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Table 1. Baseline Characteristics

| Characteristic (n=32) | Mean ± Standard Deviation |
|---|---|
| **Age (years)** | 25.7 ± 6.5 |
| **Male (n, %)** | 16 (50) |
| **Genotype (n, %)** | |
| F508del present | 30 (94%) |
| *Heterozygous* | 13 (41%) |
| *Homozygous* | 17 (53%) |
| G551 present | 3 (9%) |
| **Weight (kg)** | 57.8 ± 12.7 |
| **BMI (kg/m$^2$)** | 21.3 ± 3.7 |
| **BMI <18 (n, %)** | 7 (22) |
| **FEV1 Baseline (% predicted)** | 53 ± 19 |
| **CFTR modulator on enrollment (n, %)** | 7 (22) |
| **Hospitalized on enrollment (n, %)** | 14 (44) |
| **Baseline 25-OHD (ng/mL)** | 18.8 ± 6.1 |

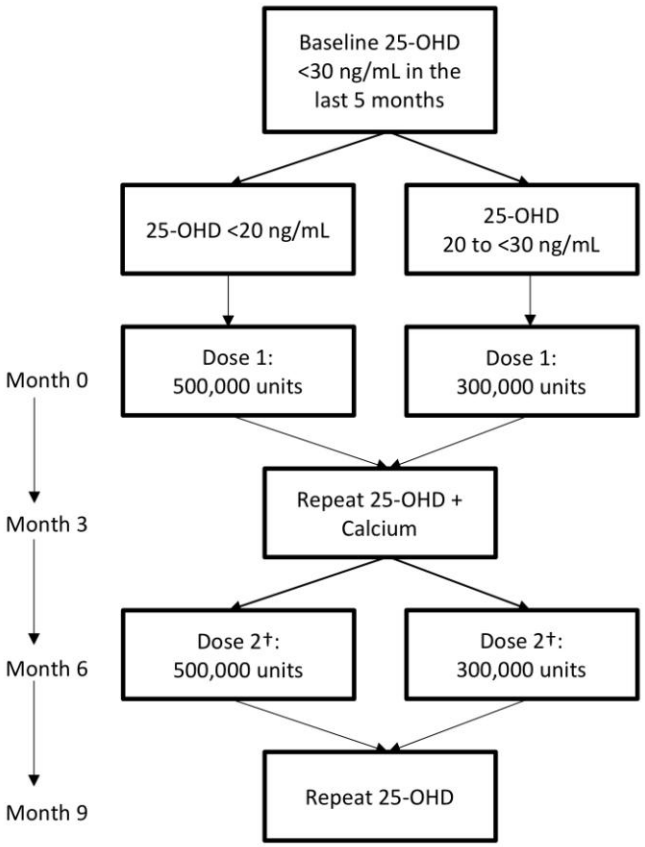
BMI = body mass index; FEV1 = forced expiratory volume at 1 second; CFTR = cystic fibrosis transmembrane conductance regulator; 25-OHD = 25-hydroxyvitamin D

Table 2. Characteristics of Responders vs Non-responders

| Characteristic | Responders (n=16) | Non-Responders (n=16) |
|---|---|---|
| **Age (years)** | 27.2 ± 7.8 | 24.1 ± 4.7 |
| **Male (n, %)** | 7 (44%) | 9 (56%) |
| **Genotype (n, %)** | | |
| F508del present | 15 (94%) | 15 (94%) |
| *Heterozygous* | 8 (50%) | 4 (25%) |
| *Homozygous* | 6 (38%) | 11 (69%) |
| G551 present | 3 (19%) | 0 |
| **Weight (kg)** | 58.9 ± 14.5 | 56.7 ± 11 |
| **BMI (kg/m$^2$)** | 21.5 ± 3.8 | 21 ± 3.7 |
| **BMI <18 (n, %)** | 3 (19%) | 4 (25%) |
| **FEV1 Baseline (% predicted)** | 52 ± 21 | 54 ± 17 |
| **CFTR modulator on enrollment (n, %)** | 4 (25%) | 3 (19%) |
| **Hospitalized on enrollment (n, %)** | 8 (50%) | 6 (38%) |
| **Baseline 25-OHD (ng/mL)** | 18.6 ± 6 | 19 ± 6.4 |

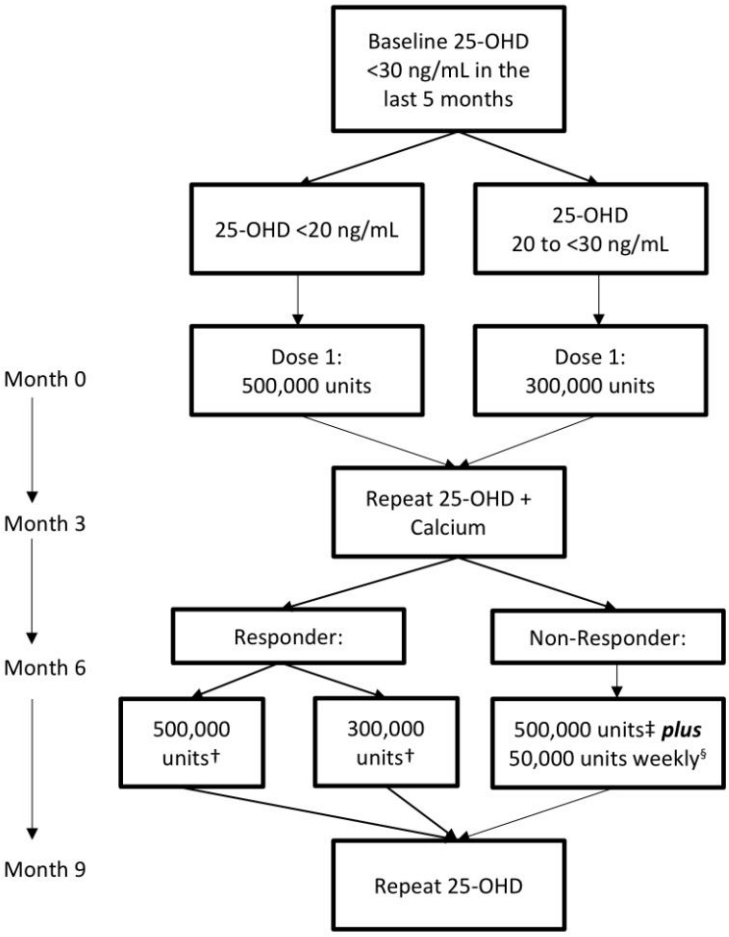
BMI = body mass index; FEV1 = forced expiratory volume at 1 second; CFTR = cystic fibrosis transmembrane conductance regulator; 25-OHD = 25-hydroxyvitamin D

Figure 1. Original Protocol



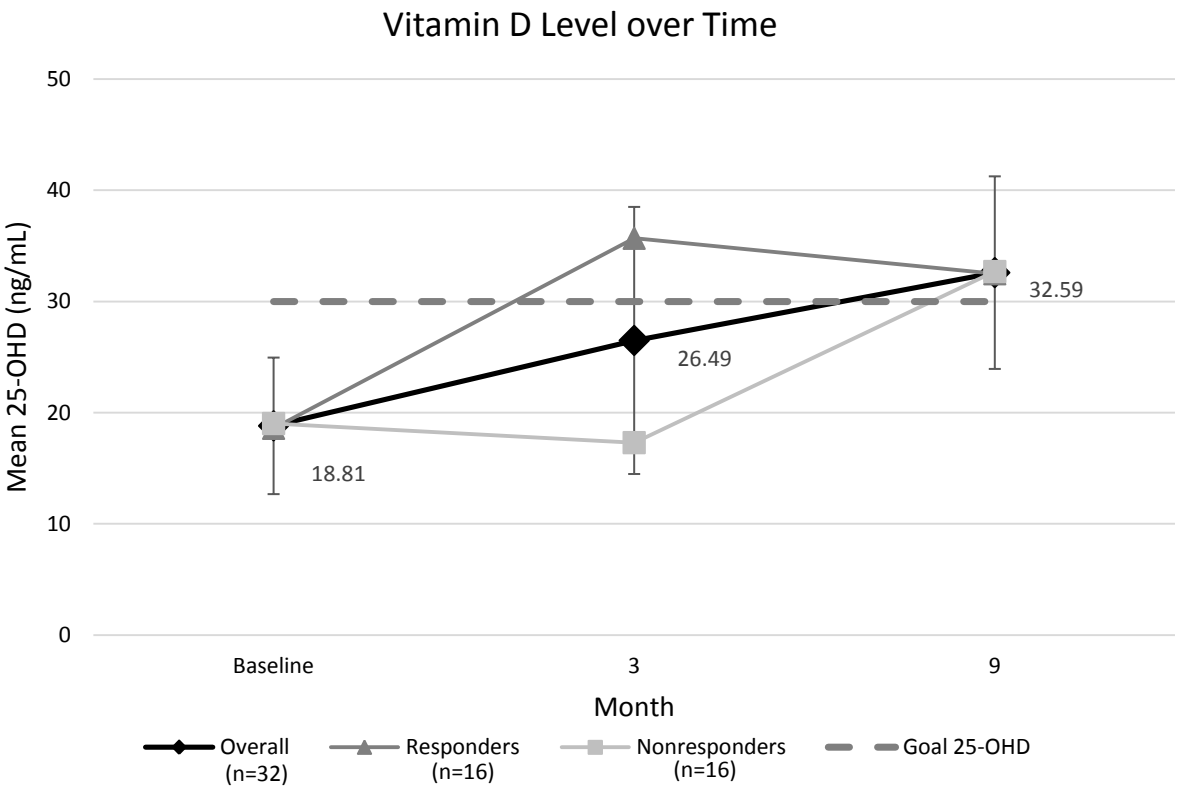

†Repeat dose received at month 0

Figure 2. Revised Protocol




†Repeat dose received at month 0; ‡Give 500,000 units regardless of dose 1;
§Given immediately following review of 25-OHD level

Figure 3. Mean increase in 25-OHD over time




Overall, p<0.001; Baseline to Month 3, p=0.011; Baseline to Month 9, p<0.001; Month 3 to 9, p>0.05

*Error bars represent standard deviation of overall mean; Goal 25-OHD as defined by CF Foundation recommendations*[6]