Study Protocol and Statistical Analysis Plan

Official Title

Accelerated Correction of Vitamin D Deficiency in Cholestatic Children: A Comparative Trial of Vitamin D2 Monotherapy Versus Combination Therapy With Calcitriol

Brief Title	Vitamin D2 Versus Vitamin D2 Plus Calcitriol in Cholestatic Children With Vitamin D Deficiency
Acronym	VITD-CHOL
NCT Number	NCT number to be assigned
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Principal Investigator	Thanaporn Nilyaem, M.D.
Institution	Pediatric Gastroenterology and Hepatology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

1. Administrative Information

Item	Description
Study Type	Interventional clinical trial
Study Design	Open-label, randomized controlled trial with ethical crossover
Allocation	Randomized allocation in a 1:1 ratio using block randomization with block size of 4
Study Phase	Phase 4
Number of Arms	2
Estimated Enrollment	Approximately 54 participants, allowing for loss to follow-up
Participant Duration	6 months

2. Study Synopsis

This clinical trial will evaluate whether adding calcitriol to standard vitamin D2 therapy improves vitamin D deficiency in children with cholestasis and chronic liver disease. Cholestasis can reduce bile salt delivery to the intestine, leading to impaired absorption of fat-soluble vitamins. Liver disease may also impair hepatic hydroxylation of vitamin D to 25-hydroxyvitamin D (25-OHD). Calcitriol is an active vitamin D metabolite and may bypass part of this physiologic limitation.

Participants will be randomized to receive vitamin D2 monotherapy or vitamin D2 plus calcitriol. The primary comparison is the change in serum 25-OHD from baseline to Month 3. Participants will be followed through Month 6 for additional biochemical outcomes and safety assessment.

3. Background and Rationale

Vitamin D deficiency is common in pediatric cholestasis and chronic liver disease. The mechanisms are multifactorial and include impaired intestinal absorption of fat-soluble vitamins due to reduced bile salts and impaired hepatic conversion of vitamin D to 25-OHD. Standard high-dose vitamin D2 therapy may correct deficiency slowly or incompletely in some cholestatic children. Combination therapy with calcitriol is hypothesized to improve biochemical correction while safety is monitored closely, particularly for hypercalcemia and hyperphosphatemia.

4. Objectives

4.1 Primary Objective

To compare the magnitude of increase in serum 25-OHD level from baseline to Month 3 between children receiving vitamin D2 monotherapy and children receiving vitamin D2 plus calcitriol.

4.2 Secondary Objectives

- To compare the proportion of participants who achieve correction of vitamin D deficiency at Month 3 and Month 6.
- To evaluate changes in parathyroid hormone (PTH), 1,25-dihydroxyvitamin D, serum calcium, and serum phosphate.
- To evaluate the safety of combination therapy, including hypercalcemia, hyperphosphatemia, and other treatment-related adverse events during the 6-month study period.
- To evaluate the relationship between vitamin D correction and changes in Pediatric End-stage Liver Disease (PELD) score and liver function tests.

5. Participant Population

Children with chronic liver disease and cholestasis who have vitamin D deficiency will be recruited from pediatric gastroenterology and hepatology outpatient and inpatient services at King Chulalongkorn Memorial Hospital.

5.1 Inclusion Criteria

- Patients younger than 18 years of age.
- Diagnosis of cholestasis, defined as direct/conjugated bilirubin >1 mg/dL for more than 1 month.
- Diagnosis of chronic liver disease.
- Vitamin D deficiency, defined as serum 25-hydroxyvitamin D (25-OHD) level <20 ng/mL.

5.2 Exclusion Criteria

- Pre-existing hypercalciuria, screened by urine calcium testing before enrollment.
- Benign or malignant tumors.
- Renal tubular defects, screened by electrolyte testing before enrollment.
- Current anticonvulsant therapy.
- Inability or failure to attend scheduled follow-up visits.

Participants whose underlying cause of cholestasis is corrected during treatment and follow-up, with direct/conjugated bilirubin decreasing to <1 mg/dL, will be withdrawn from the study.

6. Interventions and Study Arms

Arm	Arm Type	Intervention	Month 3 Treatment Review
Vitamin D2 Monotherapy	Active Comparator	Vitamin D2 40,000 IU orally once weekly for 3 months.	If serum 25-OHD remains <20 ng/mL, participants may crossover to vitamin D2 80,000 IU/week plus calcitriol 50 ng/kg/day according to protocol. If serum 25-OHD is >=20 ng/mL, current therapy is maintained.
Vitamin D2 Plus Calcitriol	Experimental	Vitamin D2 40,000 IU orally once weekly plus calcitriol 50 ng/kg/day orally for 3 months.	If serum 25-OHD remains <20 ng/mL, vitamin D2 may be increased to 80,000 IU/week while calcitriol 50 ng/kg/day is continued. If serum 25-OHD is >=20 ng/mL, current therapy is maintained.

7. Randomization and Blinding

Eligible participants who provide informed consent will be randomized in a 1:1 ratio using block randomization with a block size of 4. The trial is open-label because the interventions differ in regimen and dose adjustment. Outcome measures are objective biochemical laboratory values.

8. Study Procedures and Assessment Schedule

Participants will undergo baseline assessment, treatment allocation, Month 3 assessment with treatment review, and Month 6 final assessment. Medication adherence will be assessed by return and count of medication packages/tablets. Good adherence is defined as receipt of at least 80% of prescribed medication, moderate adherence as >50% to <80%, and poor adherence as <50%.

Assessment	Baseline	Month 3	Month 6
Clinical data and medication review	Yes	Yes	Yes
Serum 25-OHD	Yes	Yes	Yes
1,25-dihydroxyvitamin D, PTH, calcium, phosphate	Yes	Yes	Yes
Liver function tests and coagulation parameters	Yes	Yes	Yes
PELD score	Yes	Yes	Yes
Adverse event and adherence assessment	No	Yes	Yes

9. Outcome Measures

9.1 Primary Outcome Measure

Change in serum 25-OHD level from baseline to Month 3, measured in ng/mL, compared between the vitamin D2 monotherapy arm and the vitamin D2 plus calcitriol arm.

9.2 Secondary Outcome Measures

- Proportion of participants with serum 25-OHD >=20 ng/mL at Month 3.
- Proportion of participants with serum 25-OHD >=20 ng/mL at Month 6.
- Change in serum 25-OHD level from baseline to Month 6.
- Changes in serum PTH and 1,25-dihydroxyvitamin D at Month 3 and Month 6.
- Incidence of hypercalcemia and hyperphosphatemia through Month 6, according to age-specific laboratory reference ranges.
- Incidence of treatment-related adverse events through Month 6.

• Changes in PELD score and liver function tests at Month 3 and Month 6.

10. Safety Monitoring

Safety monitoring will focus on biochemical abnormalities related to vitamin D and calcitriol therapy, particularly hypercalcemia and hyperphosphatemia. Adverse events will be collected at scheduled visits and managed according to clinical judgment and institutional standards. The study team may adjust or discontinue treatment for safety concerns.

11. Sample Size

The sample size was estimated for comparison of two independent means for change in serum 25-OHD level. Assumptions were based on prior pediatric chronic liver disease data. With a 1:1 allocation ratio, 80% power, and a two-sided alpha of 0.05, the target sample size is approximately 24 participants per arm, for 48 participants total. Allowing for approximately 10% to 20% loss to follow-up, the planned enrollment is approximately 54 to 58 participants.

12. Statistical Analysis Plan

Analyses will be performed using STATA or equivalent statistical software. Statistical significance will be defined as a two-sided p-value <0.05.

12.1 Analysis Populations

The primary analysis will follow the intention-to-treat principle as feasible, including randomized participants according to assigned study arm. Per-protocol or sensitivity analyses may be performed to evaluate the impact of medication adherence and protocol deviations.

12.2 Baseline Characteristics

Continuous variables will be summarized as mean +/- standard deviation for normally distributed data or median and interquartile range for non-normally distributed data. Categorical variables will be summarized as counts and percentages. Baseline characteristics will be compared between arms using independent t-test or Mann-Whitney U test for continuous variables and chi-square or Fisher exact test for categorical variables, as appropriate.

12.3 Primary Outcome Analysis

The primary endpoint, change in serum 25-OHD from baseline to Month 3, will be compared between arms using an independent t-test if normally distributed or a Mann-Whitney U test if non-normally distributed. Mean or median differences with appropriate confidence intervals will be reported.

12.4 Secondary Outcome Analysis

The proportions of participants achieving serum 25-OHD >=20 ng/mL at Month 3 and Month 6 will be compared using chi-square or Fisher exact test. Repeated measures ANOVA or mixed-effects models may be used to evaluate biomarker changes over time. Safety outcomes will be summarized by treatment arm and compared descriptively or with exact tests when appropriate. Correlations between changes in 25-OHD and changes in PELD score or liver function tests may be assessed using Pearson or Spearman correlation depending on data distribution.

12.5 Missing Data

The extent and reasons for missing data will be described. The primary analysis will use available data, and sensitivity analyses may be considered if missing data are substantial or imbalanced between arms.

13. Data Management and Confidentiality

Participant data will be recorded using study case record forms and study identifiers. Research participant names or directly identifying information will not be included in public study documents. Access to identifiable research records will be limited to authorized study personnel according to institutional requirements.

14. Ethics

The study will be conducted in accordance with applicable ethical principles, institutional requirements, and the approved protocol. Written informed consent from parents or legal guardians, and assent from children when appropriate, will be obtained before enrollment.

15. Document Notes for ClinicalTrials.gov Upload

This document is a concise English protocol and statistical analysis plan prepared for public posting. Before final upload, the study team should confirm that the NCT number is correct, the document date and version match institutional records, and no participant identifiers are present.