NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	NDA 020862 Supplement 33
Priority or Standard	Standard
Submit Date(s)	August 20, 2024
Received Date(s)	August 20, 2024
PDUFA Goal Date	June 20, 2025
Division/Office	Division of General Endocrinology (DGE)/Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Review Completion Date	See DARRTS stamped date
Established/Proper Name	Doxercalciferol
(Proposed) Trade Name	Hectorol
Pharmacologic Class	Vitamin D analog
Applicant	Sanofi-Aventis U.S. LLC
Dosage form	Capsules
Applicant proposed Dosing Regimen	Not applicable
Applicant Proposed changes	Inclusion of pediatric information into product labeling
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Not applicable
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Not applicable
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Not applicable
Recommended Dosing Regimen	No change in dosing regimen

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Meghna Jairath
Office of Clinical Pharmacology Reviewer(s)	Li Wang, Ph.D.
Office of Clinical Pharmacology Team Leader(s)	Li Li, Ph.D.
Clinical Reviewer	Olivia Easley, MD
Clinical Team Leader	Shivangi Vachhani, MD
Cross-Disciplinary Team Leader	Shivangi Vachhani, MD
Division Director	Theresa Kehoe, MD

Additional Reviewers of Application

OPDP	Charuni Shah
DPMH	Shamir Tuckman, MD. DPMH clinical reviewer Mona Khurana, MD. DMPH team leader

OPDP=Office of Prescription Drug Promotion
DPMH = Division of Pediatrics and Maternal Health

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Li Wang, Ph.D.	OCP/DCEP	Sections: 6	**Select one:** _X_ Authored ___ Approved
	Signature: LI WANG -S Digitally signed by LI WANG -S Date: 2025.05.30 15:17:04 -04'00'			
Clinical Pharmacology Team Leader	Li Li, Ph.D.	OCP/DCEP	Sections: 6	**Select one:** ___ Authored _X_ Approved
	Signature: Li Li -S Digitally signed by Li Li -S Date: 2025.06.02 13:07:51 -04'00'			
Clinical Reviewer	Olivia Easley, MD	OCHEN/DGE	Sections: 1, 2, 3, 7, 8, 9, 10, 11, 12, 13, 14	**Select one:** _X_ Authored ___ Approved
	Signature: Olivia J. Easley -S Digitally signed by Olivia J. Easley -S Date: 2025.06.02 13:24:15 -04'00'			
Clinical Team Leader	Shivangi Vachhani, MD	OCHEN/DGE	Sections: All sections	**Select one:** _X_ Authored _X_ Approved
	Signature: See DARRTS signature page			
Associate Director for Labeling	Lai Ming Lee, PhD	OCHEN/DGE	Sections: 11	**Select one:** _X_ Authored ___ Approved
	Signature: Lai M. Lee -S Digitally signed by Lai M. Lee -S Date: 2025.06.02 13:32:45 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Cross Disciplinary Team Leader	Shivangi Vachhani, MD	OCHEN/DGE	Sections: All sections	**Select one:** _X_ Authored _X_ Approved
	Signature: See DARRTS signature page			
Division Director (Clinical)	Theresa Kehoe, MD	OCHEN/DGE	Sections: All sections	**Select one:** ___ Authored _X_ Approved
	Signature: See DARRTS signature page			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
iPTH	intact parathyroid hormone
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Hectorol (doxercalciferol) is a synthetic vitamin D2 analog available in capsule and injectable formulations. The capsule formulation is indicated for the treatment of secondary hyperparathyroidism in adult patients with Stage 3 or Stage 4 chronic kidney disease (CKD) and adult patients with CKD on dialysis. The injectable formulation is indicated for the treatment of secondary hyperparathyroidism solely in patients with CKD on dialysis.

The recommended oral capsule dosage depends on dialysis status:

- For Stage 3 or 4 CKD: Initiate dosing at 1 mcg orally once daily. Maximum dose is 3.5 mcg once daily.
- For CKD on dialysis: Initiate dosing at 10 mcg orally three times weekly at dialysis (no more frequently than every other day). Maximum dose is 20 mcg three times weekly for a total of 60 mcg weekly.

The starting dose of Hectorol injection is 4 mcg by bolus intravenous administration three times weekly at the end of dialysis (no more frequently than every other day) with a maximum dose of 18 mcg weekly.

Dosage adjustment is targeted to achieve to intact parathyroid hormone (iPTH) levels within the desired therapeutic range and serum calcium within normal limits.

The current submission contains an efficacy supplement to update section 8.4 to reflect results of the final report for post-marketing requirement (PMR) 513-1 study LPS15314 of the management of secondary hyperparathyroidism in pediatric patients ages 5 years to 18 years with Stage 3 or 4 chronic kidney disease (CKD) not yet on dialysis.

1.2. Conclusion on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness of Hectorol (doxercalciferol) for the treatment of secondary hyperparathyroidism due to CKD in pediatric patients has not been established.

The Applicant conducted a single, open-label, randomized, parallel group, active-controlled (calcitriol) trial to assess the safety and efficacy of Hectorol in treating secondary hyperparathyroidism in pediatric patients ages 5 years to 17 years with stages 3 and 4 chronic kidney disease not yet on dialysis (Trial LPS14314). However, due to recruitment challenges, the Applicant was unable to enroll an adequate number of subjects in the trial.

The primary efficacy endpoint, defined as the proportion of doxercalciferol-treated subjects who achieved two consecutive reductions in iPTH of greater than or equal to 30% from baseline to week 12, was observed in 14.3% of subjects. No formal statistical hypothesis testing was performed on the primary efficacy endpoint. However, a notably lower response rate was observed in the doxercalciferol group compared to the calcitriol group (14.3% vs. 71.4%, respectively).

Therefore, a pediatric indication cannot be granted for Hectorol at this time. The Hectorol prescribing information will be amended to include language stating that the efficacy of Hectorol has not been established for the treatment of secondary hyperparathyroidism in pediatric patients with Stage 3 or Stage 4 CKD and with CKD on dialysis.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The overall risk-benefit of Hectorol (doxercalciferol) in the treatment of children with secondary hyperparathyroidism due to chronic kidney disease is unfavorable. In the single randomized, open-label, active controlled trial in 21 pediatric patients aged ≥5 years with chronic kidney disease (CKD) stages 3 and 4 with secondary hyperparathyroidism not yet on dialysis, the product did not meet its primary efficacy endpoint (i.e., proportion of patients achieving two consecutive ≥30% reductions in intact parathyroid hormone [iPTH]). The percentage achieving the prespecified primary efficacy endpoint was 14.3% (2/14) in the doxercalciferol group compared to 71.4% (5/7) in the calcitriol group. The trial raised no safety concerns with respect to treatment with either doxercalciferol or calcitriol, and there was no meaningful difference in safety between the two treatment groups. Study result interpretation is limited, however, by the small sample size resulting from recruitment challenges.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In chronic kidney disease, secondary hyperparathyroidism develops due to phosphate retention, 1,25-dihydroxyvitamin D deficiency, hypocalcemia, and skeletal resistance to parathyroid hormone (PTH) action. • Secondary hyperparathyroidism can manifest clinically in development of bone disease such as osteitis fibrosa cystica and mixed osteodystrophy.	Secondary hyperparathyroidism can cause significant skeletal abnormalities especially in pediatric patients.
Current Treatment Options	• In children with CKD Stage 2 to 4, 25- hydroxyvitamin D is assessed and replenished as needed with oral ergocalciferol or cholecalciferol if low. In children with normal 25-hydroxyvitamin D levels and elevated PTH, an activated Vitamin D analog such as calcitriol is used instead of ergocalciferol or cholecalciferol to bypass renal conversion of 25-OH vitamin D to biologically active 1,25-OH vitamin D.	There are already existing vitamin D analogs available for treatment of pediatric secondary hyperparathyroidism due to chronic kidney disease. This condition does not represent an unmet need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Overtreatment with vitamin D can result in adynamic bone disease and osteomalacia.	
Benefit	• Hectorol, which is converted by the liver to biologically active 1,25-OH vitamin D and therefore does not require normal renal function in its recipients, could be potentially beneficial in treating secondary hyperparathyroidism in children with CKD. However, substantial evidence of effectiveness was not established in the single, open-label trial in pediatric subjects with stage 3 and 4 CKD with secondary hyperparathyroidism not yet on dialysis.	Doxercalciferol did not reduce levels of intact parathyroid hormone in most subjects treated and therefore has not displayed benefit in the pediatric population with CKD.
Risk and Risk Management	• No safety risks associated with Hectorol treatment were identified in the single small trial involving 21 participants.	Due to its lack of benefit, the overall risk-benefit profile of Hectorol in treatment of secondary hyperparathyroidism in chronic kidney disease in the pediatric population is unfavorable.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

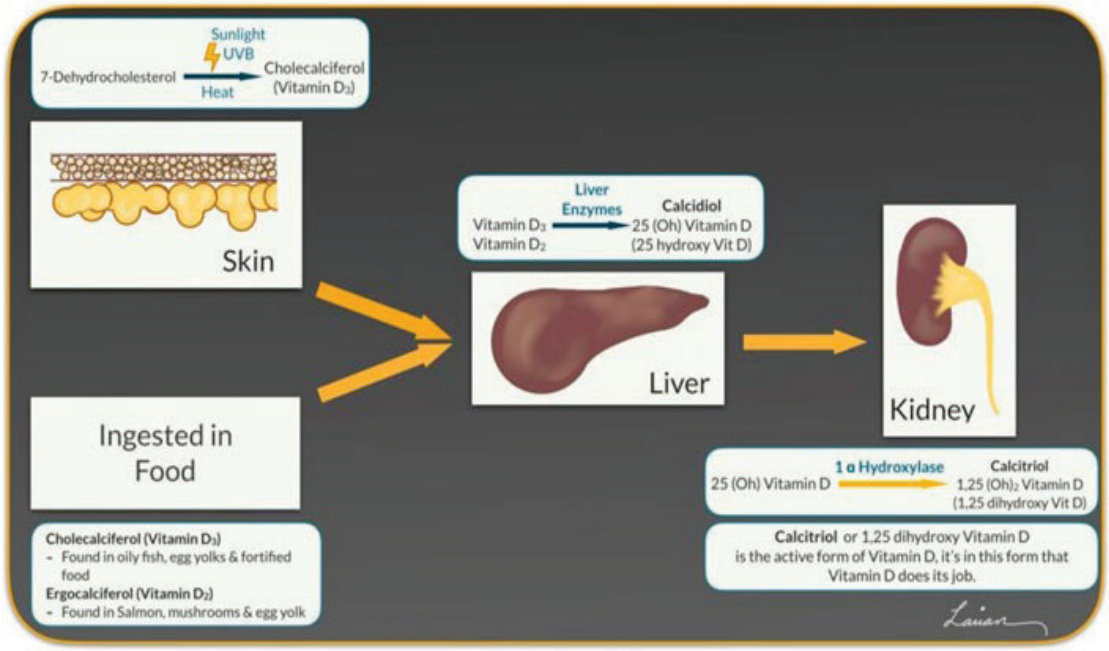
2.1. Analysis of Condition

Secondary hyperparathyroidism is a common complication of chronic kidney disease (CKD). In patients with normal renal function, vitamin D2 (also known as ergocalciferol) is absorbed into the gastrointestinal tract and converted in the liver to calcidiol [25-hydroxyvitamin (OH)D] (see Figure 1) and then undergoes hydroxylation in the kidneys to form the metabolically active calcitriol (1α,25-dihydroxy (OH_2) vitamin D).

In CKD, the kidney's ability to convert calcidiol to calcitriol is impaired, which leads to deficiency in metabolically active vitamin D. Vitamin D deficiency results in reduced gastrointestinal absorption of calcium. Parathyroid hormone levels increase as the body attempts to normalize serum calcium and phosphorous, ultimately resulting in secondary hyperparathyroidism. Figure 2 shows the interplay between vitamin D, calcium and parathyroid gland activity that occurs in the setting of reduced renal function.

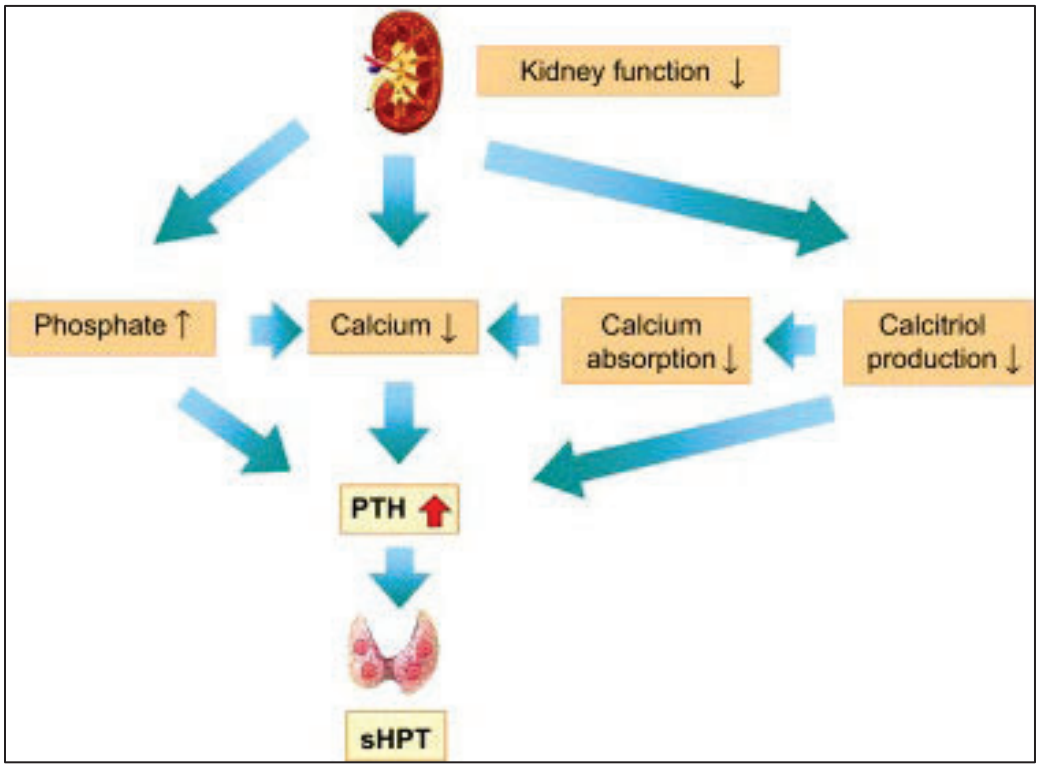
The metabolic derangements caused by secondary hyperparathyroidism lead to weakened bone (a condition known as osteitis fibrosa) and increased risk of fracture, among other complications.

Figure 1. Vitamin D synthesis



Source: https://www.hyperparathyroidmd.com/hyperparathyroidism-vitamin-d/

Figure 2 Pathway of Secondary Hyperparathyroidism development in kidney disease



Source: Patrick Biggar, Samuel K.S. Fung, Markus Ketteler, "Treatment of phosphate retention: The earlier the better?", Kidney Research and Clinical Practice, Volume 33, Issue 1, 2014, Pages 3-8, Figure 1.

2.2. Analysis of Current Treatment Options

The treatment of secondary hyperparathyroidism due to CKD is aimed at preventing development of osteitis fibrosa, reducing risk of bone fracture and minimizing parathyroid hyperplasia. Therapy involves replacing vitamin D and controlling serum phosphorous by restricting dietary phosphorous and use of phosphate binders when the former is insufficient. The 2017 kidney disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines recommends measuring and correcting 25(OH) vitamin D levels in pediatric patients with vitamin D deficiency and insufficiency and maintaining serum calcium levels in the age-appropriate normal range. The guidelines do not prioritize the use of calcimimetics, calcitriol, or vitamin D analogs to lower PTH.

Currently available vitamin D analogs for use in children with secondary hyperparathyroidism due to CKD are shown in Table 1.

Table 1. Summary of FDA-approved Pharmacologic Treatments of Pediatric Patients with Secondary Hyperparathyroidism associated with CKD

Generic name [trade name(s)]	Mechanism of Action	Method of administration	Population and indication
Paricalcitol (Zemplar)	Synthetic, biologically active vitamin D2 analog	Oral	Prevention and treatment of secondary hyperparathyroidism associated with CKD Stages 3, 4 and 5 (on dialysis) in patients ≥10 years
Paricalcitol (Zemplar) injection		Injection	Prevention and treatment of secondary hyperparathyroidism in patients ≥5 years with CKD on dialysis
Calcitriol (Rocaltrol)	Synthetic analog of calcitriol	Oral	secondary hyperparathyroidism in patients with CKD not requiring dialysis Includes all ages of pediatric population

Hectorol, which is approved for use in adult patients with secondary hyperparathyroidism associated with CKD, does not require renal hydroxylation. Instead, the drug is activated by CYP27 in the liver to form 1α,25-$[OH]_2D_2$ (major metabolite) and 1α,24-$[OH]_2D_2$ (minor metabolite).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Hectorol capsules 2.5 mcg (NDA 020862) received US approval on June 9, 1999, for the indication of "reduction of elevated iPTH levels in the management of secondary hyperparathyroidism in patients undergoing chronic renal dialysis." Hectorol Injection (NDA 021027) was approved on April 6, 2000, for the treatment of "reduction of elevated iPTH levels in the management of secondary HPT in patients undergoing chronic renal dialysis." On April 23, 2004, FDA approved efficacy supplement 6, which allowed for use of a new, lower strength of Hectorol capsules (0.5 mcg) for a new indication of "treatment of secondary hyperparathyroidism in patients with Stage 3 or Stage 4 chronic kidney disease, not yet on dialysis."

3.2. Summary of Pre-submission/Submission Regulatory Activity

On April 23, 2004, FDA approved Supplement 6, an efficacy supplement seeking approval of a new, lower strength of Hectorol capsules (0.5 mcg) for the treatment of secondary hyperparathyroidism in patients with Stage 3 or Stage 4 chronic kidney disease, not yet on dialysis. The approval of Supplement 6 triggered the requirement for a pediatric assessment as mandated by the Pediatric Research Equity Act (PREA) (21 U.S.C.355c). FDA waived the pediatric study requirement for ages 0 to 4 years. For the age group of 5 to 17 years, the pediatric study was deferred, and the approval letter included the following post-marketing requirement (PMR):

- PMR 513-1: Deferred pediatric study under PREA for the management of secondary hyperparathyroidism in pediatric patients ages 5 to 18 years with Stage 3 or 4 chronic kidney disease (CKD) not yet on dialysis (Protocol LPS14314)

The sponsor experienced recruitment challenges and requested (b) (4)

In a correspondence dated February 3, 2022, FDA acknowledged the recruitment challenges but did not agree to (b) (4). FDA further advised the sponsor to submit a complete study report once the study has been finalized.

The Applicant submitted the final study report for PMR 513-1 in supporting document 554 on March 31, 2023.

(b) (4)

In a letter dated August 24, 2023, FDA requested that the Applicant submit a labeling supplement (b) (4) The Applicant requested (b) (4), which FDA denied.

The Applicant submitted Efficacy Supplement-33, the subject of this current review, on August 20, 2024, in SD 562.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Not applicable.

4.2. Product Quality

Not applicable. No product quality data were submitted in this supplement.

4.3. Clinical Microbiology

Not applicable

4.4. Devices and Companion Diagnostic Issues

Not applicable

5 Nonclinical Pharmacology/Toxicology

Not applicable. No nonclinical data were submitted in this supplement.

6 Clinical Pharmacology

6.1. Executive Summary

Trial LPS14314 was performed to fulfill the post marketing requirements (PMRs) 513-1. PMR 513-1 required the Applicant to conduct a trial under PREA for the management of secondary hyperparathyroidism in pediatric patients ages 5 to 18 years with Stage 3 or 4 chronic kidney disease (CKD) not yet on dialysis. The primary objective of Trial LPS14314 was to evaluate the effect of Hectorol capsules in reducing elevated levels of intact parathyroid hormone, while one of the secondary objectives was to determine the pharmacokinetic (PK) profile of 1,25-dihydroxyvitamin D2 after administration of doxercalciferol. The PK population included 14 participants from the doxercalciferol group with at least one postdose concentration.

RECOMMENDATION

The Office of Clinical Pharmacology has reviewed the PK results in pediatric patients from Trial LPS14314 and determined that the observed PK information for doxercalciferol from this trial appears valid (See Section 6.2 for detailed information).

LABELING CHANGES

In the proposed drug label, the Applicant (b) (4) , the Office of Clinical Pharmacology has determined that the (b) (4) should not be included in the label.

6.2. Summary of Clinical Pharmacology Assessment

In Trial LPS14314, subjects with serial PK sampling at Week 8/10 or Sparse PK samples (baseline to Week 12), the PK profiles of 1,25-dihydroxyvitamin D2 were generally flattened with large inter-subject variabilities. The calculated PK parameters based on the serial PK sampling at Week 8/10 demonstrate high variability (~70%) for both Cmax and $AUC_{0\text{-}24h}$.

6.2.1. Pharmacology and Clinical Pharmacokinetics

DESIGN OF STUDY LPS14314

This was a Phase 3, randomized, multinational, open-label, parallel group, active comparator trial in subjects aged 5 to 18 years with chronic kidney disease (CKD) Stages 3 and 4 with secondary hyperparathyroidism (SHPT) not yet on dialysis. The trial included a Screening Period (4 days to 4 weeks), a Primary Efficacy Period (12 weeks), and a Safety Continuation Period (12 weeks). Eligible participants were randomized either to the Hectorol or Rocaltrol study treatment groups in a 2:1 ratio and were stratified by age and CKD stage at baseline. Approximately, 56 subjects in the doxercalciferol group and 28 subjects in calcitriol group were planned to be enrolled in the trial. However, only 21 subjects were randomized (doxercalciferol: 14 participants and calcitriol: 7 participants).

The starting dose of Hectorol per the package insert for adult patients with SHPT and CKD Stages 3 or 4 is 1 mcg every day for a total weekly dose of 7 mcg. For this pediatric trial, the starting dose of Hectorol and all potential titration increases were less than those used in adults and had been modeled to provide weekly exposures comparable to those observed in adults. The pediatric starting doses were: for 12 to18 year-old patients, 0.5 mcg every 2 to 3 days for a total weekly dose of 1.5 mcg; and for 5 to <12 year-old patients, 0.5 mcg every 3 to 4 days for a total weekly dose of 1.0 mcg. Dose titration was dependent on patient age (5 to < 12 years), and (12 to 18 years). For the younger age group (5 to < 12 years), patient weight (< 30 kg, or > 30 kg) was also taken into consideration. After a series of dose titrations, the maximum dose in pediatric patients 12 to 18 years old is 2.5 mcg every day for a total weekly dose of 17.5 mcg; the maximum dose in pediatric patients 5 to <12 years old and ≥30 kg body weight is 2.0 mcg every day for a total weekly dose of 14.0 mcg; and the maximum dose in pediatric patients 5 to <12 years old and <30 kg body weight is 1.0 mcg every day for a total weekly dose of 7.0 mcg.

PHARMACOKINETIC ASSESSMENT

Serial PK samples were collected post-dose at hours 1 to 3, 4 to 6, 7 to 12, and 24 to 36 hours at either Week 8 or Week 10 – choice was per the schedule availability of the site and subject.

Sparse PK samples were collected at baseline and then within 24 hours of the most recent dose of doxercalciferol at weeks 2, 4, 6, 8 or 10 (whichever week is not used for serial PK assessment) and 12.

PHARMACOKINETIC AND STATISTCAL ANALYSIS

1,25 hydroxyvitamin D2 serum concentration data were used in a separate population PK analysis. Evaluation of the 1,25-dihydroxyvitamin D2 concentration-time data obtained in this trial were conducted using a model-based approach, using NONMEM (b) (4) Version 7 Level 2 or higher). A previous adult population PK model developed with dense data obtained from 3 earlier protocols (BCI-CH-103, BCI-CH-107, and BCI-CH-117) was tested as a potential base model. Individual and population mean parameters including absorption rate constant, clearance and volume of distribution were reported. If feasible, derived parameters including area under the concentration-time curve were reported. No formal statistical evaluation of the derived parameters was conducted.

BIOANALYTICAL

1,25-dihydroxyvitamin D2 in human plasma were measured by a validated LC-MS/MS method. The bioanalytical method was developed and validated by (b) (4) The analyte was isolated from plasma with ImmuTube extraction kit and derivatization. Detection was done by tandem mass spectrometry in the multiple reaction monitoring mode using the positive ion mode. The summary of bioanalytical method and validation metrics are presented in Table 2.

Table 2: Summary Review of Bioanalytical Methods Measuring 1,25-dihydroxyvitamin D2 in Human plasma.

Parameter	1,25-dihydroxyvitamin D2
Bioanalytical method validation report	PDV0107
Validation assay range (pg/mL)	5 to 100
QCs (pg/mL)	5, 15, 50, and 75
Recovery (%)	85 to 115
Inter-day precision (% CV)	2.39 to 10.60
Inter-day accuracy (% Bias)	-2.78 to 3.04
Intra-day precision (% CV)	1.24 to 9.21
Intra-day accuracy (% Bias)	-11.67 to 6.49
Reference standard	Lot Number: 11177 (b) (4) and C3-104-260 (b) (4)
Specificity	No interference observed in the blank matrix
Freeze/thaw stability	4 freeze (-80°C)-thaw (ambient temperature) cycles
Stock stability	630 days (100 µg/mL) at -20°C
Bench-top stability	Working solution stability: ~24 hours at room temperature Sample stability: ~24 hours at ambient temperature
Processed stability	Post-Preparative Stability: ~72 hour at room temperature
Long-term storage stability	1244 days at -80°C

Source: Validation Report PDV0107
Abbreviations: CV, coefficient of variation; QC, quality control

The concentrations of 1,25-dihydroxyvitamin D2 were determined in a total of 126 human plasma samples obtained from Trial LPS14314. No concentrations could be reported for study

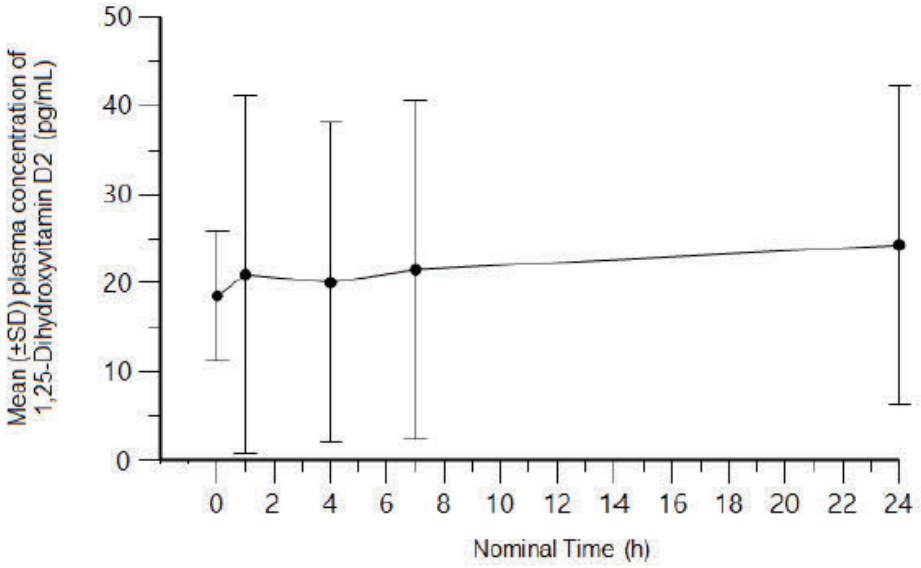
sample [redacted] (b) (4) Week10 / 0h due to insufficient sample volume. A total of 5 reassayed analyses (3.97%) were performed out of the 126 study samples. The observed accuracy (expressed as %Bias) and precision (expressed as %CV) are -5.60 to 2.40 and 3.00 to 7.03, respectively. A total of 38 study samples were selected for the incurred sample reproducibility test to demonstrate that results obtained from study sample analysis are reproducible. A total of 100.00% of the reanalyzed samples met the criteria of assay reproducibility. All samples were analyzed within the 1240 days while the long-term storage stability in human plasma was established for 1244 days.

PHARMACOKINETIC RESULTS

Serial PK samples were collected in 6 subjects. Data from one subject was excluded from noncompartmental PK analysis as the PK samples from that subject were all below lower limit of quantification (LLOQ). In two other subjects, relative nominal time was used for noncompartmental PK analysis as relative actual time of the sampling time points were not available. As shown in Figure 3, the PK profiles of 1,25 dihydroxyvitamin D2 from serial PK sampling after administration of doxercalciferol at Week 8/10 were generally flattened with large intersubject variabilities. Descriptive statistics of the plasma PK parameters of 1,25-dihydroxyvitamin D2 at Week 8/10 in participants who underwent serial sampling are shown in Table 3. The total variability (CV%) was high (~70%) for both C_{max} and $AUC_{0\text{-}24h}$.

Mean (± SD) plasma concentration-time profiles of 1,25-Dihydroxyvitamin D2 profiles at baseline and postbaseline at Weeks 2, 4, 6, 8 or 10, and 12 (Sparse PK samples) are shown in Figure 4. Similar to the PK profiles from serial PK sampling, the PK profiles of 1,25 dihydroxyvitamin D2 across visits were flattened with large intersubject variabilities.

Figure 3: Mean (± SD) 1,25-dihydroxyvitamin D2 plasma concentration versus time profiles for patients who underwent serial sampling at Week 8/10.



BLQ = below the limit of quantification; PK = pharmacokinetic
Note: N = 6, In one subject, only 3 serial PK samples were collected, and they were all below LLOQ. Concentrations for BLQ sample were considered as 0 for the calculation of descriptive statistics.
Source: 16-2-5-ddc-data [16.2.5.2.2]

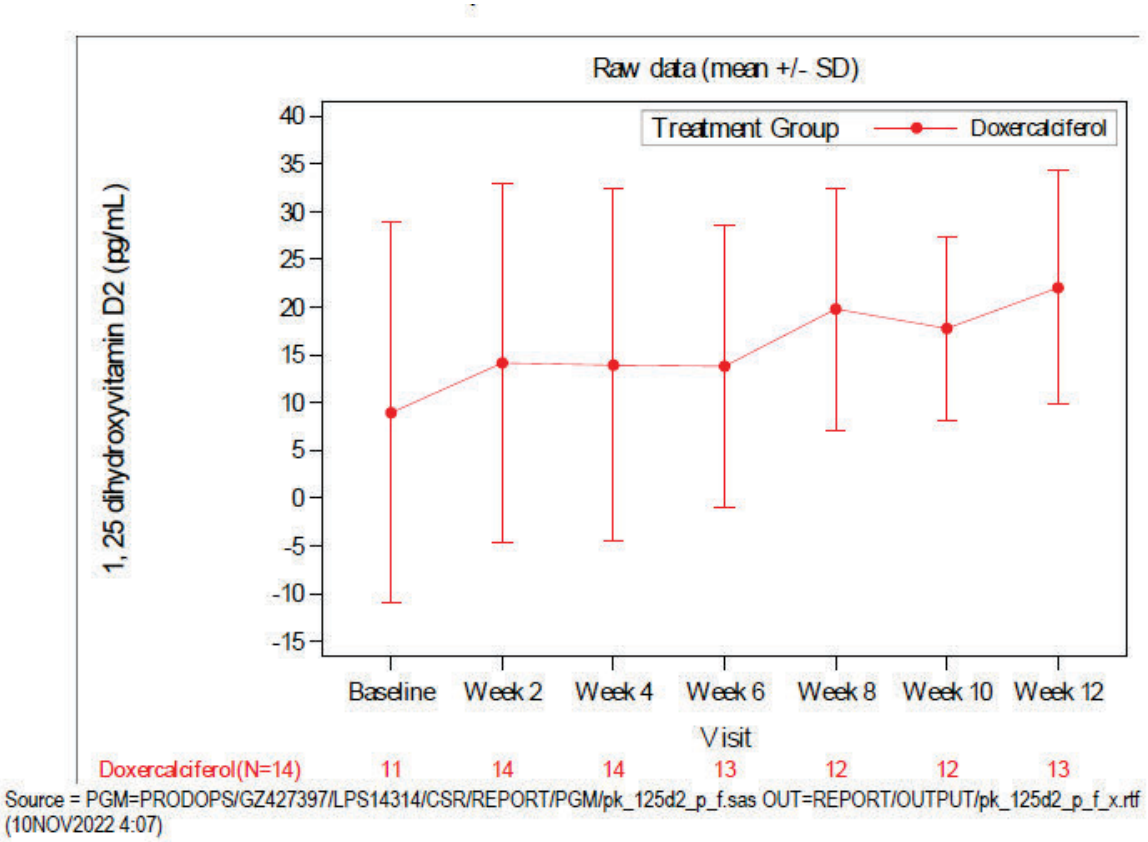
Source: Figure 7, page 62, LPS14314 CSR

Table 3: Descriptive statistics (mean ± SD, [geometric mean], [CV%]) of plasma pharmacokinetic parameters of 1,25-Dihydroxyvitamin D2 at Week 8/10.

N[a]	C_{max} (pg/ml)	t_{max} (h)	AUC_{0-24h} (h*pg/ml)	C_{trough}[b] (pg/ml)
5	27.2 ± 18.9 (22.7) [69.4]	1.07 [0.00 - 7.75]	595 ± 422 (494) [70.9]	18.6 ± 7.40 (39.9) [17.4]

AUC_{0-24h} = area under the concentration-time curve from 0 to 24 hours; Cmax = maximum plasma concentration; t_{max} = time to maximum plasma concentration.
[a] Serial PK samples were collected in 6 patients underwent serial sampling. In one patient, all concentrations were below LLOQ and this patient was excluded from noncompartmental PK analysis.
[b] N = 4; Predose samples were collected in only 4 patients.
Source: Table 25, page 64, LPS14314 CSR

Figure 4: Mean (± SD) 1,25-dihydroxyvitamin D2 plasma concentration versus time profiles across visits.



Source: Figure 9, page 63, LPS14314 CSR

CONCLUSION

- In subjects with serial PK sampling at Week 8/10 or Sparse PK samples (baseline to Week 12), the PK profiles of 1,25-dihydroxyvitamin D2 were generally flattened with large inter-subject variabilities.
- The calculated PK parameters based on the serial PK sampling at Week 8/10 demonstrate high variability (~70%) for both C_{max} and $AUC_{0\text{-}24h}$.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

No change in general dosing in the current supplement.

Therapeutic Individualization

Not Applicable.

Outstanding Issues

None.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The design of the clinical study submitted to this application is summarized in Table 4.

Table 4. Clinical Trial Relevant to this Supplement

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
LPS14314	NCT02859896	Phase 3, randomized, open-label, parallel group, with active comparator (calcitriol)	Route: Oral capsules Dosing regimen: Starting Dose • One 0.5 mcg capsule 3 times weekly (for Age 12 to 18 years) • One 0.5 mcg capsule 2 times weekly (for Age 5 to <12 years) Dose range: 0.5 mcg/week to 17.5 mcg/week	Primary efficacy endpoint: percentage of subjects with ≥ 30% reductions in iPTH from baseline up to Week 12. Safety endpoints: adverse events, vital signs, clinical laboratory assessments	• Screening Period: 4 days to 4 weeks • Primary Efficacy Period: 12 weeks • Safety Continuation Period: 12 weeks	21 subjects (14 in the doxercalciferol group and 7 in the calcitriol group)	Subjects aged 5 to 18 years with CKD Stages 3 and 4 with secondary hyperparathyroidism not yet on dialysis	35 centers in the United States and Chile.

7.2. Review Strategy

This review will focus on the information that the Applicant proposes to include in labeling, which is an update to section 8.4 Pediatric Use.

In this supplement, the Applicant has included data from a single phase 3, randomized, open-label, active comparator trial in subjects aged 5 to 18 years with CKD Stages 3 and 4 with secondary hyperparathyroidism not yet on dialysis (Trial LPS14314). However, due to challenges with recruitment, trial enrollment was terminated early (see Section 3.2). Hence, the Applicant does not propose a new indication for Hectorol. Instead, the Applicant proposes to amend Subsection 8.4 Pediatric Use of Section 8 USE IN SPECIFIC POPULATIONS of the Hectorol USPI to reflect that effectiveness was not established in the pediatric population.

This review focuses on safety and efficacy data from the phase 3 trial LPS14314 and includes an assessment of the Applicant's primary and secondary efficacy results and analyses. The safety review includes an assessment of the Applicant's safety analyses as well as analyses generated by the medical reviewer.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Open-Label, Randomized, Parallel Group Study to Assess the Safety and Efficacy of Hectorol® (doxercalciferol capsules) in Pediatric Patients with Chronic Kidney Disease Stages 3 and 4 with Secondary Hyperparathyroidism Not Yet on Dialysis [Trial LPS14314]

Trial Design

This was a phase 3, randomized, multinational, open-label, parallel group, active comparator trial in subjects aged 5 to 18 years with CKD Stages 3 and 4 with secondary hyperparathyroidism not yet on dialysis. The trial included a Screening Period (4 days to 4 weeks), a Primary Efficacy Period (12 weeks), and a Safety Continuation Period (12 weeks).

To qualify, subjects had to weigh at least 15 kg, have CKD Stage 3 or 4 (defined as estimated glomerular filtration rate [eGFR] of 15-59 mL/min/1.73 m2, inclusive) and an iPTH >100 pg/mL for CKD stage 3 or >160 pg/mL for CKD stage 4. In addition, the following screening laboratory thresholds were required:

- serum 25-OH vitamin D >30 ng/mL
- corrected calcium >10 mg/dL
- serum phosphorous >4.5 mg/dL (children 13-18 years of age) and >5.8 mg/dL for children 5-12 years of age.

Any supplemental vitamin D had to be discontinued at least 14 days prior to the baseline visit.

Subjects were randomized 2:1 to doxercalciferol or calcitriol and were stratified by age and CKD stage at baseline as follows:

- At least 30% of subjects <12 years of age and at least 30% of subjects ≥12 years of age.
- At least 30% of subjects with Stage 3 CKD (estimated glomerular filtration rate [eGFR] = 30 to 59 mL/min/1.73 m^2) and at least 30% of subjects with Stage 4 CKD (eGFR = 15 to 29 mL/min/1.73 m^2).

All subjects were to receive study drugs for 24 weeks. The starting dose of doxercalciferol differed by age sub-group, as follows:

- Ages 12 to 18 years: 0.5 mcg capsule three times weekly at a frequency of every 2 to 3 days
- Age 5 years to <12 years: 0.5 mcg two times weekly at a frequency of every 3 to 4 days.

The starting dose of calcitriol was 0.25 mcg once daily.

For both doxercalciferol and calcitriol, dosing was adjusted to the intact parathyroid hormone (iPTH) plasma levels measured bi-weekly in all subjects.

The doxercalciferol titration scheme was modeled on adult exposure data and designed to achieve comparable exposure. Titration recommendations for calcitriol were those specified in the Rocaltrol prescribing information.

The calcitriol active comparator was included for qualitative comparison purposes only. No statistical hypothesis testing occurred to compare the two groups with respect to safety or efficacy.

The Applicant planned on enrolling 56 subjects in the doxercalciferol group and 28 subjects in calcitriol group in the trial. However, there were several challenges with enrollment, and ultimately only 21 subjects were randomized (14 subjects in the doxercalciferol group and 7 subjects in the calcitriol group).

Study Endpoints

The primary efficacy endpoint was the percentage of subjects achieving 2 consecutive ≥ 30% reductions in iPTH from baseline to week 12.

The secondary efficacy endpoints were percent of change in iPTH from baseline to weeks 12 and 24, and frequency of hypercalcemia, defined as albumin corrected serum calcium >10.2 mg/dL, up to Weeks 12 and 24.

The pharmacokinetic endpoint was serum 1,25-OH vitamin D concentration time data.

The safety endpoints were adverse events, vital signs, and clinical laboratory assessments.

Statistical Analysis Plan

The calcitriol active comparator was included for qualitative comparison purposes only. No statistical hypothesis testing occurred to compare the two groups with respect to safety or efficacy.

The Statistical Analysis Plan (SAP) for this protocol was reviewed by the FDA biostatistical team in a memorandum filed to IND 031423 in DARRTS on December 2, 2014. The team noted that "this study is underpowered to show a treatment difference."

Protocol Amendments

Protocol Amendment 2 was dated March 29, 2016. The dose titration scheme and maximum dose for doxercalciferol was changed. In addition, the target PTH level in subjects receiving growth hormone was changed as growth hormone can increase levels of iPTH. There was no enrollment of subjects at the time of Amendment 2.

8.1.2. Study Results

Compliance with Good Clinical Practices

The protocol was conducted in compliance with Good Clinical Practices.

Financial Disclosure

Financial disclosure was submitted (refer to section 14.1 of this review).

Patient Disposition

A total of 21 subjects were randomized with the majority completing the study treatment period. See Table 5 below.

Table 5. Subject disposition

	Doxercalciferol (N=14)	Calcitriol (N=7)
	N(%)	N(%)
Randomized	14 (100)	7 (100
Completed study treatment period	12 (86)	7 (100)
Premature discontinuation	2 (14)	0
Adverse event	1 (7)	0
Other	1 (7)	0

Source: NDA 020862 SD 554 module 5.3.5.1 LPS14314 Study Report Body, Table 5, p. 25.

All randomized subjects were included in the full analysis set and safety populations.

Protocol Violations/Deviations

Most subjects in both treatment groups had a protocol deviation with violations occurring in more than one subject in either treatment group shown in Table 6. The primary endpoint was analyzed for both the full analysis set (FAS) and the per protocol set (PPS). The protocol violation of "Investigational Medicinal Product (IMP)administered but not as per protocol" included non-compliance with dosing regimen (N=3) and IMP re-dispensed form previous un-used or un-finished bottles (n=2).

Table 6. Major Protocol Violation occurring in at least two subjects in either treatment group

	Doxercalciferol (N=14) N(%)	Calcitriol (N=7) N(%)
Eligibility criteria violation: Presence of Chronic GI disease	4 (29) 2 (14)	1 (14) 0
Randomization procedure: IMP kit number dispensed differed from IMP kit number allocated	2 (14) 2 (14)	1 (14) 1 (14)
IMP administered but not as per protocol	4 (29)	1 (14)
Planned sample not performed (serum calcium, phosphorous, albumin)	6 (43)	6 (86)
Review of phosphate binder use not performed	6 (43)	0

Source: NDA 020862 SD 554 module 5.3.5.1 LPS14314 Study Report Body, Table 6, p. 15.

Demographic Characteristics

Most subjects were white, non-Latino boys aged 12 to 18 years. Most subjects had CKD Stage 3 at enrollment. Demographic and disease characteristics were balanced between treatment groups (Table 7).

Table 7. Demographic and Disease Characteristics

	Doxercalciferol (N=14)	Calcitriol (N=7)
Mean (SD) Age (years)	11.9 (4)	10.4 (4.7)
Age group		
	N(%)	N(%)
5-<12 years	5 (36)	4 (57)
12 to 18 years	9 (64)	3 (43)
Sex		
Male	10 (71)	5 (71)
Female	4 (29)	2 (29)
Race		
White	10 (71)	5 (71)
Black	1 (7)	1 (14)
Multiple	1 (7)	0
Unknown	1 (7)	
Not reported	1 (7)	1 (14)
Ethnicity		
Hispanic or Latino	6 (43)	2 (29)
Not Hispanic or Latino	8 (57)	5 (71)
CKD Stage		
CKD Stage 3	10 (71)	4 (57)
CKD Stage 4	4 (29)	3 (43)
iPTH level at screening (pg/mL [(n(%)]		
>100 and ≤160	7 (50)	2 (29)
>160	7 (50)	5 (71)

Source: NDA 020862 SD 554 module 5.3.5.1 LPS14314 Study Report Body, Table 7, pp26-7

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Mean extent of exposure was similar between the two groups and the majority of subjects in both groups were compliant with study medication (see Table 8)

Table 8. Extent of exposure to investigational medicinal product (IMP) and Treatment Compliance

	Doxercalciferol N=14	Calcitriol N=7
Days of IMP exposure		
Mean (SD)	163 (26)	179 (30)
Duration of IMP exposure		
N(%) with >12 weeks and ≤18 weeks	1 (7)	0
N(%) with >18 weeks and ≤24 weeks	7 (50)	4 (57)
Overall compliance (%)		
% (SD)	96 (7)	96 (5)

Source: NDA 020862 SD 554 module 5.3.5.1 LPS14314 Study Report Body, Table 10 p 32 and Table 11 p 33

Efficacy Results – Primary Endpoint

The majority of subjects in the doxercalciferol group did not achieve the primary efficacy endpoint of two consecutive ≥ 30% reductions in iPTH. The response rate in the doxercalciferol group was also lower than in the calcitriol group (see Table 9).

Table 9. Percentage of subjects achieving 2 consecutive ≥ 30% reductions in iPTH from baseline up to week 12

Statistics	Doxercalciferol (N=14)	Calcitriol (N=7)
Number	14	7
Participants achieving two consecutive ≥30% reduction in iPTH, n (%)	2 (14.3)	5 (71.4)
95% CI[a]	(1.78 to 42.81)	(29.04 to 96.33)
Percentage difference vs. Calcitriol[b]	-52.9	
95% CI of percentage difference vs. Calcitriol[b]	(-99.90 to -5.98)	

a 95% confidence interval is estimated by Clopper-Pearson method.
b Common percentage difference and 95% confidence interval is estimated by Mantel-Haenszel method stratified on randomization stratum of age group (5 to <12, 12 to 18, years of age) and randomization stratum of CKD Stage (3, 4).

Source: NDA 020862 SD 554 module 5.3.5.1 LPS14314 Study Report Body, Table 12, p. 34

The following are efficacy results according to age and CKD subgroup:

- No (0/2) subjects aged 5 to 12 years in the doxercalciferol group achieved the primary efficacy endpoint, compared to 4 (100%) subjects in that age group in the calcitriol group.
- One of 10 subjects (10%) in the doxercalciferol group and 3 of 4 subjects (75%) in the calcitriol group with CKD Stage 3 achieved the primary efficacy endpoint
- One of four subjects (25%) in the doxercalciferol group and 2 of 3 subjects (67%) in the

calcitriol group with CKD Stage 4 achieved the primary efficacy endpoint.

8.1.3. Assessment of Efficacy Across Trials

Not applicable as only a single trial was conducted.

8.1.4. Integrated Assessment of Effectiveness

To fulfill PMR 513-1, the Applicant conducted Trial LPS14314, an open-label, randomized, parallel group trial to assess the safety and efficacy of Hectorol in pediatric subjects with CKD stages 3 and 4 with secondary hyperparathyroidism not yet on dialysis. However, this trial did not establish efficacy of Hectorol in this patient population.

The Applicant initially planned on enrolling 56 subjects in the Hectorol group and 28 subjects in calcitriol group in the trial. However, due to recruitment challenges, the trial was terminated early, and ultimately only 21 subjects were randomized (14 subjects in the Hectorol group and 7 subjects in the calcitriol group).

The primary efficacy endpoint, defined as the proportion of doxercalciferol-treated subjects who achieved two consecutive reductions in iPTH of greater than or equal to 30% from baseline to week 12, was observed in 14.3% of subjects. No formal statistical hypothesis testing was performed on the primary efficacy endpoint. However, a notably lower response rate was observed in Hectorol group compared to the calcitriol group (14.3% vs. 71.4%, respectively). This substantially lower response rate suggests a potential lack of treatment effect with Hectorol in pediatric patients. However, this observation may also be attributed to the limited sample size. The trial was underpowered to begin with, and the final enrollment was further reduced, potentially impacting the reliability and generalizability of the results.

In conclusion, substantial evidence of effectiveness of Hectorol for the treatment of secondary hyperparathyroidism due to CKD in pediatric patients has not been established. Therefore, pediatric indication cannot be granted for Hectorol at this time. The Hectorol label for Hectorol will be amended to include language stating that efficacy of Hectorol has not been established for the treatment of secondary hyperparathyroidism in pediatric patients with Stage 3 or Stage 4 CKD and with CKD on dialysis.

8.2. Review of Safety

8.2.1. Safety Review Approach

The single trial submitted to this application was reviewed for safety.

8.2.2. Review of the Safety Database

Overall Exposure

A total of 14 pediatric subjects aged 5 to 17 years were enrolled and received at least a single dose of Hectorol. Twelve of the 14 subjects randomized completed the study treatment period.

Adequacy of the safety database:

The safety database of 14 subjects exposed to Hectorol is insufficient to make a meaningful determination of the drug's safety in the proposed patient population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no concerns with data integrity or submission quality.

Categorization of Adverse Events

Adverse Event of Special Interest (AESI) was defined as albumin corrected serum calcium >10.2 mg/dL, pregnancy, symptomatic overdose, ALT ≥ 3 ULN (if baseline ALT <ULN), and ALT ≥ 2x baseline (if baseline ALT ≥ ULN). Serious adverse event (SAE) was defined as any adverse event that results in death or is life-threatening, requires inpatient hospitalization or prolonging of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a medically important event such as an allergic bronchospasm, blood dyscrasis, convulsions, development of drug dependence or drug abuse, ALT >3 x ULN, suicide attempt, syncope, cancer or chronic neurodegenerative disease. An adverse event (AE) was defined as any adverse event that is not a serious adverse event or adverse event of special interest.

Routine Clinical Tests

Clinical laboratory data including serum calcium, 1,25 vitamin D, renal and liver function tests were collected as noted in Table 10. Serum calcium levels were collected every two weeks.

Table 10. Schedule of Activities

	Washout NOT required – Screening	Washout required – Screening		PRIMARY EFFICACY PERIOD							SAFETY CONTINUATION PERIOD	
VISIT	1 Week -2[d]	1a Week - 4	1b Week -2[d]	2 Week 0	3 Week 2	4 Week 4	5 Week 6	6 Week 8	7 Week 10	8 Week 12	9 Week 18	10 Week 24/ET
DAY	Day -16 to - 4	Day - 30	Day -16 to -4	Day 1	Day 15 ±3 days	Day 29 ±3 days	Day 43 ±3 days	Day 57 ±3 days	Day 71 ±3 days	Day 85 ± 3 days	Day 126 ± 7 days	Day 168 ± 7 days
Informed Consent	x	x										
Screening												
Inclusion Criteria	x	x	x	x								
Exclusion Criteria	x	x	x	x								
Patient Demography	x	x										
Medical/Surgical History	x	x										
Prior Medication	x	x										
Dietary Consult	x	x										
Randomization				x								
Treatment												
Review of phosphate binder use and diet compliance	x	x	x	x	x	x	x	x	x	x	x	x
Study Treatment(s)												
Hectorol® / Rocaltrol®				←	----------	----------	----------	----------	----------	----------	----------	→
Review of dosing compliance					x	x	x	x	x	x	x	x
Dose adjustment evaluation					x	x	x	x	x	x	x	
Drug accountability					x	x	x	x	x	x	x	x
Dispense study drug				x	x	x	x	x	x	x	x	
Efficacy												
iPTH	x		x	x	x	x	x	x	x	x	x	x
Safety												
AE /SAE monitoring (continuous post-ICF)	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x
Physical Exam	x[h]		x[h]	x						x[h]		x
Vital Signs[a]	x		x	x								x
Height and weight	x		x									x

	Washout NOT required – Screening	Washout required – Screening		PRIMARY EFFICACY PERIOD							SAFETY CONTINUATION PERIOD	
VISIT	1 Week -2[d]	1a Week - 4	1b Week -2[d]	2 Week 0	3 Week 2	4 Week 4	5 Week 6	6 Week 8	7 Week 10	8 Week 12	9 Week 18	10 Week 24/ET
DAY	Day -16 to - 4	Day - 30	Day -16 to -4	Day 1	Day 15 ±3 days	Day 29 ±3 days	Day 43 ±3 days	Day 57 ±3 days	Day 71 ±3 days	Day 85 ± 3 days	Day 126 ± 7 days	Day 168 ± 7 days
Laboratory Testings												
Pregnancy test[b]	x		x	x		x		x		x	x	x
Serum calcium, phosphorus, albumin, calcium-phosphorus product	x		x	x	x	x	x	x	x	x	x	x
Blood chemistry, hematology[e]	x		x	x								x
25-hydroxyvitamin D	x	x										x
GFR calculation	x		x									x
1,25-dihydroxyvitamin D_2 for pharmacokinetic assessment (if randomized to Hectorol®)	x[f]		x[f]	x[g]	x	x	x	x[c]	x[c]	x		

a Including blood pressure, heart rate and temperature

b Post-menarchal female patients will have a serum pregnancy test at the Week -2, and Week 12 visits and a urine pregnancy test every 4 weeks (Week 0, 4 and 8), followed by a urine pregnancy test at Week 18 and at Week 24

c Serial PK Samples will be collected from 18 Hectorol patients post-dose at hours 1 to 3, 4 to 6, 7-12, and 24-36 hours at either Week 8 or Week 10 – choice is per the schedule availability of the site and patient. At the chosen date, the dose of Hectorol® will be administered at the site. A catheter will be used to minimize the number of venipunctures. See protocol section for additional information.

d Week – 2 visits can be performed within 16 to 4 days prior to baseline (Week 0 visit).

e Hematology (red blood cell count, reticulocyte count [to be performed per local lab where applicable], hemoglobin, hematocrit, platelets, white blood cell count with differential blood count). Blood chemistry (sodium, potassium, bicarbonate, chloride, liver function tests (ALT, AST, total and direct bilirubin, alkaline phosphatase, GGTP), albumin, albumin corrected serum calcium, calcium, phosphorus, calcium-phosphorus product, blood glucose, kidney function tests (serum creatinine, blood urea nitrogen).

f Sample to be collected in all patients but analyzed only in patients randomized to Hectorol®

g Sample to be collected after randomization (in patient randomized to Hectorol®) and prior to the first dose intake

h Physcial exam to include Tanner Development Stage

Source: LPS14314 Clinical Trial Protocol 02, dated 29 March 2016, pages 11-12

8.2.4. Safety Results

Deaths

There were no deaths.

Serious Adverse Events

Three treatment emergent serious adverse events (SAEs) occurred in the doxercalciferol group compared to none in the cholecalciferol group and are described below:

- Hypertensive urgency in a 6-year-old Black male with CKD stage 3, on study day 117. The event lasted three days and the subject recovered and continued in the trial
- Bronchial hyperreactivity occurred on study day 8 in a 10-year-old white male with CKD stage 4. The event lasted six days. The subject recovered and continued in the trial.
- A 17-year-old male with CKD stage 4 experienced progression to CKD stage 5 on study day 88 at which time the subject was discontinued from the trial.

The investigators considered none of the events to be related to study drug.

Dropouts and/or Discontinuations Due to Adverse Effects

The SAE of CKD stage 5 described above was the only adverse event leading to early study discontinuation.

Treatment Emergent Adverse Events and Adverse Reactions

The nature of treatment emergent adverse events was similar between treatment groups, except for diarrhea, which did not occur in the calcitriol group (see Table 11). However, diarrhea is a common finding in pediatric patients. Hence, given the small number of subjects who experienced this AE, it is not clear whether the greater incidence of diarrhea was due to the drug, or due chance.

Table 11. Treatment Emergent Adverse Events occurring in >2 subjects in either treatment group

Preferred Term	Doxercalciferol N=14 N(%)	Calcitriol N=7 N(%)
Any TEAE	11 (79)	6 (86)
Vomiting	4 (29)	2 (29)
Diarrhea	3 (21)	0
Headache	2 (14)	2 (29)
Blood phosphorous increased	2 (14)	1 (14)
Pyrexia	1 (7)	2 (29)

Source: NDA 020862 SD 554 module 5.3.5.1 LPS14314 Study Report Body, Table 17, p. 43

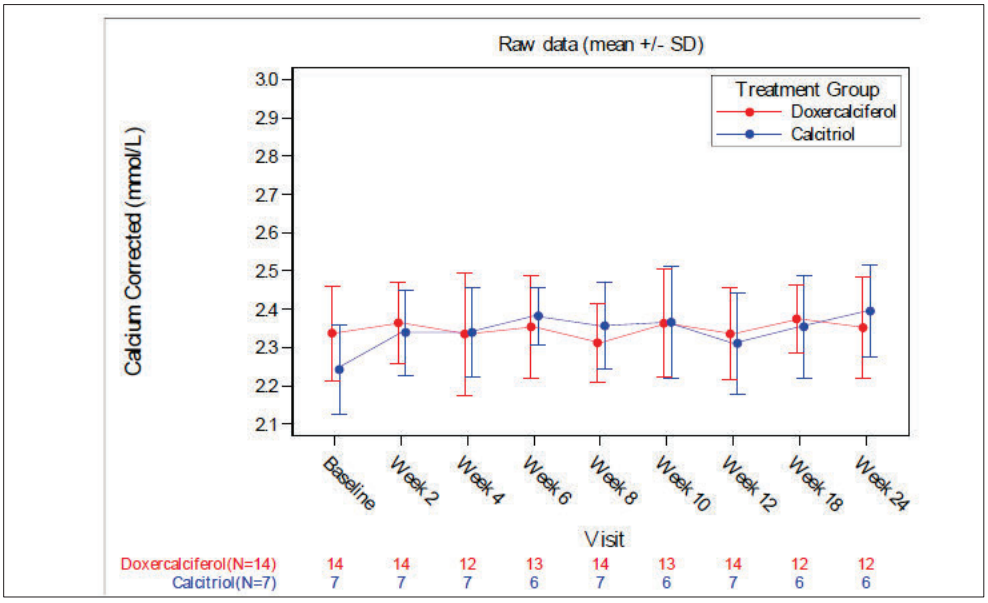
Laboratory Findings

Hypercalcemia was identified as an adverse event of special interest. One subject receiving doxercalciferol – a 13-year-old female with CKD stage 3 whose baseline corrected calcium was in the normal range, experienced Grade 1 calcium elevation on Day 29 (value of 2.6 mmol/L). Doxercalciferol dose was reduced from 0.5 mcg/day to 1.5 mcg/week and calcium had returned to the normal range by Day 43. There were no other subjects with laboratory values of hypercalcemia.

A single subject assigned to calcitriol and whose serum calcium at baseline was normal, experienced Grade 1 hypocalcemia [value of 2.075 (normal range 2.1-2.575 mmol/L)] at week 12. Calcium returned to normal by the week 18 visit. There were no other shifts from normal to below normal in serum calcium.

There was no meaningful difference between treatment groups in mean serum calcium by visit (see Figure 5).

Figure 5. Calcium corrected: Mean (+/-SD) across visits during treatment



Source: Figure 4, p. 52

Median 25-OH vitamin D at baseline was slightly higher in the calcitriol group. At week 24, the median values were similar in both groups, as was the change from baseline (see Table 12)

Median iPTH was high in both treatment groups at baseline. The Week 24 median had increased for doxercalciferol while it had decreased for calcitriol. The change from baseline was significantly greater in calcitriol than in doxercalciferol.

Table 12. Median (min, max) at baseline and week 24 and median change from baseline

	Doxercalciferol	calcitriol
25-OH vitamin D		
Baseline	102 (75, 140)	120 (76, 133)
Week 24	84 (50, 130)	92 (30, 120)
change from baseline	-27	-24
iPTH (18-80)		
baseline	152 (56, 499)	208 (99, 554)
Week 24	167 (36, 786)	69 (16, 237)
Change from baseline	4.2	-118

There were otherwise no meaningful differences in changes in laboratory parameters during treatment, or in the incidence of values outside the normal range between the two treatment groups.

Vital Signs

There was no meaningful difference in median change from baseline in vital sign parameters between treatment groups.

The protocol pre-specified value ranges for potentially clinically significant abnormalities (PCSA) in blood pressure, weight, and temperature, as shown in Table 13

Table 13. Thresholds for PCSA in Blood Pressure, Weight, and Temperature by age group category

Age range (years)	High and increase from baseline	Low and decrease from baseline
Systolic blood pressure		
2 to <6	≥101 mmHg and increase ≥20 mmHg	≤70 mmHg and decrease >20 mmHg
6 to <12	≥ 108 mmHg and increase ≥ 20 mmHg	≤80 mmHg and decrease >20 mmHg
12 to 18	≥119 mmHg and increase ≥20 mmHg	≤90 mmHg and decrease >20 mm Hg
Diastolic blood pressure		
2 to <6	≥59 mmHg and increase >10mmHg	≤34mmHg and decrease ≥10mmHg
6 to <12	≥72 mmHg and increase >10 mmHg	≤48 mmHg and decrease ≥10 mmHg
12 to 18	≥78 mmHg and increase >10 mmHg	≤54 mmHg and decrease ≥10 mmHg
Weight		≥5% decrease from baseline
Temperature (all ages)		
Rectum, ear, temporal artery		≥38 C
oral		≥37.5 C
axilla		≥37.2 C

No subject in either treatment group transitioned from normal at baseline to PCSA at week 24 with respect to SBP or weight.

One subject each in both treatment groups had normal baseline DBP that had transitioned to PCSA low at week 24. At baseline the doxercalciferol treated subject had blood pressure of 87/56 mmHg which was measured at 102/43 mmHg at week 24. The subject receiving calcitriol had baseline blood pressure of 112/66 which at week 24 was 87/48 mmHg. Subjects with chronic kidney disease are prone to blood pressure lability and in neither case is there an obvious contribution from study drug.

Another subject in the doxercalciferol group experienced elevated body temperature of 39.4° C at week 18 coincident with adverse event of streptococcal pharyngitis. Temperature had returned to normal at week 24 and was related to infection, not to study drug.

Electrocardiograms (ECGs)

ECGs were not assessed during the trial.

8.2.5. Analysis of Submission-Specific Safety Issues

No additional safety issues were identified beyond what has been reviewed.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

The study sample size of only 21 patients (14 subjects on doxercalciferol and 7 subjects on calcitriol) precludes a meaningful evaluation of the effect of demographic subgroup on drug safety or efficacy.

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable

8.2.9. Additional Safety Explorations

Not applicable.

8.2.10. Safety in the Postmarket Setting

Not applicable

8.2.11. Integrated Assessment of Safety

The safety database from the single phase 3 trial LPS14314 is not adequate for a comprehensive safety assessment of Hectorol for the treatment of secondary hyperparathyroidism due to CKD in pediatric patients. As discussed in Section 3.2, due to recruitment challenges, the Applicant terminated enrollment in Trial LPS14314 early, prior to enrolling an adequate number of subjects to appropriately characterize the safety profile of Hectorol in pediatric patients.

Within the limitations of the small population size of the trial, there did not appear to be any significant safety signals of concern or trends in the TEAEs. The incidence of TEAEs was similar between the Hectorol and calcitriol arms, except for diarrhea, which occurred at a greater incidence in Hectorol arm compared to calcitriol arm (3 [21%] vs. none). However, diarrhea is a common finding in pediatric patients. Hence, given the small number of subjects who experienced this AE, it is not clear whether the greater incidence of diarrhea was due to the

drug, or due chance. There were no clinically meaningful or unexpected changes observed in laboratory parameters during the trial.

In conclusion, the safety review did not identify significant new safety signals or additional information pertinent to the safety profile of Hectorol as described in the USPI. However, a lack of any additional safety findings in this trial does not indicate that the drug is safe in pediatric population, given that the safety database from the single phase 3 trial was not adequate. Hence, Section 8.4 (Pediatric Use) of the Hectorol label will be amended to include language stating that safety of Hectorol has not been established for the treatment of secondary hyperparathyroidism in pediatric patients with Stage 3 or Stage 4 CKD and with CKD on dialysis.

8.3. Statistical Issues

The SAP for this protocol was reviewed by the FDA biostatistical team in a memorandum filed to IND 31423 in DARRTS on December 2, 2014. The team noted that "this study is underpowered to show a treatment difference." No hypothesis testing for efficacy was prespecified.

8.4. Conclusions and Recommendations

To fulfill PMR 513-1, the Applicant conducted Trial LPS14314, an open-label, randomized, parallel group trial to assess the safety and efficacy of doxercalciferol in pediatric subjects with CKD stages 3 and 4 with secondary hyperparathyroidism not yet on dialysis.

Neither the efficacy nor the safety of Hectorol in pediatric patients with secondary hyperparathyroidism due to CKD were adequately demonstrated in Trial LPS14314, because the Applicant was not able to enroll an adequate number of pediatric subjects. The Applicant initially planned on enrolling 56 subjects in the doxercalciferol group and 28 subjects in calcitriol group in the trial. However, due to recruitment challenges, the trial was terminated early, and ultimately only 21 subjects were randomized (14 subjects in the doxercalciferol group and 7 subjects in the calcitriol group).

The efficacy data also suggest a potential lack of treatment effect with doxercalciferol in the pediatric population. The primary efficacy endpoint, defined as the proportion of doxercalciferol-treated subjects who achieved two consecutive reductions in iPTH of greater than or equal to 30% from baseline to week 12, was observed in 14.3% of subjects. No formal statistical hypothesis testing was performed on the primary efficacy endpoint. However, a notably lower response rate was observed in doxercalciferol group compared to the calcitriol group (14.3% vs. 71.4%, respectively). This substantially lower response rate suggests a potential lack of treatment effect with doxercalciferol in pediatric patients. However, this observation may also be attributed to the limited sample size. The trial was underpowered to begin with, and the final enrollment was further reduced, potentially impacting the reliability and generalizability of the results.

The safety profile of doxercalciferol was consistent with the known safety profile of doxercalciferol in adults. No new safety concerns were identified. However, a lack of any

additional safety findings in this trial does not indicate that the drug is safe in pediatric population, given that the safety database from the single phase 3 trial was not adequate. Mean 1,25-OH vitamin D concentration increased after 12 weeks of treatment with doxercalciferol, but inter-subject variability was high.

The Applicant appears to have made a good faith attempt to fulfill the PMR. Hence, PMR 513-1 can be considered fulfilled. The Pediatric Review Committee discussed this supplement on April 29, 2025, and concurred with the Division's recommendations.

Subsection 8.4 Pediatric Use of Section 8 Use in Specific Populations of Hectorol USPI will be updated to reflect that safety and effectiveness of Hectorol have not been established for the treatment of secondary hyperparathyroidism in pediatric patients with Stage 3 or Stage 4 CKD and with CKD on dialysis. The review team also did not identify any new safety signals that should be included in the USPI.

9 Advisory Committee Meeting and Other External Consultations

Not applicable.

10 Pediatrics

The trial was conducted to fulfill the PREA PMR which, as discussed below in Section 13, is considered fulfilled.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information (PI)

The Applicant proposed [redacted] (b) (4) owever, *FDA's Guidance for Industry: Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling (2019)* states that negative studies should be briefly summarized in subsection 8.4 to avoid implying that the drug (in this case, Hectorol) is safe and effective in pediatric patients. Per 21 CFR 201.57 (c)(9)(iv)(E), the regulatory pediatric use statement ("Safety and efficacy were not demonstrated …" language above) must be included the Use in Specific Populations/ Pediatric Use subsection when substantial evidence to support a pediatric indication have not been met.

Therefore, [redacted] (b) (4) deleted from section 8.4. Also, no new safety issues were identified in Trial LPS14314. Hence, the following language was incorporated to satisfy the regulatory requirement (21 CFR 201.57(c)(9)(iv)(E)] and to briefly summarize the trial that did not demonstrate safety and effectiveness in pediatric patients:

> The safety and efficacy of HECTOROL have not been established for the treatment of secondary hyperparathyroidism in pediatric patients with Stage 3 or Stage 4 chronic kidney disease (CKD) and with CKD on dialysis.
>
> Effectiveness was not demonstrated in a 12-week randomized, open-label trial in fourteen HECTOROL-treated patients, aged 5 to 17 years with chronic kidney disease (not on dialysis) and secondary hyperparathyroidism.

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

13 Postmarketing Requirements and Commitment

The submission was discussed at a meeting of the Pediatric Review Committee (PERC) on April 29, 2025.

The PeRC agreed that this product is assessed in pediatric patients 5 to 18 years of age and the PREA PMR is considered fulfilled. The PeRC agreed with the plans to update section 8.4 with a summary of the findings of the completed study.

No additional postmarketing requirements or commitments will be issued.

14 Appendices

14.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): LPS14314

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 51		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHIVANGI R VACHHANI
06/02/2025 03:06:14 PM

THERESA E KEHOE
06/03/2025 08:26:17 AM