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APPLICATION NUMBER:

208010Orig1s000

SUMMARY REVIEW

Summary Review of Class 2 Resubmission

Date	6/10/2016
From	Marina Zemskova, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	208010
Supplement#	
Applicant	OPKO Ireland Global Holding
Date of Submission	4/22/2016
PDUFA Goal Date	6/21/2016
Proprietary Name / Established (USAN) names	Royaldee/ extended-release calcifediol
Dosage forms / Strength	Capsule/ 30 mcg
Proposed Indication(s)	(b)(4) treatment of secondary hyperparathyroidism (SHPT) in (b)(4) with chronic kidney disease (CKD) stages 3 or 4 and (b)(4)
Recommended:	Approval

Memorandum

On April 22, 2016 OPKO Ireland Global Holding resubmitted a New Drug Application (NDA) for Royaldee (b)(4) formulation of calcifediol) under Section 505(b) (1) of the Federal Food, Drug, and Cosmetic Act in support of the following indication:

Treatment of secondary hyperparathyroidism (SHPT) in (b)(4) with chronic kidney disease (CKD) stages 3 or 4 and vitamin D levels less than 30 ng/ml

This NDA was originally submitted to the Agency on 9/30/2015. All data to support approval were reviewed during the previous cycles and are summarized in previous memoranda. Refer to these memoranda for details.

The Division issued a Complete Response (CR) because numerous Good Manufacturing Practices violations at the drug product manufacturing facility (b)(4) were identified during a combined surveillance and pre-approval inspection carried out on (b)(4) (refer to the Division Director and CDTL summary reviews, CMC review from 3/28/2016 and CR letter from 03/28/2016 in DARRTS). FDA's Florida District Office (FLA-DO) classified the inspection as "Official Action Indicated" and the office of pharmaceutical quality recommended a withhold action on the application.

Per the OPQ summary; "the manufacturer submitted responses to the inspection observations on (b)(4). The FLA-DO Compliance Branch proceeded to review and evaluate the inspection results, including (b)(4) response to the 483 (dated (b)(4) and the investigator's EIR (completed early (b)(4); they subsequently classified (final) the inspection as VAI. The FLA-DO Compliance Branch determined that the firm's response was largely adequate. The district will request additional responses from (b)(4) to address remaining concerns.

The FLA-DO Pre-approval Manager (PAM) notified OPF (May 11, 2016) of the final VAI classification, removed the pOAI alert in Panorama, and recommended the facility be approved to support the NDA. Based on the district's recommendation, OPF considers the facility acceptable

to support NDA 208010.”

Proprietary name

The proposed proprietary name for calcifediol, Rayaldee, was reassessed and deemed acceptable by the Office of Medication Error Prevention and Risk Management (refer to the review from 6/2/2016). A letter stating this was issued to the Applicant on 6/2/2016.

Safety Update

The safety data on (b)(4) was included in the current submission and reviewed by Dr. William Lubas. There were no deaths or serious adverse events. Dr. William Lubas concluded that there were no new safety signals in patients with CKD 3 or 4 and secondary hyperparathyroidism.

Labeling

The revised label was reviewed by the clinical reviewer (refer to the review in DARRTS from 6/8/2016), associate director for labeling, by DMEPA reviewer (refer to the review in DARRTS from 6/6/2016), patient labeling and OPDP and was found to be acceptable.

Conclusion:

The Sponsor/manufacture adequately addressed all deficiencies listed in the Division's CR letter issued on 28 March 2016.

A review of the data submitted in the original NDA concluded that the Sponsor provided substantial evidence to support the safety and effectiveness of Rayaldee in patients with CD stage 3 and 4 (refer to the CDTL review from 3/28/2016).

Lastly, no new information or data was included in the re-submission of the NDA that would change risk/benefit assessment of Rayaldee in the intended population.

Recommended Regulatory Action

I recommend approval of Rayaldee for the following indication: *treatment of secondary hyperparathyroidism (SHPT) in (b)(4) with chronic kidney disease (CKD) stages 3 or 4 and vitamin D levels less than 30 ng/ml.*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARINA ZEMSKOVA

06/10/2016

JEAN-MARC P GUETTIER

06/17/2016

Dr. Zemskova's review serves as the Divisional Summary for the class-2 re-submission. Manufacturing deficiencies have been addressed, I concur with her recommendation for approval. Refer to the DD summary in the original submission for the Divisional Summary of efficacy and safety for the product. Two pediatric studies will be required under the Pediatric Research and Equity Act post-approval (see approval letter for study details and agreed upon timelines).

Cross-Discipline Team Leader Review

Date	3/28/2016
From	Marina Zemskova, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	208010
Supplement#	
Applicant	OPKO Ireland Global Holding
Date of Submission	May 29, 2015
PDUFA Goal Date	3/29/2016
Proprietary Name / Established (USAN) names	Royaldee/ extended-release calcifediol
Dosage forms / Strength	Capsule/ 30 mcg
Proposed Indication(s)	(b)(4) treatment of secondary hyperparathyroidism (SHPT) in (b)(4) with chronic kidney disease (CKD) stages 3 or 4 and (b)(4)
Recommended:	Complete Response

1. Introduction

On May 29, 2015 OPKO Ireland Global Holding submitted a New Drug Application (NDA) for Royaldee under Section 505(b) (1) of the Federal Food, Drug, and Cosmetic Act. Royaldee is a (b)(4) formulation of calcifediol (25-hydroxycholecalciferol, 25-OH vitamin D3).

The Sponsor has obtained a right of reference to NDA 018312 for Calderol (an immediate release calcifediol formulation) and references nonclinical studies contained within that NDA to support approval of the new formulation. Calderol was approved in 1980 for the treatment of metabolic bone disease or hypocalcemia associated with chronic renal failure in patients undergoing renal dialysis and was withdrawn from the market in 2001 for commercial reasons and not for safety or efficacy reasons.

The proposed indication for Royaldee is:

(b)(4) treatment of secondary hyperparathyroidism (SHPT) in (b)(4) with chronic kidney disease (CKD) stages 3 or 4 and (b)(4)

In this CTDL review I will summarize the findings from primary reviews and discuss issues identified by each disciplines. This review will also discuss the main efficacy and safety findings from the two pivotal clinical studies, focusing on the study population (i.e. vitamin D insufficient patients with chronic kidney disease) and pre-specified primary endpoint which

was a percentage of patients who had decrease in intact parathyroid hormone (iPTH) levels by $\geq 30\%$.

2. Background

Secondary hyperparathyroidism (SHPT) and mineral metabolism abnormalities (e.g., calcium and phosphorus) that occur in the setting of chronic kidney disease (CKD) may lead to bone disease (abnormalities in bone turnover, mineralization, and strength) and extra-osseous calcifications (deposition of calcium in the kidney, cardiovascular system). Poor bone health could lead to increased fracture risk and calcification of cardiovascular tissues such as the myocardium, conduction system, valves, arterioles and arteries could result in cardiovascular pathology such as arrhythmia, coronary artery disease or other events.

To prevent poor bone health and extra-osseous calcification in patients with chronic kidney disease, the 2009 Kidney Disease Improving Global Outcomes (SHPT) therapeutic guidelines¹ recommend that subjects with CKD stage 3-5 not on dialysis and iPTH levels above the normal reference range be evaluated and treated for factors that contribute to elevation in PTH including hyperphosphatemia, hypocalcemia and Vitamin D deficiency. Treatment of SHPT with Vitamin D or its analog occurs alongside treatment of other prevalent mineral abnormalities (hyperphosphatemia, hypocalcemia) also implicated in the bone disease and mineral metabolism disorders associated with chronic kidney disease.

Royaldee is a (b)(4) vitamin D3 analog (25-OH vitamin D3, calcifediol). Thus, compared to inactive vitamin D analogs (cholecalciferol and ergocalciferol), Royaldee does not have to be activated in the liver by 25 hydroxylation.

Similar to natural Vitamin D and other Vitamin D analogs, the main function of calcifediol is the regulation of calcium and phosphate homeostasis, which occurs mainly via conversion of vitamin D to its active metabolite, 1,25-dehydroxycholecalciferol (1,25-OH vitamin D, calcitriol), and binding to the vitamin D receptors in a variety of tissues including parathyroid gland. Vitamin D inhibits the synthesis and secretion of parathyroid hormone (PTH), and subsequently reduces circulating PTH. This constitutes the physiologic rationale for vitamin D analog use in the treatment of secondary hyperparathyroidism in the settings of chronic kidney disease.

Patients with SHPT and advanced CKD (usually stage 5) are treated with active vitamin D analogs (1,25-OH vitamin D) because failing kidneys are unable to convert inactive vitamin D to its active form. Patients with stage 3 and 4 CKD have sufficient remaining kidney function to convert inactive vitamin D into its active form. Thus, in patients with stage 3 and 4 CKD and low vitamin D stores, replenishing vitamin D with an agent like calcifediol would result in raising total body stores of vitamin D, active vitamin D levels and calcium levels. These effects would in turn decrease PTH levels. Thus, central to this application is whether the

¹ KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009 Aug;(113):S1-130.

Sponsor has demonstrated that treatment with the vitamin D analog, Rayaldee, decreases iPTH in patients with CKD and SHPT who were found to have low vitamin D levels.

Regulatory Background

The following are the major regulatory interactions that took place between DMEP and OPKO Ireland Global Holding regarding the Rayaldee development program for the secondary hyperparathyroidism indication:

1) Pre-IND meeting (December 18, 2006).

Retrospectively, this meeting was very important because it set the overall direction of the Rayaldee Phase 3 clinical program. (b)(4)

(b)(4) and pointed out that the goal of vitamin D therapy is to treat the SHPT. (b)(4)

(b)(4) and that the primary endpoint should be PTH level, (b)(4)
As stated above 25-OH vitamin D needs to be converted to active vitamin D and the effect on PTH is generally attributed to active vitamin D.

2) IND 075162 was opened on October 2, 2007 with a protocol for a Phase 1 clinical trial (CTAP101-CL-1005) to evaluate PK, PD and safety of CTAP101 (Rayaldee) in healthy subjects and subjects with stage 3 or 4 CKD and vitamin D insufficiency.

3) End-of-Phase 2 meeting (EOP2; February 14, 2012)

The development program for Rayaldee was discussed during this meeting. Multiple disagreements between the Division and the Sponsor and uncertainties regarding proposed Phase 3 clinical program were raised during this meeting. Disagreements with regards to the proposed indication, patient population, size of planned clinical program, the ability to bridge Rayaldee to the findings of safety and efficacy of Calderol were discussed. The Division also disagreed with the (b)(4)

(b)(4)
Due to the multiple complex issues raised by the application and unresolved issues, the Division recommended submitting the Phase 3 study protocol under the "special protocol assessment" process.

The need for thorough QTc study was also discussed during the meeting; it was agreed that dedicated QTc study is not necessary and ECG should be measured during the Phase 3 study.

4) As per the Division's recommendations, the Sponsor submitted a request for a special protocol assessment (SPA) of Phase 3 study protocol (CTAP101-CL-3001) on May 15, 2012. After the reviewing the protocol, the Division issued an agreement letter on August 30, 2012. The Division and the Sponsor reached overall agreement on the proposed study design.

Some of the trial design attributes required for the agreement were:

- the study will be a double-blind, placebo control study
- the proposed primary endpoint will be a percentage of patients who achieve decrease in iPTH level by $\geq 30\%$ at the end of the study
- one of the proposed secondary endpoint will be a percentage of patients who has vitamin D 25-OH level within normal range at the end of the study
- selected patient population will be patients with CKD stage 3 or 4, iPTH levels > 85 ng/ml and 25-OH vitamin D levels < 30 ng/ml
- the sample size estimate for each CKD stage (105 patients) is satisfactory, the dropout rate of 20% is incorporated into the sample size calculations and the assumption used in the sample size calculations is acceptable
- the primary analysis will be conducted on Intent to Treat population and patients with missing primary endpoint data will be treated as treatment failures.

5) Pre-NDA meeting (October 8, 2014).

The Division and the Sponsor agreed that NDA will be filed under 505 (b) (1) because the Sponsor has obtained a right of reference to the entire Calderol NDA. Overall, the meeting focused on NDA's content and format and the completeness of the different NDA modules.

5) NDA submission: May 29, 2015.

6) Amendment – Safety Update Report (4 month): September 24, 2015.

3. CMC/Device

The Office of Pharmaceutical Quality (OPQ) review recommends Complete Response because of the multiple deficiencies identified at (b)(4) facility during the inspection (refer to the review in DARRTS, 3/28/2016).

There are no other deficiencies identified by the other review members of the OPQ team.
There are no recommendations for Phase 4 studies.

The active ingredient in Rayaldee, calcifediol, has a molecular weight of 400.6 g/mol. The CMC review indicates that the Sponsor obtained right of reference to NDA 018312 (Calderol) and to the relevant DMF (b)(4) for all CMC information on the drug substance and drug product. This information was reviewed and found to be acceptable.

Rayaldee is manufactured as extended-release capsules and formulated to contain 30 mcg of calcifediol; excipients are mineral oil, monoglycerides and diglycerides, paraffin, hypromellose, lauroyl polyoxylglycerides, dehydrated alcohol and butylated hydroxytoluene. The capsule shell contain modified starch, carrageenan, sodium phosphate, dibasic, sorbitol sorbitan solution, FD&C Blue #1, titanium dioxide and purified water. The soft capsule shell is manufactured by (b)(4) utilizing a proprietary encapsulation technology. Details on the capsule shell are obtained from (b)(4) DMF (b)(4) for which the Sponsor obtained right of reference. The regulatory drug product specifications were reviewed by CMC reviewer and were found to be adequate based on the supporting release and stability data and ICH guidelines for this type of dosage form.

An expiry of 24 months was granted when stored at room temperature, (b) (4)

4. Nonclinical Pharmacology/Toxicology

The applicant conducted several non-clinical studies to support the use of Rayaldee. These studies included pharmacokinetic and toxicokinetic studies, two 6-month dog studies to compare the toxicology of an immediate release formulation to the (b) (4) formulation (Rayaldee), one 28-day mice study to determine the tolerability of Rayaldee up to 1000 mcg/day and a 6-month carcinogenicity study in the Tg-rasH2 mice. All other required studies (including single dose toxicology studies, in vitro mutagenicity studies, reproductive and developmental toxicity studies) were conducted and reviewed previously under NDA 018312 (Calderol; immediate release calcifediol formulation) to which the Sponsor obtained right of reference.

The scientific justification to support reliance on Calderol data was found to be valid by the pharmacology/toxicology team on the basis that the active ingredient, calcifediol, in Rayaldee and Calderol formulations are the same, and that the impurity profiles of both formulations (Rayaldee and Calderol) are similar. Lastly, Dr. Espandiarì also reviewed the safety of all ingredients (including (b) (4) ingredients, carrageenan and (b) (4) starch, as requested by the Office of Technical Quality) contained in the proposed capsule shell formulation and also considered these ingredients to be safe.

The toxicology profile observed with Rayaldee in animals is consistent with that of an exaggerated pharmacodynamic response. Hypercalcemia, hypercalciuria and mineralization of soft tissue (heart and kidney) were the main toxicology findings; the incidence and severity of these findings correlated with serum calcifediol levels. Dr. Espandiarì notes however that no toxicities were observed at calcifediol exposure 5.6 and 1.8 fold higher than levels observed in clinical studies at (b) (4) doses of 30 and 60 mcg/day, respectively.

Dr. Espandiarì also concluded that the findings from carcinogenicity study demonstrated no drug-related neoplastic changes.

Please see Dr. Parvaneh Espandiarì review dated February 8, 2016, for details of the nonclinical program supporting approval of this NDA. She and pharmacology/toxicology supervisor, Dr. C. Lee Elmore, deem the nonclinical data acceptable in support of approval of Rayaldee for the treatment of secondary hyperparathyroidism in patients with stage 3 or 4 CKD and vitamin D (b) (4) provided labeling accurately reflects the nonclinical findings and their recommendations on use of the product. No postmarketing trials are being proposed by this discipline.

I concur with Drs. Espandiarì's and Elmore's assessment. There does not appear to be any nonclinical issue that would preclude approval.

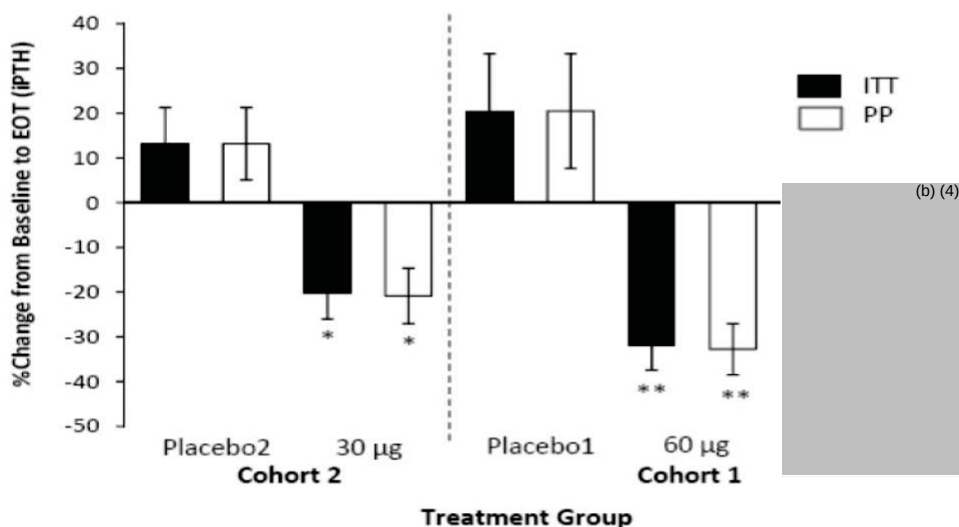
5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was completed by Dr. Ritesh Jain, and Pharmacometrics review was completed by Dr. Lian Ma. Both reviewers recommended approval of Rayaldee without additional Phase 4 studies. For detailed discussion, please refer to their Clinical Pharmacology review in DARRTS (2/26/2016).

Reviewers concluded that pharmacokinetic (PK) data from a multiple dose Phase 2 trial (CTAP101-CL-2008) in patients with CKD stage 3 and 4 and SHPT and population pharmacokinetic (PopPK) analysis from Phase 2 and Phase 3 pivotal trials (CTAP101-CL-3001 and CTAP101-CL-3002) provided acceptable PK data for labeling purposes. The mean baseline-adjusted C_{max} values from the Phase 2 study (CTAP101-CL-2008) were 28, 60, and (b) (4) ng/mL following 30mcg, 60mcg and 90mcg once daily Rayaldee doses, respectively. Mean exposures (baseline-adjusted AUC_{0-6w} to calcifediol), were dose proportional over 30 to 90 mcg doses when compared across dose groups. Median elimination half-life (t_{1/2}) was between 24 to 36 days across all dose groups. PopPK analysis revealed an elimination half-life of approximately 25 days for calcifediol in patients with CKD, volume of distribution (Vd/F) of 30.1 L. It took approximately 8 to 9 weeks to reach the steady state calcifediol levels.

Data from Phase 2 study (CTAP101-CL-2008) demonstrated that the exposures were dose proportional: Rayaldee administered at daily doses of 30, 60 and 90 mcg for 6 weeks produced mean plasma iPTH changes from baseline of -20, -32 and (b) (4)%, respectively (Figure 1).

Figure 1: Mean ($\pm$ SE) Percent Change in Plasma iPTH from Baseline by Treatment Group and Analysis Population at end of treatment (EOT) (Study CTAP101-CL-2008).

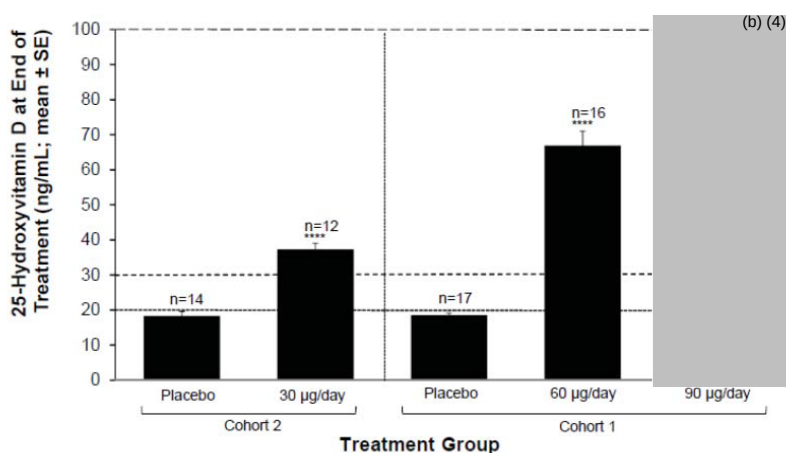


*p<0.005 **p<0.001 ***p<0.0005
Source: Clinical Pharmacology review, figure 2, page 17.

The daily dose of 30 mcg resulted in an increase in mean serum total 25-OH vitamin D concentrations to 37 ng/mL and the daily dose of 60 mcg increased serum total 25-OH vitamin D to a mean of 67 ng/mL (within the appropriate target range of 30 to 100 ng/mL for patients

with stage 3 or 4 CKD; dose of 90 mcg (b) (4).

Figure 2: Mean ($\pm$ SE) Serum Total 25-Hydroxyvitamin D by Treatment Group at EOT in the PP Population (Study CTAP101-CL-2008)



**** Significantly different from placebo, $p < 0.0001$

Note: The three horizontal dashed lines indicate the lower limit of normal per the Institute of Medicine (lower) and K/DOQI (middle), and the upper limit of the laboratory reference range (upper) [Ross et al 2011; K/DOQI 2003; Guideline 7].

Source: Clinical Pharmacology review, figure 3, page 18.

Intrinsic factors (e.g. weight/body mass index, age, renal function) that could influence exposure and activity were evaluated. Age, gender, race, body weight, diabetic status and eGFR had no clinically relevant effect on the PK of Rayaldee. Hepatic impairment was not evaluated in Rayaldee program. Calcifediol is a (b) (4) vitamin D3 analog and does not have to be activated in the liver by 25 hydroxylation. Thus, Dr. Jain concluded that hepatic impairment should not have any effect on the exposure or the efficacy of the calcifediol.

The absolute bioavailability of Rayaldee following oral administration in healthy subjects was approximately 25% based on the results from the Phase 1 absolute bioavailability study in healthy subjects (CTAP101-CL-1011) using the dose of 900 mcg. Phase 1 food effect study using 450 mcg Rayaldee dose in healthy volunteers demonstrated that the administration of Rayaldee with high-fat meals resulted in a significantly higher exposure of calcifediol compared to the exposure of calcifediol administered in a fasted state. However, the clinical pharmacology reviewers considered the results of both studies to be exploratory because the studies used a supra therapeutic doses of Rayaldee and PK linearity for dose beyond 90 mcg was not demonstrated in this NDA. (b) (4)

Lastly, Dr. Jain recommends to administer Rayaldee at bedtime because this regimen has been studied in Phase 3 pivotal studies.

The Sponsor did not conduct any clinical studies to investigate the distribution, metabolism or excretion of calcifediol (as was agreed during EOP2 meeting) and provided available data

from the published literature. Dr. Jain summarized the following information regarding the distribution, metabolism and excretion of calcifediol obtained from the literature²:

- calcifediol is metabolized by the following three routes: conversion to calcitriol by cytochrome P-450 25-hydroxyvitamin D hydroxylase (CYP27B1) in the kidney, parathyroid gland, and other tissues; hepatic catabolism to water-soluble forms excreted in bile as glucuronide conjugates; and conversion to 24,25-OH vitamin D3 and calcitroic acid by cytochrome P-450 CYP24A1
- more than 98% of calcifediol in plasma circulates as bound to plasma protein.

Drug-drug interactions were not studied in Rayaldee clinical program. The following information regarding drug-drug interaction potential of calcifediol is obtained from the approved vitamin D analogs labels and from the literature:

- Cholestyramine is reported to reduce the absorption of fat-soluble vitamin D, and thus may impair the absorption of calcifediol from Rayaldee capsules.
- Co-administration of anticonvulsants (e.g., phenytoin and phenobarbital) is reported to reduce plasma levels of calcifediol by accelerating its metabolism.
- the co-administration of cytochrome P450 inhibitors that may inhibit the catabolic enzymes of calcifediol and its metabolites (CYP24 and CYP27B1), such as ketoconazole may alter the plasma levels of calcifediol.

The Clinical Pharmacology reviewers have recommended approval of both the 30 mcg dose and the 60 mcg dose; the starting dose of Rayaldee should be 30 mcg with up-titration to 60 mcg after 3 months. These recommendations are based on the dose response data from Phase 2 study (CTAP101-CL-2008) and efficacy and safety results from two Phase 3 pivotal trials (to be further discussed in sections 7 and 8). The dose titration at 12 week intervals is recommended based on the estimation that the steady state of calcifediol to occur at 12 weeks. The proposed titration criteria, i.e. iPTH (b) (4) and calcium < 9.8 mg/dl are based on the following observation. The pooled data of Phase 3 pivotal studies demonstrated that only 20% of subjects remained on 30 mcg at week 12 (time of dose escalation) compared to 80% of subjects on 60 mcg. Dr. Ma compared the exposures between patients who stayed on 30 mcg and those whose dose was escalated to 60 mcg and concluded that the lower concentrations were not the main driver for lack of biochemical control by week 12, but rather consistent with patients baseline biochemical characteristics of the disease (patients who were up-titrated at week 12 had higher iPTH levels and lower calcium levels at baseline).

Lastly, the reviewers recommend that the up-titration should be allowed beyond 3 months for patients who stayed on 30 mcg dose and achieved iPTH control at 3 month, but lost response lately during the therapy based on the results of Phase 3 studies: the proportion of patients who stayed at 30 µg dose and achieved 30% PTH reduction was 42% at week 12, and reduced to 26% at the efficacy assessment period.

There do not appear to be any Clinical Pharmacology issues that would preclude approval. I agree that both the 30 mcg and 60 mcg dose are approvable.

² Clinical Pharmacology review, page 6 (DARRTS 2/26/2016)

6. Clinical Microbiology

Not applicable. No Clinical Microbiology information is included in this NDA.

7. Clinical/Statistical- Efficacy

The Rayaldee clinical development program included three Phase 1, two Phase 2, two pivotal Phase 3 studies and one extension study.

This memorandum will focus on the design and the results of the two Phase 3 randomized, double-blind, placebo-controlled, multi-center, 26-week pivotal studies (CTAP101-CL-3001 and CTAP101-CL-3002, referred to as studies 3001 and 3002 in this review), because these trials include the most comprehensive assessment of efficacy and safety of Rayaldee to treat secondary hyperparathyroidism in the intended population (i.e., patients with stage 3 or 4 CKD and (b)(4)). All other studies will be referenced as needed.

The design of both Phase 3 pivotal studies was identical; thus I will focus attention on the design of study 3001 only.

Study CTAP101-CL-3001

Study 3001 was a randomized, double blind, placebo-controlled, multicenter (44 sites in US), 26-week study that investigated the use of Rayaldee for the treatment of secondary hyperthyroidism in adults with stage 3 and 4 CKD and vitamin D (b)(4).

As stated above, the design (exclusion and inclusion criteria, endpoints, size of the study and analysis plan for this pivotal study were agreed upon under a special protocol assessment agreement issued on August 30, 2012.

The primary objective of the study was to evaluate the efficacy of Rayaldee versus placebo in reducing plasma iPTH by $\geq 30\%$ from pre-treatment baseline.

The secondary objectives of the study were to evaluate the efficacy of Rayaldee versus placebo in increasing serum total 25-OH vitamin D levels to > 30 ng/ml and to evaluate safety of Rayaldee in the intended population.

Patient population

Patients > 18 years old with CKD stage 3 (defined as $eGFR \geq 30$ and < 60 mL/min/1.73m²) or 4 (defined as $eGFR \geq 15$ and < 30 mL/min/1.73m²) who were diagnosed with secondary hyperparathyroidism (defined as elevated iPTH levels of ≥ 85 pg/ml and < 500 pg/ml on two occasions) were eligible to participate in the study.

The selected lower inclusion criterion for iPTH levels of > 85 pg/ml is consistent with KDIGO³

³ KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney

guidelines (KDIGO guideline 4.2.2) which recommend that subjects with iPTH levels above the normal reference range receive treatment with vitamin D analogs to control SHPT and its complication, renal osteodystrophy. Of note, to definitely diagnose renal osteodystrophy a bone biopsy (gold standard) is required. However, the Division agreed with that imposing a requirement that predialysis patients undergo baseline and end of treatment bone biopsies to document improvement in bone histology as part of a study of SHPT would impact study feasibility (refer to SPA agreement).

In order to participate in the study patients were also required to have normal serum calcium (≥ 8.4 mg/dl and < 9.8 mg/dl) and phosphorus ≥ 2.0 mg/dl and < 5.0 mg/dl levels for two screening visits. Subjects were allowed to continue taking elemental calcium < 1000 mg/day and vitamin D (ergocalciferol or cholecalciferol) < 1600 IU/day. Use of calcium-based phosphate binders was allowed in doses up to 1000 mg/day of elemental calcium; noncalcium-based phosphate binders were allowed to be used at the discretion of the Investigator. Phosphate binder and calcium therapy was to remain constant during the study.

Lastly, only patients with vitamin D insufficiency (defined as 25-OH vitamin D > 10 ng/ml and < 30 ng/ml) were allowed to participate in the study. The overall rationale for the selecting patients with low vitamin D levels for this trial was that the low vitamin D levels are associated with secondary hyperparathyroidism and, as per KDIGO guidelines, patients with elevated iPTH levels should be evaluated for low vitamin D levels first and treated with vitamin D, since correction of vitamin D levels might decrease iPTH levels into the normal range. As pointed out by Dr. Lubas, the selection of subjects with low vitamin D levels serves as an enrichment strategy, since such patients are more likely to lower their PTH with an improvement in their stores of vitamin D.

(b)(4)

Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009 Aug;(113):S1-130.

⁴ Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Jul;96(7):1911-30.

⁵ IOM. Dietary reference intake for calcium and vitamin D. Washington, DC: The National Academies Press; 2011.

Study design

The study was comprised of screening period, a 6-month treatment period and a 1-week follow up period. All patients were randomized to receive Rayaldee or placebo in a 2:1 ratio, and randomization was stratified by CKD stage.

The starting dose was 1 capsule (30 mcg) daily at bedtime; this regimen was continued for 12 weeks. The dose was allowed to be increased once (to 60 mcg) during the study, at the 12-week visit, if all of the following criteria had been met: plasma iPTH was >70 pg/ml, serum total 25-OH vitamin D was ≤ 65 ng/ml and serum calcium was <9.8 mg/dl (using the average values for visits 6 and 7). The dose was allowed to be decreased (to 30 mcg QD or to 30 mcg three times a week) at any time during the study if any of the following criteria were met on two consecutive visits: iPTH <30 pg/ml, or serum calcium >10.3 mg/dl or serum phosphorus >5.5 mg/dl or serum total 25-OH vitamin D >100 ng/ml. Any subject whose dose was suspended for serum calcium ≥ 11 mg/dl and who was taking the study drug 3 times weekly or whose plasma iPTH values >900 pg/ml on 2 consecutive visits after dose titration was to be discontinued from the study.

Retrospectively, the use of 25-OH vitamin D level ≤ 65 ng/mL for dose titration is unclear. As per Endocrine Society guideline (2011), the “sufficient” levels of vitamin D in healthy population are > 30 ng/ml; the supplementations with vitamin D are relatively safe until the serum levels of 25-OH vitamin D are > 100 ng/dl⁶. Moreover, high vitamin D levels (even above 100 ng/ml) may be associated with different safety profile in patients with impaired renal function who are unable to convert 25-OH vitamin D to active 1,25-OH vitamin D, and, thus, may be better tolerated without a significant risk of hypercalcemia. The safety of 25-OH vitamin D levels > 65 ng/ml in patients with CKD in the trials was demonstrated by pharmacometrics reviewer’s (Dr. Lian Ma) analysis of data from 11 patients who did not have further dose titration at week 12 because of 25-OH vitamin D levels > 65 ng/ml- these patients did not have abnormal calcium, phosphorus or oversuppressed iPTH levels. Dr. Ma also noted that CKD stage did not modify the effect of the drug on 25-OH vitamin D level over time.

⁶ Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Jul;96(7):1911-30.

Primary efficacy outcome

The primary efficacy endpoint was a responder analysis examining the number of subjects in the Intent to Treat (ITT) population who experienced a mean decrease of $\geq 30\%$ in plasma iPTH from baseline in the efficacy assessment period (EAP); iPTH values were obtained at four consecutive visits (week 20 through week 26).

Subjects missing 3 out of 4 iPTH values in the EAP were classified as non-responders in the primary analysis. Dr. He confirmed that the Sponsor's method of handling missing data was acceptable and that the percentage of patients missing at least 3 out of 4 measurements in the EAP was 11-17% in both treatment groups (CKD stage 3 or 4).

The selection of iPTH as surrogate endpoint to establish clinical benefit deserves further discussion.

- As summarized in Dr. Lubas's review, all currently marketed vitamin D analogs were approved for the treatment of SHPT in patients with CKD stage 3-5 based on their iPTH lowering effects (mean decrease in iPTH levels or decrease $> 30\%$).
- Elevated iPTH levels in patients with CKD are associated with metabolic bone disease and risk for soft tissue calcifications and, vitamin D analogs improve biochemical endpoints associated with SHPT and metabolic bone disease (PTH, calcium, phosphorus, 25-OH vitamin D, 1,25-OH vitamin D, alkaline phosphatase, bone turnover markers, etc.) with rare and manageable side effects. The improvement in iPTH may translate into improved bone histology and prevention of soft tissue calcifications and ultimately lead to improvement in clinical outcomes (i.e. bone fractures and decrease end-organ damage). Although there are no data from prospective clinical trials directly demonstrating that reduction in iPTH levels with vitamin D is associated with improved clinical outcomes (such as bone fractures, cardiovascular disease, etc.), the Division has accepted iPTH reduction as a surrogate marker of benefit. First, past and current treatment guidelines for chronic kidney disease management (KDIGO 2009) have and continue to recommend treating factors that contribute to secondary hyperparathyroidism (hyperphosphatemia, vitamin D insufficiency, hypocalcemia) with the aim of addressing mineral and bone disorder of CKD. Second, large trials of long duration would be required to examine the effect of vitamin D treatment on hard outcome measures (i.e., fractures years down the road). The current KDIGO guidelines (2009) recommend treating patients with iPTH levels above the normal reference range not on dialysis with vitamin D analogs, calcium supplements and phosphate binders, since correction of electrolyte and vitamin D abnormalities may improve the iPTH levels. Absent new scientific data informing the benefits and risks of normalizing iPTH, calcium, phosphorus and vitamin D in the setting of CKD the Division continues to accept PTH reduction as a surrogate to determine efficacy of vitamin D analogs.
- Thus, as noted in Dr. He's review, the Sponsor was advised during EOP2 meeting to select

(b)(4)

- The agreement between the Sponsor and the Division on the selection of iPTH as the efficacy endpoint and on responder analysis looking at the percentage of subjects having achieved at least a 30% reduction in iPTH during EAP (weeks 20 to 26) was finalized under SPA.

Baseline Demographics and Disposition

A total of 429 patients with CKD stage 3 or 4 were enrolled in the two pivotal studies and received Rayaldee (285 patients) or placebo (144 patients).

Of these, 213 subjects were randomized in Study 3001 (72 received placebo and 141 received Rayaldee), and 216 subjects were randomized in study 3002 (72 received placebo and 144 received Rayaldee). Completion rate was approximately 80%-86% in both studies based on the last visit assessment.

The two randomized groups were relatively well balanced at baseline with respect to main demographic and disease characteristics in both studies. The mean age of patients was 64.4-66.8 years; the primary cause of CKD was diabetes mellitus, followed by essential hypertension in both studies. Mean iPTH level was higher in patients with CKD stage 4 (in study 3001-169 pg/ml in Rayaldee group, and 157 pg/ml in placebo group; in study 3002- 167 pg/ml in Rayaldee group and 169 pg/ml in placebo group) compared to CKD stage 3 (in study 3001-125 pg/ml in Rayaldee group, and 127.3 pg/ml in placebo group; in study 3002- 132 pg/ml in Rayaldee group and 141 pg/ml in placebo group); the observed difference is most likely due to the more advanced renal disease in patients with CKD stage 4. All patients had baseline 25-OH vitamin D level < 30 ng/ml (mean values 18.8- 20.8 ng/ml).

Efficacy results

The statistical review for efficacy was performed by Dr. Jiwei He. Efficacy findings were also discussed in Dr. William Lubas review. The efficacy findings are summarized below. For a more detailed discussion of the efficacy findings, see Dr. He's review and Dr. Lubas's review.

Dr. He verified the Sponsor's results for the primary analysis and confirmed that both pivotal studies demonstrated superiority of Rayaldee versus placebo in terms of reduction of iPTH from baseline (Table 1).

Table 1 Primary efficacy results (iPTH) for Rayaldee in patients with SHPT, stage 3 or 4 CKD and vitamin D insufficiency

Study	Treatment arm	Patients, n ¹	Change in mean plasma iPTH from Baseline to End of Study, ² mean % (SD)	Responders, n (%)	p-value ³
CTAP-CL-3001	Placebo Rayaldee	72 141	5.11 (29.56) -22.80 (26.41)	6 (8.3) 46 (32.6)	< 0.001
CTAP-CL-3002	Placebo Rayaldee	72 144	3.70 (24.49) -21.33 (26.20)	5 (7.0) 49 (34.1)	< 0.001
Pooled	Placebo Rayaldee	144 285	4.42 (27.10) -22.05 (26.26)	11 (7.6) 95 (33.3)	< 0.001

¹ ITT population, same as randomized² Among the subjects with 2 or more measurements during the efficacy assessment period³ Cochran-Mantel-Haenszel test controlling for CDK stage

Source: Dr. He's statistical Review, table 1

Both studies demonstrated that approximately one third of patients with CKD stage 3 or 4 (31.4-34.4%) achieved at least a 30% mean reduction in iPTH from baseline during EAP compared to 5.4-11 % of patients in placebo group (Table2).

Table 2. Number and percentage of patients with iPTH reduction > 30% at EAP in the ITT population in Study 3001 and Study 3002.

	Rayaldee, n (%)		Placebo, n(%)		p value ^a
	Responders, n (%)	Non-responders, n (%)	Responders, n (%)	Non-responders, n (%)	
	Study CTAP101-CL-3001				
CKD Stage 3	n=71		n=36		0.012
	24 (33.8)	47 (66.2)	4 (11.1)	32 (88.9)	
CKD Stage 4	n=70		n=36		0.003
	22 (31.4)	48 (68.6)	2 (5.6)	34 (94.4)	
Total	n=141		n=72		<0.001
	46 (32.6)	95 (67.4)	6 (8.3)	66 (91.7)	
	Study CTAP101-CL-3002				
CKD Stage 3	n=80		n=35		0.005
	27 (33.8)	53 (66.3)	3 (8.6)	32 (91.4)	
CKD Stage 4	n=64		n=37		0.001
	22 (34.4)	42 (65.6)	2 (5.4)	35 (94.6)	
Total	n=144		n=72		<0.001
	49 (34.1)	95 (65.9)	5 (7)	67 (93)	

^aCochran-Mantel-Haenszel test,

Proportion of responder in Rayaldee group is highlighted in yellow, proportion of responders in placebo group is highlighted in green

Source: Dr.He's review, tables 7 and 8, modified

Dr. He conducted additional statistical tests and concluded that the effect of Rayaldee on iPTH reduction did not differ between CKD stage 3 and 4 and that the creatinine clearance did not modify the treatment effect on iPTH.

Secondary endpoints

Dr. He verified that the analysis carried out on secondary endpoints was acceptable (sequential method with pre-specified prioritization) and that the results of this analysis were supportive for the conclusion drawn from the trials' primary endpoint.

Briefly, the proportion of responders in the per protocol (PP) population was also significantly higher in Rayaldee group compared to placebo group; the proportion of responders in PP population was similar in both trials and similar to the proportion of responders in ITT population (Table 3).

Table 3. Number and percentage of patients with iPTH reduction > 30% at EAP in the PP population in Study 3001 and Study 3002.

Population in Study 3001 and Study 3002.					
	Rayaldee, n (%)		Placebo, n(%)		p value ^a
	Responders, n (%)	Non-responders, n (%)	Responders, n (%)	Non-responders, n (%)	
	Study CTAP101-CL-3001				
CKD Stage 3	n=58		n=33		0.004
	24 (41.4)	34 (58.6)	4 (12.1)	29 (87.9)	
CKD Stage 4	n=57		n=29		<0.001
	22 (38.6)	35 (61.4)	1 (3.4)	28 (96.6)	
Total	n=115		n=62		<0.001
	46 (40)	69 (60)	5 (7.8)	57 (92.2)	
	Study CTAP101-CL-3002				
CKD Stage 3	n=65		n=29		0.006
	25 (38.5)	40 (61.5)	3 (10.3)	26 (89.7)	
CKD Stage 4	n=54		n=31		<0.001
	22 (40.7)	32 (59.3)	2 (6.5)	29 (93.5)	
Total	n=119		n=60		<0.001
	47 (39.6)	72 (60.4)	5 (8.4)	55 (91.6)	

^aCochran-Mantel-Haenszel test,

Proportion of responder in Rayaldee group is highlighted in yellow, proportion of responders in placebo group highlighted in green

Source: Dr.He's review, tables 9 and 10, modified

The proportion of subjects in the ITT population who achieved total 25-OH vitamin D levels > 30 ng/ml during EAP was significantly greater in Rayaldee group compared to placebo group (p<0.001) (Table 4). In PP population, mean serum 25-OH vitamin D levels increased over time in the Rayaldee group, reaching a plateau around 65 ng/ml compared to mean serum 25-OH vitamin D levels that remained below 30 ng/ml in placebo group at the end of the study during the both studies (refer to Dr. Lubas's review, figure 3, page 47 and figure 6, page 54).

Table 4. Number and percentage of patients with 25-OH vitamin D > 30 ng/ml at EAP in the ITT population in Study 3001 and Study 3002.

	Active, n (%)		Placebo, n(%)		p value ^a
	Subjects with normal 25-OH D levels (> 30 ng/ml), n (%)	Subjects with low 25-OH D levels (< 30 ng/ml), n (%)	Subjects with normal 25-OH D levels (> 30 ng/ml), n (%)	Subjects with low 25-OH D levels (< 30 ng/ml), n (%)	
	Study CTAP101-CL-3001				
CKD Stage 3	n=71		n=36		
	55 (77.5)	16 (22.5)	2 (5.6)	34 (94.4)	<0.0001
CKD Stage 4	n=70		n=36		
	58 (82.9)	12 (17.1)	0 (0)	36 (100)	<0.0001
Total	n=141		n=72		
	113 (80.2)	28 (19.8)	2 (2.8)	70 (97.2)	<0.0001
	Study CTAP101-CL-3002				
CKD Stage 3	n=80		n=35		
	67 (83.8)	13 (16.2)	1 (2.9)	34 (97.1)	<0.0001
CKD Stage 4	n=64		n=37		
	53 (82.8)	11 (17.2)	4 (10.8)	33 (89.2)	<0.0001
Total	n=144		n=72		
	120 (83.3)	24 (16.7)	5 (6.8)	69 (93.2)	<0.0001

^aCochran-Mantel-Haenszel test

Source: Dr. He's tables 11 and 12; modified

Lastly, all patients who were responders in the Rayaldee group also had 25-OH vitamin D levels > 30 ng/ml (as per Dr. He's exploratory analysis). This is consistent with KDIGO recommendations that vitamin D levels should be evaluated and treated first in patients with CKD and elevated iPTH levels, since such treatment may decrease iPTH levels.

Exploratory endpoints

Both trials also included several exploratory endpoints; two of them, 1,25-OH vitamin D levels (active metabolite of vitamin D) and bone turnover markers, deserve brief discussion. However, it should be noted, that even though descriptive analysis of mean changes in these biomarkers demonstrated some between-group differences (Rayaldee vs. placebo), the clinical meaningfulness of these comparisons are difficult to interpret since both studies were not powered to determine changes in these markers.

- Vitamin D converts to its active metabolite 1,25-OH in order to exert its effect on iPTH, calcium and phosphorus homeostasis, thus, the improvement of 1,25-OH vitamin D levels is mechanistically necessary for the treatment of SHPT. Conversion is impaired in patients with impaired renal function, thus, the expected increase in 1,25-OH vitamin D levels might be less in patients with advanced renal failure (i.e. CKD stage 4). Indeed, both

studies demonstrated that there was a numerical increase in 1,25-OH vitamin D levels in patients treated with Rayaldee compared to placebo indicating that patients have sufficient residual kidney function to convert vitamin D to its active metabolite (refer to figure 5, page 53 and figure 7, page 55 of the Clinical Review). As expected, the improvement in 1,25-OH vitamin D levels was more pronounced in patients with CKD stage 3 treated with Rayaldee compared to patients with CKD stage 4; patients with CKD stage 3 also had higher levels of 1,25-OH vitamin D at baseline. However, it is unclear whether the magnitude of these changes is associated with improvement in SHPT, since the optimal (and “normal”) levels of 1,25-OH vitamin D in this patient population are unknown and neither studies were designed to evaluate the relationship between 1,25-OH vitamin D and iPTH levels.

- Similar observations are made with respect to changes in bone biomarkers (bone specific alkaline phosphatase, procollagen 1 N-terminal propeptide, and type 1 collagen C-telopeptide). Although a favorable trend was observed for bone formation and bone resorption biomarkers with Rayaldee relative to the placebo in patients with CKD stage 4 only, it is unclear if the magnitude of the observed changes is associated with a clinical benefit (i.e. improvement in bone histology and fracture rates). No difference in bone markers were observed between Rayaldee arm and placebo arm in patients with stage 3 CKD. Lastly, given the short duration of the trial which, lasted only 26 weeks, it is insufficient time to see meaningful effect on bone turnover markers. Overall, data from the pivotal trial are not designed to allow an assessment of Rayaldee on bone structure or morphology.

During an open-label single-arm extension trial, CTAP-CL-3003, the treatment effect observed with Rayaldee in studies 3001 and 3002 was observed to be maintained up to 52 weeks. Although data from extension trial provide some evidence of persistence of Rayaldee effect for up to 1 years, the quantitative efficacy data obtained from such an open-label, uncontrolled trial should not be used for labeling because, by the very nature of its design, the trial selected a patient population likely to have benefited from the drug, a control group is lacking and the data is confounded by concomitant therapy with other vitamin D analogs.

In conclusion, the efficacy analyses conducted in the CTAP101-CL-3001 and CTAP101-CL-3002 trials demonstrate that Rayaldee can decrease iPTH level and improve vitamin D 25-OH levels in patients with CKD stage 3 and 4 and secondary hyperparathyroidism. I agree with Dr. He's conclusion that the efficacy results from the two Phase 3 pivotal studies support claim of using Rayaldee for treatment of SHPT in patients with CKD stage 3-4 and (b) (4)

8. Safety

In Studies 3001, 3002, and 3003, 324 patients were treated with Rayaldee for > 6 months, and 169 patients were treated with Rayaldee (30 mcg or 60 mcg) for > 12 months. This level of exposure was considered to be acceptable under SPA to support chronic dosing. This number of patients exposed to the drug for 6 months and 12 months is also in agreement with the ICH

E1 recommendations for minimum requirements of patient exposure needed to characterize the safety of chronically administered drugs before approval (300 patients to be treated for 6 months and 100-for one year).

Deaths

In pivotal studies, there were a total of 7 deaths in patients treated with Rayaldee (4 in study 3001, 3 in study 3002) compared to 1 death in placebo group (acute myocardial infarction in study 3002). The causes of death in Rayaldee groups were: urosepsis (1), wound infection (1), cardiac arrest (2), cardiac disorder (1), and acute respiratory failure (1). The only death that occurred in more than one patient treated with Rayaldee was cardiac related death (3 in Rayaldee group and 1 in placebo group). The small numerical imbalance in cardiac related deaths in Rayaldee and placebo group seemed to be most likely due to the design of the studies (imbalanced 2:1 randomization): there were 2 cardiac related death in Rayaldee group vs. 1 cardiac related death in placebo group in study 3002 and only 1 case of cardiac arrest in patient treated with Rayaldee in study 3001. Case narrative review revealed the patients who died had pre-existing conditions that could have contributed to the death and causality attribution was confounded.

There were an additional 4 deaths during the uncontrolled open label extension study 3003 (all patients were treated with Rayaldee): cardiac arrest (2), sepsis, congestive heart failure, however no firm conclusion regarding causal relationship of the events of death with the drug can be drawn in the absence of controlled group and presence of multiple confounding factors in this population (use of other vitamin D analogs, age, underlying serious medical conditions, etc.).

In conclusion, all death narratives were reviewed by Dr. Lubas, who concluded that the deaths were most likely not drug- related and that the observed difference was not outside the possibility of chance. I agree with Dr. Lubas's conclusion that there are no safety concerns at this time. Overall, the deaths from cardiac and infectious causes are not unexpected events in this high risk population with chronic renal failure and other underlying serious conditions (diabetes, hypertension, dyslipidemia, cardiovascular disease, immunosuppression, etc.).

Serious Adverse Events (SAE)

Fifty two subjects on Rayaldee and 23 subjects on placebo reported at least one serious adverse event (in study 3001: 12 subjects on placebo and 30 subjects on Rayaldee; in study 3002: 11 subjects on placebo and 22 subjects on Rayaldee). The only SAEs that occurred more frequently in patients treated with Rayaldee compared to patients treated with placebo were congestive heart failure and creatinine increase. The pooled analysis of data from the studies 3001 and 3002 demonstrated that 9 subjects in Rayaldee (3.2%) group vs. 0 subjects in placebo (0%) group had congestive heart failure and 8 subjects in Rayaldee group (2.8%) vs. 0 subjects in placebo group had a serious event of blood creatinine increased, respectively. Outcome of case narrative review for both of these events is discussed in the dedicated sections below.

Eighteen Rayaldee-treated and six placebo-treated patients discontinued studies prematurely due to the adverse events. The most frequent AEs that led to the study discontinuation in

Royaldee group were: infections (urosepsis (2), pneumonia (1), wound infection (1)) and cardiac arrest (2); all other AEs occurred in one patient each (including hypercalcemia, CHF, fluid overload, renal impairment and blood creatinine increase).

Common Adverse Reactions

A total of 67.4% of Royaldee-treated subjects and 69.4 % of the placebo-treated subjects reported at least one treatment-emergent adverse event. No hypersensitivity reactions during Royaldee administration were reported in clinical program.

Table 5. Summary of Treatment Emergent AE pooled from the 26-week Placebo-Controlled Studies reported in more than 2% of Royaldee-treated subjects and with greater frequency than in placebo-treated subjects (ITT population).

Adverse events	Placebo , n=144 N (%)	Royaldee, n=285, N (%)
Anemia	3.5 (5)	4.9 (14)
Blood creatinine increase	1.4 (2)	4.9 (14)
Nasopharyngitis	2.8 (4)	4.9 (14)
Dyspnea	2.8 (4)	4.2 (12)
Cardiac failure congestive	0.7 (1)	3.5(10)
Cough	2.1 (3)	3.5(10)
Constipation	2.8 (4)	3.2(9)
Bronchitis	0.7 (1)	2.8 (8)
Hyperkalemia	0.7 (1)	2.5 (7)
Fall	2.1 (3)	2.1 (6)
Osteoarthritis	0.7 (1)	2.1 (6)

Source: Sponsor's table submitted to the NDA on 2/23/2016 in response to the Division's information request.

Congestive heart failure (CHF)

Congestive heart failure was not prospectively defined and the events were not adjudicated using standardized measures but spontaneously reported by investigators.

The Sponsor reported a total of 11 subjects who developed CHF in studies 3001 and 3002: 10 subjects were treated with Royaldee and 1 subject was treated with placebo. Of these, 9 cases were reported as SAE (all in Royaldee group) and 2 cases as non-serious AEs (1 in Royaldee group and 1 in placebo group).

SAEs of CHF

The Sponsor reported a total of 9 subjects treated with Royaldee (0 subjects in placebo group) who developed SAE of CHF. However, Dr. Lubas reviewed the safety data from both studies and identified 5 more cases of SAE of CHF: 4 in Royaldee group and 1 in placebo group (reported as "cardiac failure acute", "fluid overload" and "pulmonary edema"). Thus, a total of 14 patients with SAEs of congestive heart failure were identified: 13 (4.5%) subjects in Royaldee group (7 subjects in study 3001 and 6 subjects in 3002 study) and 1 patient (0.7%) in placebo group (study 3002). Dr. Lubas reviewed all narratives of CHF cases and found that, two of 13 subjects in Royaldee group (one in study 3001 and one in study 3002) had CHF

reported prior to the first dose. Thus, only 11 subjects developed CHF during treatment with Rayaldee. The observed numerical imbalance of the CHF cases was not also the same in both study and was more pronounced in study 3001 (6 subjects on Rayaldee vs. 0 subjects on placebo) compared to study 3002 (5 on Rayaldee vs. 1 on placebo). Multiple factors including advanced age (>60 years old), underlying serious medical conditions predisposing to the cardiac complications (CKD, DM, coronary artery disease, hypertension, peripheral vascular disease, etc.), other precipitating factors (noncompliance with diuretics, pacemaker dysfunction, infections) have been identified in all 11 patients. Moreover, 10/11 patients had pre-existing CHF. All these confounding factors make causality assessment challenging in this patient population with a high baseline risk of CHF. Majority of patients recovered, did not require dose adjustment during the event and were able to continue treatment with Rayaldee (only 2 patients discontinued the study due to CHF). No dose dependence was noted; some of these patients were able to be advanced to 60 mcg without further events and some of these patients continued to have CHF events even after the drug has been discontinued. One patient died because of CHF, however CHF and death occurred after the drug has been discontinued. Lastly, no safety signals associated with CHF were identified in non-clinical studies.

In conclusion, I agree with Dr. Lubas's conclusion that no new safety issue was identified at this time and that all patients with CKD should be regularly monitored for cardiac adverse events and fluid overload as per standard care in this population.

Blood creatinine increase

Again, as stated in the above section, blood creatinine increase or renal failure was not prospectively defined and the events were not adjudicated using standardized measures but spontaneously reported by Investigators.

The Sponsor reported a total of 16 subjects who had an event of "blood creatinine increase" in studies 3001 and 3002: 14 subjects were treated with Rayaldee and 2 subjects were treated with placebo. Of these, 8 cases were reported as SAE (all in Rayaldee group) and 8 cases as non-serious AEs (4 in Rayaldee group and 2 in placebo group).

SAEs of blood creatinine increase

A total of 8 patients treated with Rayaldee had SAE of blood creatinine increase. Dr. Lubas reviewed narratives of these cases and concluded that the majority of these cases were due to the fluid overload or aggressive use of diuretics (and not to the drug itself) and 6/8 patients recovered with proper hydration and continued treatment with Rayaldee (without change in dose in the majority of patients). The drug was prematurely discontinued in 2/8 patients who were also diagnosed with acute renal failure. However, one of these patients had also precipitating factors (dehydration, gastroenteritis); the diagnosis of renal failure in the other patient was unclear- he was diagnosed with acute renal failure and started on dialysis even though his creatinine did not change from baseline. Dr. Lubas also indicated that there was no evidence of vitamin D toxicity in all cases as demonstrated by the normal serum calcium levels and 25-OH vitamin D levels < 100 mcg/dl. The changes in blood creatinine levels from baseline were analyzed further in overall study population; there were no clinically meaningful changes in mean blood creatinine levels from baseline in Rayaldee group compared to placebo group at the end of the study (increase in mean creatinine by 0.1 mg/dl in both groups in study

3001 and by 0.1 mg/dl in placebo group and by 0.2 mg/dl in Rayaldee group in study 3002). More importantly is that there were also no significant changes in eGFR from the baseline at the end of the study in study population: in study 3001, mean eGFR decreased by 0.3 ml/min/1.73 m² in Rayaldee group and by 0.6 ml/min/1.73 m² in placebo group; in study 3002, mean eGFR decreased by 1.2 ml/min/1.73 m² in Rayaldee group and by 1.4 ml/min/1.73 m² in placebo group. Lastly, no safety signals related to changes in creatinine or worsening of renal function was identified in nonclinical studies.

Overall, it is not unusual for creatinine and renal function to fluctuate in this study population due to the progression of the disease itself and/or presence of concomitant diseases and precipitating factors (e.g. dehydration, infection) or use of nephrotoxic medications. I agree with Dr. Lubas's conclusion that the data are not consistent with a drug-related kidney injury signals but most likely reflect other causes.

Laboratory Parameters

Hypercalcemia and hyperphosphatemia

There is a known risk of hypercalcemia and hyperphosphatemia during the treatment with all vitamin D analogs. Thus, the Clinical Review paid special attention to the occurrence of out-of-range calcium and phosphorus values and related adverse events, and conducted several analyses in order to characterize the frequency and severity of such findings.

Serum Calcium

As shown in the table below, the mean levels of serum calcium increased from baseline to final visit by a statistically significantly greater extent in Rayaldee group compared with placebo group. Visual comparison of scatterplots in Dr. Lubas's review (Figure 15, page 102) indicate multiple values in the abnormal range in both treatment groups, but no obvious outliers at the end of the study. However, the increase in calcium levels was small and most likely not clinically meaningful. The greater changes in Rayaldee groups might be explained by vitamin D mechanism of action.

Table 6. Mean change from baseline to final visit in serum calcium (pooled data from studies 3001 and 3002) by the treatment group and stage (ITT population)

Serum calcium, mg/dl	CKD Stage 3		CKD Stage 4		Total	
	Placebo	Rayaldee	Placebo	Rayaldee	Placebo	Rayaldee
Mean Baseline value (SD),	N=71 9.3 (0.26)	N=151 9.3 (0.32)	N=73 9.2 (0.29)	N=134 9.2 (0.28)	N=144 9.2 (0.28)	N=285 9.2 (0.32)
Mean Final value (SD),	N=66 9.4 (0.29)	N=138 9.4 (0.38)	N=68 9.3 (0.4)	N=129 9.4 (0.46)	N=134 9.3 (0.3)	N=267 9.4 (0.4)
Mean change from baseline (SD)	0.1 (0.25)	0.2 (0.26)	0.1 (0.33)	0.2 (0.38)	0.1 (0.3)	0.2 (0.3)

Source: Sponsor's table 22, Summary of Clinical Safety, modified.

Twelve percent of patients treated with Rayaldee and 7% of patients treated with placebo in pivotal studies had elevated calcium levels above upper normal limit (10.2 mg/dl). More importantly, the majority of these patients had only single elevation of calcium that returned to

the normal values during the next visit without dose adjustment. Only 6 subjects (2%) in Rayaldee group and 0 subjects in placebo group had hypercalcemia (predefined as calcium level > 10.3 mg/dl on 2 consecutive visits) during the study; the events resolved with dose reduction. Majority of the patients with elevated calcium levels were asymptomatic and had calcium levels < 11.5 mg/dl. There were a total of three AEs reported as hypercalcemia in Phase 3 pivotal trial (2 in Rayaldee group and 1 in placebo group); however it is unknown whether these patients were symptomatic or the AEs were reported based on the calcium levels only. Of these three subjects, only one subject had SAEs of hypercalcemia (12.5 mg/dl) and was withdrawn from the study due to hypercalcemia. The subject was asymptomatic and event resolved after the drug was discontinued. No firm conclusion regarding causal relationship of the event with the drug can be drawn at this time: this subject had normal vitamin D levels during the event (38 ng/ml) and had other precipitating factors (infection and acute renal failure).

Overall, I agree with Dr. Lubas's conclusion that the risk of hypercalcemia is low in the intended patient population during the treatment with Rayaldee with proper monitoring of calcium levels.

Serum phosphorus

Mean serum phosphorus levels greater increased from baseline to the final visit in Rayaldee group (from 3.7 mg/dl to 3.9 mg/dL in Rayaldee group) compared to placebo group (remained unchanged (3.8 mg/dl)). There were no statistically significant difference between the treatment groups and mean changes from baseline were overall small (0.2 mg/dl in Rayaldee group vs. 0.1 mg/dl in placebo group) and most likely not clinically meaningful. Visual comparison of scatterplots in Dr. Lubas's review (Figure 16, page 104) also demonstrated that it seems to be more outliers in Rayaldee group with phosphorus levels > 6 mg/dl in study 3002 that might affect the mean values at the end of the treatment. Lastly, the slightly higher phosphorus levels in Rayaldee group may also be explained by vitamin D mechanism of action on phosphorus homeostasis.

There were no difference in the rate of hyperphosphatemia (defined as value > 5.5 mg/dl) between treatment groups: 25 subjects (9%) in Rayaldee group and 13 subjects in placebo group (9%) had at least one elevated phosphorus level above the predefined threshold in the pivotal studies; the levels normalized during the next visit without the dose adjustment in the majority of subjects. Only one subject on Rayaldee was diagnosed with protocol-defined hyperphosphatemia (phosphorus level > 5.5 mg/dl on 2 consecutive visits) during the study; the event resolved and subjects continued treatment. No SAEs of hyperphosphatemia were reported during the treatment with Rayaldee and no subjects were withdrawn from the studies due to hyperphosphatemia. I agree with Dr. Lubas's conclusion that the risk of hyperphosphatemia did not increase with Rayaldee treatment in patients with CKD stage 3 or 4.

Oversuppression of iPTH levels and risk of adynamic bone disease

There is a concern with all vitamin D analogs that oversuppression of iPTH levels may lead to adynamic bone disease, fractures and bone pain in patients with SHPT and CKD. However, the specific levels of iPTH that is associated with this complication are unknown.

Dr. Lubas identified 7 patients in pivotal studies with at least one iPTH level < 30 pg/ml (threshold established by the Sponsor for the dose decrease): 1 patient in placebo group (0.7%)

and 6 patients in Rayaldee group (2%). Of these, only two patients (in Rayaldee group) had two consecutive iPTH levels < 30 pg/ml (criteria for dose reduction); all other patients had iPTH levels > 30 pg/ml at the next visit without the dose adjustment. Of 6 patients with suppressed iPTH levels, only one patient who was on Rayaldee 30 mcg had iPTH level < 15 pg/ml (lower normal limit of iPTH); the level increased to 30 pg/ml during the next visit without dose adjustment. More importantly, majority of these patients who was treated with Rayaldee had 25-OH vitamin D levels < 100 ng/ml (1 patient with single iPTH level of 26 pg/ml had 25-OH vitamin D level 105 ng/ml) and normal calcium levels (1 patient on Rayaldee had elevated calcium level of 10.8 mg/dl), and all of them had normal phosphorus levels. None of these patients had bone pain or fractures.

Additionally, Dr. Lubas identified 26 subjects in open-label extension study 3003 who had at least one iPTH level < 30 pg/ml. However, approximately 50% of these subjects were treated concomitantly with other active vitamin D analogs (calcitriol, paricalcitol, doxercalciferol) that most likely contributed to the suppressed iPTH levels and causality attribution was confounded. None of these patients had bone pain or bone fractures.

Overall, it is unknown whether low iPTH levels in the pivotal Rayaldee studies were associated with adynamic bone disease; none of these patients had bone biopsy and low iPTH levels are not uniformly predictive of bone histologic states, especially when considered alone (i.e. without concomitant abnormalities in calcium, phosphorus levels or use of medications affecting bone structure such as bisphosphonates).

Overall, I agree with Dr. Lubas's recommendations that the treatment with Rayaldee should avoid oversuppression of iPTH levels. However, I do not agree with the recommendations that the dose titration should be based (b) (4)

Thus, I favor the language that recommends the dose titration in order to maintain iPTH levels within (b) (4) normal range rather than (b) (4).

Other laboratory parameters

There were no clinically meaningful differences between treatment groups in the change from baseline to final visit in any other laboratory parameters (hematology, clinical chemistry, urinalysis, urinary calcium, phosphate, etc.).

Vital signs

There were also no significant changes in vital signs between the treatment groups.

In conclusion, the safety observations made during the Rayaldee clinical program in patients with CKD stage 3 and 4 are consistent with the known safety profile established for the whole class of vitamin D analogs. No new, population specific, safety signals were identified in the Rayaldee program.

9. Advisory Committee Meeting

No AC meeting was held.

10. Pediatrics

No pediatric patients were studied as part of the Rayaldee development program. The Applicant has submitted a proposed pediatric study plan which was reviewed and discussed by the Pediatric Review Committee on February 17, 2016. The proposed pediatric study plan includes a waiver for patients < 1 month, and deferred pediatric studies for older pediatric patients until safety and efficacy have been established in adults and a (b) (4) formulation of calcifediol (b) (4) suitable for use in pediatric patients has been developed. The initial pediatric study plan proposed a PK/PD study and two safety and efficacy studies (b) (4)

However, we recommend that the Sponsor conduct a single safety and efficacy study in children 1 month- 17 years old and also include children 1 month- 2 years old in PK/PD study to characterize the PK/PD of Rayaldee in this age group of patients. There is a risk that the safety and efficacy study in children 1 month-2 year old with CKD 3-4 might be terminated preliminary due to the poor enrollment; CKD is rare in this age group. The results of PK/PD study needs to be submitted and reviewed by Division prior to the initiation of the second study evaluating safety and efficacy of Rayaldee in pediatric patients with CKD stage 3-4 and SHPT. The list of required pediatric studies was communicated to the Sponsor via email on 3/03/2016. The Sponsor accepted the proposed pediatric plan and sent a copy of the PMR studies to the Division with proposed milestone dates via email on 3/16/2016.

11. Other Relevant Regulatory Issues

OSI inspection

A clinical inspection summary was completed by Dr. Cynthia F. Kleppinger on January 28, 2016. Four principal investigators were investigated. The audit resulted in one Voluntary Action Indicated letter and three No Action Indicated decisions. The inspection of the Sponsor also resulted in Voluntary Action Indicated letter due to the regulatory violations, however, the review concluded that these violations “are unlikely to significantly impact primary safety and efficacy analyses and data from the Sponsor appears to be acceptable”. Overall, the review concluded that “the inspectional findings support validity of the data as reported by the Sponsor under this NDA”.

Financial Disclosure

FDA 3453 form was submitted confirming that the applicant of the pivotal studies, CTAP101-CL-3001 and CTAP101-CL-3002 and the open label extension CTAP101-CL-3003 did not enter into any financial arrangement with the listed clinical investigators that could influence the outcome of the trials (refer to Dr. Lubas’s review).

Interdisciplinary Review Team (IRT) for QT Studies Consultation

As agreed during EOP2 meeting (on 2/14/2012), the dedicated QTc study was not required; however, the Division recommended to monitor ECG during the Phase 3 study.

The IRT consultant reviewed ECG pooled data and clinical pharmacology data in NDA submission and confirmed that thorough QT study is not required (DARRTS 9/16/2015) based on the fact that mean calcifediol C_{max} at the 90 mcg/day dose (85.6 ng/ml) established in study CTAP101-CL-2008 in patients with CKD and SHPT “is not extremely higher” than the normal calcifediol range reported in the literature (30-74 ng/ml).

The consultant also noted that the purpose of ECG monitoring in the studies was mainly for safety purposes and not for effect size quantification, thus there was no adequate information regarding Rayaldee effect on QTc interval. However, the consultant agrees with the Sponsor conclusion that there was no substantial difference in ECG safety between the Rayaldee and placebo treatment groups and did not recommend any additional labeling.

12. Labeling

Proprietary name

The proposed proprietary name for CTAP101 is Rayaldee. This was reviewed and deemed acceptable by the Office of Medication Error Prevention and Risk Management. A letter stating this was issued to the Applicant on August 25, 2015.

Labeling

Agreement on the final labeling language has not been reached at the time this review was completed.

However, the following should be changed in the label:

- The indication should be restricted to the adult population with CKD stage 3-4 and SHPT, (b)(4)
- The intended population should not be defined as (b)(4) due to the reasons discussed in section 7. I think that indications should be rather restricted to the population with specific baseline characteristics (such as vitamin D levels < 30 ng/ml) reflecting the patient population evaluated in Rayaldee clinical program.
- Limitation of use should be included in the label stating that the drug should not be used in patients with CKD stage 5 and in patients on dialysis. The safety and efficacy of Rayaldee has not been evaluated in this patient population; the efficacy of Rayaldee might be significantly decreased in these patients due to the advanced renal failure and inability of kidneys to convert 25-OH vitamin D to its active form.

- (b)(4)

- The option of up-titration beyond 3 months for achieving additional iPTH reduction in patients who remained on dose of 30 mcg daily after 3 months should be included in the label.
- Section 6 (Adverse reactions) should include table of adverse reactions that occurred in > 1.4% patients treated with Rayaldee compared to placebo (pooled data from Phase 3 pivotal studies). The description of hypercalcemia and hyperphosphatemia events that occurred during the studies should include all patients with abnormal laboratory values (i.e. calcium and phosphorus), and not only number of adverse events reported by the Investigators.
- The results from individual pivotal studies should be included in the label in order to demonstrate the consistency of results across the studies ((b) (4))
- The label should include only results from the prespecified primary and secondary endpoints in ITT population.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Complete Response because an OPQ investigation identified multiple deficiencies at (b) (4) facility during the inspection. Satisfactory resolution of these deficiencies is required before this application may be approved.

Additional recommendations:

I recommend that the proposed indication for Rayaldee should be modified as follows (pending the satisfactory resolution of the facility's deficiencies and agreement on the final labeling language):

treatment of secondary hyperparathyroidism (SHPT) in (b) (4) with chronic kidney disease (CKD) stages 3 or 4 and 25-hydroxyvitamin D levels less than 30 ng/ml.

(b) (4) (b) (4)

I agree that proposed indication should be limited to the population of patients with vitamin D levels < 30 ng/ml, reflecting the patient population evaluated in Rayaldee clinical program. However, this population should not be defined as (b) (4) for the reasons described in section 7.

Lastly, I recommend to limit the proposed indication to adult population only with SHPT and CKD stage 4 or 5. The Rayaldee clinical program assessed efficacy and safety of the drug in adult population only. (b) (4)

- Risk Benefit Assessment

The data submitted in support of Rayaldee provides sufficient information to conclude that the benefits of use in patients with CKD stage 3 and 4 outweigh the risk associated with the drug.

Benefit:

Both pivotal trials, 3001 and 3002, have demonstrated that Rayaldee was superior to placebo in reducing iPTH levels; mean percent change from baseline to final visit in serum iPTH levels was -22% in Rayaldee group and 4 % in placebo group (pooled data).

Approximately 33 % of patients with CKD stage 3 or 4 and vitamin D levels < 30 ng/ml treated with Rayaldee and 11% of patients treated with placebo had decrease in iPTH > 30% from baseline at the end of the study. Rayaldee program also demonstrated that a majority of patients with low vitamin D levels at baseline, treatment with Rayaldee restored vitamin D levels to the normal range (80-83% of patients) compared to placebo (3-6% of patients). This is consistent with the current 2009 KDIGO guidelines that recommend that subjects with elevated iPTH levels above the normal reference range should be evaluated and treated for hyperphosphatemia, hypocalcemia and Vitamin D deficiency first as these may improve the iPTH levels and prevent mineral and bone disease associated with CKD.

Overall, Rayaldee has demonstrated an ability to control SHPT as measured by decreases in iPTH level, similar to other vitamin D analogs approved for the treatment of secondary hyperparathyroidism in patients with CKD. All currently marketed vitamin D analogs were approved based on their effects on iPTH levels. The Division treats a vitamin D induced decreases in serum iPTH in patients with low vitamin D levels and SHPT as an acceptable surrogate of efficacy in patients with CKD and secondary hyperparathyroidism. Treatment of mineral and hormonal disorders associated with CKD that could contribute to bone disorders specific for this population can, in the absent of scientific data to the contrary, be reasonably expected to translate into improvement clinical outcomes. We however recognize that in the absence of high quality scientific evidence (derived from prospective outcomes studies) to describe the relationship between serum iPTH response to an intervention and outcome measures uncertainty around the magnitude of clinical benefits derived from these interventions exist.

Risk:

The potential risks associated with Rayaldee treatment in patients with CKD stage 3 or 5 have been relatively well characterized in the Rayaldee clinical program and do not outweigh the expected benefit. Overall, the safety profile of Rayaldee was similar to those associated with other vitamin D analogs currently approved for the treatment of SHPT in patients with CKD.

No new safety signals emerged.

No hypersensitivity reactions were identified.

The major identified risks include hypercalcemia, hyperphosphatemia and oversuppression of iPTH (that might be associated with adynamic bone disease and increased risk of fractures). In two pivotal trials, 12% of subjects on Rayaldee had at least one elevated calcium level, 9% of patients treated with Rayaldee had at least one elevated serum phosphorus level, and 2% of subjects treated with Rayaldee had at least one iPTH level < 30 pg/ml. These mineral abnormalities and iPTH levels improved in the majority of patients without dose adjustment or with dose reduction; none of these patients were symptomatic.

Overall, the incidence of hypercalcemia, hyperphosphatemia and oversuppression of iPTH observed with Rayaldee was low in the clinical program and did not exceed the incidence of these AEs observed with other approved vitamin D analogs. More importantly, these risks can be mitigated through product labeling, appropriate patient selection, monitoring and timely introduction of treatment and/or discontinuation of the drug.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

The following pediatric postmarketing studies are required to be conducted by the Sponsor:

- A repeat dose, dose ranging PK/PD study evaluating Rayaldee in predialysis patients with stage 3 or 4 CKD with SHPT and 25-OH vitamin D levels < 30 mcg/L and ages 1 month to less than 18 years.
- A 16-week, randomized, placebo-controlled, double-blind, efficacy and safety study evaluating Rayaldee in predialysis patients with stage 3 or 4 CKD with SHPT and 25-OH vitamin D levels < 30 mcg/L and ages 1 month to less than 18 years.

- Recommended Comments to Applicant

The action letter will communicate the deficiencies identified in the OPQ review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARINA ZEMSKOVA
03/28/2016

JEAN-MARC P GUETTIER
03/28/2016
I concur.