Cross-Discipline Team Leader Review

Date	5/22/2017
From	Marina Zemskova, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA (b) (4) and NDA 21688/S-23
Applicant	Amgen
Date of Submission	11/23/2016
PDUFA Goal Date	5/23/2017
Proprietary Name / Established (USAN) names	Sensipar
Dosage forms / Strength	(b) (4)
Proposed Indication(s)	(b) (4)
Recommended:	NDA (b) (4): (b) (4) NDA 21688/S-23: Approval pending labeling agreement

1. Introduction

On November 23, 2016 Amgen submitted New Drug Application (NDA) (b) (4) for (b) (4)

(b) (4)

The application included PK/PD, efficacy and safety data from pediatric studies submitted in response to a Written Request (WR).

The Sponsor proposes (b) (4). Thus, in addition to NDA (b) (4) the Sponsor also submitted an efficacy supplement to NDA 21688 for the proposed labeling changes (to update the appropriate sections of the Sensipar label with pediatric information) for the original NDA.

Sensipar is an oral calcimimetic that, in the presence of extracellular calcium, enhances the activation of calcium-sensing receptors (CaSR) in parathyroid tissues and suppresses the secretion of parathyroid hormone (PTH). Sensipar is approved as an oral tablet in three

strengths 30, 60, and 90 mg for the treatment of SHPT in adult patients with CKD on dialysis (Amgen, NDA 021688, approved in 2004). Sensipar is also approved for the treatment of hypercalcemia in patients with parathyroid carcinoma and for hypercalcemia in patients with primary hyperparathyroidism, however, these indications are not relevant to the current application for Sensipar, and thus, will not be discussed in this memorandum.

2. Background

Secondary hyperparathyroidism and mineral metabolism abnormalities (e.g., calcium and phosphorus) 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 that could result in cardiovascular pathology such as arrhythmia, coronary artery disease or other events. Secondary hyperparathyroidism in children may also lead to skeletal deformities and growth retardation.

Advanced stage kidney disease (end stage renal disease in particular) is a rare condition in childhood with an estimated worldwide median incidence of 9 per million of the age-related population[1]. Children are priority candidates for kidney transplantation; the majority of pediatric patients undergo kidney transplantation at earlier stages of renal disease and/or before SHPT and its complication develops. Thus, the number of pediatric patients with SHPT due to CKD is much smaller compared to the adult population with CKD and SHPT. The prevalence of pediatric patients with SHPT remains unknown; as per Sponsor, "point prevalence estimates using USRDS and DaVita databases for 2015 indicate that < 1000 patients 0-18 years of age on dialysis…will develop SHPT"[2]. Pediatric patients who develop SHPT require medical treatment to control iPTH and mineral abnormalities. The recommendations for the treatment of SHPT associated with CKD are similar in adults and children. To prevent skeletal and cardiovascular complications in patients with SHPT and CKD, the 2005 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines in children[3] and 2009 Kidney Disease Improving Global Outcomes (KDIGO) therapeutic guidelines in adults[4] recommend that subjects with CKD and iPTH levels above the target range be treated with Vitamin D or its analog alongside treatment of other prevalent mineral abnormalities (hyperphosphatemia, hypocalcemia) associated with chronic kidney disease..

Active vitamin D and vitamin D analogs are the first line treatment and are the only agents recommended by KDOQI and approved by FDA for the treatment of SHPT in pediatric

[1] Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. Pediatr Nephrol. 2012 Mar;27(3):363-73.
[2] NDA (b) (4) Section 2.5, Clinical Overview.
[3] KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children With Chronic Kidney Disease. http://www2 kidney.org/professionals/KDOQI/guidelines_pedbone/
[4] 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.

patients with CKD. Vitamin D analogs effectively decrease iPTH levels in pediatric patients; however, all vitamin D analogs are associated with hypercalcemia.

Calcimimetics decrease iPTH and lower serum calcium. Currently, use of calcimimetics for the treatment of SHPTH is recommended (2009 KDIGO) [4] and approved in adults only. There are no currently approved calcimimetics for the treatment of SHPT in children with CKD. As per Sponsor, a calcimimetic may be an effective adjunct to the treatment of SHPT in pediatric patients.

Regulatory Background

This section summarizes the major regulatory interactions for the Sensipar pediatric development program for the (b) (4).

1. Written Request

In May 2007, the Sponsor submitted a Proposed Pediatric Study Request (PPSR) to the Agency seeking issuance of a WR for Sensipar for the treatment of pediatric patients with SHPT and CKD on hemodialysis. The WR was denied at that time and the Agency requested that the Sponsor first conduct a juvenile dog toxicity study to support the pediatric program.

The Sponsor resubmitted a PPSR in December 2009. The Agency issued a WR on 5/5/2010 requesting the Sponsor to evaluate whether use of Sensipar in the treatment of secondary hyperparathyroidism (SHPT) in pediatric patients 28 days to 18 years with end stage kidney disease receiving dialysis was safe and effective. As per the WR, the efficacy and safety of Sensipar had to be evaluated in pediatric clinical studies, since the efficacy of Sensipar in pediatric patients could not be extrapolated from adults "because the course of the disease is significantly different than the course of the disease in adult population".

The original WR included: (1) a pediatric PK study in children 28 days to 6 years of age (Study 1: 20090005) and (2) a 30-week randomized, double-blind, placebo-controlled efficacy and safety study in 100 children ages 28 days to 18 years with CKD and SHPT with 26-week open-label safety extension study (Study 2: 20070208) In addition, the Sponsor was asked to review and submit a summary of published literature on Sensipar use in pediatric children with CKD and SHPT. Lastly, the WR also asked the Sponsor to develop an age-appropriate formulation; to test this formulation for efficacy and safety in the studied pediatric population(s); and to seek marketing approval for that age-appropriate formulation.

The original WR was amended 5 times, the sixth amendment was denied by the Agency:

- Amendment 1 (submitted on 6/24/2010, approved on 12/14/2010)

With the first amendment to the WR, Amgen requested to remove the younger subgroup of patients, age 28 days to 6 years, from safety and efficacy Study 2 due to recruitment difficulties (multiple venipunctures, rarity of the disease, shorter time to transplantation, etc.) and instead to conduct an independent smaller safety and tolerability study in children 28 days to 6 years of age with CKD and SHPT to evaluate the risk of hypocalcemia associated with the use of Sensipar in at least 15 patient-completers (Study 3: 20110100).

The Agency agreed that the efficacy in pediatric patients < 6 years old with CKD and SHPT may be extrapolated from adult information and from pediatric information obtained from Study 2 in older children. However, the Agency requested that the iPTH-lowering effect of Sensipar be evaluated as a secondary endpoint in Study 3.

- Amendment 2 (requested on 1/20/2011, approved on 3/25/2011)

The second amendment clarified specific requirements in the WR with respect to: the requested size of the national registry study, the number of patients in PK study 1, the number of patients required to complete Study 2 (70 patients to complete the double-blind part of the st and at least 30 patients to complete the open-label part of the study), and, the age-appropriate definition of hypocalcemia in Study 3.

Full Clinical Hold (PCH) for all pediatric studies due to pediatric death

On Jan 31, 2013, FDA was informed by Amgen about a 14- year patient in Study 2 had died on (b) (6). On January 31, 2013, FDA notified Amgen by telephone to suspend dosing in all pediatric studies. On February 7, 2013, the Agency issued a clinical hold letter for all pediatric studies with Sensipar. The cause of death was determined to be multifactorial including missed hypocalcemia (possibly due to treatment with cinacalcet) and prolonged QT interval (refer to safety section below).

Amgen did not contact the Agency to discuss the future development of the Sensipar pediatric program until July 8, 2013. The parties held a teleconference on September 4, 2013, during which the Sponsor proposed to discontinue the pediatric clinical program (b) (4) However, the Division disagreed with the Sponsor and stated that "the data generated to date are insufficient to allow a robust assessment of the safety and efficacy of Sensipar in children" and that the drug "should be studied adequately".

After the Agency's complete review of the fatal case and discussion with Amgen, new safety revisions to decrease the risk of hypocalcemia were incorporated into all Amgen's pediatric clinical protocols. These safety revisions included (but were not limited to): weekly monitoring using ionized calcium to allow for real-time dose adjustment, more restrictive limits on serum calcium levels incorporated into dosing algorithms, revision to the inclusion/exclusion criteria for subjects with prolonged QTc interval at baseline, exclusion of drugs that can prolong the QTc interval, etc.

After the fatal event that led to the long clinical hold (14 months) Study 2 was terminated and Amgen agreed to perform a new randomized, open-label, 20-week study with a control arm randomized to standard of care (Study 4: 20130356; see Amendment 3 below). Study 4 was designed to evaluate safety and efficacy of Sensipar in pediatric patients 6 to 18 years old with CKD and SHPT using the new safety measures described above.

The Full Clinical Hold was lifted on 12/13/2013 and a single dose study (study 1) was allowed to proceed. However, the Agency issued a new Partial Clinical Hold for all multiple dose pediatric studies (teleconference from 12/13/2013, Agency's Clinical Hold Letter from 12/14/2013). In order to resolve the deficiencies, the Sponsor was required to incorporate new safety revisions to decrease the risk of hypocalcemia in Study 3 (Study 20110100) and to

submit a finalized protocol for Study 4 (Study 20130356). The design of the new study was extensively discussed between Agency and the Sponsor during type A meeting on February 4, 2014. The Agency expressed a concern that the shorter duration of a new study (Study 4, 20 weeks) compared to the 30-week duration of Study 2 might limit the ability to obtain an adequate assessment of the safety and efficacy of Sensipar, especially at higher doses (due to a shorter duration of the titration phase).

- Amendment 3 (requested on 3/31/2014, approved on 7/29/2014)

The third amendment addressed the above discussed changes to the pediatric program, i.e. that Study 2 could be terminated and analyzed with available data. Because Study 2 was prematurely discontinued and applicant had insufficient data to robustly evaluate pediatric efficacy and safety, the Agency requested that a new 20-week, open-label study of Sensipar versus standard of care with enhanced monitoring for hypocalcemia be conducted in patients 6-18 years old (Study 4: 20130356).

The timeframe for the submission of the WR study reports was revised; the new deadline became November 25, 2016.

- Amendment 4 (submitted on 12/12/2014, approved on 4/9/2015) and Amendment 5 (submitted on 6/19/2015, approved on 10/14/2015)

In the fourth and fifth amendments the applicant sought to reduce the sample size for the efficacy assessment because patients enrolled in Study 4 could not complete the full 20 weeks. **Instead of 48 patients with 20 weeks** of data, the Agency agreed to accept **40 patients with at least 12 weeks** of data as long as all 40 patients could be included in the final primary endpoint determination. To deal with missing data at 20 weeks the Division agreed that the efficacy endpoint could be measured at weeks 11 and 12 and not at weeks 17 to 20 as originally planned. Amgen agreed to analyze the data as requested in the U.S. specific protocol though they continued to plan to measure the end point at weeks 17 to 20 as part of their own analysis, which they planned to submit to countries outside the U.S.

- Amendment 6 (requested on 12/3/2015, **denied** 12/24/2015)

Amgen did not recruit a sufficient number of patients into the safety and tolerability study for young (28 days to 6 years) pediatric patients (*Study 3: 20110100*). However, to be able to file the WR and obtain additional exclusivity Amgen proposed a sixth amendment to the WR to change the number of young pediatric patients required to complete the study from 15 patients at 26 weeks or transplanted at or after week 12 to the number of completers in the study at the time (4 completers). It was unclear to the Agency why the Applicant recruited such a small number of patients 28 days- 6 years old and had only 4 completers in the Study 3 despite the long duration of the study (since 2010) and whether the applicant truly attempted to aggressively recruit patients into their study; therefore, the Division was unwilling to further modify the WR as the original public health objectives of issuing the request would be unlikely to be met.

The final WR included the following requirements that needed to be fulfilled in order to obtain needed pediatric information on Sensipar:

- PK/PD information and safety information on use of Sensipar in pediatric patients < 18 years old and efficacy information on use of Sensipar in patients 6-18 years old should be obtained from the following clinical trials:
  - **Study 1** - PK/PD study in pediatric patients 28 days-6 years old
  - **Study 2** – double-blind, randomized, placebo-controlled study evaluating safety and efficacy of Sensipar in pediatric patients 6-18 years old with CKD and SHPT (terminated prematurely with 40 patients enrolled and analyzed);
  - **Study 3** - an open-label, single-arm study evaluating safety of Sensipar in at least 15 completers 28 days-6 years old (who completed 26 weeks of the study or 12 weeks of the study and underwent kidney transplantation).
  - **Study 4** - open-label, randomized, controlled study evaluating safety and efficacy of Sensipar in at least 40 patients 6-18 years old with CKD and SHPTH who complete 12 weeks of the study
- Efficacy in pediatric patients 28 days-6 years old should be extrapolated from information gathered from adults and in the studies outlined in WR; an exposure-response analysis supporting this extrapolation should be submitted to the Agency.
- An age-appropriate formulation should be developed and tested in the studies described above
- Summary of the published literature on use of Sensipar in pediatric patients and safety information from any national registry on pediatric patients treated with and without Sensipar should be submitted

2. Pre-NDA meeting, 9/21/2016

During this meeting, the Division and the Sponsor had an extensive discussion regarding the NDA content and format to be submitted to the Agency in support of the (b) (4) , and pediatric exclusivity.
The Agency requested that a new separate NDA be submitted for (b) (4) .
The Sponsor requested again to submit a final amendment (amendment 6) to the WR to adjust the number of patients studied in Study 3 from fifteen to four. The Sponsor stated they were not able to meet the WR requirements for a variety of reasons including difficulty with patient recruitment given the small size of the study population, difficulty with patient retention, the fact that the study was placed on a partial clinical hold in February 2013 for 14 months, and study closure in June 2016 in order to be able to submit the study report within the necessary time frame to obtain pediatric exclusivity prior to patent expiration. The Agency denied the requested modification to the WR and indicated that a final determination whether the submitted studies meet the terms of the WR would be made during the review of the application.

3. Sensipar (b) (4) was granted Orphan Drug designation for the treatment of secondary hyperparathyroidism in pediatric patients with CKD on dialysis on 9/7/2016 by the Office of Orphan Products Development.

4. **NDA (b) (4) and NDA 21688/S-23 with a request for a pediatric exclusivity determination for Sensipar were submitted on November 23, 2016.**

NDA (b) (4) was submitted for (b) (4).
NDA 21688/S-23 (efficacy supplement; labeling changes) was submitted to incorporate new pediatric data information obtained from the studies conducted in response to WR into the label for Sensipar.

Priority review was granted for NDA (b) (4) because the (b) (4) .

5.CMC/Device

(b) (4)

(b) (4)

6.Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology / toxicology review was completed by Dr. Parvaneh Espandiari and Dr. C. Lee Elmore (refer to the review in DARRTS from 4/28/2017). There are no outstanding nonclinical issues and the pharmacology/toxicology reviewers recommend approval of (b) (4) with no requirements for post-approval nonclinical studies.

All (including single dose toxicology studies, in vitro mutagenicity studies, reproductive and developmental toxicity studies) but one required studies were conducted and reviewed previously under NDA 021688 (Sensipar tablets).

The Sponsor conducted one 6-month juvenile study in normocalcemic dogs to support the clinical pediatric studies. The results of this study have been already submitted to the Agency and reviewed under IND 109361 (refer to the review in DARRTS). Briefly, the toxicology findings were consistent with the known pharmacological effects of Sensipar in healthy animals, i.e. decrease in iPTH and calcium levels. The reviewers concluded that these toxicities were not anticipated to occur in states of hypercalcemia associated with SHPT. No new or concerning toxicities were identified in this study.

The reviewers also concluded (b) (4)

7.Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was completed by Dr. Sang M. Chung and Dr. Jayabharathi Vaidyanathan. The reviewers concluded that the clinical pharmacology information, including the response analysis submitted in this application, "**does not provide adequate data to support efficacy and safety of Sensipar in the pediatric population"**. For detailed discussion, please refer to their Clinical Pharmacology review in DARRTS (5/1/2017).

The reviewers' recommendations are based on the results of review of the Sponsor's PK/PD data and analyses obtained from the following sources:

- Two PK/PD single dose studies in pediatric patients:
  - Study 20030227 using fixed 15 mg dose (half 30 mg tablet) evaluating Sensipar PK/PD parameters in pediatric patients 6-18 years old
  - Study 20090005 (Study 1 in WR) using 0.25 mg/kg weight-based dose (5 mg capsules) evaluating PK of new dosage form in children < 6 years old. Study 20090005 also evaluated the PK of single dose of Sensipar following the different route of administration (oral vs. via gastrostomy or nasogastric tubes)
- Study 20070208 (Study 2 in WR), dose titration study evaluating safety and efficacy of Sensipar in children 6-18 years with CKD on dialysis
- Study 20110100 (Study 3 in WR) evaluating safety of multiple Sensipar doses in children 28 days-6 years old with CKD and SHPT
- Population pharmacokinetic analysis (PopPK) using combined data from all pediatric studies and historical adult data (4 studies) to support efficacy of Sensipar in children < 6 years old
- Physiologically-based PK (PBPK) modelling to support efficacy of Sensipar in pediatric patients < 1 years old.

Based on the review of the above data, Dr. Chung concluded that:

- Effective dosing regimen of Sensipar in pediatric patients 6-18 years old has not been established in the clinical studies.

The reviewers indicated that the proposed starting weight-based dose of Sensipar (0.2 mg/kg) was acceptable from a clinical pharmacology perspective because the exposure following weight-based dosing was less variable compared to that following the fixed dose administration and might be associated with lower hypocalcemia risk. However, the overall clinical relevance of body weight-based dosing proposed by the Sponsor remains unknown and effectiveness of Sensipar at studied doses has not been established in pediatric clinical program because of the following deficiencies:

The actual doses used in multiple dose efficacy studies were not individual weight-based doses as planned by the Sponsor. The actual doses used in these studies were based on the total body weight range (e.g., 2.5 mg for 12.5-25 kg children, 5 mg for 25-49 kg children, etc.; refer to Dr. Chung's review Table 3) because of the available dosage form strengths (i.e. 1, 2.5 and 5 mg capsules). Thus, there might be a significant difference between the proposed weight based starting dose and actual administered dose: for example, a starting weight-based dose for 49-kg patient is 9.8 mg, however patient is administered 5 mg dose (50% lower dose) based

on total body weight range. This dosing based on total body weight range might have resulted in significant between-subject variability in Sensipar exposure and possible under or overdosing in the pediatric studies.
The results did not provide sufficient evidence that the doses used in these studies were effective in decreasing iPTH by > 30% in patients 6-18 years old (refer to Efficacy section below).

- Efficacy of Sensipar in children 28 days-6 years old has not been established based on the results of extrapolation analysis from adult data and available pediatric data in children > 6 years old.
The reviewers concluded that the results of the Sponsor's PopPK analyses do not support the efficacy of Sensipar in pediatric patients 28 days-6 years old.

Although simulated Sensipar PK characteristics in adults and children 28- days-6 years old were comparable, inter-individual variability in Sensipar PK and PD parameters was higher in pediatric patients compared to adult parameters. The reviewers concluded that because of high inter-individual variability and small numbers of subjects, the Sponsor's simulation results do not support the claim that the target therapeutic response can be achieved following multiple oral doses of > 15 mg in children 28 days-6 years (large inter-individual variabilities result in wide prediction intervals). The assessment of the results of Sponsor's simulation of the different models for dose titration (based on monitoring corrected calcium weekly, modifying ionized calcium monitoring, etc.) is also complicated due to the high inter-individual variability in Sensipar PK parameters.

- Efficacy of Sensipar in children <28 days old has been established based on the results of the results of PBPK analysis.

The results of PBPK modeling were also not acceptable because "empirical modeling approach (i.e., using a minimal, one-compartment model with adjustment through sensitivity analysis) [was used] to provide reasonable prediction for two compartment characteristics of Sensipar PK". In addition, PK parameters were evaluated in a single patient < 1 year old in the pediatric clinical program, thus, the reviewers concluded that "predictability of the age-dependent change on Sensipar PK for pediatric patients aged less than 1 year is not fully validated and thus not acceptable for extrapolation of efficacy and (b) (4)

- Data submitted to support the safe and effective administration of Sensipar capsule via gastrostomy or nasogastric tube was also insufficient.

As per the Clinical Pharmacology reviewers, no conclusions could be made regarding the comparability of Sensipar PK parameters following different routes of administration (oral vs. via tubes) due to the limited sample size and large variability in PK parameters (refer to Dr. Chung's review, Figure 3). Thus, the reviewers recommen (b) (4)
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- Bioequivalence (BE) between 5 mg Sensipar powder packed in capsule (new dosage form; 6 capsules) and 30 mg tablet (approved dosage form; 1 tablet).

The Sponsor conducted a BE study (20070293) to demonstrate bioequivalence between capsule containing Sensipar powder (six 5 mg capsules) and approved tablet (30 mg) in healthy adult volunteers. Dr. Chung analyzed the results of the study and concluded that two formulations are bioequivalent when the content of the capsule is sprinkled over the food as demonstrated by the least squares means (LSM) ratio between the two formulations that met bioequivalence criteria (80-125% for the AUC_{0-t} and C_{max}):

- **AUC_{0-t}:** 0.997 (90% CI 93.5% - 106.2%)
- **C_{max}:** 1.037 (90% CI 95.5% - 112.6%)

However, Dr. Chung indicated that Sensipar exposure was lower when capsules were **swallowed as whole** and was not bioequivalent to the Sensipar exposure following treatment with tablets or when Sensipar powder was sprinkled over the food.

I agree with Clinical Pharmacology conclusions.

8.Clinical Microbiology

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

9.Clinical/Statistical- Efficacy

The Sponsor included in this application the results obtained from two randomized controlled Phase 3 studies conducted as per WR (Study 20070208, referred to as Study 2 and Study 20130356, referred to as Study 4 from here on in) to support the claim (b) (4) .

The efficacy of Sensipar in children < 6 years old with CKD on dialysis was planned to be extrapolated from the adult data and data in older children using PopPK analyses; the results of this extrapolation are discussed in the Clinical Pharmacology section.

Drs. Susie Sinks (biostatistician) and William Lubas (clinical reviewer) reviewed the efficacy results obtained from the pediatric clinical program and recommended (b) (4) . The statistical and clinical reviewers concluded that **none** of the above studies provide sufficient evidence to support (b) (4)

Since the above recommendations are based on the results of two phase 3 studies, I will briefly summarize the design and the results of these trials below. I will also briefly discuss the design of Phase 2 study 20110100 in this section (Study 3 in WR) for the completeness of the review;

however, the results of this study will be discussed in the next section, since the study was designed to evaluate safety only.

Other studies conducted within the Sensipar Capsule pediatric clinical program will not be discussed in detail in this memorandum and will be referenced as needed only.

Study 20070208 (Study 2)

Study 2 was a multicenter (26 sites in 9 countries including US), dose titration study evaluating safety and efficacy of Sensipar in children with CKD on dialysis. The study consisted of 2 periods: a 30-week randomized, double-blind, placebo-control period followed by 30-week open label period (all subjects received Sensipar).

I will focus on the design and results of the 30-week double-blind, placebo control period as the objective of the study was to evaluate the efficacy of Sensipar versus placebo in reducing plasma iPTH levels from pre-treatment baseline in pediatric patients ages 6 to 18 years with CKD on hemodialysis treated with Sensipar for 30 weeks during a double-blind treatment period.

Eligible Participants

Patients eligible to participate in the study were children 6-18 years old with CKD receiving dialysis for at least 2 months who were diagnosed with secondary hyperparathyroidism (defined as iPTH level ≥ 300 pg/ml).

The selected lower inclusion criterion for PTH levels (mean level of greater than or equal to 300 pg/ml) is consistent with KDOQI[5] guidelines in children which recommend maintaining PTH levels in the range of 200-300 pg/ml (Guideline 9B) and to initiate treatment with vitamin D analogs (based on serum calcium and phosphorus levels) to avoid progression to levels outside of this range and thereby reduce the risk of renal osteodystrophy. It should be noted that, the diagnosis of renal osteodystrophy is a histological diagnosis made on bone biopsy. None of the patients in the pediatric studies had bone biopsies performed.

In order to participate in the study patients were also required to have serum calcium ≥8.8 mg/dl and phosphorus ≥ 4 mg/dl (≥ 3.5 mg/dl in children 12-18 years old) levels. Subjects were allowed to continue taking calcium supplements, phosphate binders, and vitamin D analogs throughout the study; the doses were allowed to be modified as required. Subjects who had new or worsening of pre-existing seizures were excluded from the study.

Study design

The double-blind phase of the study included screening period, a 30-week double-blind treatment period (including 24-week dose titration phase and 6-week efficacy assessment phase (EAP) during fixed dose administration). All patients were randomized to receive Sensipar or matching placebo in a 1:1 ratio. Randomization was also stratified by age group: 6-12 years of age and 12-18 years of age.

[5] KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children with Chronic Kidney Disease. http://www2 kidney.org/professionals/KDOQI/guidelines_pedbone/

The following Sensipar formulations were used in all pediatric studies: capsule containing powder to be sprinkled over the food (5 mg) and currently approved tablets (30, 60 and 90 mg). For doses < 5 mg, the content of 5 mg capsule was mixed with water or syrup and the appropriate volume of the solution was administered to the patient. It should be noted, that (b) (4) in pediatric population, only 5 mg capsule was used in the study.

The starting dose in Study 2 was ≤ 0.20 mg/kg daily. A maximum daily dose was 4.2 mg/kg and not to exceed 180 mg. The study implemented a dose titration schedule and safety monitoring for hypocalcemia that is already approved and used in adults with CKD on dialysis (as per current Sensipar label) based on corrected calcium levels. Briefly, each administered dose was allowed to be increased every 4 weeks sequentially (the sequential doses were 2.5, 5, 10, 15, 30, 60, 90, 120 and 180 mg) if all of the following criteria had been met: plasma iPTH >300 pg/ml, serum calcium >8.4 mg/dl and gastrointestinal symptoms or symptoms of hypocalcemia were absent. Each administered dose was required to be decreased at any time during the study if any of the following criteria were met: iPTH <150 pg/ml or serum calcium < 8.4 mg/dl or subject is symptomatic. Dosing had to be discontinued at any time if patient became symptomatic, calcium < 8 mg/dl, or iPTH<100 pg/ml. Following any change in the drug dose, iPTH and calcium had to be monitored for 5-7 days after the change.

It should be noted that the titration schedule in this study was based on the laboratory values of calcium obtained 1 week prior to the next dosing titration visit; no calcium levels were available on the day of the dosing titration visit. Thus, there is a risk that the dose titration might have occurred in patient who had unrecognized hypocalcemia during the last week prior to the next titration visit. Indeed, one patient died during the study. Even though the cause of death in this case was determined to be multifactorial, one of the potential causes of death was unrecognized hypocalcemia (serum calcium level was 5.3 mg/dl; refer to safety section below).

Primary efficacy outcome

The primary efficacy endpoint was a responder analysis examining the number of subjects in the Full Analysis Set population (FAS: defined as all subjects who were randomized at baseline and had at least one post-baseline iPTH assessment) who completed the study and experienced a mean decrease of ≥ 30% in plasma iPTH from baseline during the efficacy assessment period (EAP; weeks 25 to 30).

Reduction in iPTH over six months is used as a surrogate of clinical benefit (reduced risk of bone and mineral metabolism disorders associated with end stage renal disease) to support the approval of drugs to treat secondary hyperparathyroidism and has been accepted by the Division. The Division's approach is consistent with expert opinions described in past and current treatment guidelines for chronic kidney disease management (KDOQI 2005- in children and KDIGO 2009-in adults, respectively) which recommend treating elevated PTH and factors that contribute to secondary hyperparathyroidism (hyperphosphatemia, vitamin D insufficiency, hypocalcemia) to prevent mineral and bone complications of CKD.

There are the following concerns with the evaluation of primary endpoint in the study:

-Use of last observation carried forward (LOCF)
In patients who discontinued the study prematurely and/or had missing data during EAP, the mean of last two available iPTH values were used as the end of the treatment concentrations; a single iPTH value was used if only one post-baseline iPTH level was available
- Definition of "completers"
Patients who were considered study "completers" at the end of the trial did not have to be treatment completers, i.e. to be treated with Sensipar till EAP. This design and use of LOCF made it possible for subjects to have iPTH evaluations prior to EAP and to be counted as responder or non-responder based on LOCF, and then discontinue treatment prematurely at this point due to AEs or other reasons.
-Sample size
Lastly, the Sponsor originally calculated that a sample size of 100 patients will provide 99% power to detect the pre-specified difference in the proportion of patients with iPTH decrease of > 30% during EAP between treatment arms (60% for the Sensipar and 15% for the placebo; similar to the difference observed in adult pivotal trials). Study 2 was terminated early due to a pediatric death; and, less data were collected than originally planned (only 43 patients were randomized; refer to regulatory section above). However, the Agency agreed to review the study with available data (Amendment 3 to WR from 7/29/2014).

Baseline Demographics and Disposition
A total of 43 patients were enrolled, randomized, and received at least one dose of Sensipar (22 patients) or placebo (21 patients) and, were included in the FAS dataset. Sixteen of 43 subjects (37%) completed the 30-week double-blind treatment period (5 subjects in Sensipar group (22.7%) and 11 subjects in placebo group (52.4%)). Of 16 study completers, 5 children were 6-12 years old (30%). A total of 12 subjects were enrolled in the open-label part of the study; of these, 10 received at least one dose of Sensipar in the open-label phase and 4 completed the open-label phase (1 subject previously received Sensipar and 3 subjects previously received placebo).
Twenty-seven subjects (63%) discontinued the double-blind part of the study prematurely; the most common reason for discontinuation was early study termination (12 subjects: 7 subjects in Sensipar group and 5 subjects in placebo group) followed by kidney transplant (6 subjects in Sensipar group and 2 subjects in placebo group). AE was a reason for early study discontinuation in 1 subject treated with Sensipar (death; refer to safety section below).

The two randomized groups were relatively well-balanced at baseline with respect to their main demographic and disease characteristics. The mean age of patients was 13 years (range 6-18 years). Mean iPTH level was 795.8 pg/ml (median 684 pg/ml) in placebo group, and 757.1 pg/ml (median 676) in Sensipar group. Mean calcium and phosphorus levels were ~9.9 mg/dl and 6.4-6.6 mg/dl at baseline respectively. Up to 95% of patients were on vitamin D supplements at baseline.

Efficacy results
Dr. Shuxian Sinks reviewed the primary statistical analyses used to support the establishment of efficacy of Sensipar in pediatric population. Efficacy findings are also reviewed and discussed in Dr. William Lubas's review. For detailed discussions of the efficacy findings see both of these reviews. My memorandum provides a summary of the main efficacy findings.

Primary Analysis

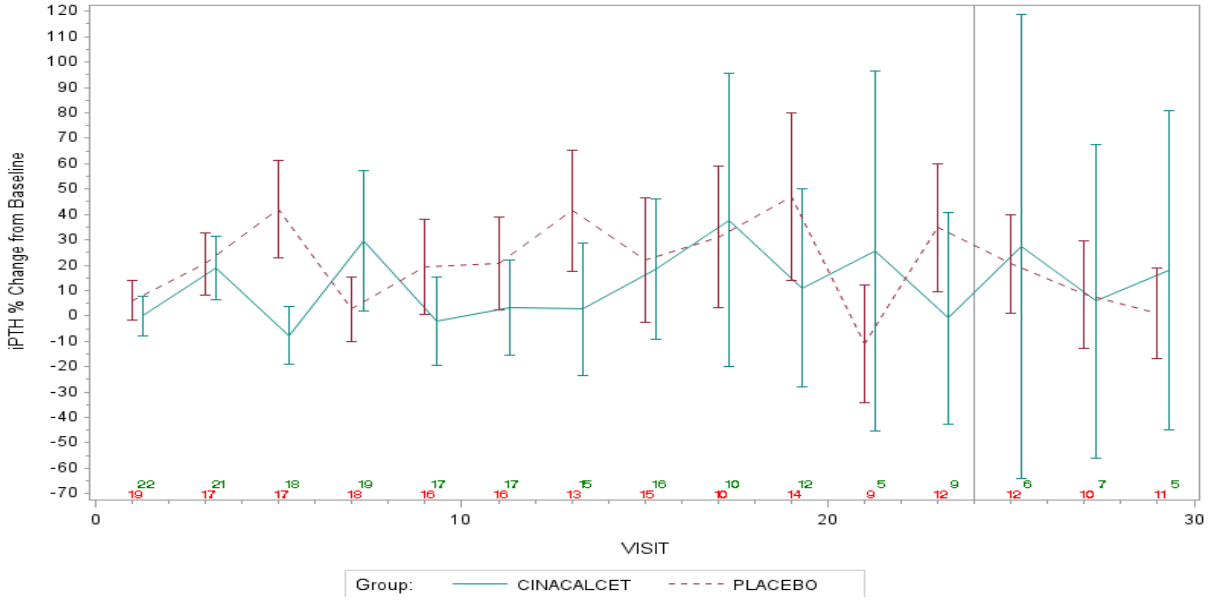
The Sponsor conducted the primary analysis in the FAS population using LOCF missing data approach and including all data collected prior to the suspension of Sensipar. The results of this analysis demonstrated that the responder rate (i.e. patients who had >30% iPTH reduction from baseline) was significantly higher in the Sensipar group compared to placebo group: odds ratio of 4.26 (95% CI: 0.99, 18.3; p-value=0.017).
The Sponsor's use of LOCF method for analyses relied on assumption that the treatment benefit for subject discontinued early remained the same as last observed value. Dr. Shuxian Sinks disagreed with the Sponsor's primary analysis using LOCF. Her concerns were that the results of primary analysis are significantly affected by the large amount of missing data during EAP (ranging from up to 52.4 % in placebo group to up to 77.3% in Sensipar group depending on timing of EAP) and that the Sponsor's assumption is "implausible.., as iPTH achieved while on treatment might not be sustained after stopping treatment". Thus, the Sponsor was requested to repeat the primary analysis handling the missing data in a fashion that corresponded to the original intended conduct of the study design (but not the actual conduct of the study); and, handling the missing data based on the assumption that the reason for subject's early study discontinuation is missed at random (MAR). The results of the repeated analysis (Sponsor's response to the information request from 3/10/2017) demonstrated that response rate was only 41.5% in Sensipar group and 24.2% in placebo group; the difference was no longer statistically significant (p=0.36). Dr. Sinks also repeated the primary analysis using ITT population (that include all randomized patients regardless of discontinuation) and confirmed that there was no statistically significant difference in response rate between Sensipar and placebo groups: odds ratio of 1.25 (95CI: 0.28, 5.59, p=0.77). Dr. Sinks concluded that the large amount of missing data affects the reliability of the study results and complicates the study conclusion regarding the clinically meaningful efficacy of the drug relevant to clinical practice.

Dr. Sinks also performed a sensitivity analysis using a tipping point analysis in the ITT population (that include all randomized patients regardless of discontinuation) to evaluate the potential impact of the missing data on the reliability of the efficacy results based on LOCF Briefly, this analysis provides a range of estimates of treatment effect under varied assumptions about possible outcomes of the patient dropouts; the demonstration of efficacy would be reliable despite the missing data if "tipping point" from significance to non-significance is unlikely happened in the real clinical setting. The results of her analysis demonstrated that the Sponsor's results of primary analysis using LOCF are "implausible and unreasonable" due to the large amount of the missing data (Dr. Sinks's review Table 11). Dr. Sinks analyzed the iPTH lowering effect of Sensipar in subgroups of patient who dropped out of the study prematurely and in those who completed the study ((Figures 1-3). The results of this analysis demonstrated that the Sponsor's conclusion regarding Sensipar superiority in lowering iPTH level (based on LOCF method) most likely was driven by the data obtained from large number of patients who did not complete the study (Figures 2).

Lastly, the small number of completers, large variability in iPTH reduction among subjects and use of vitamin D analogs during the study (that has iPTH-lowering effect and might

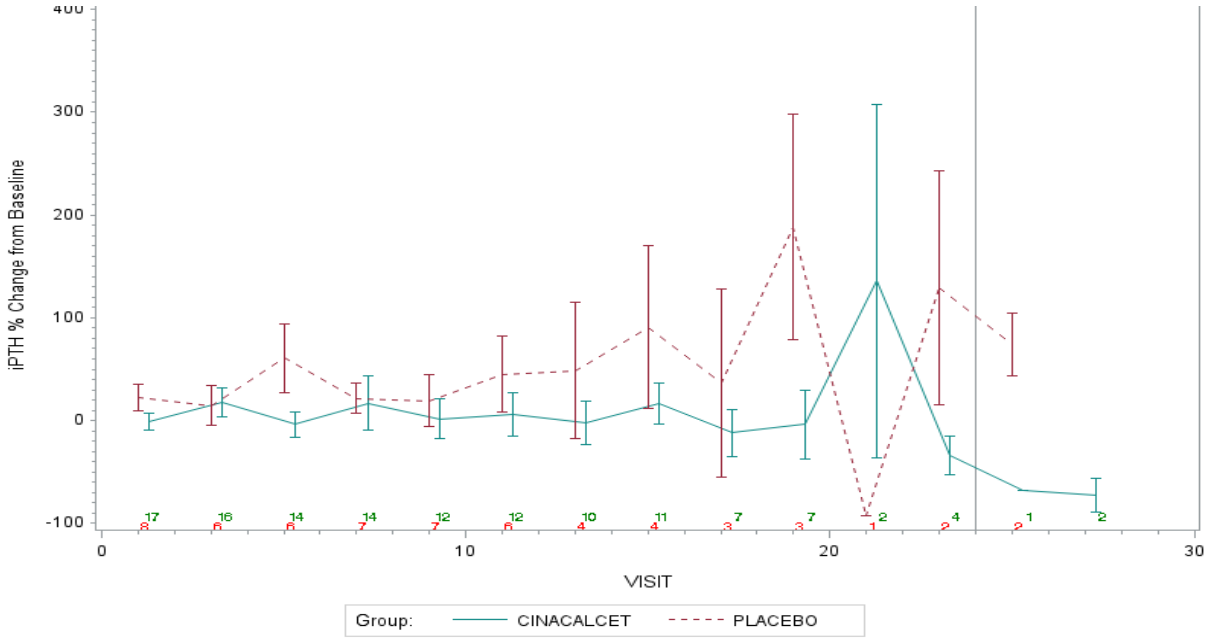
contribute to the observed efficacy of Sensipar in both groups) complicates further the evaluation of efficacy of the drug in the pediatric population.

Figure 1. iPTH % Change from Baseline for Study 20070208 (All Observed Data)



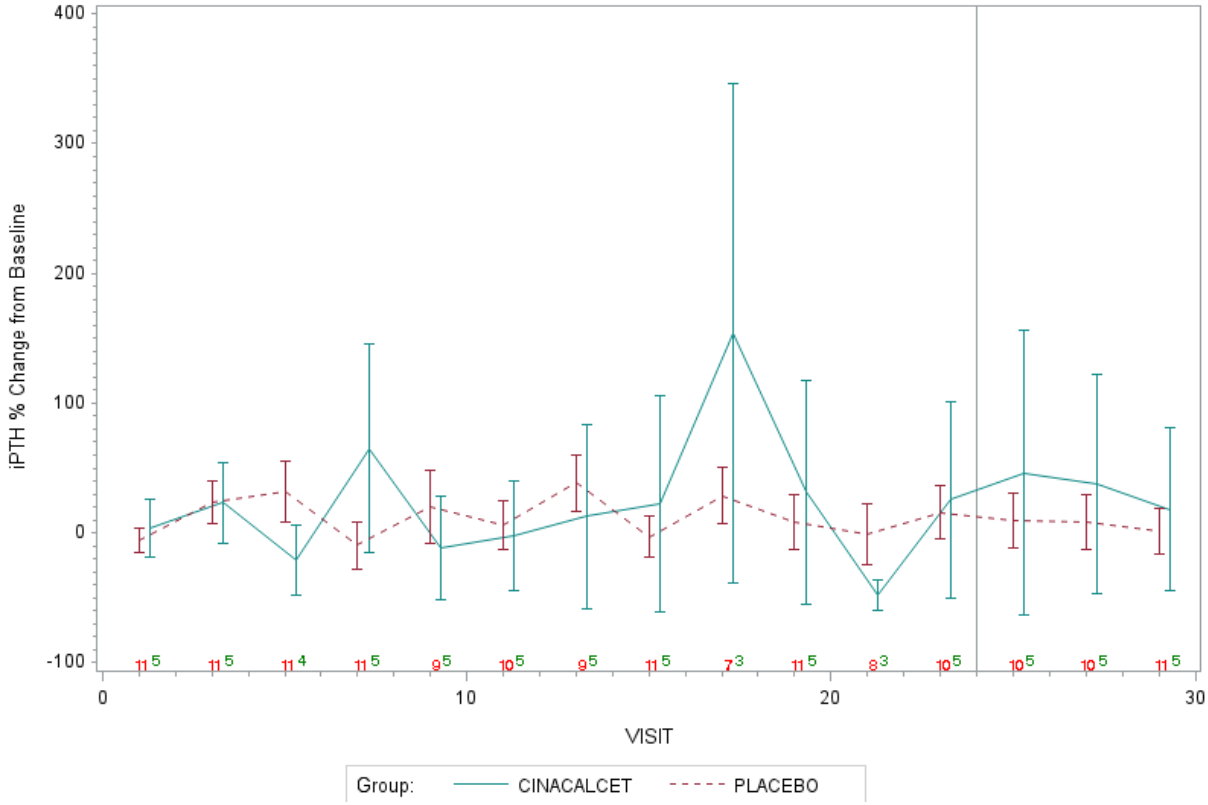
Source: Biostatistician's review, figure 3.

Figure 2. iPTH (%) Change from Baseline (Subjects Discontinued early)



Source: Biostatistician's review, figure 4

Figure 3. iPTH % Change from Baseline for Study 20070208 (Subjects Completed EAP)



Source: Biostatistician's review, figure 4

Secondary analyses

The results of the secondary analysis do not provide any supportive evidence regarding the efficacy of Sensipar in pediatric patients. Thus, these results are summarized only for the completeness of this review.

The secondary endpoints were: proportion of patients with iPTH levels < 300 pg/ml, mean change in iPTH from baseline during EAP, percent change in corrected and ionized calcium and phosphorus from baseline during EAP, growth velocity etc.
Dr. Sinks reviewed the results of these analyses and concluded that "… superiority [of Sensipar] is questionable" and the results of secondary analyses do not support the efficacy of Sensipar in pediatric patients: the Sponsor used a hierarchical testing procedure to test the primary and secondary endpoints and the results of the Sponsor's repeated analysis and Dr. Sinks's analysis of primary endpoint did not reach statistical significance.

In children, secondary hyperparathyroidism may also lead to growth retardation. Thus, the Sponsor included the evaluation of growth velocity as a secondary endpoint in the study. There was no clinically meaningful difference in the improvement in growth velocity between treatment groups (LS Mean estimate 3.3 in Sensipar group vs. 3.1 in placebo group). Moreover, the evaluation of growth velocity was performed earlier during the study than originally planned (planned at 30 and 60 weeks). The short duration of the treatment with Sensipar (< 6 months) in the majority of children, concomitant treatment with growth hormone

and PTH-lowering drugs (vitamin D analogs) and small sample size with high drop-out rate further complicates the assessment of growth velocity in these patients.

I agree with Dr. Sinks and Dr. Lubas that even though some of these analyses demonstrated small differences of unknown clinical significance in secondary endpoints between treatments groups, the clinical meaningfulness of these comparisons are difficult to interpret since the secondary endpoints are not tested for statistical significance and no correction for multiplicity was made for testing of secondary endpoints.

In conclusion, I agree with the biostatistical and clinical reviewers that the results of Study 20070208 did not provide substantial evidence of efficacy of Sensipar in children 6-18 years old with SHPT and CKD; the results of the Sponsor's analyses are unreliable and significantly affected by missing data and other confounding factors as described above. Moreover, the dosing regimen used in the study that was based on corrected calcium levels raises significant safety concerns regarding this regimen due to missed low calcium levels and the associated death (refer to Safety Section below).

Study 20130356 (Study 4)

Because Study 2 was terminated prematurely due to a fatality and had insufficient data to robustly evaluate efficacy and safety of Sensipar in pediatric patients 6-18 years old, the Agency requested that a new open-label study evaluating efficacy and safety of Sensipar versus standard of care in pediatric patients 6-18 years old with enhanced monitoring for hypocalcemia be conducted (refer to Type A meeting minutes from 2/5/2014 and WR Amendment 3 approved on 7/29/2014).

Study 4 was a multicenter (32 sites in 14 countries including US), open-label, active control study evaluating safety and efficacy of Sensipar in children 6-18 years old with CKD on dialysis.

The objective of the study was to evaluate the efficacy of Sensipar versus standard of care (SOC: vitamin D analogs, calcium supplements and phosphate binders) in reducing plasma iPTH levels by 30% from baseline in pediatric patients 6-18 years old with CKD on hemodialysis treated with Sensipar for 20 weeks or until the time of renal transplantation.

Patient population

The enrollment requirements for this study were similar to the enrollment criteria used in Study 2: patients 6-18 years old with CKD receiving dialysis, iPTH level ≥ 300 pg/ml and serum corrected calcium ≥8.8 mg/dl were eligible to participate in the study. However, due to the pediatric death in Study 2, the following additional inclusion and exclusion criteria were implemented in this study to mitigate risks associated with drug-induced hypocalcemia: ionized calcium was required to be obtained and to be > 1.05 mmol/L on first day of drug administration, patients with QT interval abnormalities, and patients receiving concomitant medications known to prolong the QT interval or to prolong Sensipar exposure (e.g., CYP3A4 inhibitors) were excluded from the study.

As in Study 2, subjects continued taking calcium supplements, phosphate binders, and vitamin D sterols throughout the study; the doses were allowed to be modified as required (in both

groups, SOC group and Sensipar group).

Study design
The study included a screening period, 20-week (or till the time of the renal transplant) open-label treatment period and 4-week follow up period.

All patients were randomized to receive Sensipar (tablets or capsules) in addition to standard of care (vitamin D analogs, calcium and phosphate binders) or standard of care alone in a 1:1 ratio. Randomization was also stratified by age group: 6-12 years of age and 12-18 years of age.

The study used 5 mg capsule and 30 mg tablet formulations. The starting dose (≤ 0.20 mg/kg daily) and sequential doses in this study and in Study 2 were the same; the dose was allowed to be increased every 4 weeks. However, because of the occurrence of hypocalcemia observed with the titration regimen used in Study 2, additional safety monitoring was implemented in this study to mitigate the risk for hypocalcemia:

- Half of maximum daily dose used in study 2 was allowed in Study 4 (2.5 mg/kg, and not to exceed 60 mg in study 4 vs. 4.2 mg/kg in study 2).
- Safety monitoring was enhanced by the monitoring of real-time ionized calcium levels weekly. Dose titration was based not only on plasma iPTH >300 pg/ml and serum calcium >8.4 mg/dl, but also on ionized calcium levels obtained prior to dose titration (> 1.05 mmol/L). Administered dose was required to be discontinued if patient became symptomatic, calcium < 8 mg/dl, ionized calcium < 1.0 mmol/L or iPTH<100 pg/ml.
- If subject required administration of drugs known to prolong QT interval, CYP3A4 inhibitors or CYP2D6 substrates during the study, Sensipar had to be withheld.
- If a subject's dosing was interrupted during the study at any time, the dose of Sensipar was withheld until corrected calcium was > 8.4 mg/dl, ionized calcium > 1.05 mmol/L and subject was asymptomatic

Primary efficacy outcome
The primary efficacy endpoint was the same as in Study 2, i.e. a responder analysis examining the number of subjects in the FAS who experienced a mean decrease of ≥ 30% in plasma PTH from baseline during the efficacy assessment period (i.e., weeks 11 to 15).

The Sponsor's proposed evaluation of primary efficacy outcomes for Study 4 addressed some of the Agency's concerns raised with the Study 2 analyses (refer to the discussion above) including:

- Definition of study "completers"
- In Study 4, subjects who completed at least 12 weeks of treatment before undergoing renal transplant were considered to have completed the study.
- Missing data in this study was imputed using non-responder imputation method (subjects who did not have value at week 11 or 15 were considered non-responders), as opposed to LOCF, which was used as the primary analysis method for missing data in Study 2.

However, the overall duration of Study 4 was shorter compared to Study 2: 20 weeks vs. 30 weeks, respectively. It should be also noted that during the negotiation of WR (amendments 4

and 5, refer to regulatory section), the time of the efficacy assessment was changed from week 17-20 to week 11-15 in order to avoid a large amount of anticipated missing data. The Agency expressed a concern at that time that early evaluation of efficacy in the proposed study (compared to evaluation of efficacy in Study 2 at week 30) might limit the study's ability to provide an adequate assessment of the safety and efficacy of Sensipar, especially at higher doses (due to the shorter duration of titration phase).

Study 4 was closed on 6/23/2016: as per Sponsor, "the end of study date was chosen to allow for all enrolled subjects to contribute to the primary endpoint assessment".

Baseline Demographics and Disposition
A total of 55 patients were enrolled and randomized (27 patients in Sensipar group and 28 patients in SOC group) into the study and were included in FAS. Of these 55 patients, 2 patients in Sensipar group did not receive study drug. Thirty six of 55 subjects (65.5%) were study completers (16 subjects in Sensipar group (59%) and 20 subjects in SOC group (71%)). Nineteen subjects (35%) discontinued the study prematurely; the most common reason for discontinuation was the Sponsor's decision to close the study (10 subjects: 4 subjects in Sensipar group and 6 subjects in placebo group) followed by kidney transplant (2 subjects in Sensipar group and 3 subjects in placebo group). No subjects discontinued the study prematurely due to AEs.

The mean age of patients was 12-13 years. Children randomized to SOC group had more severe SHPT compared to Sensipar group as determined by iPTH levels: mean iPTH levels were 1228 pg/ml (median 1122 pg/ml) and 945.7 pg/ml (median 662.7), respectively. This imbalance in baseline disease severity may affect the comparison of iPTH levels between groups as patients with less severe disease might achieve disease control sooner and at lower doses. Mean calcium and phosphorus levels were ~9.8 mg/dl and 5.6 mg/dl at baseline respectively; mean ionized calcium level was 1.2 mmol/L.
Up to 74% of patients in both treatment groups were using vitamin D sterols at baseline.

Efficacy results

Primary analysis
The primary analysis conducted by the Sponsor in the FAS population (55 patients),in which subjects with missing data at EAS were analyzed as non-responders, demonstrated that there was **no** statistically significant difference between treatment groups in the proportion of subjects who achieved a > 30% reduction in iPTH from baseline during week 11-15: 25.9 % of patients treated with Sensipar and 17.9% of patients treated with SOC had a reduction in iPTH level by > 30% at week 12-15 (p=0.48).

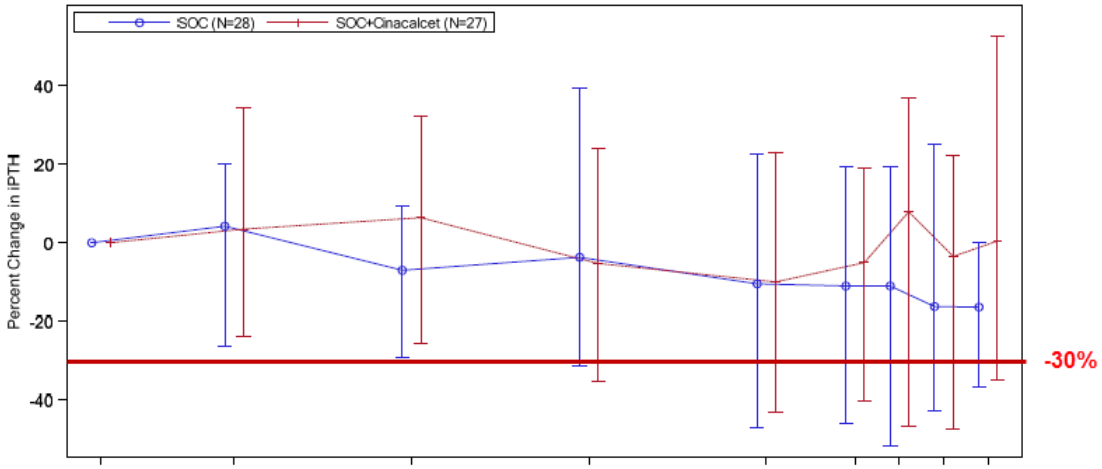
There was a substantial amount of missing data presented in this study: 14% in SOC group and 26% in Sensipar group during week 11-15; and 35.7% - 48.1% at week 17-19 depending on time of assessment and treatment group.

It should be noted that 80% of subjects in the Sensipar group were also receiving vitamin D analogs during the study. Vitamin D analogs have a PTH-lowering effect, which further

confounds the study results. Thus, observed decrease in iPTH levels during the study might be due to SOC (in particular, to vitamin D analogs) that has been used by both treatment groups.

Secondary analyses
The secondary endpoints (i.e., change in iPTH, calcium, phosphorus, etc. from baseline at the end of the study) were similar in study 2 and study 4.
The analyses of the secondary endpoints in study 4 do not support the claim that (b) (4) Moreover, it appears that there was more noticeable decrease in iPTH levels in subjects in SOC group compared to subjects in Sensipar group (Figure 4).

Figure 4. Median (IQR) % change in iPTH from Baseline by Study Visit



SOC (N=28)	28	27	27	24	24	17	16	18	19
SOC+Cinacalcet (N=27)	25	24	21	20	19	16	14	14	11

iPTH = intact parathyroid hormone; IQR = interquartile range; SOC = standard of care
Source: Dr. Lubas's review.

In addition, more subjects in SOC group had iPTH level < 300 pg/ml during week 17-20 compared to Sensipar group (18% in SOC group vs. 7% in Sensipar group). However, the overall clinical meaningfulness of these comparisons are difficult to interpret since no correction for multiplicity was made for testing of secondary endpoints and the secondary endpoints were not tested for statistical significance. The small sample size with high dropout rate and large variability in iPTH reduction among subjects complicates further the analysis.

Exploratory analyses
The trial included evaluation of growth velocity from baseline to week 20 as exploratory endpoint. Descriptive analysis of mean growth velocity did not demonstrate clinically meaningful difference in growth velocity between treatment groups (3.67 cm/year in Sensipar group vs. 3.42 cm/year in SOC group). An interpretation of the results of this analysis is further complicated by the short duration of the treatment with Sensipar (< 20 weeks) in the majority of children, concomitant treatment with growth hormone and PTH-lowering drugs (vitamin D analogs), absence of the data on growth velocity at baseline, small sample size with high drop-out rate, etc.

In conclusion, Study 4 failed to demonstrate that Sensipar was superior to SOC in meeting pre-specified target PTH reduction thresholds and did not provide convincing and substantial evidence to demonstrate the clinical benefit of Sensipar in the intended population at the achieved doses.
It should be noted that efficacy of the drug has been evaluated at very low drug exposures: mean doses were 0.3 mg/kg/day at week 11-15 and 0.4 mg/kg/day at week 17-20; mean maximum dose 0.7 mg/kg/day.
The reasons for the lack of dose optimization in the trial are unclear. One contributor may be a short duration of the study and a longer period of time (> 15 weeks) might be required for safe and optimal dose titration. The Sponsor also indicated that the major reasons for not achieving adequate Sensipar exposure and corresponding iPTH reduction was an enhanced safety monitoring based on ionized calcium levels and high pre-set ionized calcium threshold levels. However, all these factors were not addressed in the study and whether the drug is ineffective itself or lack of efficacy is due to small sample size, large amount of missing data, imbalance in severity of the disease between groups (presence of more severe disease in SOC group), tight titration schedule, short duration of the study, drug-related intolerability (e.g. more hypocalcemia events were recorded in subjects treated with Sensipar) remains unknown.

Study 20110100 (study 3)
For the completion of this section, I will discuss here the design of this study. The safety findings from this study will be discussed in the next section of this memorandum.

Study 20110100 was a Phase 2, 26-week, open-label, single-arm, multicenter (14 cites in US and Europe) study to evaluate the safety of Sensipar in children 28 days-6 years old with CKD on dialysis.

The primary objective of the study was to evaluate the safety of Sensipar with focus on the primary safety concern of hypercalcemia. Serum calcium values < 9 mg/dl for children < 2 years old and < 8.4 mg/dl for children > 2 years old were used to estimate the risk of hypercalcemia.

Patient population
Patients 28 days-6 years old with CKD on dialysis were eligible to participate in the study. The eligibility criteria were similar to the criteria used in studies 2 and 4 (e.g. PTH values, use of concomitant medications). In order to participate in the study corrected serum calcium had to be ≥9.4 mg/dl in children < 2 years old (> 8.8 mg/dl in children > 2 years old), phosphorus > 5 mg/dl in children < 2 years old (> 4.5 mg/dl in children > 2 years old).
The eligibility criteria for this study were modified after the Clinical Hold has been lifted: the patients were required to have normal ionized calcium level on day of first dose administration (> 1.3 mmol/l in children < 2 years old and > 1.05 mmol/l in children > 2 years old); subjects with abnormal QTc interval or concomitantly treated with drugs prolonging OTc interval were excluded from the trial. As in other pediatric studies, subjects were allowed to continue taking vitamin D analogs, calcium supplements and phosphate binders; the doses were allowed to be modified as required.

Study design
The study comprised of screening period, a 24-week treatment period followed by 2- week follow up period. All patients received Sensipar orally and standard of care (vitamin D, calcium and phosphate binders). Only Sensipar capsule for sprinkle on the food formulation (5 mg) was used in the study.

The doses and dose titrations were modified during the conduct of the study because of clinical hold due to pediatric death.
-The starting dose was ≤ 0.25 mg/kg daily before clinical hold and ≤ 0.2 mg/kg daily after clinical hold. Every 4 weeks, each administered dose was allowed to be increased sequentially.

- The dose titration schedules and dose discontinuation rules were the similar to those used in study 2 before clinical hold (based on total corrected serum calcium levels) and to those in study 4 after clinical hold (based on the f ionized calcium). The maximum dose of Sensipar was 4.5 mg/kg before clinical hold and 2.5 mg/kg/day or 60 mg after the clinical hold.

The WR stated that data from at least 15 patients who complete the study was required in order to obtain sufficient safety information on chronic use of Sensipar in this age group. "Study completers" were defined as subjects who completed 26 weeks of study or terminated study after week 12 due to kidney transplantation. Similar to the definition of the completers in study 2, patients who were considered "study completers" at the end of the trial did not have to be treatment completers, i.e., to be treated with Sensipar till EAP. This design made it possible for subjects to have safety evaluations (including calcium levels) during "washout period" after the drug has been discontinued.

Because of the clinical hold, the results of this study are presented for all subjects and separately for subjects who were on study before (cohort 1) and after (cohort 2) the clinical hold.

Baseline Demographics and Disposition
A total of 18 patients with CKD on dialysis were enrolled in the study; of these, one subject did not receive Sensipar. Of 18 patients, 8 patients were enrolled before partial clinical hold (cohort 1) and 10 were enrolled after the partial clinical hold (refer to regulatory section above). Fourteen subjects discontinued the study early; the most common reason for disconsolation was partial clinical hold (5 patients) or study termination (5 subjects), followed by kidney transplant (2 subjects); 2 subjects withdrew informed consent. No subjects discounted the study preliminary due to the AEs.

Seventeen subjects were included in FAS, Safety Analysis Set and Calcium Analysis Set; one subject who did not receive Sensipar was excluded from all analyses.

Four patients completed the study (i.e., were enrolled in the study till EAP): 3 subjects completed 26 weeks (2 subjects in cohort 2 and 1 subject in cohort 1), and 1 subject in cohort 1 completed 12 weeks and received a renal transplant. However, the duration of treatment with Sensipar in these subjects was shorter compared to their overall participation in the study: 3 subjects received Sensipar for < 16 weeks (12, 15 and 16 weeks, respectively). The 4th subject

received Sensipar initially for 7 weeks, and then for another 5 weeks; the interval between two treatment periods was > 1 month.

The mean age of patients was 36 months (median 33 months). Only few patients were < 2 years old (3 subjects including one patient who was 1 year old). The majority of children (15) were > 2 years old. Mean iPTH level was high, 1299 pg/ml (median 1288 pg/ml) and was consistent with more severe disease in this patient. Mean serum calcium was 10.15 mg/dl (median 10.15 mg/dl), mean serum phosphorus was 6.2 mg/dl (median 5.75 mg/dl). Eighty-nine percent of patients were using vitamin D sterols at baseline.

Assessment of efficacy in children 28 days- 6 years old
Because of the difficulties in recruiting a sufficient number of pediatric patients on hemodialysis, the Agency agreed that efficacy might be extrapolated using PopPK with available adult data and data obtained from the efficacy and safety trials of Sensipar in pediatric patients > 6 years old. However, as discussed in Clinical Pharmacology section of this memorandum, the results of PopPK and PBPK analysis did not provide sufficient evidence that the drug is effective in children < 6 years old in decreasing iPTH levels.

The Sponsor evaluated changes in iPTH levels as a secondary endpoint in this study. Despite the Sponsor's conclusion that the treatment effect was observed in the majority of patients, the quantitative data obtained from this open label uncontrolled study does not provide any additional useful information to support the proposed claim that Sensipar is effective in children < 6 years old. The trial was small, with only 4 completers and a high dropout rate, the study was not powered to determine changes in iPTH, the exposure to Sensipar was short (ranging from 4 weeks to 16 weeks), etc. As Dr. Lubas noted in his review, use of vitamin D analogs that might have contributed to the decrease in iPTH levels further confounds the efficacy results of the study. I agree with Dr. Lubas's conclusion that the results of this study did not provide any useful information to support the efficacy of the drug in this age group.
The safety review focuses on three pediatric trials discussed in the efficacy section, study 2, 3 and 4. The studies were reviewed in depth by Dr. Lubas who summarized all safety data obtained from this submission. Refer to Dr. Lubas's review for details. In this memorandum, I will briefly summarize only serious adverse events, fatal cases, adverse events of special interest, i.e. hypocalcemia, and whether the Sponsor provided sufficient safety information to demonstrate safe chronic use of Sensipar in intended population.

11. Safety

The safety review focuses on three pediatric trials discussed in the efficacy section, study 2, 3 and 4. The studies were reviewed in depth by Dr. Lubas who summarized all safety data obtained from this submission. Refer to Dr. Lubas's review for details. In this memorandum, I will briefly summarize only serious adverse events, fatal cases, adverse events of special interest, i.e. hypocalcemia, and whether the Sponsor provided sufficient safety information to demonstrate safe chronic use of cinacalcet in intended population.

Safety Data in pediatric patients 6- 18 years old with CKD and SHPT (from study 2 and study 4).

These studies included a total of 53 subjects > 6 years old who received at least one dose of cinacalcet; of these 28 subjects received cinacalcet in Study 2 and 25 subjects received cinacalcet in study 4. There was a high dropout rate in both studies: 63% of patients who revived cinacalcet or placebo in study 2 and 35% of subjects who received cinacalcet or SOC in study 4 discontinued the trial early. The majority of subjects discontinued the trials because of study termination.

Exposure to cinacalcet

Overall, these studies provided very limited safety data with regards to long-term use of the drug at the proposed doses in children 6-18 years old with CKD.

The majority of children in both studies had exposure to cinacalcet for < 12 weeks (Table 1): median duration of treatment was 100 days in study 2 (mean 129 days) and 140 days in study 4 (mean 164 days). This exposure is shorter compared to the expected treatment duration in studies 2 and 4 (30 weeks and 20 weeks, respectively).

Table 1. Summary of Exposure to Sensipar.

Duration of exposure by category	Study 20070208 (N=28 [a]) N (%)	Study 20130356 (N=25 [b]) N (%)
≥ 4 weeks	24 (85)	23 (92)
≥ 8 weeks	20 (71)	22 (88)
≥ 12 weeks	17 (60.7)	21 (84)
≥ 16 weeks	13 (46.4)	18 (72)
≥20 weeks	9 (32.1)	13 (52)
≥ 24 weeks	7 (25)	9 (36)
≥ 36weeks	4 (14.3)	7 (28)
≥ 48 weeks	3 (10.7)	2 (8)

[a] The Sponsor summarized the data obtained from 22 subjects who were initially randomized to Sensipar group in double blind phase of the study and from 6 subjects who were initially randomized to the placebo in double blind phase but were switched to Sensipar in open-label part of the study together in this column.

[b] The Sponsor summarized the data from subjects who received Sensipar in study 20130356 and from those patients who completed study 20130356 (and were treated with Sensipar or placebo) an continued treatment with Sensipar in open label study 20140159

Source: the Sponsor's Summary of Clinical Safety, 2.7.4, table 3, modified.

The majority of children in both studies were exposed to low therapeutic doses: mean maximum doses were 40 mg/day (median 17.9 mg/day) in study 2, and 23.5 mg/kg (15 mg/kg) in study 4, respectively. It should be also noted that the starting dose was ½ of the equivalent effective adult starting dose. The selection of pediatric starting doses was based on safety parameters, i.e. to reduce the risk of hypocalcemia (refer to Clinical Pharmacology Section); thus the starting dose was not selected as the lowest effective dose.

In conclusion, there was insufficient exposure at appropriate doses in a limited number of patients to characterize the safety profile of Sensipar for chronic use in pediatric patients > 6 years old.

Death

There were two deaths in pediatric clinical program (one death in study 2 and one death in the extension study 20140159):

- Subject 20866012001

A 14-year old child enrolled in Study 2 died during the week 23 while receiving 90 mg of Sensipar once a day. The cause of death in this case was determined to be multifactorial and included hypocalcemia (corrected serum calcium of 5.3 mg/dl; not picked up during monitoring), baseline prolonged QT interval (patient was treated with Zofran- medication with known QT prolonging effect), concurrent illness (fever, nausea, dehydration, anemia, asplenia and concurrent treatment with immunosuppressive medications). This fatality case is concerning because a contribution of Sensipar to this event cannot be excluded (severe hypocalcaemia and prolonged QTc interval).

- Subject 10021001002 (Case CZECT2016085584).

A 2-year old boy who participated in study 201310100 for 4 months was enrolled in the extension study 20140159. Subject died a month later due to bronchopneumonia (as per final autopsy report). Corrected calcium level at time of death was 8.24 mg/dl. However, this patient also had a possible GI bleed (described as vomiting with coffee-ground material) at time of death. It should be noted that calcimimetics (etelcalcetide and Sensipar) are associated with increased risk of GI bleed in patients with CKD and current labels for these product include the description of GI bleeding. Thus, GI bleeding caused by Sensipar in this patient cannot be ruled out at this time.

Serious Adverse Events (SAE)

A total of 13 subjects treated with Sensipar experienced SAEs in these studies: 9 subjects in study 2 (18 SAEs) and 4 subjects in study 4 (10 SAEs). The only SAEs that were reported in >1 patient treated with Sensipar were hypertension and hypocalcemia. Two patients in study 2 (vs. 1 patient in placebo group) and 1 patient in study 4 (vs. 0 patients in SOC group) developed hypertension. A total of two SAEs of hypocalcemia were reported in study 2: 1 subject in double-blind phase (discussed in section death) and 1 subject in the open-label phase (discussed in AEs of special interest section).
All other SAEs occurred in one patient each.

Common Adverse Reactions

In study 2, 82% of subjects in Sensipar group and 86% of subjects in placebo group had at least one AE. In study 4, a total of 84% (21/25) of Sensipar-treated subjects and 56.7 % (17/30) of the SOC-treated subjects reported at least one AE. The most common AEs that occurred in subjects treated with Sensipar were vomiting (7 subjects in study 2), hypocalcemia (12 subjects: 6 subjects in study 4 (24%) and 6 subjects in study 2 (23%)), muscle spasm (6 subjects: 3 subjects in study 2 and 4, each), nausea (7 subjects: 4 subjects in study 2 and 3

subjects in study 4), and headache (4 subjects: 3 subjects in study 2 and 1 subject in study 4). All other AEs occurred in ≤ 3 subjects each.

AE of special interest: hypocalcemia

There is a known risk of hypocalcemia associated with use of calcimimetics. Severe hypocalcemia might be associated with cardiac arrhythmias, seizures, and death.

There were the following findings with regard to calcium levels and AEs of hypocalcemia in these studies (refer to Dr. Lubas's review for details):

- Changes in mean calcium values:

In study 2, the LS mean of percent change in mean corrected serum calcium during EAP was 4.6% in the Sensipar group and -1% in placebo group.
In Study 4, the mean levels of serum calcium decreased from baseline to week 17-20 by a 0.28 mg/dl in Sensipar group and increased by 0.06 mg/dl in SOC group.
Overall, these changes were small and of unknown clinical significance. Observed decrease in calcium levels in Sensipar group is not unexpected and is consistent with mechanism of action of the drug. The interpretation of these changes is further complicated by small sample size, large amount of missing data, and liberal use of vitamin D and calcium supplements in both groups during the study.

- The incidence of hypocalcemia (as defined by predefined calcium and/or ionized calcium levels):

In study 2, the incidence of hypocalcemia was higher in Sensipar group compared to placebo group: seven subjects (32%) in Sensipar group and 3 (14%) subjects in SOC group had at least one calcium level below 8.4 mg/dl (predefined calcium level). Of 7 subjects with hypocalcemia in Sensipar group, 5 subjects had corrected calcium level < 8 mg/dl and 3 subjects had corrected calcium < 7.5 mg/dl.
In study 4, with increased serum calcium monitoring, the rates of hypocalcemia were lower compared to study 2. Overall, 6 subjects (24%) in Sensipar group and 2 (7%) subjects in SOC group had at least one calcium level below 8.4 mg/dl (predefined calcium level). Of 6 subjects with hypocalcemia in Sensipar group, one subject had corrected calcium level < 7.5 mg/dl. The incidence of hypocalcemia was higher when the diagnosis was based on ionized Ca levels: fifteen subjects in Sensipar group (60%) and 16 subjects in SOC group (55%) had ionized Ca level < 1.05 mmol/L (predefined ionized Ca levels). Of 15 subjects with low ionized Ca level in Sensipar group, 5 subjects had ionized Ca < 0.94 mmol/L.

- Hypocalcemia reported as AE

In study 2, 9 subjects had reported AEs of hypocalcemia during double-blind period of the study (5- in Sensipar group and 4- in placebo group), and 4 subjects had AE of hypocalcemia in open-label period. Two subjects had SAEs of hypocalcemia (see discussion below)
In study 4, hypocalcemia was reported as AE in 7 subjects (28%) in Sensipar group and in 3 subjects (10%) in SOC group. Symptomatic hypocalcemia was reported in 4 subjects treated with Sensipar (tingling, muscle cramps, etc.); no seizures were reported. No deaths or SAEs due to hypocalcemia were reported in the study.

- Death and SAE associated with hypocalcemia

A total of 2 subjects treated with Sensipar in pediatric clinical program had SAE of hypocalcemia (both subjects were enrolled in study2):

- Subject 20866012001 (described in Death section)- in double blind phase of the study
- Subject 20866016001 (case USACT2012064841): in open-label phase of the study.

A 13 years old male who was treated with Sensipar 30 mg had ionized calcium 0.8 mmol/l with normal corrected calcium level and symptoms of agitation, confusion, sweating (due to high blood pressure as per Investigator). Hypocalcemia resolved in 2 days.

Overall, the limited safety data (due to the small sample size, high dropout rate, insufficient exposure to Sensipar, etc.) is obtained from these two studies that complicates the assessment of safety profile of Sensipar in children 6-18 years old and does not allow to make a definite conclusion regarding safe chronic use of the drug in the intended population. In addition, multiple confounding factors (underlying medical conditions, concomitant medications, etc.) complicate this assessment further.
Moreover, there is a serious safety concern associated with risk of severe hypocalcemia in children > 6 years old. However, the appropriate titration schedule to mitigate the risk of hypocalcemia was not established in these trials. The titration regimen in study 2 based on corrected calcium level was associated with two serious AEs of hypocalcemia (including fatal case). Even though there were no SAEs of hypocalcemia in study 4 (when lower doses and slower titration schedule based on tighter monitoring of calcium levels was used), these doses were associated with lack of efficacy of the drug in intended population. Overall, it is not possible to draw a definite conclusion as to whether the regimens and the doses used in this study were safe without demonstration of the drug efficacy in these trials.

In conclusion, I agree with Dr. Lubas, that the safety profile of Sensipar in children 6-18 years old has not been established based on the data from these trials.

Safety Data in pediatric patients 28-6 years old with CKD and SHPT

The Sponsor's assessment of safety of Sensipar in this age group is based on the data obtained from WR study 3, 20-week single arm study evaluating safety of Sensipar in patients < 6 years old, from retrospective chart review (study 20090198) and from WR single dose PK/PD study in patients < 6 years old (study 2009005).

Study 3

Study 3 was the only multiple dose study prospectively evaluating safety of Sensipar in children < 6 years old. As per WR, the Agency concluded that at least 15 patients who complete the study (and thus, has sufficient exposure to the drug) would be required to properly evaluate the safety of the product in this age group.

Exposure to Sensipar
Overall, the study was small and the exposure to Sensipar at appropriate doses in this study was insufficient to characterize the safety profile of the product intended for chronic use in this population:

- This study included a total of 17 subjects 28 days- 6 years old who received at least one dose of Sensipar; however, only 4 patients completed the study. The majority of patients (14) discontinued the trial early. The majority of subjects discontinued the trial because of study termination (10 subjects). The majority of children were > 2 years old, thus the information from younger children is even more limited (from 3 subjects). Thus, the Sponsor had overall insufficient number of the completers in the study.
- The duration of the exposure was overall short in the study.

The exposure to Sensipar in the pivotal adult studies in patients with CKD was 6 months. Even though, it was not expected that children will be treated with Sensipar for 6 months because of the shorter course of the disease, it was expected that the duration of the exposure will be longer than observed. It was expected that the majority of patients will stay on the study and will be treated with Sensipar for 26 weeks with only few patients terminate study early due to kidney transplant.

However, the majority of children in this study had exposure to Sensipar for < 16 weeks: median duration of treatment was 83 days (mean 66 days) in 7 subjects and 106 days (mean 101 days) in 10 subjects. Even though there were 4 "completers" in the study (i.e. subjects who remained on the study till EAP), these patients also had short duration of exposure: 3 patients received Sensipar for 12, 15 and 16 weeks, respectively. Treatment in the fourth subject was interrupted multiple times: this subject received continuous treatment for 3, 2 and 7 weeks with drug interruptions for 2 and 8 weeks between treatments (equal to washout period). Of these 4 subjects, 2 had drug disconsolation due to low PTH (< 70 pg/ml); low PTH in this population is of concern and might be associated with adynamic bone disease. It should be noted, that the protocol was designed to evaluate safety of Sensipar

- The doses used in the study were low.

The starting dose was selected as a safe dose and not as the lowest effective dose: mean 0.17 mg/kg (median 0.179 mg/kg). As per label, the minimum effective adult dose is 0.5 mg (30 mg for 60 kg-subject).

The maximum achieved median doses before clinical hold were 0.5 mg/kg (7.6 mg); mean 0.98 mg/kg (11.2 mg). The maximum achieved median doses after clinical hold (when more restrictive titration scheme has been implemented) were 0.5 mg/kg (5 mg); mean 0.55 mg/kg(6.95 mg). The maximum dose in the majority of subjects (7/17 subjects, 41%) was 5 mg. For the comparison, the maximum adult weigh based dose is 30 mg/kg (180 mg for 60-kg adult).

Three of 4 completers achieved maximum dose of < 10 mg; of these, 2 patients had multiple dose interruptions due to safety reasons (i.e. low iPTH, < 70 pg/ml). On the other hand, the fourth subject, a 1-year old patient, was on a maximum dose of 12.6 mg and 18.9 mg during week 12 and 16, respectively; this exposure seems to be too high considering patient's age.

There was no death in study 3

However, a 2.5 year old boy who participated in study 3 and continued treatment with Sensipar in the extension study died (refer to Death section above).

SAE

Nine subjects treated with Sensipar developed SAEs. The most frequent SAEs were hypertension (2) and device complications (2), all other SAEs occurred in one subject each. One subject in study 3 developed SAE of seizures; however, seizures were most likely not

drug/hypocalcemia related (occurred in 2 weeks after drug discontinuation and calcium level was normal).

Common AEs
Ninety-four percent of subjects (16/17) developed at least one adverse event; the incidence of adverse events was similar between subjects enrolled before and after clinical hold. These AEs were: cough (4), hypertension (4), upper respiratory tract infection (4), vomiting (4), device complications (3), diarrhea (3), pyrexia (3), viral infection (3) and bronchitis (2).

AE of special interest: hypocalcemia
No subjects had low corrected calcium levels (< 9 mg/dl in children < 2 years old and < 8.4 mg/dl in children > 2 years old) as prespecified in the study. A total of three subjects < 2 years old had low ionized calcium level: 2 subjects had ionized calcium < 1.125 mmol/l and one subject had ionized calcium < 0.94 mmol/l. One case of asymptomatic hypocalcemia was reported as AE (calcium level and patient's age are not reported).

Dr. Lubas also analyzed overall changes in calcium levels in this study and noted that the decrease in mean calcium level in cohort 1 was overall small and of unknown clinical significance and there was no decrease in calcium level in cohort 2. The absence of the expected decrease in mean calcium levels in cohort 2 (due to the calcium-lowering mechanism of action of Sensipar) and the absence of AEs of hypocalcemia might be due to the lower exposure to Sensipar and stricter calcium monitoring in cohort 2. In addition, the allowed titration of vitamin D analogs and calcium supplements to mitigate the risk of hypocalcemia and to achieve iPTH target levels during the study might underestimate the risk of Sensipar-induced hypocalcemia.

In conclusion, the limited data derived from 4 study completers (who were treated with Sensipar for < 16 weeks) and from 13 patients treated for 12 weeks do not provide sufficient information to conclude that the proposed doses are safe for chronic use in children < 6 years old.
Overall, the study was small with high dropout rate before week 12 and of short duration. All children, including "completers," in this study were exposed to Sensipar at low doses for generally short periods of time. Lastly, the evaluation of safety of Sensipar in this population is further complicated by multiple confounding factors including serious medical conditions and use of concomitant medications (including titration of calcium supplements and vitamin D analogs).

Other sources of safety information on use of Sensipar in children < 6 years old

Dr. Lubas reviewed the data obtained from other sources that were submitted as supportive evidence of the safety of Sensipar in pediatric patients 28 days- 6 years old with CKD and SHPT and concluded that this data did not provide robust evidence of safety:

- The safety data obtained from Study 1 does not support the safety of the chronic use of Sensipar: the study was a single dose study at lowest safe dose (not at effective dose).
- The retrospective chart review (study 20090198) that included 23 patients does not provide useful information regarding safe use of Sensipar in children < 6 years old. This study is

retrospective and is deficient in the amount and quality of safety data provided. Collection of safety data was not standardized, and/or prospectively planned for this study. There are multiple uncertainties with regard to exposure (dose, duration, etc.), to how the adverse events collected and/or reported, etc. Due to the retrospective nature of the trial, it is not possible to verify that investigators systematically accounted for all deaths, serious adverse events, discontinuations, common adverse events, vital sign or laboratory abnormalities that occurred while the patients were receiving Sensipar. In addition, there were two reports of SAE of hypocalcemia reported in this study.

12. Advisory Committee Meeting

No AC meeting was held.

13. Pediatrics

- **The Division did not recommend granting pediatric exclusivity**

The Division did not recommend granting pediatric exclusivity since Amgen did not fairly respond to the WR. Amgen's studies did not satisfy the requests in the WR, nor did they not supply sufficient information to conclude that Sensipar is safe and effective in pediatric patients with CKD and SHPT.

The Division's recommendations are based on the review of data from 4 studies conducted to satisfy WR and included in this NDA (discussed above). The Division determined that the requirements of the WR had not been satisfied with respect to the submitted data for Study 3 - 20110100-*Treatment of secondary hyperparathyroidism in pediatric subjects age 28 days to < 6 years with CKD receiving hemodialysis or peritoneal dialysis (Study 3)*. According to the WR a minimum of 15 patients were required to complete the 26-week of the study or 12 weeks of the study 12 weeks of the study if they had been enrolled in the study for at least 12 weeks and underwent renal transplant. Moreover, the Division reviewed the available data from this study and other data submitted by Amgen and concluded that the limited data do not provide sufficient information to conclude that the proposed doses of Sensipar are safe in children < 6 years old.

> Data from studies conducted under the WR submitted by the Sponsor in this NDA and the Division's recommendations were discussed by the Pediatric Exclusivity Board on April 18, 2017. The Pediatric Exclusivity Board agreed with the Division's recommendations.

- **NDA (b) (4) received a waiver for pediatric studies under PREA on May 10, 2017**

Pediatric Review Committee also reviewed the proposed label and agreed with the Division's recommendations to remove (b) (4) from the label.

It should be noted, that the original NDA for Sensipar (NDA 21688) received a waiver for pediatric studies under PREA in 2004 because necessary studies were impossible or highly

impracticable due to the small number of pediatric patients with CKD (refer to Pediatric Page in DARRTS from 2004).

14. Other Relevant Regulatory Issues

A clinical inspection summary was completed by Dr. Damon Green on April 4, 2017. Three principal investigators were investigated. The audit resulted in No Action Indicated decisions for all three sites. Refer to Dr. Lubas's review for details.

15. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

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

(b) (4)

NDA 21688/S-23: Approval pending labeling agreement (refer to Labeling section above).

The information relevant to the (b) (4) has to be removed from the label. Pediatric information should be restricted to Pediatric Use section (section 8.4), because the data from pediatric studies was inconclusive to establish the efficacy or safety of Sensipar in the intended population.

- Risk Benefit Assessment

NDA (b) (4)

The applicant did not demonstrate that Sensipar results in a meaningful decrease in iPTH level after either 3 or 6 months of use in pediatric patients in patients 28 days-18 years old with CKD on dialysis.

The efficacy or safety of chronic use of Sensipar in pediatric patients 6-18 years old has not been established, because:

- Two controlled studies failed to demonstrate that treatment with Sensipar significantly reduces baseline iPTH levels compared to placebo or standard of care in patients 6-18 years old with CKD on dialysis
  - Study 20070208, double-blind, placebo-controlled efficacy study was stopped early because of a potential drug-related risk (i.e., hypocalcemia). The study failed to demonstrate a statistically significant difference in iPTH decrease from baseline

between groups when the analysis of the primary endpoint was repeated appropriately addressing missing data by using originally planned analysis, i.e., when the missing data was addressed accordingly to the original intended conduct of the study design, and not accordingly to the actual conduct of the trial.
- Study 20130356, open-label standard of care comparator efficacy study (with enhanced safety monitoring for hypocalcemia) failed to show an effect of Sensipar versus comparator.

- The Sponsor did not provide sufficient evidence that use of Sensipar is safe at the proposed doses and titration regimen in this population. The major safety concerns with Sensipar use in all patients are related to hypocalcemia and include serious adverse events such as: seizures, cardiac arrhythmias and sudden cardiac death. There was a pediatric death in Study 20070208 associated with severe hypocalcemia missed by the safety monitoring used in the trial; one more serious adverse event of hypocalcemia was reported in the extension trial.

<u>The efficacy or safety of chronic use of Sensipar in pediatric patients 28 days- 6 years old has not been established, because:</u>

- The efficacy of Sensipar in pediatric patients 28 days- 6 years cannot be extrapolated from the adult data and data obtained from older children because of the following:
- The results of the PopPK analyses are inconclusive because of high inter-individual variability in Sensipar PK and PD parameters in pediatric patients compared to adult that result in wide prediction interval. Thus, the results of this analysis do not support the claim that the target therapeutic response can be achieved following multiple oral doses in children 28 days-6 years.
- The proposed doses in pediatric patients 28 days-6 years are not supported by the data obtained from older children because of high inter-individual variability in Sensipar PK parameters and because the efficacy of the drug at the proposed doses has not been established in the older children population.
- The Sponsor did not provide sufficient information to conclude that the proposed doses of Sensipar are safe in children < 6 years old
- Study 20110100, open-label, uncontrolled safety study provided only limited data regarding long-term use of Sensipar in the intended population. The data was derived from 4 patient-completers continuously treated with Sensipar for < 16 weeks and 13 patients treated for < 12 weeks. The doses achieved in the study were also too low.
- Study 20090005 was a single dose study using a subtherapeutic dose and does not inform safety of Sensipar for chronic use of the drug in the intended population
- The retrospective chart review has limited value in informing the risks of the drug due to the limitations and biases of retrospective review (selection of patients, reporting the results, monitoring, etc.).

(b) (4)

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

- Recommended Comments to Applicant

The action letter will communicate the deficiencies identified in the clinical, statistical, clinical pharmacology and labeling reviews.

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
05/22/2017

JEAN-MARC P GUETTIER
05/22/2017