EXHIBIT B

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805.447.1000
www.amgen.com

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Khushboo Sharma
CDER Formal Dispute Resolution Project Manager
10903 New Hampshire Avenue
White Oak Building 22, Room 6486
Silver Spring, MD 20993-0002

Janet Woodcock
CDER Director
10903 New Hampshire Avenue
White Oak Building 51, Room 6133
Silver Spring, MD 20993-0002

Re: SENSIPAR® (cinacalcet hydrochloride) tablets, for oral use
NDA 021688 Supplement Number 023
NDA 209962

FORMAL DISPUTE RESOLUTION REQUEST

Attn: Janet Woodcock, Director, Center for Drug Evaluation and Research
Khushboo Sharma, CDER Formal Dispute Resolution Project Manager

Dear Ms. Sharma and Dr. Woodcock:

I am writing on behalf of AMGEN Inc. (Amgen) to appeal a recent decision by the Pediatric Exclusivity Board (the Board) to deny pediatric exclusivity for Sensipar® (cinacalcet hydrochloride) tablets.

I. BACKGROUND OF THIS REQUEST

Previously, on May 5, 2017, Amgen submitted a formal dispute resolution request in this same matter. That request was rejected on May 19, 2017, on the grounds that it was premature to seek dispute resolution prior to the Board issuing a final determination as to pediatric exclusivity for Sensipar. The Board issued its final decision and explained its decision to us by letter on May 22, 2017 (Denial Letter). Accordingly, the decision is now ripe for dispute resolution.

The facts were presented in our May 5, 2017 dispute resolution request. However, after ongoing discussions with the review division and review of the denial letter, we offer the following factual statement regarding this request:

Amgen is the holder of new drug application (NDA) 021688 for Sensipar tablets, a calcium-sensing receptor agonist indicated for Secondary Hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on dialysis, Hypercalcemia in adult patients with Parathyroid Carcinoma (PC), and Hypercalcemia in adult patients with primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but who are unable to undergo parathyroidectomy. There is an unmet medical need for medicines to treat secondary HPT in children, and a public health benefit to providing information on pediatric dosing, safety, and

efficacy in the Sensipar Prescribing Information (PI). For these reasons, FDA issued a Written Request (WR) for cinacalcet in May of 2010.

Amgen not only responded to FDA's Written Request for pediatric studies by that date; it exceeded the scope of FDA's request. In total, Amgen performed nine studies over the span of roughly eleven years, together covering 103 pediatric patients who received at least one dose of Sensipar in interventional clinical trials, along with an additional 113 patients who received Sensipar in either a registry or chart review.[1] As part of this effort, Amgen completed three pharmacokinetic studies to determine an appropriate pediatric dose for Sensipar. In addition, Amgen completed a prospective registry study performed by the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), a pediatric literature summary, and a pediatric post-marketing case summary to describe real world pediatric use, as specified by the WR. Amgen also conducted a retrospective chart review to describe the use of cinacalcet in pediatric subjects aged 0 to < 6 years with secondary HPT and CKD receiving dialysis. This was not part of the WR but did provide safety information for pediatric patients < 6 years of age treated with cinacalcet. Furthermore, Amgen provided population PK and exposure-response (PK/PD) analyses, and a Bayesian extrapolation analysis. As agreed, Amgen also developed an appropriate pediatric formulation and established its bioavailability. The formulation development and studies were conducted over a period of 11 years, indicative of Amgen's commitment to meet the specific requests of the agency.

Having conducted the requested studies in accordance with applicable scientific principles in the timeline described in the WR, Amgen submitted two applications to FDA on November 23, 2016 in accordance with the agency's submission requirements. Supplemental NDA 021688/023 was an efficacy supplement to update the approved Sensipar labeling with a pediatric indication and other information concerning the pediatric studies. NDA 209962 was filed requesting approval of the new oral dosage form that was developed for cinacalcet in pediatric patients. NDA 209962 also included the final reports from the pediatric studies, requested approval for an indication in pediatric patients with secondary HPT receiving dialysis, and presented a formal request for a pediatric exclusivity determination. Submission of the reports of the pediatric studies on November 23, 2016 triggered a statutory 180-day period for FDA to determine whether the pediatric study reports fairly respond to the WR.[2] That 180-day period ended on May 22, 2017.

In a letter dated May 22, 2017, FDA denied pediatric exclusivity to Sensipar. The denial letter stated that "Amgen has met the literal terms of the WR for Studies 1, 2, and 4," but concluded that "Amgen's failure to provide sufficient safety data in the 28 day to < 6 year old age group prevents FDA from drawing any conclusions about the safety of the product in patients < 6 years of age when used as intended," and that the submission thus failed to fairly respond to the WR. Now that Amgen has received an unfavorable decision, Amgen again asks the Center Director to review and resolve the dispute.

II. DESCRIPTION OF THE MATTER TO BE RESOLVED

A. Legal Standard

The Best Pharmaceuticals for Children Act (BPCA) established a statutory regime whereby NDA sponsors can earn a six-month period of exclusivity that attaches to patent and regulatory exclusivities.[3] Under the BPCA, if FDA "determines that information relating to the use of a new drug product in the pediatric population may produce health benefits in that population," FDA may issue a Written Request.[4] By the Written Request, FDA asks a sponsor to conduct and submit reports of studies "to determine if the use of a drug could have

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1 SENSIPAR NDA 209962 § 1.9.3, Request for Pediatric Exclusivity Determination), at 7-8, tbl. 2.

2 *See* 21 USC 355a(d)(3).

3 *See* 21 USC 355a.

4 *Id.* at 355a(b)(1), (c)(1).

meaningful health benefits in the pediatric population."[5] The Written Request must include a timeframe for the studies and ask the sponsor to propose pediatric labeling resulting from the studies.[6]

If a sponsor conducts the studies sought by FDA in the WR and submits reports of the study results to FDA, the agency has 180 days to either accept or reject the reports. FDA's "only responsibility" in accepting or rejecting the reports is to determine whether (1) "the studies fairly respond to the written request," (2) the studies "have been conducted in accordance with commonly accepted scientific principles and protocols," and (3) the studies "have been reported in accordance with the requirements of the [agency] for filing."[7] If each of the criteria is met, FDA must accept the reports, at which point the six-month extension of exclusivity and patent protection automatically applies.[8]

Whether the studies ultimately support approval for use for children – that is, whether they successfully demonstrated safety and efficacy – is irrelevant to FDA's decision to accept the studies and recognize the six additional months of pediatric exclusivity.[9] Even an inconclusive study can and does fairly respond to a WR and thereby qualifies for pediatric exclusivity.[10] And if the reports are accepted, the six-month extension of exclusivity and patent protection automatically applies.[11]

Finally, the "fairly responds" statutory standard does not require absolute conformity between the WR and the study results. As a court has held,

> A denial of pediatric exclusivity for failure to meet a single term of a written request would not be in accordance with section 355a(d)(3), which plainly does not require compliance with every single provision of a written request, but requires only that a pediatric study "fairly respond" to a written request. Nor would it be consistent with the statutory standard to deny pediatric exclusivity because of disappointment with data submitted by a manufacturer if the study as a whole is a fair response to the written request.[12]

The specific example interpreted by the court in that case is virtually identical and should be followed here. Merck filed the action in response to denial of pediatric exclusivity for Mevacor. The WR for Mevacor required two studies: a study on the use of Mevacor in adolescent males, and a supplemental study on the use of Mevacor in adolescent females.[13] As FDA reported to the court, the WR for Mevacor required Merck to study 35 girls for at least six months.[14] Only five girls completed the six-month timeline of the study.[15] Nevertheless, the court

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5 *Guidance for Industry, Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act* (Sept. 1999) (withdrawn Aug. 7, 2013 (78 FR 48175)) (*Pediatric Exclusivity Guidance*) at 4.

6 21 USC 355a(d)(1)(A).

7 *Id.* at 355a(d)(3).

8 *Id.* at 355a(b)(1), (c)(1) (exclusivities and patent protection extended if pediatric study reports are "accepted").

9 *See id.*

10 *See* Section 8.4 for Zomig (zolmitriptan) NDA 020768, Orencia (abatacept) BLA 125118, and Ortho Tri-Cyclen (ethinyl estradiol; norgestimate) NDA 019697.

11 *Id.* at 355a(b)(1), (c)(1) (exclusivities and patent protection extended if pediatric study reports are "accepted").

12 *Merck & Co. v. FDA*, 148 F. Supp. 2d 27, 30 (DDC 2001).

13 *Id.* at 29.

14 *See* Def. Mem. in Opp. to Pl.'s Mot. for a TRO and Prelim. Inj. at 11, *Merck & Co. v. FDA*, 148 F. Supp. 2d 27 (D.D.C. 2001) (No. 14).

concluded that Merck's studies "fairly respond[ed]" to the written request, and FDA subsequently awarded the drug pediatric exclusivity.

B. FDA's Written Request for Sensipar

Amgen submitted a Proposed Pediatric Study Request (PPSR) for Sensipar in May 2007. After consultation between the parties, FDA issued Amgen a WR on May 5, 2010. Over the next five years, Amgen and the agency agreed to amend the WR five times, most recently on October 14, 2015. The first amendment was made to allow extrapolation of efficacy to children from 28 days to < 6 years of age and, thus, to add a new multiple-dose safety study in this younger population. The second amendment clarified terminology in the WR regarding the patient population to be included in the registry, the objective of one of the PK studies, and the definition of study completion in another study. The third amendment was made following a 14-month partial clinical hold that occurred during the program. Significant changes were needed to the WR because one study was terminated and a new study was added. The fourth amendment clarified the number of completers in one study (the number of children to be enrolled was not changed). Finally, the fifth amendment made changes to align the WR with protocol changes to the endpoints and statistical analysis in one study.

As amended, the Written Request asked Amgen to conduct four studies:

Study 1: A single-dose PK/PD study in pediatric patients ages 28 days to < 6 years with chronic kidney disease and secondary hyperparathyroidism receiving dialysis.

Study 2: A 30-week, randomized, double-blind, placebo-controlled, safety and efficacy study with a 30-week, open-label, safety extension in pediatric patients ages 6 years to < 18 years with chronic kidney disease and secondary hyperparathyroidism receiving dialysis. This study will include an assessment of pharmacokinetic (PK) parameters using a sparse sampling design. Study 2 has been terminated early and will be analyzed with available data.

Study 3: A 26-week or time-until-transplantation (whichever comes first), open-label, safety study in pediatric patients ages 28 days to < 6 years. The final protocol including starting dose, dose titration scheme, and exclusion criteria will have to be approved by the agency before this study is initiated.

Study 4: A 20-week, randomized, open-label, controlled study in pediatric subjects between the ages of 6 and < 18 years, with secondary hyperparathyroidism and chronic kidney disease who are receiving either hemodialysis or peritoneal dialysis.[16]

The WR also required Amgen to perform an open-label extension study for Study 4, a published literature review, and a summary of demographic and drug use data from a national registry. Additionally, the WR stated that efficacy in subjects 28 days to < 6 years of age should be extrapolated from studies in adults and pediatric studies in the WR. The program was initiated under IND 56010 (the cinacalcet IND for the treatment of secondary HPT in adults), but was continued under IND 109361 – a separate IND specific to the treatment of secondary HPT in pediatric patients.

After a report of a fatality in Study 20070208 (WR Study 2) during the course of the pediatric program, FDA placed a partial clinical hold on IND 109361 for 14 months, from February 2013 to April 2014. The cause of death was multifactorial, and a contribution of Sensipar to the death could not be excluded. The individual was

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15 *Id.*

16 WR Amendment 5 at 2. FDA also requested in the WR an open-label extension protocol. The extension protocol called for an open-label extension protocol to Study 4 to assess longer term safety of cinacalcet for at least 7 additional months. Interim results were submitted with the marketing application. While not a term of the Written Request, final results of this extension study will be submitted upon completion of the protocol.

noted to be severely hypocalcemic at the time of death. Changes to the clinical program as a result of the partial clinical hold were incorporated into the WR. Among other changes, FDA altered the WR to state that Study 2 would be terminated and analysis would be based on available data. Amgen and FDA also agreed to lower the proposed Sensipar dose and to introduce a slower titration scheme.[17]

At the time of the fatality, Amgen met with FDA and proposed terminating the studies due to safety risk. FDA did not agree. The agency stated that "we continue to believe that cinacalcet can be useful for the management of secondary hyperparathyroidism in the pediatric population and that the cinacalcet pediatric program should continue with enhanced titration and monitoring safeguards."[18] FDA further stated "we have learned a lot from the analysis of the clinical data collected during the pediatric program," and responded to Amgen's concern about difficulty retaining patients in the study that "FDA underst[ands] the sponsor's concern that most pediatric patients get early transplants if at all possible so this limits the number of patients and the length of exposure to this drug in the pediatric population."[19] Responding to the changes agreed upon by FDA and Amgen, Amgen continued the pediatric studies following the fatality.

C. Amgen's Pediatric Studies

In nearly every respect, the studies performed by Amgen fulfilled FDA's WR to the letter or exceeded its terms.

In Study 1, FDA asked for one pharmacokinetic study in patients aged 28 days to less than 6 years.[20] Amgen responded with three pharmacokinetic studies: one in patients 28 days to less than 6 years; one in patients aged 6 to 18 years; and one in adults to assist in developing PK/PD models to support a pediatric dosing regimen.[21] In Study 2, FDA ultimately requested a double-blind study in at least 40 patients, with at least 14 completing the double-blind portion of the study, at least 2 completing the open-label extension, and at least 25% of patients aged 6 to 12 years.[22] Amgen responded with a double-blind study of 43 patients, with 16 completing the double-blind portion, 4 completing the open-label extension, and 31.3% of patients aged 6 to 12 years.[23] In Study 4, FDA asked for a second efficacy study of at least 48 subjects, with at least 40 completing 12 weeks of the study.[24] Amgen responded with an efficacy study of 55 subjects, with 49 completing 12 weeks of the study.[25] Additionally, the dates for closure of Studies 3 and 4 were selected to allow all enrolled subjects to complete week 15 and contribute to the primary efficacy and safety endpoints of the studies.

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17 The weight-based maximum dose was reduced in both Studies 3 and 4, but the fixed dose maximum dose was never to exceed 180 mg even in Study 2. This was primarily achieved by decreasing the number of titrations. The starting dose only reduced in Study 3 and was always $\leq$ 0.20 mg/kg in Studies 2 and 4.

18 Memorandum of Meeting Minutes, Type A Meeting, Sept. 4, 2013.

19 *Id.*

20 Oct. 14, 2015 Revised WR.

21 SENSIPAR NDA 209962 § 1.9.3 Request for Pediatric Exclusivity Determination. In the WR, FDA also stated that efficacy in patients 28 days to < 6 years of age can be extrapolated from the studies in the WR and studied in adults. FDA further said that an exposure-response analysis was to be submitted to support the extrapolation. Safety data in the 28 day to < 6 years of age population was to come from the other sources of data in the WR, including Study 3. This analysis was completed.

22 Oct. 14, 2015 Revised WR.

23 Amgen Annotated Written Request for Pediatric Exclusivity Determination.

24 Oct. 14, 2015 Revised WR.

25 Amgen Annotated Written Request for Pediatric Exclusivity Determination.

In addition, FDA asked for an open-label extension protocol including subjects who participated in Study 4, and Amgen responded with an open-label extension study including subjects who participated in Study 3 and Study 4, with 42 subjects enrolled.[26] FDA asked for a summary of published literature on Sensipar use in pediatric patients and a summary of drug-use data from a national registry.[27] Amgen responded with the summary of published literature, a final study report of a prospective cohort registry study which included 538 pediatric patients up to 21 years of age (90 of which received Sensipar), and a retrospective chart review to describe the use of Sensipar in 23 patients less than 6 years old in clinical settings.[28] Amgen measured every requested endpoint and conducted all requested analyses of the data. Regarding Study 1, Study 2, Study 4, the open-label extension study, the literature review, and the retrospective registry study, Amgen fully met and exceeded the express terms of the Written Request and submitted additional real world evidence. As a matter of fact, Amgen provided more data for this population than any other sponsor had previously provided or been asked to provide.[29]

Only one study, Study 3, failed to fully meet the express terms of the WR by falling short of its target of 15 completing patients. Amgen was able to recruit 18 patients, study 11 of them for more than 12 weeks, and have 4 meet the definition of study completion.[30] Prior to the imposition of the clinical hold, Amgen was able to recruit 8 patients into the study. Notably, 5 of the 8 had to discontinue investigational product when the study was placed on partial clinical hold at the end of January 2013, at which time FDA directed Amgen to suspend dosing in all pediatric studies.[31] When finally permitted to resume the study in April 2014, Amgen was able to recruit 10 more patients, all but two of whom were enrolled for more than 13 weeks. However, recruitment continued to be hampered by challenges inherent to the study population of patients under age six with kidney failure. These patients are the highest priority for kidney transplants, which made identifying eligible patients for the study even more challenging. Based on feedback from the study sites, many families focused their efforts on finding a donor rather than beginning the cumbersome process of enrollment in a clinical study, including the repeated blood draws associated therewith. Recruitment was also frustrated by few general nephrologists accepting pediatric patients, and the general paucity of pediatric nephrologists.[32] In light of these difficulties, Amgen implemented a comprehensive program for recruitment and retention that included initiating a large number of sites, engaging site management organizations (including NAPRTCS), offering home health services to ease the burden on patients, providing extensive site support, organizing additional investigator meetings, and modifying the protocol to simplify procedures in response to site personnel feedback.

Amgen twice asked FDA to amend the WR to account for these difficulties, and also asked FDA to extend the filing date from November 23, 2016, to December 8, 2016, to provide more time for Study 3 to continue.[33] But

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26 SENSIPAR NDA 209962 § 1.9.3 Request for Pediatric Exclusivity Determination.

27 Oct. 14, 2015 Revised WR.

28 SENSIPAR NDA 209962 § 1.9.3 Request for Pediatric Exclusivity Determination; Amgen Annotated Written Request for Pediatric Exclusivity Determination.

29 *See, e.g.*, Calcijex WR (a single study in 35 patients aged 13-18 years, of which 20 were treated with Calcijex); Zemplar WR (a single study in 29 patients, of which 15 were treated with Zemplar; no patients less than 5 years old were enrolled).

30 SENSIPAR NDA 209962 § 1.9.3 Request for Pediatric Exclusivity Determination.

31 *See* Denial Letter at 4.

32 Amgen General Correspondence: Type C Meeting Request to Discuss the Pediatric Program and Written Request Requirements, Dec. 3, 2015.

33 *See* Type C Meeting Request (Dec. 3, 2015); *see also* Pre-sNDA Response to FDA Preliminary Comments (Sept. 21, 2016) (FDA again denies amendment to the WR to account for enrollment difficulties).

FDA refused, saying "we will not have any more discussion on this."[34] As a result, Amgen terminated the study in June 2016 in order to meet the November 2016 deadline to file final study reports. At that time, 5 of the 10 subjects in the second cohort were still undergoing treatment, cutting short their contribution to the overall data set. Patients enrolled in the trial at the time of discontinuation were offered the option of enrolling in an open label study to continue their therapy, but these patients no longer contributed to the corpus of data for Study 3. Despite these setbacks, Amgen was able to provide data on 17 patients, 11 of whom completed more than 12 weeks and 4 of whom met the definition of study completion, for an aggregate of 1473.9 patient-days of treatment and a mean duration of exposure of 86.7 days (12.4 weeks).[35]

The data in Study 3 were sufficient to evaluate the primary endpoint. The Study 3 protocol stated that "[w]ith a planned sample size of 15 completers overall..., the width of the 2-sided 90% CI around the estimate of the proportion of subjects achieving the primary endpoint is no more than 0.42."[36] Although the lower number of completers in Study 3 reduced exposure in this study, the primary endpoint was able to be evaluated in the 17 patients who enrolled in the study and received at least one dose of Sensipar. The actual estimated proportion for the primary endpoint was 0, and the actual 90% confidence interval was 0.0,0.162 (i.e., 0%, 16.2%).[37] In addition, other safety parameters in Study 3 included (as specified in the WR) an evaluation of adverse events, vital signs, ECGs, and laboratory parameters.[38]

Furthermore, safety was evaluated in 14 additional children in Study 1 (single dose study), 23 additional children in the Retrospective Observational Study, and 9 children in the prospective cohort registry study. In total, safety information was provided for 63 patients (in Study 1, Study 3, the Retrospective Chart Review Study, and the prospective cohort registry study) under 6 years of age with exposure to cinacalcet.[39] The duration of exposure to cinacalcet in children < 6 was 1 day for all 14 patients < 6 in Study 1[40] and a mean of 274.2 days (39.2 weeks) (range of 34 to 1036 days) for the 23 patients < 6 in the Retrospective Chart Review Study.[41] Beyond these patients, in the study of NAPRTCS registry data, 14 of the 90 subjects treated with cinacalcet were under 6 years of age. None of the studies identified any unexpected safety concerns, and the safety profile was consistent with that observed in adults.[42] In sum, the totality of the evidence when the studies are viewed together yielded adequate experience in patients under age 6 to characterize the safety profile of cinacalcet in this population.

In total, the studies included 103 patients who received at least one dose of cinacalcet in interventional clinical trials and real world evidence from 113 patients who received cinacalcet in a registry (Study 20120116) or chart review (Study 20090198). In preparation for and support of the studies performed for the WR, Amgen also developed an age-appropriate formulation and established its bioavailability. In total, 9 clinical studies were performed over the span of approximately 11 years. In addition to the clinical studies, Amgen also conducted population pharmacokinetics and pharmacokinetics / pharmacodynamics modeling studies and a Bayesian

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34 Letter from Meghna Jairath, FDA, to Sabina Buntich, Amgen, Meeting Denied (Dec. 24, 2015).

35 Study 20110100 CSR Table 12.1. Mean duration of exposure is 86.7 days (86.7 days x 17 patients = 1473.9 patient-days).

36 *Id.*, Protocol Section 10.2.

37 *Id.*, CSR Section 12.9.

38 *Id.*, CSR Section 12.

39 Study 20090005, CSR Table 9.2.

40 *Id.*, CSR Section 8.1.

41 Study 20090198, CSR Table 1.

42 Study 20090005, CSR Section 12; Study 20110100, CSR Section 12; Study 20090198, CSR, at 4.

extrapolation analysis, which allowed for qualitative and quantitative extrapolation of pediatric effectiveness. The studies' size and scope are particularly notable given the low prevalence of pediatric patients with secondary HPT – it is currently estimated that there are fewer than 1000 patients 0 to < 18 years of age on dialysis with SHPT in the United States.[43] Of these, approximately 300 patients are estimated to be 0 to 5 years of age, 220 are 6 to 12 years of age, and approximately 430 patients are 13 to < 18 years of age.[44]

Amgen's pediatric study program was sufficient to generate the following components for the NDA:

- Chemistry, Manufacturing, and Controls information for an age-appropriate formulation developed for pediatric use (1, 2.5, and 5 mg capsule dosage forms).
- Reports from two juvenile toxicity studies conducted upon FDA recommendation (Studies 109584 and 110057).
- Bioavailability/bioequivalence study report of the 5 mg cinacalcet capsule dosage form (6 capsules total), administered with contents (granules) sprinkled onto applesauce or swallowed whole with applesauce, compared with the 30 mg commercial Sensipar tablet, swallowed whole with applesauce, in healthy adult subjects (Study 20070293).
- Final CSRs for Studies 20090005, 20070208, 20110100, and 20130356 (WR Studies 1, 2, 3, and 4, respectively). All reports included information on the representation of pediatric subjects of ethnic and racial minorities.
- Interim CSR from Study 20140159, the open-label extension protocol to Studies 20110100 and 20130356 (WR Studies 3 and 4).
- A summary of demographic and drug-use data from NAPRTCS national registry with > 6000 registered pediatric dialysis patients. A prospective registry was performed to evaluate safety information for 538 pediatric dialysis patients, including 90 patients treated with cinacalcet (Study 20120116).
- A retrospective chart review in 23 patients < 6 years of age (Study 20090198).
- Population PK and exposure-response (PK/PD) analyses using data from Studies 20090005, 20070208, and 20110100 (WR Studies 1, 2, and 3) that relate the time course of plasma cinacalcet concentrations with the changes in serum calcium (safety) and PTH (efficacy) levels and support the dosing recommendations proposed for pediatric patients. Results also support consistency in PK and PD of cinacalcet between adults and children and meet the WR requirement to submit exposure-response analysis to support extrapolation of efficacy in pediatric patients 28 days to < 6 years of age.
- A Bayesian extrapolation analysis that infers the treatment effect of cinacalcet on PTH from the adult population to the overall pediatric population and to children ages 28 days to < 6 years with CKD and secondary HPT receiving dialysis.
- A summary of the published literature on the use of cinacalcet in pediatric patients.

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[43] No published data exist on the prevalence of pediatric patients with secondary HPT; however point prevalence estimates using USRDS and DaVita databases for 2015 indicate that < 1000 patients 0 to < 18 years of age on dialysis (491 for hemodialysis and 475 for peritoneal dialysis) will develop secondary HPT (data on file, Amgen). Of these, approximately 300 patients are estimated to be 0 to 5 years of age, 220 aged 6 to 12 years and approximately 430 aged 13 to < 18 years.

[44] *Id.* For this reason, Sensipar was designated as an orphan drug on September 8, 2016 for treatment of secondary hyperparathyroidism (HPT) in pediatric patients with chronic kidney disease receiving dialysis.

- A summary report evaluating all pediatric postmarketing adverse event reports regarding cinacalcet that are available to Amgen.
- Proposed pediatric labeling to incorporate the findings of the studies, including information on dosing, safety, efficacy, PK, PK/PD, product excipients, and storage and handling.
- Study datasets from Studies 20070208, 20110100, 20130356, and 20140159, as well as datasets supporting the Integrated Summary of Safety, and Bayesian analysis (according to Study Data Tabulation/Clinical Data Interchange Standards Consortium standards).

Even with the differences in the number of completers in Study 3, Amgen's pediatric program when viewed as a whole was sufficient to achieve the goal of assessing the dosing, safety, and efficacy of using cinacalcet in all pediatric subsets requested in the WR, including the safety subset in Study 3. By this or any measure, the program fairly responds to FDA's WR as amended, and qualifies for pediatric exclusivity under the Act. Amgen's response exceeded the WR requirements in many ways, including the addition of valuable real-world evidence.

D. The Pediatric Exclusivity Board Denies Sensipar Pediatric Exclusivity

Despite the submissions detailed above, the Pediatric Exclusivity Board denied exclusivity to Sensipar in a letter dated May 22, 2017. In the denial letter, the Board stated that in determining whether a submission "fairly responds," the board "considers whether the submission is sufficient to enable it to approve pediatric labeling (including negative pediatric labeling) for *all of the age groups and indications* requested based on the studies conducted."[45] The Board found that the statutory purpose of pediatric exclusivity is to generate clinical information that results in a "*health benefit*" to pediatric populations.[46] The Board further found:

> The legislative history makes clear (and the Agency's experience confirms) that for FDA-regulated products, the health benefit is obtained when the information that a physician needs to properly prescribe a medication is described in the product's labeling. Thus, the provision attempts to ensure that when [pediatric exclusivity] is granted for studies, FDA also may approve labeling describing the results of the studies and *providing adequate information for use of the drug* in relevant pediatric populations.[47]

The Board then denied exclusivity to the studies, not because of how the studies were conducted, but because the data "were insufficient to allow FDA to adequately characterize the risks for cinacalcet for its chronic intended use in [the younger] age group."[48]

The Board conceded that "Amgen has met the literal terms of the WR for Studies 1, 2, and 4."[49] However, it found that the response, as a whole, failed to fairly respond based on a single "criterion": "the absence of any robust source of safety information" in children aged 28 weeks to < 6 years old.[50] The Board found that "many of the non-completers who received cinacalcet in Study 3 were exposed to doses that were too low to adequately characterize the safety of the product for its intended [chronic] use" due to the low starting dose and slow titration

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45 Denial Letter at 4 (emphasis added).

46 *Id.* at 2 (emphasis added).

47 *Id.* (emphasis added).

48 *Id.* at 7.

49 *Id.*

50 *Id.* at 10.

study design for Study 3.[51] Of particular note, revisions to the dosing regimen in Study 3 were implemented at FDA's recommendation as an additional safety measure to permit Study 3 to resume following the fatality in Study 2 and subsequent 14-month clinical hold.[52]

The Board also rejected "supportive safety information from Study 4" in pediatric patients because of "inadequate cinacalcet titration,"[53] even though it noted Study 4 complied with the terms of the WR.[54] The Board also dismissed real world safety data from 23 patients aged 28 days to < 6 years in a retrospective chart review, with a mean time of exposure of 274.2 days, because this retrospective chart review, like all retrospective chart reviews, was "subject to the limitations and biases of retrospective observational chart review, which included voluntary participation, selection bias, uncertainty with regard to how the product was used, uncertainty with regard to exposure in terms of dose and duration of exposure, uncertainty with regard to dosing regimen used (i.e., administration schedule and titration), uncertainty surrounding the completeness of ascertainment and reporting of safety data, and missing data."[55] Accordingly, the Board appears to be rejecting all retrospective chart reviews as sources of evidence. Given the Agency's renewed emphasis on encouraging the development of real world evidence through observational studies and the use of such evidence to support regulatory submissions,[56] the Board's rejection of a supporting role for the observational studies was surprising in light of FDA's renewed emphasis on real world evidence. Finally, the Board also did not address the 12 patients aged 28 weeks to < 6 years old who received Sensipar in the PK study or the patients < 6 years of age in the NAPRTCS study or the literature review, which provided significant dosing, safety, and efficacy data.

The Board thereby concluded that the studies as a whole did not fairly respond to the WR because the data was inadequate to provide robust safety information to support adequate labeling for the chronic use of Sensipar in one age subpopulation.

E. The Pediatric Exclusivity Board Did Not Apply the Clear Statutory Standard

The Board's purported basis for denying pediatric exclusivity does not comport with the plain language of the statute. Instead, the Board has asserted multiple ambiguous standards that are found nowhere in the statute or relevant agency guidance. For this reason, the Board's decision to deny pediatric exclusivity to Amgen was improper and should be reversed.

1. The Statutory Standard is Clear

As described above, the BPCA established a regulatory structure to incentivize NDA sponsors to conduct studies in pediatric populations. FDA may issue a Written Request to an NDA sponsor if the agency "determines that information relating to the use of a new drug product in the pediatric population may produce health benefits

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51 *Id.* at 8.

52 *See* Memorandum of Meeting Minutes, Type A Meeting, Sept. 4, 2013; Complete Response to Partial Clinical Hold, § 1.11.3, at 5 (describing the reduction of the maximum dose in the treatment protocol and a revised treatment schedule).

53 Denial Letter at 9.

54 *Id.* at 7.

55 *Id.* at 9.

56 *See, e.g.*, Robert M. Califf, Melissa A. Robb, Andrew B. Bindman, et al., *Transforming Evidence Generation to Support Health and Health Care Decisions*, 375 N. Engl. J. Med. 2395 (2016).

in that population."[57] The Written Request must include a timeframe for the studies and ask the sponsor to propose pediatric labeling resulting from the studies.[58]

Once the sponsor has conducted and submitted the results of the requested studies, the agency's role is limited. First, the agency must determine if the studies qualify for pediatric exclusivity. In doing so, the agency's only responsibility is to determine whether the studies (1) "fairly respond" to the Written Request, (2) were "conducted in accordance with commonly accepted scientific principles and protocols," and (3) have been reported in accordance with applicable filing requirements.[59] Second, if the Board concludes that the sponsor has met these three criteria, the agency must award pediatric exclusivity.[60]

Finally, the agency must order the product's labeling to include information about the study results.[61] In this regard, the statute expressly recognizes that pediatric studies may not be successful. Whatever the results of the studies, FDA must include in the product's labeling information about the study results and FDA's conclusion regarding whether the pediatric study "does *or does not* demonstrate that the drug that is the subject of the study is safe and effective, including *whether such study results are inconclusive*, in pediatric populations or subpopulations."[62]

2. The Board Departed from the Clear Statutory Standard

Notwithstanding the clear statutory directive, the Board applied a different set of standards to Amgen in this case. In particular, the agency's denial letter discusses at least two different standards the Board purportedly used to evaluate Amgen's pediatric study reports: a "full response" standard[63] and a "characterization of safety" standard.[64] Both of these standards depart from the statutory text to create a higher bar to obtaining pediatric exclusivity than intended by Congress as evidenced by the statute. The agency admits that these standards do not flow directly from the statute, but from the Board's interpretation of the BPCA's scant legislative history as well as the "structure and context of ...Section 505A...."[65] Using these extra-statutory standards, the Board denied pediatric exclusivity to Amgen.

For example, the Board writes that "if a specific number of patients is requested or a specific study duration or endpoint is specified to ensure that the study will generate adequate data to provide a health benefit, failure to comply with these elements of the WR may result in a denial of exclusivity."[66] As the Board has applied this standard to Amgen, it amounts to a requirement that Amgen "fully respond" to every element of the WR in order to earn pediatric exclusivity. The Board's application of this standard to Amgen directly contravenes the statutory language.

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57 *Id.* at 355a(b)(1), (c)(1).

58 21 USC 355a(d)(1)(A).

59 *Id.* at 355a(d)(3).

60 *Id.* at 355a(b)(1), (c)(1) (exclusivities and patent protection extended if pediatric study reports are "accepted").

61 *Id.* at (j).

62 *Id.* at (j) (emphasis added).

63 *See* Denial Letter at 2.

64 *See id.* at 7.

65 *Id.* at 1.

66 *Id.* at 2.

In addition, the agency asserts that Study 3 did not "fairly respond" to the WR because the studies did not "provid[e] an appropriate safety assessment."[67] Elsewhere in the letter, the agency acknowledged that its denial of Amgen's proposed WR amendment in December 2015 was caused by the agency's concern that the lower number of patients "would not be expected to provide sufficient information to establish the safety of the product in the younger patient population."[68] This feedback was not communicated to Amgen at the time. Similarly, the agency contends – with no evidence or cited authority to support its statements – that "[t]he legislative history makes clear (and the Agency's experience confirms) that for FDA regulated products, the health benefit is obtained when the information that a physician needs to properly prescribe a medication is described in the product's labeling."[69] Again, nothing in the statute conditions pediatric exclusivity on a complete characterization of the safety of the pediatric population or individual subpopulations.

Whether these alternative standards are to be found in the legislative history or not (and the Board's denial letter provides no compelling evidence that they are), they are not expressed in the statute. Congress made clear that a sponsor need not comply with every term of a WR, nor must a sponsor definitively establish safety and/or efficacy in the pediatric population(s).[70] And Congress made a perfectly rational choice in determining how to align the benefits of the BPCA's regime with its statutory requirements. The statutory requirements recognize the importance of incentivizing studies in pediatric populations given the higher hurdles faced by sponsors in designing and executing studies in such small patient populations. In the case of cinacalcet in particular, the population of children in the US on dialysis and suffering from secondary HPT between the ages of 6 months and 6 years at any time is estimated at only 300 patients.[71] When dealing with such small numbers of patients, it is extraordinarily challenging to recruit sufficient patients to demonstrate the safety profile for a drug with statistical certainty. In denying Amgen exclusivity here, the Board acted to undermine this express incentive from Congress and may caution future sponsors against undertaking long and difficult pediatric studies.

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67 *Id.* at 10.

68 *Id.* at 9.

69 *Id.*

70 We note that FDA has often granted pediatric exclusivity where neither safety nor effectiveness could be established in one or more pediatric subpopulations. *See, e.g.*, PI for Spiriva Respimat Inhalation Spray (tiotropium bromide) (Feb. 15, 2017) (safety and efficacy established in pediatric patients aged 6 to 11, but "safety and efficacy have not been established in pediatric patients less than 6 years of age"); PI for Ofirmev (acetaminophen) (Jan. 27, 2017) (Including information about studies of patients less than 2 years of age, but concluding that safety and efficacy had not been established for this age group); PI for Entocort EC (budesonide) (Apr. 29, 2016) (finding safety and effectiveness established in pediatric patients aged 8 to 17 years who weigh more than 25 kg, but finding "safety and effectiveness have not been established in pediatric patients less than 8 years of age"); PI for Emend (aprepitant) (Aug. 28, 2015) (finding safety and efficacy in pediatric patients 12 years of age and older, but finding "no commercially available dosage form appropriate for patients less than 12 years of age and weighing less than 30 kg"); PI for Oxycontin extended release tablets (oxycodone hydrochloride) (Aug. 13, 2015) (finding safety and efficacy established in patients 11 to 16 years old, but insufficient numbers of patients less than 11 years enrolled to establish safety); PI for ProAir RespiClick (albuterol sulfate) (Mar. 31, 2015) (finding safety and efficacy for children 12 - 17 years old, but safety and effectiveness profile "not established" in patients younger than 12 years); PI for Dymista (azelastine hydrochloride and fluticasone propionate) (Feb. 20, 2015) (finding safety and efficacy in patients aged 6 to 11 years, but insufficient efficacy results in patients aged 4 - 5 years, and insufficient safety and efficacy data in patients below the age of 4 years).

71 Amgen notes that the WRs for other products intended to treat secondary HPT describe significantly smaller studies than requested of Amgen. *See, e.g.*, Calcijex WR (a single study in 35 patients aged 13-18 years, of which 20 were treated with Calcijex); Zemplar WR (a single study in 29 patients, of which 15 were treated with Zemplar; no patients less than 5 years old were enrolled).

F. The Board Erred in Concluding that Amgen Did Not Fairly Respond to the Written Request

On receipt of the study reports, FDA has only three responsibilities – to determine (1) that the reported data "fairly responds" to the Written Request; (2) that the studies have been conducted in accordance with commonly accepted scientific principles and protocols, and (3) that the data has been filed in accordance with FDA's requirements.[72] The Board's letter raised no objection with regard to the latter two criteria, and the denial of pediatric exclusivity is based solely on the Board's contention that Study 3 does not "fairly respond" to the WR.

Thus, notwithstanding the totality of the evidence submitted by Amgen, the Board concluded that pediatric exclusivity must be denied because "[a]n insufficient number of patients 28 days to < 6 years of age completed WR Study 3 and clinical data in the submission were insufficient to allow FDA to adequately characterize the risks of cinacalcet for its chronic intended use in this age group." In addition, the Board noted that Amgen has "not fairly responded to the amended WR as a whole" given its failure to present "any robust source of safety information in" the younger age group.[73]

1. Amgen "Fairly Responded" to the Written Request

Even a cursory review of the totality of the information described in the Annotated Written Request for Pediatric Exclusivity Determination leads to the conclusion that Amgen "fairly respond[ed]" to the terms of the Written Request. Amgen performed the four studies described in the WR and submitted the results to FDA. As outlined in the WR, this program included additional non-clinical studies recommended by FDA, clinical studies evaluating the safety and efficacy of cinacalcet in children 6 to < 18 years of age (Studies 20070208 and 20130356 and extension protocol 20140159), and studies evaluating single and multiple dose safety and pharmacokinetics in children 28 days to < 6 years of age (Studies 20090005 and 20110100). For this younger age group, in accordance with the WR, efficacy was extrapolated from information gathered from adults and other pediatric studies,[74] and an exposure-response analysis was performed to support this extrapolation.

As discussed above, the studies included 103 patients who received at least one dose of cinacalcet in interventional clinical trials and 113 patients who received cinacalcet in a prospective cohort registry (Study 20120116) or retrospective chart review (Study 20090198). In preparation for and support of the studies performed for the WR, Amgen also developed an age-appropriate formulation and established its bioavailability.

As a result of the studies that it conducted, Amgen proposed extensive information for the cinacalcet labeling regarding the safety and effectiveness of the drug in the pediatric populations studied. When it became clear that the Division would not grant a pediatric indication or approve the pediatric oral dosage form, Amgen limited its labeling negotiations to Section 8.4 Special Populations. As approved, that labeling states that "[t]he safety and efficacy of Sensipar have not been established in pediatric patients." The final labeling includes a brief description of WR Studies 2, 3, and 4 with the total number of pediatric patients (62) dosed with Sensipar in these three studies. The labeling also notes that dosing with Sensipar was stopped in WR Study 2 because of a fatality, which was determined to be multifactorial, although a contribution of Sensipar to the death could not be excluded. The labeling also noted that "changes to Sensipar dosing after the fatality were implemented" in WR Studies 3 and 4. Finally, the labeling concluded that the data in WR Studies 3 and 4 "were insufficient to establish the safety and efficacy of Sensipar for the treatment of secondary HPT in pediatric patients with CKD on dialysis."

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72 21 USC 355a(d)(3).

73 Denial Letter at 7.

74 The extrapolation was two-fold adult to pediatric and adult and older pediatric to younger pediatric group. This used the adult phase 3 registrational trials (Studies 20000188, 20000183, and 20000172) and the pediatric WR Study 3 and WR Study 2. The Bayesian extrapolation analysis provided further evidence supporting the partial extrapolation of treatment effect of cinacalcet from adult to pediatric subjects.

This description is similar to the labeling of other drugs that have received exclusivity.[75] Thus, it is clear that the Board has diverged from the agency's prior interpretation of the standard and has failed to adequately consider its own regulatory precedent.

2. Amgen Took Great Pains to Conduct Study 3 in Accordance with the Terms of the WR

It is difficult to assess the magnitude of Amgen's efforts and the results it submitted in November 2013 without recognizing the effects of the partial clinical hold (PCH). The PCH was in effect for 14 months spanning portions of 2013-2014 and delayed the pediatric program by over a year. It had a direct impact on Amgen's ability to enroll Study 3 for which the agency requested that a minimum of 15 patients be treated for 26 weeks. In particular, 8 pediatric subjects had been enrolled prior to the partial clinical hold, but 5 of those subjects had to discontinue treatment when the partial clinical hold was instituted. Only 1 of those patients met the definition for completing the study. Following the resumption of enrollment after the PCH was lifted, an additional 10 children were enrolled, but only 3 of those made it to completion.

Despite these difficulties, Amgen made every effort to fully enroll the study. Subject enrollment was held open for more than three years – from January 2012 to June 2016. Amgen implemented a comprehensive program for recruitment and retention that included initiating a large number of sites, engaging site management organizations (including NAPRTCS), offering home health services to ease the burden on patients, providing extensive site support, organizing additional investigator meetings, and modifying the protocol to simplify procedures in response to site personnel feedback. When Amgen raised these issues with the agency, FDA encouraged the company to continue the trial. The agency also rejected Amgen's proposals to amend the Written Request when it was clear that study 3 would not obtain its full complement of completers. Instead, FDA directed Amgen to "use [its] discretion moving forward."[76]

In its letter, the Board notably omits any discussion of the effect of the clinical hold on Amgen's ability to enroll sufficient patients in Study 3. Instead, the agency states only that it "acknowledg[ed] the challenges with recruitment." This omission is particularly glaring, where the administrative record shows that the agency recognized the importance of Amgen's studies and stated that it had "learned a lot" from the trials prior to the fatality in Study 2.[77] The agency knew or could have easily foreseen at that time that the clinical hold would reduce the number of completers in study 3.

Despite these challenges, the totality of evidence from the studies meets the statutory standard of fairly responding to the Written Request. Although the targeted number of completers was not achieved in Study 3, sufficient data were collected in the overall pediatric study program, including WR Study 3, to satisfy the primary objectives of the study, which were to evaluate the safety and tolerability of cinacalcet in pediatric patients ages 28 days to < 6 years and to characterize the PK profile in pediatric patients, and to therefore satisfy the overall objectives of the Written Request.

3. In Denying Pediatric Exclusivity to Amgen, the Board Ignored its Precedent

As mentioned, in a case very similar to this one, the Board – in consultation with the same division that reviewed Sensipar – denied pediatric exclusivity to Merck for its product Mevacor (lovastatin) (NDA 019643). When Merck challenged this determination, a court held that the Board had impermissibly interpreted the plain language of the pediatric exclusivity statute. The facts of the Merck case are strikingly similar to Amgen's. The Mevacor WR called for a study in "approximately 35 girls" aged 10-17 who would receive treatment of at least six

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[75] *See, e.g.*, Section 8.4 for Zomig (zolmitriptan) NDA 020768, Orencia (abatacept) BLA 125118, and Ortho Tri-Cyclen (ethinyl estradiol; norgestimate) NDA 019697.

[76] Letter from Meghna Jairath, FDA, to Sabina Buntich, Amgen, Meeting Denied (Dec. 24, 2015).

[77] September 2013 Meeting Minutes.

months' duration. Merck enrolled only 5 girls in this study, or approximately 14% of its target enrollment. On the basis that Merck had not met this term of the WR, the Board denied pediatric exclusivity.

Merck immediately sought emergency relief in federal court. In its decision to extend a TRO staying the effectiveness of FDA's denial, the court concluded that "the Board's determination is 'not in accordance with law' because it invokes a standard not specified in the statute."[78] In particular, the court held that the statutory "fairly respond" standard "plainly does not require compliance with every single provision of a written request."[79] Finally, the court concluded that it would not "be consistent with the statutory standard to deny pediatric exclusivity because of disappointment with data submitted by a manufacturer if the study as a whole is a fair response to the written request."[80] Following the court's decision, the Board awarded pediatric exclusivity to Merck.

Here, Amgen is in a virtually identical situation. For the reasons described above, Amgen was only able to enroll 17 patients in its study, and only 4 out of the requested 15 patients met the definition for completing the study, or approximately 27% of the target number of completers. And, as with Merck, FDA refused to consider data gathered on patients who enrolled for the majority of the study period but not the full period. Nevertheless, Amgen conducted 4 studies under the WR, and the agency concedes that Amgen "met the literal terms" for Studies 1, 2, and 4.[81] Thus, the Board's denial of pediatric exclusivity rests entirely on its conclusion that "[a]n insufficient number of patients 28 days to < 6 years of age completed WR Study 3 and clinical data in the submission were insufficient to allow FDA to adequately characterize the risks of cinacalcet for its chronic intended use in this age group."[82] Concluding that "this criterion" was not met, the Board denied exclusivity.

Moreover, FDA has previously used patients in a retrospective observational study to supplement a safety assessment when a pediatric study was unable to meet its enrollment goal. Orencia (abatacept) was the subject of an amended WR that required the enrollment of 180 patients with juvenile idiopathic arthritis (JIA) in children 6 years of age or older.[83] The sponsor "was unable to provide data on the previously agreed 180 patients" enrolled for the full study, so it supplemented the safety dataset with retrospective observational studies.[84] FDA did not amend the WR to conform to the lower enrollment numbers.[85] Nevertheless, the agency concluded that "the data submitted in this supplement, while not technically meeting the specifics of the PWR, are adequate and fulfills the intent of the Pediatric Written Request."[86] Not only did the agency find that less-than-perfect compliance could meet the terms of the WR; it also found that adequate compliance could be achieved by supplementing an under-enrolled study with data from a retrospective observational study.

In contrast, the language of the Board's denial letter to Amgen makes clear that the Board expected full compliance with each and every requirement of the cinacalcet WR. The Board denied exclusivity because of a failure to meet one criterion – completion of a study in younger patients. Thus, it concluded that Amgen had not "fairly responded to the amended WR as a whole." In so concluding, the Board clearly applied a standard found nowhere in the statute, guidance documents, or even the agency's own precedent. It is precisely that narrow,

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78 *Merck*, 148 F. Supp. 2d at 30.

79 *Id.*

80 *Id.*

81 Denial Letter at 7.

82 *Id.*

83 *See* Dr. Keith Hull, Addendum to Primary Clinical Review of Supplement 211, BLA 125118, at 7 (March 24, 2017).

84 *Id.*

85 *Id.*

86 *Id.*

extra-statutory analysis that the court found unlawful in reversing the agency's decision regarding Mevacor. Amgen respectfully requests that the Center Director do the same here and reverse the Board's erroneous denial of pediatric exclusivity.

G. The Agency Failed to Follow the Amendment Procedures Set Forth in the WR

It is longstanding agency practice to issue amendments to pediatric WRs. To that end, the Sensipar WR instructed Amgen to "submit proposed changes and the reasons for the proposed changes to your application," if Amgen sought to amend its WR.[87] Following these procedures, Amgen sought – and FDA granted – five amendments to the initial WR. Amgen sought a sixth amendment in the fall of 2015, after it was clear that study 3 would not meet the required number of completers by the deadline of November 2016.

However, the Division refused Amgen's request to meet, saying that it is time-consuming and cumbersome to make changes to the WR; moreover, the Division refused Amgen's request to amend the WR. The Board now asserts – for the first time – that the Division was concerned that "the amendment would not be expected to provide sufficient information to establish the safety of the product in the younger patient population"[88] As discussed above, the studies were never designed to "establish the safety" of the product nor were they designed to "provide sufficient information" about the product.

Neither the Division nor the Board informed Amgen in December 2015 that the agency considered that Amgen's data were insufficient to establish the safety of Sensipar in the younger patient population. Nor did the agency inform Amgen at that time that the Board would evaluate Amgen's eligibility for pediatric exclusivity against this novel and unknown standard. This contributes to the inexorable conclusion that Amgen is now being denied exclusivity because it failed to meet standards about which it was not informed and could not have learned of through routine agency channels, such as guidance, correspondence, and precedence.

H. Conclusion

The Board denied pediatric exclusivity for Sensipar by departing from the clear statutory standard enacted by Congress. In doing so, the Board also departed from its own precedent and discounted the substantial clinical and real-world evidence assessing pediatric use of Sensipar. Based on the totality of the evidence, we respectfully request that the Center Director review and reverse the decision of the Pediatric Exclusivity Board to deny pediatric exclusivity for Sensipar.

III. STEPS PREVIOUSLY TAKEN TO RESOLVE THE DISPUTE

Amgen has worked diligently with FDA to assure that the studies fairly responded to the WR, beginning in the development of the pediatric studies and continuing through the agency's evaluation of the submitted applications.

During clinical development, Amgen was able to adequately enroll WR Study 3 but was not able to obtain enough completers, due in part to the clinical hold and in part to other factors, including pediatric patients dropping out before their term was complete because pediatric patients on dialysis are prioritized for kidney transplants. Amgen was permitted to modify the protocol to simplify procedures in response to site personnel feedback, and FDA directed Amgen to continue the program. In December 2015, FDA declined Amgen's meeting request to further discuss the ongoing clinical studies and the enrollment challenges that Amgen was having. FDA declined a second modification request in September 2016. On multiple occasions, FDA advised Amgen that the agency would not further amend the WR and would not participate in further discussion on the topic. Amgen completed the program and submitted results of the studies to FDA.

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87 WR 5 at 3.

88 Denial Letter at 9.

Amgen's first indication that the review division might not view Amgen's studies favorably came in a draft labeling mark-up from the Division, received on May 1, 2017, only 21 days before the statutory 180-day deadline. There, the division omitted the proposed pediatric indication and did not include any data from the pediatric studies in the labeling, except for information about the single fatality. Amgen was given 48 hours to respond. Once the Division agreed to discuss Amgen's proposed labeling and the statutory requirement that the Agency include a description of Amgen's pediatric program in the labeling, Amgen submitted proposed language for Section 8.4 of the PI regarding pediatric experience with the drug on May 8, 2017.

Correctly anticipating that the labeling changes might portend a dispute over pediatric exclusivity, Amgen filed a formal dispute resolution request on May 5, 2017. That request was rejected on May 19, 2017, on the grounds that it was premature to seek dispute resolution prior to the Pediatric Exclusivity Board issuing a final determination as to pediatric exclusivity for Sensipar.

Amgen continued to negotiate with the review division until the two sides finally agreed on draft labeling on May 22. Nevertheless, on the same day, the Board denied Amgen pediatric exclusivity. Now, in order to be afforded relief, Amgen is requesting dispute resolution to assure this important issue is correctly resolved.

IV. PROPOSED POSSIBLE SOLUTIONS AND EXPECTED OUTCOMES

Amgen is requesting that the agency grant pediatric exclusivity to Sensipar on the basis that the pediatric studies, taken as a whole, fairly respond to the WR.

V. IDENTITY OF THE DIVISION ISSUING THE DECISION

The decision was issued by Dr. Peter Stein, Deputy Director of the Center for Drug Evaluation and Research and Chair of the Pediatric Exclusivity Board, in consultation with CDER's Pediatric Exclusivity Board and the Division of Metabolic and Endocrine Drug Products.

VI. ADVISORY COMMITTEE REVIEW

Amgen is not requesting advisory committee review at this time.

VII. LIST OF DOCUMENTS PREVIOUSLY SUBMITTED

- NDA 209962
- NDA 021688 supplement 023
- FDA Written Request for Pediatric Studies, Amendment 5
- IND 56010
- IND 109361
- Letter to the Review Division responding to proposed labeling changes (May 2, 2017)
- Responses to proposed labeling changes (May 2, 2017), (May 8, 2017) (Section 8.4 only), (May 9, 2017), (May 17, 2017), (May 18, 2017), (May 22, 2017)
- Formal Dispute Resolution Request, May 5, 2017

VIII. STATEMENT REGARDING NEW INFORMATION

No new information has been submitted in support of this formal dispute resolution request.

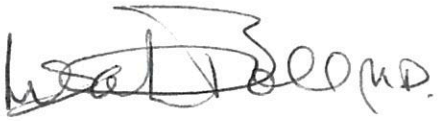
IX. SPONSOR CONTACT INFORMATION

Dr. Steven K. Galson, M.D., M.P.H.
Sr. Vice President, Global Regulatory Affairs & Safety
805-447-4988
sgalson@amgen.com
One Amgen Center Drive
Thousand Oaks, CA
91320-1799

If you have any questions or need additional information, please contact me at my direct line at 805-447-4988 or by electronic mail at sgalson@amgen.com.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Senior Vice President
Global Regulatory Affairs
Amgen



Lisa Bollinger, M.D.
Vice President
Regulatory Affairs
Amgen

cc: Elizabeth Dickinson
FDA Chief Counsel

Peter Stein, M.D.
Chair, Pediatric Exclusivity Board

Meredith Manning
Hogan Lovells US LLP

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805.447.1000
www.amgen.com

May 5, 2017

Khushboo Sharma
CDER Formal Dispute Resolution Project Manager
10903 New Hampshire Avenue
White Oak Building 22, Room 6486
Silver Spring, MD 20993-0002

Re: **SENSIPAR® (cinacalcet) tablets, for oral use**
NDA 021688 Supplement Number 023
NDA 209962

FORMAL DISPUTE RESOLUTION REQUEST
AND REQUEST FOR A TYPE A MEETING

Attn: **Jean-Marc Guettier, Director, Division of Metabolic and Endocrine Drug Products**
Khushboo Sharma, CDER Formal Dispute Resolution Project Manager

Dear Ms. Sharma and Dr. Guettier:

I am writing on behalf of AMGEN Inc. (Amgen) to preserve its ability to lodge an appeal of a pending decision by the Pediatric Exclusivity Board to deny pediatric exclusivity for SENSIPAR® (cinacalcet) tablets and thereby to secure Amgen's entitlement to pediatric exclusivity under the statute.

I. BACKGROUND AND TIMING OF THIS REQUEST

Amgen is the holder of new drug application (NDA) 021688 for SENSIPAR (cinacalcet) tablets, a calcium-sensing receptor agonist indicated for Secondary Hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on dialysis, Hypercalcemia in adult patients with Parathyroid Carcinoma (PC), and Hypercalcemia in adult patients with primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but who are unable to undergo parathyroidectomy. There is an unmet medical need for medicines to treat secondary HPT in children, and a public health benefit to providing information on pediatric dosing, safety, and efficacy in the Sensipar Prescribing Information (PI). For these reasons, FDA issued a Written Request (WR) for cinacalcet in May of 2010.

In accordance with the Written Request, Amgen completed a well-designed pediatric clinical study program consisting of four clinical studies and an extension study to investigate the use of cinacalcet for the treatment of secondary HPT in pediatric patients with CKD requiring maintenance dialysis. In addition, Amgen completed a prospective registry study performed by the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), a pediatric literature summary, and a pediatric post-marketing case summary to describe pediatric off-label use, as specified by the WR. As agreed, Amgen also developed an appropriate pediatric formulation and established its bioavailability. The formulation development and studies were conducted over a period of 11 years, indicative of Amgen's commitment to meet the specific requests of the agency.

Having conducted the requested studies in accordance with applicable scientific principles and completed the studies in the timeline described in the WR, Amgen submitted two applications to FDA on November 23, 2016 in accordance with the applicable submission requirements. Supplemental NDA 021688/023 proposed to add to the labeling a pediatric indication and other information concerning the pediatric studies. NDA 209962 seeks approval for the novel pediatric dosage form and included a formal request for a pediatric exclusivity determination. Submission of the reports of the pediatric studies on November 23, 2016 triggered a statutory 180-day period for FDA to determine whether the pediatric study reports fairly respond to the WR.[1] That 180-day period ends on May 22, 2017.

Recent unanticipated statements by the Division of Metabolic and Endocrine Drug Products (the Division) regarding pediatric labeling, and implications for the Pediatric Exclusivity Board (PEB), suggest that FDA may be inclined not to grant pediatric exclusivity to Sensipar, despite the fact that the studies fairly respond to the Written Request. Amgen has worked diligently with the Division to try to resolve this issue, but now cannot wait for a final decision to be rendered at the statutory 180-day date, because doing so would prevent Amgen from challenging an adverse decision. Section 505A of the Food, Drug, and Cosmetic Act (FDCA) states that pediatric exclusivity does not extend the preclusive effect of a listed patent if the pediatric exclusivity is awarded any less than nine months before the patent expires.[2] A critical patent covering Sensipar expires on March 8, 2018, meaning that pediatric exclusivity must be granted by June 8, 2017 or the six-month extension will not be applied to this patent. Amgen has worked diligently to complete and timely submit the results of these pediatric studies in order to ensure that pediatric exclusivity would apply to this patent. Although an initial decision in accordance with the 180-day deadline would occur before June 8, dispute resolution of an unfavorable decision may not, because FDA's dispute resolution goal is to provide a response within 30 calendar days.[3] Accordingly, Amgen is requesting dispute resolution now in order to preserve Amgen's rights under the statute.

Amgen recognizes that the Division may not have reached a final decision on the request for determination of pediatric exclusivity, and may not disclose any final decision until May 22, 2017. Due to the extraordinary circumstances in this matter, however, Amgen respectfully requests that the agency begin consideration of this submission at this time, in order to permit a timely response that protects Amgen's rights. Amgen has worked with the agency for a decade in the development and execution of the pediatric study program, and it was only made aware of the review division's concerns with days remaining on the clock to effectively seek resolution of this potential dispute. In order to permit effective relief, Amgen requests that the agency begin reviewing the relevant material for dispute resolution at this time, with the knowledge that an adverse decision by the PEB could be finalized shortly, but too late to permit dispute resolution before the statutory deadline for reaching pediatric exclusivity is reached. For the same reason, Amgen also requests expedited consideration of the dispute resolution request. In addition, Amgen reserves all rights to seek immediate judicial review as needed to protect Amgen's rights.

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1 *See* 21 USC 355a(d)(3).

2 *Id.* at 355a(b)(2).

3 *See* the letter "PDUFA Reauthorization Performance Goals and Procedures; Fiscal Years 2013 Through 2017" from the Secretary of Health and Human Services to the Chairman of the Committee on Health, Education, Labor, and Pensions of the Senate and the Chairman of the Committee on Energy and Commerce of the House of Representatives, at section V.A.1: Timelines for Reviewing Formal Dispute Resolution Requests for Human Drug Applications Covered by PDUFA or BsUFA.

II. DESCRIPTION OF THE MATTER TO BE RESOLVED

A. Legal Standard

The Best Pharmaceuticals for Children Act (BPCA) established a statutory regime whereby NDA sponsors can earn six-month extensions on patent and regulatory exclusivities.[4] Under the BPCA, if FDA "determines that information relating to the use of a new drug product in the pediatric population may produce health benefits in that population," FDA may issue a Written Request.[5] By the Written Request, FDA asks a sponsor to conduct and submit reports of studies "to determine if the use of a drug could have meaningful health benefits in the pediatric population."[6] The Written Request must include a timeframe for the studies and ask the sponsor to propose pediatric labeling resulting from the studies.[7]

If the sponsor agrees to the Written Request, conducts the requested studies, and submits the results, FDA must accept the submitted reports if the agency determines that the studies (1) "fairly respond to" the Written Request, (2) were "conducted in accordance with commonly accepted scientific principles and protocols," and (3) have been reported in accordance with applicable filing requirements.[8] The statute explicitly states that these are the sole criteria for determining whether FDA accepts the reports, and if they are met, the agency must accept the reports.[9] And if the reports are accepted, the six-month extension of exclusivity and patent protection automatically applies.[10] In this regard, the studies need not be successful for the applicant to obtain pediatric exclusivity, because that is not an appropriate factor in FDA's determination of whether to accept the reports. This is reflected in the requirement that, if FDA concludes that the pediatric study "does or does not demonstrate that the drug that is the subject of the study is safe and effective, including whether such study results or inconclusive, in pediatric populations or subpopulations," the agency must order the product's labeling to include information about the study results and FDA's conclusion in that regard.[11]

B. Amgen's Pediatric Studies

Amgen submitted a Proposed Pediatric Study Request (PPSR) for Sensipar in May 2007. In response, FDA issued Amgen a Written Request on May 5, 2010. That Written Request was amended five times, most recently on October 14, 2015. As amended, the Written Request asked Amgen to conduct four studies:

> Study 1: A single-dose PK/PD study in pediatric patients ages 28 days to < 6 years with chronic kidney disease and secondary hyperparathyroidism receiving dialysis.
>
> Study 2: A 30-week, randomized, double-blind, placebo-controlled, safety and efficacy study with a 30-week, open-label, safety extension in pediatric patients ages 6 years to < 18 years with chronic kidney disease and secondary hyperparathyroidism receiving dialysis. This study will include an assessment of pharmacokinetic (PK) parameters using a sparse sampling design. Study 2 has been terminated early and will be analyzed with available data.

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4 *See* 21 USC 355a.

5 *Id.* at 355a(b)(1), (c)(1).

6 *Guidance for Industry, Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act* (Sept. 1999) (withdrawn Aug. 7, 2013 (78 FR 48175)) (*Pediatric Exclusivity Guidance*) at 4.

7 21 USC 355a(d)(1)(A).

8 *Id.* at 355a(d)(3).

9 *Id.* (identifying FDA's "only responsibility in accepting or rejecting reports").

10 *Id.* at 355a(b)(1), (c)(1) (exclusivities and patent protection extended if pediatric study reports are "accepted").

11 *Id.* at (j).

Study 3: A 26-week or time-until-transplantation (whichever comes first), open-label, safety study in pediatric patients ages 28 days to < 6 years. The final protocol including starting dose, dose titration scheme, and exclusion criteria will have to be approved by the agency before this study is initiated.

Study 4: A 20-week, randomized, open-label, controlled study in pediatric subjects between the ages of 6 and < 18 years, with secondary hyperparathyroidism and chronic kidney disease who are receiving either hemodialysis or peritoneal dialysis.[12]

The program was initiated under IND 56010 (the cinacalcet IND for the treatment of secondary HPT in adults), but was continued under IND 109361 – a separate IND specific to the treatment of secondary HPT in pediatric patients. After the report of a fatality in Study 20070208 (WR Study 2) during the course of the pediatric program, FDA placed a partial clinical hold on IND 109361 for 14 months, from February 2013 to April 2014. Changes to the clinical program as a result of the partial clinical hold were incorporated into the WR.

C. Amgen's Studies Fairly Respond to the WR

As described in the Annotated Written Request for Pediatric Exclusivity Determination, the studies conducted by Amgen "fairly respond to" the terms of the Written Request and will form the basis for pediatric information in the proposed product labeling. For these reasons, FDA must award pediatric exclusivity to Sensipar.

Amgen performed the four studies described in the WR and submitted the results to FDA. As outlined in the WR, this program included additional non-clinical studies requested by FDA, clinical studies evaluating the safety and efficacy of cinacalcet in children 6 to < 18 years of age (Studies 20070208 and 20130356 and extension protocol 20140159), and studies evaluating single and multiple dose safety and pharmacokinetics in children 28 days to < 6 years of age (Studies 20090005 and 20110100). For this younger age group, in accordance with the WR, efficacy was extrapolated from information gathered from adults and other pediatric studies, and an exposure-response analysis was performed to support this extrapolation. In total, the studies included 103 patients who received at least one dose of cinacalcet in interventional clinical trials and 113 patients who received cinacalcet in a registry (Study 20120116) or chart review (Study 20090198). In preparation for and support of the studies performed for the WR, Amgen also developed an age-appropriate formulation and established its bioavailability. In total, 9 clinical studies were performed over the span of approximately 11 years. In addition to the clinical studies, Amgen also conducted population pharmacokinetics and pharmacokinetics / pharmacodynamics modeling studies and a Bayesian extrapolation analysis, which allowed for qualitative and quantitative extrapolation of pediatric effectiveness. The studies' size and scope are particularly notable given the low prevalence of pediatric patients with secondary HPT – it is currently estimated that there are fewer than 1000 patients 0 to < 18 years of age on dialysis in the United States.[13] Of these, approximately 300 patients are estimated to be 0 to 5 years of age, 220 are 6 to 12 years of age, and approximately 430 patients are 13 to < 18 years of age.[14]

The partial clinical hold in 2013-2014 delayed the pediatric program by over a year and may have led WR Study 3 to fall short of the enrollment targets described in the Written Request. In particular, the agency requested that a

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[12] WR Amendment 5 at 2. FDA also requested in the WR an open-label extension protocol. The extension protocol called for an open-label extension protocol to Study 4 to assess longer term safety of cinacalcet for at least 7 additional months. Interim results were submitted with the marketing application. While not a term of the Written Request, final results of this extension study will be submitted upon completion of the protocol.

[13] No published data exist on the prevalence of pediatric patients with secondary HPT; estimates were generated from point prevalence estimates using USRDS and data from a large US dialysis provider (DaVita).

[14] *Id.* For this reason, Sensipar was designated as an orphan drug on September 8, 2016 for treatment of secondary hyperparathyroidism (HPT) in pediatric patients with chronic kidney disease receiving dialysis.

minimum of 15 patients be treated for 26 weeks, but patients who received a kidney transplant after 12 weeks could be considered completers.[15] Although Amgen enrolled 18 subjects, only 11 were enrolled for at least 12 weeks and only 4 completed the study (three completed 26 weeks and 1 completed 12 weeks before receiving a kidney transplant). The difficulties in enrollment likely resulted from the partial clinical hold that was in place during conduct of the trial, the relatively small size of the eligible patient population. In addition, other contributing factors included parents' preference to focus their efforts on obtaining a kidney transplant for their child rather than participating in a clinical trial, as well as investigator and patient concerns regarding hypocalcemia and the additional burdens imposed by participation in a clinical trial (e.g., the imposition of weekly ionized calcium testing). In particular, 8 pediatric subjects had been enrolled at the time of the partial clinical hold, but 7 of those subjects discontinued the study and were not completers. Following the resumption of enrollment in the study after the partial clinical hold was lifted, an additional 10 children were enrolled, but only 3 of these were completers.

Despite these difficulties, Amgen made every effort to fully enroll the study. Subject enrollment was held open for more than three years – from January 2012 to June 2016. Amgen implemented a comprehensive program for recruitment and retention that included initiating a large number of sites, engaging site management organizations (including NAPRTCS), offering home health services to ease the burden on patients, providing extensive site support, organizing additional investigator meetings, and modifying the protocol to simplify procedures in response to site personnel feedback. When Amgen raised these issues with the agency, FDA encouraged the company to continue the trial.[16] The agency also rejected Amgen's proposals to further amend the Written Request when it was clear that study 3 would not obtain its full complement of completers, because the agency indicated that further amendments to the Written Request would not be allowed.[17] Instead, FDA directed Amgen to "use your discretion moving forward."[18]

Despite these challenges, the totality of evidence from the studies meets the statutory standard of fairly responding to the Written Request. In particular, WR Study 3 was a safety study in pediatric patients aged 28 days to < 6 years. Per the WR, efficacy in this age group was always intended to be partially extrapolated from information gathered from adults and the other three studies described by the WR. Although the targeted number of completers was not achieved, sufficient data were collected in the overall pediatric study program, including WR Study 3, to satisfy the primary objectives of the study, which were to evaluate the safety and tolerability of cinacalcet in pediatric patients ages 28 days to < 6 years and to characterize the PK profile in pediatric patients.

The smaller number of completers in WR Study 3 was the only discrepancy between the sNDA data package and the contents of the WR, as amended. Importantly, the statutory standard does not require absolute conformity between WR and study results. As a court has held,

> A denial of pediatric exclusivity for failure to meet a single term of a written request would not be in accordance with section 355a(d)(3), which plainly does not require compliance with every single provision of a written request, but requires only that a pediatric study "fairly respond" to a written request. Nor would it be consistent with the statutory standard to deny pediatric

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15 *See* WR Amendment 5 at 4.

16 *See* FDA Preliminary Meeting Comments, Type A Meeting, submitted Sept. 2, 2013.

17 *See, e.g.*, Type C Meeting Denial, Dec. 24, 2016 ("In regards to the WR, we will not have any more discussion on this, please review our last correspondence on the WR amendment 5 dated October 14, 2015 and use your discretion moving forward."); Memorandum of Meeting Minutes, Type B Pre-NDA Meeting, Sept. 21, 2016, at 5.

18 *Id.*

> exclusivity because of disappointment with data submitted by a manufacturer if the study as a whole is a fair response to the written request.[19]

Furthermore, even if the agency decides not to approve Sensipar for use in a pediatric population, the statute clearly intends that exclusivity must be recognized where, as here, a sponsor conducts and submits reports of pediatric studies that fairly respond to FDA's request.

Amgen's pediatric study program was sufficient to generate the following components for the NDA:

- Chemistry, Manufacturing, and Controls information for an age-appropriate formulation developed for pediatric use (1, 2.5, and 5 mg capsule dosage forms).
- Reports from two juvenile toxicity studies conducted upon FDA recommendation (Studies 109584 and 110057).
- Bioavailability/bioequivalence study report of the 5 mg cinacalcet capsule dosage form (6 capsules total), administered with contents (granules) sprinkled onto applesauce or swallowed whole with applesauce, compared with the 30 mg commercial Sensipar tablet, swallowed whole with applesauce, in healthy adult subjects (Study 20070293).
- Final CSRs for Studies 20090005, 20070208, 20110100, and 20130356 (WR Studies 1, 2, 3, and 4, respectively). All reports included information on the representation of pediatric subjects of ethnic and racial minorities.
- Interim CSR from Study 20140159, the open-label extension protocol to Studies 20110100 and 20130356 (WR Studies 3 and 4).
- A summary of demographic and drug-use data from NAPRTCS national registry with > 6000 registered pediatric dialysis patients. A prospective registry was performed to evaluate safety information for 538 pediatric dialysis patients, including 90 patients treated with cinacalcet (Study 20120116).
- Population PK and exposure-response (PK/PD) analyses using data from Studies 20090005, 20070208, and 20110100 (WR Studies 1, 2, and 3) that relate the time course of plasma cinacalcet concentrations with the changes in serum calcium (safety) and PTH (efficacy) levels and support the dosing recommendations proposed for pediatric patients. Results also support consistency in PK and PD of cinacalcet between adults and children.
- A Bayesian extrapolation analysis that infers the treatment effect of cinacalcet on PTH from the adult population to the overall pediatric population and to children ages 28 days to < 6 years with CKD and secondary HPT receiving dialysis.
- A summary of the published literature on the use of cinacalcet in pediatric patients.
- A summary report evaluating all pediatric postmarketing adverse event reports regarding cinacalcet that are available to Amgen.
- Proposed pediatric labeling to incorporate the findings of the studies, including information on dosing, safety, efficacy, PK, PK/PD, product excipients, and storage and handling.
- Study datasets from Studies 20070208, 20110100, 20130356, and 20140159, as well as datasets supporting the Integrated Summary of Safety, and Bayesian analysis (according to Study Data Tabulation/Clinical Data Interchange Standards Consortium standards).

Even with the differences in the number of completers in Study 3, Amgen's pediatric program was sufficient to achieve the goal of assessing the safety and efficacy of using cinacalcet in all pediatric subsets requested in the WR,

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[19] *Merck & Co. v. FDA*, 148 F. Supp. 2d 27, 30 (DDC 2001).

including the safety subset in Study 3. By this or any measure, the program fairly responds to FDA's WR, as amended, and qualifies for pediatric exclusivity under the Act.

D. Pediatric Exclusivity Was Intended to Incentivize Studies Like Those Amgen Conducted

Congress implemented the pediatric exclusivity provisions of the Act to incentivize manufacturers to generate data in pediatric populations, especially where that data would be difficult to obtain because of small population size, difficult study design, or uncertainty concerning the adverse event profile of the study drug in pediatric patients.[20]

Failure to grant pediatric exclusivity to Amgen's studies would be contrary to law, but it would also jeopardize the incentive structure developed around pediatric studies. In this case, Amgen invested significant time – 11 years – and undertook significant risk to generate data in the pediatric use of cinacalcet.

At present, there are no FDA-approved products indicated specifically for the management of secondary HPT in pediatric patients with CKD receiving dialysis. One drug, calcitriol injection, is indicated generally for the treatment of secondary HPT in patients on dialysis but does not carry a specific pediatric indication, and information on pediatric use in the label is limited to a single 12-week study of pediatric patients aged 13 and older.[21] Calcitriol tablets are also available, but the tablets have never been subject to a controlled study in pediatrics, and dosing recommendations are based on studies of adult patients and non-placebo controlled studies of pre-dialysis pediatric patients.[22] There are no data for calcitriol of the type that Amgen generated for cinacalcet: clinical experience from multiple studies, including studies in pediatric patients as young as 8 months old. Nor are there any other cinacalcet products that could serve as a source of pediatric data. As a result, practitioners treating HPT in pediatric patients receiving dialysis are currently left with no choice but to administer a drug without a pediatric formulation, pediatric labeling, or reports of pediatric studies.

It was to address this concern that FDA urged Amgen to undertake this development program (toxicology, PK, formulation development, and clinical studies) and to continue the study program even after the pediatric death in the initial study.[23] Moreover, no other study can be expected to improve or add to the data Amgen has gathered. Manufacturers of generic cinacalcet, if one were approved, would have no incentive to undertake an eleven-year development and study program; nor would innovators undertake such a program without the incentive of pediatric exclusivity. Given that the enrollment challenges will never get easier, the Amgen studies represent the furthest that the data can be expected to develop. The Act recognizes such efforts with pediatric exclusivity, and FDA should not withhold it here.

III. STEPS PREVIOUSLY TAKEN TO RESOLVE THE DISPUTE

Amgen has worked diligently with FDA to assure that the studies adequately met the WR, beginning in the development of the pediatric studies and continuing through the agency's evaluation of the submitted applications.

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[20] *See, e.g.*, FDA, Best Pharmaceuticals for Children Act and Pediatric Research Equity Act, July 2016 Status Report to Congress, at 1 ("To incentivize sponsors to conduct pediatric studies of drugs when the Agency believes the studies may produce benefits in pediatric populations, BPCA allows FDA to issue WRs to sponsors to conduct studies and establishes a framework whereby sponsors can qualify for 6 months of additional marketing exclusivity.").

[21] *See* Prescribing Information (PI) for calcitriol injection, (updated May 14, 2013).

[22] *See* Prescribing Information (PI) for calcitriol capsule, (updated May 14, 2013).

[23] *See* FDA Preliminary Meeting Comments, Type A Meeting, submitted Sept. 2, 2013 ("No, we do not agree (that the study should be discontinued), we continue to believe that cinacalcet can be useful for the management of secondary hyperparathyroidism in the pediatric population and that the cinacalcet pediatric program should continue with enhanced titration and monitoring safeguards.").

During clinical development, Amgen was able to adequately enroll WR Study 3 but was not able to obtain enough completers, due in part to the clinical hold and in part to other factors, including pediatric patients dropping out before their term was complete because pediatric patients on dialysis are prioritized for kidney transplants. When Amgen first became aware of the completion issue, it proactively approached FDA and inquired about modifications to ensure WR Study 3 could satisfy the purpose of the investigation. Amgen was permitted to modify the protocol to simplify procedures in response to site personnel feedback, and FDA directed Amgen to continue the program. In December 2015, FDA declined Amgen's meeting request to further discuss the ongoing clinical studies and the enrollment challenges that Amgen was having. On multiple occasions, FDA advised Amgen that the agency would not further amend the WR and would not participate in further discussion on the topic. Amgen completed the program as it was able and submitted results of the studies to FDA.

Amgen's first indication that the review division might not view Amgen's studies favorably came in a draft labeling mark-up from the Division, received on May 1, 2017, only 21 days before the statutory 180-day deadline. There, the division omitted the proposed pediatric indication and did not include any data from the pediatric studies in the labeling, except for information about the single fatality during the program. Amgen was given 48 hours to respond and immediately asked for a telephone conference to better understand the Division's concerns in order to respond appropriately. However, Amgen's meeting request was immediately denied by the Division. Instead, Amgen responded within the required 48-hour window with draft labeling that restored the pediatric study information and a response document justifying the inclusion of the pediatric information and accompanying pediatric exclusivity. This submission prompted a discussion with the Division, and the Division invited Amgen to submit proposed language for Section 8.4 of the PI regarding pediatric experience with the drug. Amgen will make this submission on May 8, 2017.

As a result, the review division has given every indication that it will deny Amgen's pediatric indication and proposed pediatric oral dosage form for Sensipar. Thus, the company is concerned that its request for exclusivity will similarly face a skeptical audience. As explained above, forcing Amgen to wait to request formal dispute resolution until a final decision is issued at the 180-day deadline, on May 22, will effectively deny Amgen relief. Pediatric exclusivity must be issued more than 9 months before the expiration of the patent or exclusivity to which pediatric exclusivity will attach. Amgen has taken every avenue available to timely complete the studies, submit its application, and resolve the labeling dispute with FDA. Now, in order to be afforded relief, Amgen is requesting dispute resolution to assure this important issue is resolved in a timely way. For the same reasons, Amgen also requests expedited consideration of this request, with a response no later than May 22, 2017. Unless a decision is made on this request by that date, Amgen will assume it has exhausted its administrative remedies and that it is free to seek judicial relief.

IV. PROPOSED POSSIBLE SOLUTIONS AND EXPECTED OUTCOMES

Amgen is requesting that the agency independently assess, based on the record, whether the pediatric study program and studies submitted in these applications fairly respond to the WR. If FDA agrees that the studies fairly respond, Amgen respectfully requests that the agency grant pediatric exclusivity as soon as possible, and in no event later than May 22.

V. IDENTITY OF THE DIVISION ISSUING THE DECISION

The decision was issued by CDER's Pediatric Exclusivity Board, in consultation with the Division of Metabolic and Endocrine Drug Products.

VI. ADVISORY COMMITTEE REVIEW

Amgen is not requesting advisory committee review at this time.

VII. LIST OF DOCUMENTS PREVIOUSLY SUBMITTED

- NDA 209962
- NDA 021688 supplement 023
- FDA Written Request for Pediatric Studies, Amendment 5
- IND 56010
- IND 109361
- Letter to the Review Division responding to proposed labeling changes (May 2, 2017)
- Response to proposed labeling changes (May 2, 2017)

VIII. STATEMENT REGARDING NEW INFORMATION

At this time, no new information has been submitted in support of this formal dispute resolution request. The last deciding official at the Division of Metabolic and Endocrine Drug Products, working with the Pediatric Exclusivity Board, had the opportunity to review all of the material now being relied upon for this formal dispute resolution request, as listed in Part VII, *supra*. As the Division reaches a final decision on the exclusivity determination, Amgen may be required to supplement this record with its own meeting minutes to provide a record of discussions with Division personnel regarding resolution of the partial clinical hold and denial of the requests to amend the WR. As the Division was a participant in these conversations, the relevant personnel are familiar with the content of the documents.

IX. SPONSOR CONTACT INFORMATION

Dr. Steven K. Galson, M.D., M.P.H.
Sr. Vice President, Global Regulatory Affairs & Safety
805-447-4988
sgalson@amgen.com
One Amgen Center Drive
Thousand Oaks, CA
91320-1799

If you have any questions or need additional information, please contact me at my direct line at 805-447-4988 or by electronic mail at sgalson@amgen.com.

Sincerely,

Dr. Steven K. Galson

cc: Elizabeth Dickinson
FDA Chief Counsel

Peter Stein, M.D.
Chair, Pediatric Exclusivity Board

Meredith Manning
Hogan Lovells US LLP

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021688/S-023
NDA 209962

CORRESPONDENCE

Amgen Inc.
Attention: Juliana Sholter, MS, RAC
Manager, Regulatory Affairs
601 13th Street NW, 12th Floor
Washington, D.C. 20005

Dear Ms. Sholter:

Please refer to your Supplemental New Drug Application (NDA) and New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sensipar (cinacalcet hydrochloride) Tablets and Capsules for Sprinkling, respectively.

Pediatric exclusivity (PE) is denied for studies conducted on cinacalcet hydrochloride, under section 505A of the Act. The reasons for this determination are described below.

I. Legislative/Regulatory Background

The basis of a denial of PE can best be understood in light of the structure and context of the PE provisions of Section 505A of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. § 355a (as amended).

As required by Section 505A, the PE process begins with FDA drafting and issuing a Written Request (WR) for information relating to the use of a drug in the pediatric population that may produce health benefits in that population. The Agency has a meaningful opportunity to obtain pediatric information through the PE process, so each WR is designed, within the limits of good science and ethics, to elicit information on the use of the entire active moiety in relevant pediatric populations that will result in labeling for those populations. The Agency drafts each WR to obtain studies that will allow the Agency to determine whether and how the drug should be used in pediatric patients and will permit drug products containing the active moiety to be fully labeled for pediatric populations for whom the drug has been (or is likely to be) prescribed.

In determining the scope of a WR, FDA asks: (1) Is there a health benefit to studying this drug for the proposed indication in the pediatric population; (2) In what age groups in the pediatric population does this indication occur; (3) What information does the Agency currently have regarding use of this drug for this condition in relevant pediatric age groups; and (4) What studies are necessary to fill in the gaps in pediatric information in the Agency's possession and to fully label drug products containing the active moiety for relevant pediatric populations?

The PE, if granted, attaches to all patents and exclusivity protecting the sponsor's drug products containing the active moiety, not just to protections on the particular product, indication, or population studied. A sponsor who obtains PE thus gets six additional months of potential delay of competition for every one of its products containing the active moiety that has existing patent protection or exclusivity. Because of the broad scope of the benefit, WRs are generally crafted to elicit all of the information needed to label all of the sponsor's drug products containing that active moiety for use in relevant pediatric populations.

In reviewing a submission in response to a WR, the statute states that the Secretary's "only responsibility" in accepting or rejecting the reports is to determine "whether the studies fairly respond to the written request, have been conducted in accordance with commonly accepted scientific principles and protocols, and have been reported in accordance with the requirements of the Secretary for filing." Section 505A(d)(3) of the FD&C Act.

The Pediatric Exclusivity Board (Board) considers a number of factors when assessing, as required by statute, whether the studies "fairly respond" to a WR.

First, the Board considers the purpose of the PE provision as described in the statute, with reference to the legislative history. The statute makes clear that its purpose is to generate clinical information on the use of drug products in children that will result in a health benefit to pediatric populations. The legislation was enacted to provide an incentive for sponsors to conduct studies to fill in the gaps in safety and efficacy information in product labeling regarding the use of drug products in relevant pediatric populations. The legislative history refers to pediatric populations as "therapeutic orphans" on whom therapies approved for adults are frequently used, but for whom approved and properly labeled therapies are lacking. S. Rep. No. 105-43, at 51 (1997). The legislative history makes clear (and the Agency's experience confirms) that for FDA-regulated products, the health benefit is obtained when the information that a physician needs to properly prescribe a medication is described in the product's labeling. Thus, the provision attempts to ensure that when PE is granted for studies, FDA also may approve labeling describing the results of the studies and providing adequate information for use of the drug in relevant pediatric populations. Id. at 52.

Second, when the pediatric studies are submitted and an exclusivity determination requested, the Board evaluates the information sought in the WR (including any amendments) and the objectives stated in the WR. The Board asks whether the studies were designed and carried out by the sponsor in a way likely to meet those objectives specified in the WR and underlying the exclusivity provision as a whole. The Board looks at the specific requirements that the WR imposed to support these objectives. For example, if a specific number of patients is requested or a specific study duration or endpoint is specified to ensure that the study will generate adequate data to provide a health benefit, failure to comply with these elements of the WR may result in a denial of exclusivity. Denial is likely if, in the absence of compliance, the studies are not expected to be interpretable or will not provide information that otherwise yields a health benefit to pediatric populations. In such cases, the studies are regarded by FDA as not having "fairly respond[ed]" to the WR. In making this determination, the Board also will look at the nature of the drug or class of drugs, the nature of the use (*e.g.*, chronic vs. short term), the adverse event profile in adults, and the nature of the gaps in the existing labeling.

Ultimately, the Board considers a "fair response" to the WR to be one that responds to the specific elements in the WR in light of the objective stated in the WR and the overall purpose of the PE legislation. In determining whether a submission "fairly responds" to a WR, FDA considers whether the submission is sufficient to enable it to approve pediatric labeling (including negative pediatric labeling) for all of the age groups and indications requested based on the studies conducted. Where a WR is capable of more than one interpretation, the Board considers a fair response to be one that interprets the WR in a manner likely to generate information that will provide a health benefit (including meaningful pediatric labeling) in the relevant populations that the WR asked the sponsor to study. If the studies submitted fairly respond to the WR, the Board will recommend that PE be granted (assuming the other statutory requirements for PE are met). If, on the other hand, the sponsor responds to the WR in such a way that the possibility of a health benefit (including meaningful pediatric labeling) from the studies conducted is not likely, the Board is likely to conclude that the submission does not "fairly respond" to the WR.

II. Summary of Factual Background

FDA originally issued a WR on May 5, 2010, to obtain the information needed to understand (and describe in labeling) the safety and effectiveness of the long term use of cinacalcet in children 28 days to < 18 years of age. The main objective of WR was to establish the benefits of cinacalcet use for the chronic treatment of hyperparathyroidism (HPT) secondary to end-stage renal disease in pediatric patients receiving either hemodialysis or peritoneal dialysis, and to adequately characterize the risks associated with this intended use in pediatric patients. The clinical studies included in the WR were to generate the clinical data necessary to label cinacalcet for use in children 28 days to < 18 years of age.

The following facts summarize the interactions between FDA and Amgen pertinent to this WR:

- On May 4, 2007, Amgen submitted a Proposed Pediatric Study Request (PPSR) to IND 056010.
- On June 20, 2007, A teleconference between FDA and Amgen was held to discuss the PPSR.
- On June 29, 2007, Amgen submitted a summary of the discussions held at the June 20, 2007, teleconference (IND 56010).
- On September 4, 2007, FDA denied issuance of a Written Request but encouraged Amgen to submit a new PPSR that addressed the recommendations made at the June 20, 2007, teleconference and in the denial letter.
- On April 11, 2008, Amgen submitted a new 5 mg pediatric capsule presentation to IND 56010.
- On May 23, 2008, FDA in an email communication asked that this new presentation be handled in a new IND (109361).
- On June 20, 2008, Amgen requested feedback from FDA on a key juvenile chronic toxicology study to support the conduct of pediatric studies for a new PPSR.
- On July 23, 2008, FDA responded to Amgen's questions on the key juvenile chronic toxicology study to support the conduct of pediatric studies for a new PPSR.

- On December 22, 2009, Amgen submitted a new Proposed Pediatric Study Request for cinacalcet to IND 056010.
- On March 17, 2010, A teleconference between FDA and Amgen was held to address FDA questions related to the new PPSR.
- On April 25, 2010, Minutes of the discussions for the March 17, 2010, teleconference were submitted to IND 56010.
- On May 5, 2010, FDA issued a WR for cinacalcet.
- On June 24, 2010, Amgen requested modification of, and submitted a proposed first amendment to, the WR.
- On September 7, 2010, A teleconference between FDA and Amgen was held to discuss proposed changes to the WR.
- On September 15, 2010, Minutes of the discussions for the September 7, 2010, teleconference were submitted to IND 56010.
- On December 14, 2010, FDA issued an amended WR to allow for extrapolation of efficacy in patients 28 days to 6 years of age. Therefore, a new safety study (Study 3) was added to account for this change (because additional safety information is required when extrapolation of efficacy is accepted).
- On February 08, 2011, Amgen submitted correspondence to IND 109361 requesting clarification of FDA's December 14, 2010 WR amendment.
- On March 25, 2011, FDA amended the WR a second time to adjust the number of patients in Studies 1 and 2 and responded to Amgen's January 20, 2011, list of clarifying questions.
- On June 7, 2011, Amgen submitted draft protocol 20110100 (WR Study 3) requesting FDA review and comments.
- On June 28, 2011, FDA responded to Amgen's June 7, 2011, request for draft protocol 20110100 (WR Study 3) review and comments.
- On December 27, 2012, a 14-year old patient enrolled in WR Study 2 (20070208) died
- On January 31, 2013, Amgen notified FDA by email of their intent to submit "Dear Investigator Letters" notifying investigators in WR Study 2 (20070208) and Study 3 (20110100) of their intent to immediately suspend dosing in both studies based on a preliminary review of the fatality. Amgen also notified FDA that the fatality had erroneously been reported to IND 056010.
- On January 31, 2013, FDA notified Amgen by telephone to suspend dosing in all pediatric studies and asked that the treatment allocation for the case be revealed.
- On February 7, 2013, FDA issued a clinical hold letter for pediatric studies and asked that Amgen submit details of the fatality and other pertinent information related to pediatric safety.
- On July 8, 2013, Amgen requested a meeting with FDA to seek agreement on Amgen's plan to discontinue the WR studies, on Amgen's assessment that the data collected in the clinical pediatric program was sufficient to inform product labeling, and on potential modifications to the WR to reflect that Amgen can qualify for pediatric exclusivity without conducting any additional pediatric studies.
- On September 4, 2013, a teleconference between FDA and Amgen was held to address Amgen's July 8, 2013 questions to FDA. FDA did not agree that the data collected in the cinacalcet pediatric program was sufficient to inform product labeling and did not agree to amend the WR to eliminate the need for Amgen to conduct further pediatric studies.

- On October 5, 2013, Minutes of the September 4 2013 teleconference were issued.
- On December 13, 2013, FDA notified Amgen that they could resume dosing pediatric patients in the single dose WR Study 1 (20090005) and asked the applicant to submit a finalized protocol for WR Study 4 (20130356) to resolve the hold on dosing pediatric patients in multiple dose studies.
- On December 20, 2013, Amgen submitted a meeting request to seek FDA agreement on a plan to resume the cinacalcet pediatric program with added dosing safeguards and their intent to seek an amendment to the WR.
- On February 4, 2014, FDA met with Amgen to discuss Amgen's plan to resume the pediatric program and to seek an amendment to the WR.
- On March 14, 2014, FDA notified Amgen that they could resume dosing in pediatric patients in the multiple dose studies (including WR Study 4 (20130356)).
- On March 31, 2014, Amgen requested a third amendment to the WR.
- On July 29, 2014, FDA issued a third amendment to the WR that allowed early termination of WR Study 2 and added WR Study 4 to support an adequate evaluation of safety and efficacy in patients 6 years to < 18 years of age, given the early termination of WR Study 2.
- On December 12, 2014, Amgen requested for a fourth amendment to the WR to reduce the required number of completers in WR Study 4.
- On April 9, 2015, FDA amended the WR a fourth time, allowing for a reduction in the number of completers in WR Study 4.
- On June 19, 2015, Amgen submitted a request to amend the WR a fifth time to redefine the efficacy assessment phase and make it easier for the WR term to be met, to remove language related to the statistical power required for WR Study 4 to meet its objective, and the requirement that Amgen seek FDA agreement on the final statistical analysis plan prior to study completion.
- On October 14, 2015, FDA issued a fifth amendment to the WR allowing for Amgen's requested changes to Study 4.
- On December 3, 2015, Amgen requested that FDA amend the WR for a sixth time to reduce the number of completers required in the WR for Study 3 and Study 4.
- On December 24, 2015, FDA declined to amend the WR for a sixth time as Amgen had requested (see Section III below).
- On July 1, 2016, Amgen requested a meeting to discuss their intent to submit an NDA for a pediatric indication.
- On September 21, 2016, a meeting between FDA and Amgen was held to discuss the overall cinacalcet pediatric development program and Amgen's intent to submit an NDA for a pediatric indication.
- On November 23, 2016, Amgen submitted NDAs 209962 and 021688/S-023 with a request for a pediatric exclusivity determination for cinacalcet.

III. Basis for Denial of Pediatric Exclusivity for Cinacalcet

The following four studies are included in the WR as amended and were conducted under IND 109361:

1. WR Study 1 (20090005): An open-label, single-dose, pharmacokinetics (PK) and pharmacodynamics (PD) study to characterize the single-dose PK and PD profiles and the safety of a single dose of cinacalcet in pediatric patients ages 28 days to less than 6 years with chronic kidney disease (CKD) and secondary HPT receiving dialysis.

2. WR Study 2 (20070208): A 30-week, randomized, double-blind, placebo-controlled, efficacy and safety study with a 30-week, open-label, safety extension in pediatric patients ages 6 years to less than 18 years with CKD and secondary HPT receiving dialysis. This study was to include an assessment of pharmacokinetic (PK) parameters using a sparse sampling design. Study 2 was terminated early and was to be analyzed with available data.

3. Study 3 (20110100): A 26-week or time-until transplantation (whichever comes first), open-label, safety study in pediatric patients ages 28 days to less than 6 years with CKD and secondary HPT receiving dialysis to evaluate the safety of cinacalcet and characterize the PK profile in pediatric patients.

4. Study 4 (20130356): A 20-week, randomized, open-label, controlled efficacy and safety study in pediatric patients ages 6 years to less than 18 years with CKD and secondary HPT receiving dialysis. An open-label extension protocol to Study 4 was to assess longer term safety of cinacalcet for at least 7 additional months.

To place the studies in the amended WR in perspective, we note that the initial (unamended) WR requested two studies:

1. A single-dose PK study in pediatric patients ages 28 days to less than 6 years with CKD and secondary HPT receiving dialysis. This study had to enroll enough patients to properly evaluate PK in two age groups: 28 days to less than 3 years, and 3 years to less than 6 years.

2. A 30-week, randomized, double-blind, placebo-controlled, efficacy and safety study in patients 28 days to less than 17 years of age that was to be followed by a 26-week single arm, open-label, safety extension. This study was to enroll a minimum of 100 patients.

As stated above, Amgen requested that FDA amend this WR six times.

In the first amendment, among other things, FDA revised Study 2 to allow for the extrapolation of efficacy to younger patients (28 days to less than 6 years) from data gathered for older pediatric patients (6 to l8 years) and removed the younger age group from the scope of that study. Because additional safety information is required when extrapolation of efficacy is accepted, a third study was added to adequately characterize the risks of cinacalcet in the younger patient population during long-term use. Accordingly, this study (Study 3) would be a 26-week (or time until transplantation, whichever happened first) open-label study in patients 28 days old to less than 6 years. FDA requested that a minimum of 15 patients complete Study 3 and specified that patients who terminate the study prematurely to undergo kidney transplant may be considered completers if they have been enrolled for at least 12 weeks.

In the second amendment, among other things, FDA relaxed some of the requirements for Study 1, and clarified that while 100 patients should be enrolled in Study 2, 70 patients were required to complete the 30-week double-blind portion, and that 30 patients were required to complete the open-label extension.

The third amendment, among other things, acknowledged that Study 2 had been terminated early and available data would be analyzed. It decreased the number of patients in Study 2 from 100 to 40 to account for the early termination. It also added Study 4, which would have at least 48 patients.

The fourth and fifth amendments, among other things, included a reduction in the number of patients who were required to complete Study 4, and a reduction in the exposure time required to define completion. In amendment 4, FDA agreed to lower the number of patients required to complete Study 4 from 48 patients with 20 weeks of data to a minimum of 40 patients with at least 12 weeks of data. In amendment 5, FDA agreed to loosen the definition for the efficacy assessment phase for Study 4, to remove language related to the required power for Study 4 and to remove language requiring that Amgen seek FDA agreement on the final statistical analysis plan prior to study completion.

Amgen then requested that FDA amend the WR a sixth time, proposing to further decrease the number of completers required in Study 3 and Study 4. FDA denied this amendment request because the number of patients enrolled in Study 4 had already been reduced in previous amendments and because reducing the number of required completers in Study 3 as Amgen proposed was not likely to yield sufficient information to adequately characterize the safety of the product for its intended chronic use in patients 28 days to 6 years of age, and therefore was unlikely to satisfy the purpose of the WR (see further discussion below).

Amgen's pediatric studies submitted in response to the October 14, 2015 amended WR for cinacalcet (NDAs 209962 and 021688/S-023) did not meet the terms of the WR, and in particular failed to meet the criteria for Study 3 of the WR, as detailed below. Moreover, even though Amgen has met the literal terms of the WR for Studies 1, 2, and 4, considering Amgen's submission in its entirety, the Board concludes that Amgen has not fairly responded to the amended WR as a whole. The Board reaches this conclusion based on a review of the record relating to the amended WR and after conferring with the Division of Metabolism and Endocrinology Products (Division) on its assessment of the data in the submission. The basis for this conclusion is summarized below.

An insufficient number of patients 28 days to < 6 years of age completed WR Study 3 and clinical data in the submission were insufficient to allow FDA to adequately characterize the risks of cinacalcet for its chronic intended use in this age group.

Study 3 was designed to evaluate the safety and tolerability of cinacalcet in pediatric patients ages 28 days to < 6 years of age when used chronically as intended in patients undergoing dialysis, and to characterize the cinacalcet PK profile in these pediatric patients.

The amended WR provides the number of patients required to be studied for Study 3:

"A minimum of 15 patients must complete this 26-week study. Patients who terminate the study prematurely to undergo a kidney transplant may be considered completers to satisfy this study requirement minimum if they have been enrolled in the study for at least 12 weeks."

Cinacalcet is titrated by increasing the dose until it is effective, and is intended to be used chronically in dialysis patients. Safety data for a minimum of 15 patients completing 26 weeks was considered by FDA to be a critical amount of information required to determine whether the product is safe in young pediatric patients for chronic use. Study 3 was set up as a 26-week trial because the protocol relied on a very gradual cinacalcet dosing strategy. The starting dose selected was low, in order to minimize risks to participants, and was not expected to have a therapeutic effect. The dose of cinacalcet was to be increased every 4 weeks according to protocol-specified instructions until the therapeutic target defined in the protocol was reached, or until Week 20 if the therapeutic target was not reached. The design of the trial thus anticipated that attainment of effective doses could necessitate up to five dose increases and take up to 20 weeks. The selected duration of the study ensured that at least 4 weeks (i.e., from Week 20 to 24) of safety data at effective doses would be available from subjects who completed the trial (i.e., completers). Accordingly, the study was designed to provide safety information during both cinacalcet titration and at stable effective doses. In setting the Study 3 exposure (number of patients and duration), the Division also understood that data from Study 4 in older children ($\geq$ 6 years of age to < 18 years) would provide supportive safety information in younger patients assuming that Study 4 provided a robust assessment of safety in those older age children. Such a supporting safety assessment required that an adequate number of older children be included in Study 4 and that cinacalcet dosing be sufficient to attain a therapeutic effect, indicating adequate exposure to the medication. Thus, two sources of safety information on cinacalcet in younger children were to be evaluated: safety information from Study 3 as the primary source, with supportive safety information collected in older patients from Study 4.

In considering whether the WR criteria related to Study 3 were met, the Division reviewed all available data submitted in Amgen's report. The Division noted that only 4 patients were completers with 3 completing 26 weeks and 1 subject, who received a kidney transplant, completing 12 weeks of treatment. *Thus, only 4 patients out of the 15 (or 27%) required by the WR for Study 3 completed the study.* Of note, more than half (i.e., 9 out of 17) of all of the subjects who were enrolled and exposed to cinacalcet failed to complete the study; and, 5 out of those 9 subjects failed to complete due to study closure in June 2016, when Amgen terminated the study. These failures to complete the study resulted in limiting exposure time to cinacalcet and the study not achieving the requested number of completers, as stated in the protocol. Moreover, many of the non-completers who received cinacalcet in Study 3 were exposed to doses that were too low to adequately characterize the safety of the product for its intended use: the safety data collected for most individuals reflect low dose exposure for a majority of the time those individuals were in the study, and does not reflect titration to effect as the protocol specified. Finally, the duration of exposure was also insufficient to adequately characterize the safety of the product for chronic use. Importantly, only a single completer was exposed to cinacalcet for the full duration. The median duration of exposure was only 12 weeks. As noted above, the WR specified that Study 3 should, at a minimum, include 15 completers that should

ideally have been exposed to cinacalcet for 24 weeks,[1] and the median exposure for the 18 patients enrolled fell far short of this minimum level.

As noted above, two sources of safety information on younger children (i.e., those 28 days to < 6 years of age) had been anticipated: results from Study 3 and supportive safety information from Study 4. In addition to the inadequate exposure from Study 3, discussed above, supportive safety information from Study 4 was also limited due to inadequate cinacalcet titration. Study 4 demonstrated no significant therapeutic effect with cinacalcet treatment relative to placebo. The lack of evident efficacy suggests that cinacalcet dosing in this study provided lower than clinically relevant exposures, markedly limiting the utility of safety information relevant to the older age group in this study, as well as supportive information for the younger children in Study 3.

Amgen proposed a sixth amendment to the WR on December 3, 2015 that would have reduced the number of young pediatric patients required to complete Study 3 to reflect the number of anticipated completers. Amgen claimed that this reduction was necessary due to the following issues:

- 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 due to a pediatric fatality;
- 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.

Although acknowledging the challenges with recruitment, the Division was concerned that the significantly lower patient numbers proposed in the amendment would not be expected to provide sufficient information to establish the safety of the product in the younger patient population. Therefore, the Division denied this amendment on December 24, 2015.

To attempt to address the deficiencies described above in the safety database in younger children (28 days to < 6 years), Amgen included additional safety data in 23 patients in a retrospective chart review. However, these data have only limited value to inform about the risks of the drug for its intended use. This retrospective case review is subject to the limitations and biases of retrospective observational chart review, which include voluntary participation, selection bias, uncertainty with regard to how the product was used, uncertainty with regard to exposure in terms of dose and duration of exposure, uncertainty with regard to the dosing regimen used (i.e., administration schedule and titration), uncertainty surrounding the completeness of ascertainment and reporting of safety data, and missing data. Amgen acknowledges these limitations in its submission of these data: "Although a research plan was developed prospectively for this chart review, this review shares similar limitations to other retrospective observational analyses, i.e., propensity for missing data, accuracy and completeness of data quality, and chart selection determination." Although such information can provide supportive

[1] The Division was willing to consider a minimum exposure duration of 12 weeks for a small subset of subjects who underwent a kidney transplant, but the Division expected only a few patients to be in this category, given that Amgen estimated that less than 30% of subjects would get a transplant and the inclusion / exclusion criteria for the study excluded patients who were scheduled for a kidney transplant.

information, this cannot replace the missing robust safety information from a randomized, controlled clinical trial such as Study 3.

In summary, Amgen's failure to provide sufficient safety data in the 28 day to < 6 year old age group prevents FDA from drawing any conclusions about the safety of the product in patients < 6 years of age when used as intended. If the totality of safety information Amgen submitted had provided an appropriate safety assessment in younger children and supported a label description—even if the exact minimum number of patients had not been met in Study 3—this element of the WR could have been adequately satisfied and Amgen's response could be considered a fair response to the WR as a whole. However, in the absence of any robust source of safety information in this vulnerable age group (again, considering Study 3, supportive information from Study 4, and other sources of information), the Board concludes that this criterion was not met. Accordingly, the Board concludes that Amgen has failed to fairly respond to the WR.[2]

IV. Conclusion

Amgen did not fairly respond to the amended WR for cinacalcet. Amgen's failure to meet an important element of the WR also resulted in the lack of sufficient safety data for pediatric patients < 6 years of age with secondary HPT and CKD receiving dialysis. The lack of sufficient safety data in this population has led to the inability to clearly establish the safety profile of the drug for pediatric patients in accordance with objectives of the amended WR. Accordingly, PE is denied for cinacalcet.

In accordance with section 505A(k)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a), as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA), a submission of a pediatric study report seeking exclusivity requires the Secretary to make available to the public the medical, statistical, and clinical pharmacology reviews of the same.

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Peter Stein, M.D.
Deputy Director
Office of New Drugs
Center for Drug Evaluation & Research

[2] We note that there may be an alternative basis for denial of PE based on the non-completion of a study or studies that were subject of this WR, see section 505A(h) of the FD&C Act, but, since the Board concludes that Amgen has not fairly responded to the WR under section 505A(d)(3) of the FD&C Act, the Board has not reached the separate question under section 505A(h) in making its decision.

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/s/

PETER P STEIN
05/22/2017
Concur with determination