2. SYNOPSIS

Name of Sponsor: Amgen Inc., Thousand Oaks, CA

Name of Finished Product: Sensipar® or Mimpara®

Name of Active Ingredient: Cinacalcet (cinacalcet hydrochloride; cinacalcet HCl; AMG 073; N-[1-(R)-(1-naphthyl)ethyl]-3 [3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride)

Title of Study: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Using Cinacalcet to Correct Hypercalcemia in Renal Transplant Recipients With Autonomous Hyperparathyroidism

Investigators and Study Centers: This study was conducted at 33 centers in 11 countries (Australia, Austria, Belgium, Canada, France, Germany, Italy, Poland, Spain, Switzerland, and USA). Centers and principal investigators are listed in Section 16.1.4.

Publications: None

Study Period: 15 October 2009 (first subject enrolled) to 16 April 2013 (last subject completed follow-up visit)

Development Phase: 3

Objectives: The primary objective was to demonstrate the efficacy of cinacalcet for correcting hypercalcemia in kidney transplant recipients with autonomous hyperparathyroidism (HPT).

The key secondary objectives were to assess the efficacy of cinacalcet for increasing bone mineral density (BMD) at the femoral neck and to evaluate the efficacy of cinacalcet for raising serum phosphorus levels. Other secondary objectives were:

- to evaluate the impact of cinacalcet on kidney transplant function
- to evaluate the efficacy of cinacalcet for reducing corrected total serum calcium levels
- to evaluate the efficacy of cinacalcet for reducing plasma intact parathyroid hormone (iPTH) levels
- to assess the impact of cinacalcet on urinary calcium and phosphorus excretion
- to assess the safety and tolerability of cinacalcet (including evaluations of adverse events, acute rejection, kidney transplant failure, and hypocalcemia)

Exploratory objectives are listed in Protocol Section 1.3 (Section 16.1.1 of this report).

Methodology: This was a randomized, phase 3, double-blind, placebo-controlled, multicenter study. The study consisted of a 30-day screening phase, a 20-week dose-titration phase, a 6-week efficacy assessment phase (EAP), a 26-week blinded maintenance phase, and a 4-week post-treatment follow-up phase. After screening, eligible subjects were randomized at a 1:1 ratio to the cinacalcet or placebo group at a starting dose of 30 mg orally once daily. The randomization was stratified according to the corrected total serum calcium levels (≤ 11.2 mg/dL [2.80 mmol/L] and > 11.2 mg/dL [2.80 mmol/L]). Enrollment into the low calcium stratum (≤ 11.2 mg/dL [2.80 mmol/L]) was limited to no more than 70% of enrolled subjects, to ensure at least 30% of enrolled subjects were in the high calcium stratum (> 11.2 mg/dL [2.80 mmol/L]).

Possible doses of investigational product included 30, 60, 90, 120, and 180 mg of cinacalcet or placebo orally once daily. Subjects were eligible for a dose increase once every 4 weeks during the dose-titration phase and at study visits during the maintenance phase. Dose escalation was permitted during the EAP. Dose escalation was based on corrected total serum calcium values, iPTH values, and subject safety assessment.

Number of Subjects Planned: Approximately 100 subjects.

Diagnosis and Main Criteria for Eligibility: Eligible subjects were men or women ≥ 18 years of age at the start of screening who had received a kidney transplant ≥ 9 weeks at time of screening and ≤ 24 months before first dose (could be the first or a repeat kidney transplant). Subjects could receive the first dose of investigational product no sooner than 12 weeks post-transplant and no later than 24 months post-transplant.

During the screening period, subjects were required to have a stable, functioning kidney transplant, defined as Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 (chronic kidney disease stage 3 or better), mean corrected total serum calcium > 10.5 mg/dL (2.63 mmol/L), and iPTH > 100 pg/mL (10.6 pmol/L).

Subjects were ineligible for the study if any of the following key criteria were met:

- received cinacalcet therapy post-transplant for more than 14 days cumulatively
- anticipated parathyroidectomy within 6 to 12 months after randomization
- ongoing use of bisphosphonates or use within 6 months before screening
- ongoing use of 1,25-dihydroxyvitamin D3 [$1,25(OH)_2D_3$] (including other active vitamin D metabolites or analogs) or use within 30 days before screening
- ongoing use of calcium supplements or use within 30 days before screening

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Subjects randomized to cinacalcet received a starting dose of 30 mg orally once daily. Possible sequential doses of cinacalcet for titration were 30, 60, 90, 120, and 180 mg.

Manufacturing batch numbers are provided in Section 16.1.6.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Subjects randomized to the control group received placebo tablets that were presented in identical containers (bottles) and had the same appearance as cinacalcet tablets for the same dose level.

Manufacturing batch numbers are provided in Section 16.1.6.

Duration of Treatment: Approximately 60 weeks, which included a 30-day screening phase, a 20-week dose titration phase, a 6-week EAP, a 26-week blinded maintenance phase, and a 4-week post-treatment follow-up phase.

Study Endpoints: The primary endpoint was the achievement of mean corrected total serum calcium value < 10.2 mg/dL (2.55 mmol/L), during the EAP (weeks 21 to 26).

Key secondary endpoints were percent change in the BMD at the femoral neck measured by dual X-ray absorptiometry (DXA) scan from baseline to week 52 and absolute change in mean serum phosphorus from baseline to the EAP.

Other secondary endpoints were:

- absolute change in kidney transplant function assessed using MDRD eGFR from baseline to week 52
- absolute change in mean corrected total serum calcium from baseline to the EAP
- absolute change in mean iPTH from baseline to the EAP
- absolute change in urine phosphorus levels from baseline to the EAP

All other secondary endpoints, safety endpoints, and exploratory end points are listed in Protocol Section 10.2 (Section 16.1.1 of this report).

Statistical Methods: The proportion of subjects with a mean calcium value < 10.2 mg/dL (2.55 mmol/L) during EAP was compared between the 2 treatment groups using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline corrected total serum calcium level (≤ 11.2 mg/dL [2.80 mmol/L] and > 11.2 mg/dL [2.80 mmol/L]). The primary analysis was based on the full analysis set.

Change and percent change from baseline in BMD parameters, mean corrected total serum calcium, iPTH, and phosphorus and kidney transplant function during the EAP or week 52 were summarized and compared between the 2 treatment groups using an analysis of covariance with baseline corrected total serum calcium level as a covariate.

To control for multiple comparisons, hierarchical testing procedure (Westfall, 1999) was planned to test the primary and key secondary endpoints. The primary endpoint was to be tested at a significance level of 0.05 first. If the primary endpoint achieved significant result, the 2 key secondary endpoints were to be tested using the same hierarchical method; the percent change in BMD would be tested first, if the result achieved statistical significance, the change in serum phosphorus would be tested.

All other secondary endpoints were tested at a significance level of 0.05, without adjustment for multiplicity, while exploratory endpoints were summarized descriptively.

Safety analyses used the safety analysis set. All adverse events occurring during the study were coded using the latest version of the Medical Dictionary for Regulatory Activities dictionary and the subject incidences were tabulated. Laboratory parameters were summarized for each treatment group using descriptive statistics at each measurement time point.

Summary of Results:

Subject Disposition: A total of 179 subjects were screened, of which 114 subjects were randomized. All of the subjects who were randomized received at least 1 dose of the investigational product. Of the 114 subjects randomized, 57 subjects received cinacalcet and 57 subjects received placebo.

A total of 104 (91.2%) subjects (52 [91.2%] from the cinacalcet group and 52 [91.2%] from the placebo group) completed the study. Ten (8.8%) subjects (5 [8.8%] each, from the cinacalcet and placebo group) discontinued the study. The most frequent reason for study discontinuation in both the groups was withdrawal of consent (full consent withdrawn; 2 [3.5%] subjects each, in the cinacalcet and placebo groups).

A total of 17 (14.9%) subjects (6 [10.5%] from the cinacalcet group and 11 [19.3%] from the placebo group) discontinued investigational product. The most frequent reasons for investigational product discontinuation were requirement for alternative therapy (0 subjects in the cinacalcet group, 5 [8.8%] subjects in the placebo group), withdrawal of consent (full consent withdrawn; 2 [3.5%] subjects each in the cinacalcet and placebo groups, adverse event (2 [3.5%] subjects in the cinacalcet group and 1[1.8%] in the

placebo group), and partial consent withdrawn (0 subjects in the cinacalcet group and 2 [3.5%] in the placebo group).

Baseline Demographics:

Sex: 63 (55.3%) men; 51 (44.7%) women

Age: mean (Standard Deviation[SD]) = 52.3 (10.3) years old

Race: 93 (81.6%) white; 9 (7.9%) black; 3 (2.6%) Hispanic; 5 (4.4%) Asian; 2 (1.8%) Native Hawaiin or Other Pacific Islander; and 2 (1.8%) other.

Efficacy Results: Overall, 78.9% subjects in the cinacalcet group and 3.5% subjects in the placebo group achieved the primary endpoint of mean corrected total serum calcium value < 10.2 mg/dL [2.55 mmol/L] during the EAP; the difference (cinacalcet - placebo) in the proportions was 75.44% (95% confidence interval[CI] [63.83%, 87.05%]). The odds ratio (cinacalcet/placebo) was 91.41 (95% CI [18.76, 445.41]). The CMH test stratified by baseline corrected total serum calcium level yielded a Chi-Square test statistic of 66.437 with a p-value < 0.001, which was a statistically significant result for the primary endpoint. Results of the sensitivity and sub-group analyses were consistent with the primary analysis.

The median (Quartile 1[Q1], Quartile 3[Q3]) percent change in BMD at the femoral neck from baseline to week 52 was 1.24% (-1.52%, 4.70%) in the cinacalcet group as compared with 1.05% (-1.80%, 3.51%) in the placebo group. The least square mean estimate for the difference in the percent change in BMD between the 2 treatment groups (cinacalcet – placebo) was 1.41% (95% CI [-1.10%, 3.93%]). A test of treatment effect adjusting for baseline corrected total calcium level yielded a p-value of 0.266, indicating that there was no statistically significant effect of cinacalcet treatment on this endpoint. Since the first key secondary endpoint (BMD) was not statistically significant, no hypothesis testing was performed on the second key secondary endpoint of serum phosphorus. The p-values were therefore considered as nominal. The serum phosphorus mean (SD) change from baseline to EAP was 0.52 (0.54) mg/dL for the cinacalcet group and 0.07 (0.48) mg/dL for the placebo group. The least square estimate for the difference in the absolute change in mean serum phosphorus between the 2 treatment groups (cinacalcet – placebo) was 0.45 mg/dL (95% CI [0.26, 0.64]), and the nominal p-value for treatment effect was < 0.001.

Patient-reported Outcomes Results: No notable differences were observed in symptoms of joint pain, bone pain, or memory trouble between the 2 treatment groups, as measured by the Kidney Disease Quality of Life symptom list, from baseline to end of EAP.

Safety Results:

All 114 subjects who were randomized received at least 1 dose of investigational product and were included in the safety analysis set. The mean (SD) duration of exposure in the cinacalcet group was 339.1 (77.8) days; the average daily dose (mean [SD]) in the cinacalcet group was 61.65 mg/day (31.21 mg/day).

A total of 51 (89.5%) subjects in the cinacalcet group and 53 (93.0%) subjects in the placebo group reported at least 1 treatment-emergent adverse event during the study. Fifteen (26.3%) subjects from the cinacalcet group and 19 (33.3%) from the placebo group had serious adverse events. One (1.8%) subject from the cinacalcet group had a fatal adverse event of metastatic adenocarcinoma of the lung which was not considered related to investigational product. One (1.8%) subject from the placebo group had an adverse event leading to study discontinuation. Adverse events led to discontinuation of

investigational product for 2 (3.5%) subjects in the cinacalcet group (foot fracture; metastatic lung adenocarcinoma) and 3 (5.3%) subjects in the placebo group (1 subject had infective arthritis and musculoskeletal pain; 1 subject had joint stiffness, musculoskeletal stiffness, and myalgia; and 1 subject had benign parathyroid tumor, thyroid adenoma, and nephrocalcinosis; these events led to discontinuation of the investigational product).

The most frequently (> 10%) reported treatment-emergent adverse events by preferred term were (cinacalcet, placebo): diarrhea (9 [15.8%], 3 [5.3%]), cough (8 [14.0%], 3 [5.3%]), urinary tract infection (8 [14.0%], 7 [12.3%]), nasopharyngitis (7 [12.3%], 8 [14.0%]), nausea (7 [12.3%], 6 [10.5%]), fatigue (6 [10.5%], 7 [12.3%]), and peripheral oedema (6 [10.5%], 8 [14.0%]).

Adverse events of special interest were (cinacalcet, placebo): hypersensitivity (4 [7.0%], 3 [5.3%]); hypotension (1 [1.8%], 2 [3.5%]); cardiac failure (1 [1.8%], 1 [1.8%]); acute pancreatitis (1 [1.8%], 0 [0.0%]); drug related hepatic disorders (1 [1.8%], 2 [3.5%]); nervous system disorders (excluding seizures); (13 [22.8%], 11 [19.3%]); fractures (1 [1.8%], 2 [3.5%]); and neoplastic events (1 [1.8%], 3 [5.3%]).

Conclusions: In renal transplant recipients with hypercalcemia due to autonomous HPT, cinacalcet demonstrated efficacy in reducing calcium levels in this population. A statistically significantly higher proportion of subjects in the cinacalcet group achieved the primary endpoint of mean corrected total serum calcium value < 10.2 mg/dL (2.55 mmol/L) during the EAP (78.9% subjects in the cinacalcet group and 3.5% subjects in the placebo group; the difference [cinacalcet – placebo] in the proportions was 75.44%; 95% CI [63.83%, 87.05%]). The odds ratio (cinacalcet:placebo) was 91.41 (95% CI [18.76, 445.41]). The CMH test stratified by baseline corrected total serum calcium level yielded a Chi-Square test statistic of 66.437 with a p-value < 0.001.

The first key secondary endpoint of percent change in BMD at the femoral neck measured by DXA scan from baseline to week 52 (median [Q1, Q3]) was 1.24% (-1.52%, 4.70%) in the cinacalcet group in comparison to 1.05% (-1.80%, 3.51%) in the placebo group, though statistically there was no significant difference between the 2 treatment groups. The least square estimate for the difference in the percent change in BMD between the 2 treatment groups (cinacalcet – placebo) was 1.41% (95% CI [-1.10%, 3.93%]); a test of treatment effect yielded a p-value of 0.266. Hence, no hypothesis testing was performed on the second key secondary endpoint of absolute change in mean serum phosphorus from baseline to week 52. Although not statistically tested, nominal p-values also suggested a concomitant decrease in iPTH and increase in phosphorus. The observed changes in the biochemical profile are consistent with the mechanism of action for calcimimetics and its effect on parathyroid function. There was no apparent effect on the renal transplant function as measured by eGFR. There were no unexpected safety signals raised in this study and the adverse event profile was consistent with the established identified and potential risks. No new safety findings for cinacalcet were noted.

In summary, cinacalcet demonstrated efficacy and safety for correcting hypercalcemia in renal transplant recipients with autonomous HPT.