2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Cinacalcet HCl (Sensipar®/Mimpara®)

Name of Active Ingredient: Cinacalcet

Title of Study: A Randomized Double-blind Placebo-controlled Study to Evaluate the Efficacy and Safety of Cinacalcet for the Treatment of Hypercalcemia in Subjects with Primary Hyperparathyroidism Unable to Undergo Parathyroidectomy

Investigators and Study Centers: The study was conducted at 29 centers in United States, Australia, Canada, Hungary, Poland, Portugal, and Russian Federation. Name and affiliation of principal or coordinating investigator are provided in Section 16.1.4.

Publication: None

Study Period: 10 March 2010 (first subject enrolled) to 21 December 2012 (last subject completed follow-up)

Development Phase: 3

Objectives:

The primary objective was to demonstrate the efficacy of cinacalcet for normalizing corrected total serum calcium concentration in subjects with primary hyperparathyroidism (HPT) who meet criteria for parathyroidectomy on the basis of corrected total serum calcium level, but who are unable to undergo parathyroidectomy.

The secondary objective was to demonstrate the efficacy of cinacalcet for reducing corrected total serum calcium and plasma parathyroid hormone (PTH) levels.

The safety objective was to assess the safety and tolerability of cinacalcet.

Methodology: This was a randomized, double-blind, placebo-controlled study which consisted of a 30-day screening phase, a 12-week placebo-controlled dose-titration phase, and a 16-week placebo-controlled efficacy assessment phase (EAP). Subjects who completed 28 weeks on study were to continue into an open-label safety extension phase for 24 weeks of investigational cinacalcet treatment.

Subjects who qualified for the study were to be randomized in a 1:1 ratio to oral cinacalcet or placebo stratified by bisphosphonate use. The starting dose for cinacalcet was 30 mg twice a day (BID) on day 1.

A dose titration could be performed once every 3 weeks during the placebo-controlled dose-titration phase based on corrected total serum calcium concentration and safety assessments obtained the previous week. Doses could have been sequentially increased to 60 mg BID, 90 mg BID, and 90 mg 3 times a day (TID) as outlined in the dose-titration schema in the protocol (Section 16.1.1).

During the placebo-controlled EAP, doses of investigational product could be increased or decreased as needed (based on study visits every 4 weeks) to maintain a corrected total serum calcium concentration within the normal range.

During the open-label safety extension phase, subjects received investigational cinacalcet at a starting dose of 30 mg BID at week 28. Doses could have been sequentially increased to 60 mg BID, 90 mg BID, and 90 mg TID as outlined in the dose-titration schema in the protocol (Section 16.1.1). The doses of investigational cinacalcet could have been increased or decreased as needed to maintain a corrected total serum calcium concentration within the normal range through week 52.

Further details are provided in Section 3.1 of the protocol (Section 16.1.1).

Number of Subjects Planned: 140 subjects

Diagnosis and Main Criteria for Eligibility: Main criteria for eligibility included: age ≥ 18 years with a diagnosis of primary HPT and inability to undergo parathyroidectomy. Key exclusion criteria were symptoms attributable to hypercalcemia requiring immediate medical intervention, administration of drugs that increase serum calcium concentration, initiated bisphosphonate therapy or changed bisphosphonate dose within 12 weeks before the date of informed consent, and current administration of drugs for ventricular tachycardia. Further details are provided in Section 4 of the protocol (Section 16.1.1).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Cinacalcet was provided as light green film-coated tablets in 30, 60, and 90 mg [redacted] equivalents, graduated in size, smallest to largest. Cinacalcet was administered orally at a starting dose of 30 mg BID and titrated to a maximum dose of 90 mg TID, as required.

Manufacturing batch numbers are provided in Section 16.1.6.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Placebo tablets had the same appearance as cinacalcet tablets for the respective dose level.

Manufacturing batch numbers are provided in Section 16.1.6.

Duration of Treatment: The study consisted of a 30-day screening phase, 12-week placebo-controlled dose-titration phase, and a 16-week placebo-controlled EAP. Subjects who completed 28 weeks on study were to continue into an open-label safety extension phase for 24 weeks of cinacalcet treatment for a total of 52 weeks study duration.

Study Endpoints:

Primary Endpoint

- achievement of a mean corrected total serum calcium concentration ≤ 10.3 mg/dL (2.57 mmol/L) during the EAP (weeks 16, 20, 24, and 28)

Secondary Endpoints

- achievement of a ≥ 1 mg/dL (0.25 mmol/L) reduction in corrected total serum calcium concentration from baseline to the EAP (mean of weeks 16, 20, 24, and 28)
- percent change in corrected total serum calcium concentration from baseline to the EAP (mean of weeks 16, 20, 24, and 28)
- percent change in plasma PTH concentration from baseline to the EAP (mean of weeks 16, 20, 24, and 28)

Safety Endpoints

- nature, frequency, severity and relationship to treatment of adverse events

The exploratory objectives are provided in the Section 10.2 of the protocol (Section 16.1.1).

Statistical Methods:

The final analysis for efficacy assessment was based on data from the first 28 weeks of the study (placebo-controlled, double-blinded). In addition, safety and other study data collected from weeks 28 to 52 were reported for all subjects who were treated with open-label cinacalcet during this extension phase of the study.

The full analysis set (FAS) was used for analysis of the primary and secondary efficacy endpoints and included all subjects randomized to treatment. The safety analysis set was used for all safety reporting and evaluation of safety endpoints during the placebo-controlled phase of the study (first 28 weeks). This set included those subjects who received at least 1 dose of investigational product. The safety extension analysis set is a subset of the safety analysis set and included all subjects who received at least one dose of investigational cinacalcet, which was dispensed to all subjects continuing on study to the open-label safety extension phase commencing at visit week 28.

Summary of Results:

The planned study population was 140 subjects; however despite changes to the protocol to include subjects more reflective of the population at large, the target population for the study remained smaller than anticipated. The sample size was revised from 140 to 66 subjects and the study enrollment was terminated early.

Subject Disposition: A total of 67 subjects were enrolled and randomized; 33 subjects to the cinacalcet group and 34 subjects to the placebo group. All randomized subjects received ≥ 1 dose of investigational product. Eight subjects (12%) (3 [9%] placebo, 5 [15%] cinacalcet) discontinued from the double-blind phase; 7 subjects (10%) (3 [9%] placebo and 4 [12%] cinacalcet) discontinued from the titration phase and 1 (1%) subject (in the cinacalcet group) discontinued from the EAP. The most common reason for discontinuation from the double-blind phase was withdrawal of consent (2 [6%] subjects in the placebo group and 3 [9%] subjects in the cinacalcet group).

Of the 67 subjects originally enrolled into the study, 57 (85%) subjects started the open-label phase. Thus, in addition to the 8 subjects who discontinued from the double-blind phase, 2 additional subjects from the placebo group completed the double-blind phase but did not enter the open-label phase. Three subjects discontinued from the open-label phase. One subject (1%) discontinued from the titration phase (due to an adverse event) and 2 (3%) subjects discontinued from the open-label follow-up phase (due to withdrawal of consent and protocol specified criteria). One additional subject discontinued the follow-up period after completing the open-label phase. In total, therefore, 14 (21%) subjects (8 [24%] placebo and 6 [18%] cinacalcet) discontinued from the study.

Baseline Demographics:

Sex: In the placebo group, 27 (79.4%) subjects were women and 7 (20.6%) were men. In the cinacalcet group, 25 (75.8%) subjects were women and 8 (24.2%) were men.

Age: The subjects in the cinacalcet group were slightly younger as compared with those in the placebo group. The mean (standard deviation [SD]) age was 69.5 (13.0) years for the subjects in the cinacalcet group and 75.0 (8.9) years for the subjects in the placebo group.

Ethnicity/Race: The majority of the subjects (33 [97.1%] in the placebo group and 28 [84.8%] in the cinacalcet group) were white.

Efficacy Results:

Primary Endpoint:

- During the EAP, 25 (75.8%) subjects in the cinacalcet group as compared with 0 (0.0%) subjects in the placebo group achieved a mean corrected total serum calcium concentration ≤ 10.3 mg/dL (2.57 mmol/L). The difference in response rates between the treatment groups was statistically significant ($p < 0.001$).

Secondary Endpoints:

- During the EAP, 28 (84.8%) subjects in the cinacalcet group as compared with 2 (5.9%) subjects in the placebo group achieved a ≥ 1 mg/dL (0.25 mmol/L) decrease from baseline in mean corrected total serum calcium concentration. The difference in response rates between the 2 treatment groups was statistically significant ($p < 0.001$).
- The least square (LS) mean (standard error of the mean [SEM]) percent change from baseline in corrected serum total calcium concentration was –15.21% (1.00%) for the 33 subjects in the cinacalcet group and -1.66% (0.99%) for the 34 subjects in the placebo group. The difference between the treatment groups was statistically significant ($p < 0.001$).
- The LS mean (SEM) percent change from baseline in plasma PTH level was -23.80% (4.18%) for the cinacalcet group and -1.01% (4.05%) for the placebo group. The difference between the treatment groups was statistically significant ($p < 0.001$).

Safety Results:

Double-blind phase

- The incidence of treatment-emergent adverse events (TEAEs) was higher in the cinacalcet group (27 [81.8%]) compared with the placebo group (20 [58.8%]).
- The most commonly reported adverse events (≥10% in the cinacalcet treatment group) were nausea, muscle spasms, back pain, diarrhea, and headache. With the exception of back pain, these adverse events are all listed as adverse drug reactions in the prescribing information for cinacalcet in secondary HPT.
- The incidence of treatment-emergent serious adverse events was comparable between the 2 groups: 3 (9.1%) subjects in the cinacalcet group and 4 (11.8%) subjects in the placebo group. None of the serious adverse events were considered treatment-related.
- The incidence of adverse events of special interest during the double-blind treatment phase was not notably different from the known profile of cinacalcet.
- One subject from the cinacalcet group had a fatal adverse event of decreased appetite. This event was considered to be unrelated to the investigational product and was confounded by the use of haloperidol.
- The withdrawal rate from investigational product due to TEAEs was similar between the 2 groups: 2 subjects in the cinacalcet group withdrew due to overdose of cinacalcet and decreased appetite and 1 subject in the placebo group withdrew due to coronary artery occlusion. The event of overdose was considered related to cinacalcet; the other 2 events were considered as not related to the investigational product.

No clinically significant abnormalities in clinical laboratory measures were noted except for the changes observed in corrected serum calcium, plasma parathyroid hormone, and phosphorus levels in the cinacalcet group, which were consistent with the mechanism of action of cinacalcet. No specific trends were noted in any laboratory abnormalities and/or toxicities.

No clinically significant findings for blood pressure, pulse, respiration, electrocardiogram (ECG), or temperature were noted.

Open-label phase

- Treatment-emergent adverse events were reported for 39 (68.4%) subjects.
- Serious treatment-emergent adverse events were reported for 8 (14.0%); none were considered treatment-related.
- The incidence of adverse events of special interest was not notably different from the known profile of cinacalcet.
- Two (6.9%) subjects discontinued investigational product due to an adverse event (1 subject each, hypocalcemia and pulmonary embolism). Neither event was considered related to investigational product.

No clinically significant abnormalities in clinical laboratory measures were observed and no specific trends were noted in any laboratory abnormalities and/or toxicities.

No clinically significant findings for blood pressure, pulse, respiration, ECG, or temperature were noted.

Conclusions:

There was a statistically significant benefit in the primary and all secondary efficacy endpoints for the cinacalcet group relative to the placebo group. Subjects randomized to cinacalcet sustained lowering of serum calcium concentration for up to 52 weeks.

The observed adverse event profile in this study was generally consistent with the known safety profile of cinacalcet in the treatment of primary hyperparathyroidism as listed in the prescribing information, with no new safety risks identified.