2. SYNOPSIS

Name of Sponsor: Amgen Inc. Thousand Oaks, CA

Name of Finished Product: Sensipar® (US) or Mimpara® (Europe)

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

Title of Study: Bone Histomorphometry Assessment for Dialysis Patients with Secondary Hyperparathyroidism of End Stage Renal Disease (BONAFIDE Study)

Investigator(s) and Study Center(s): This study was to have been conducted at 55 study centers in North America, Europe, Turkey, and Macedonia; however, only 30 centers enrolled subjects. A complete list of investigators is provided in Appendix 4.

Publication(s): None

Study Period: 22 May 2006 (first subject enrolled) to 13 May 2011 (last subject's last visit)

Development Phase: 2

Background:

Secondary hyperparathyroidism (HPT) develops early in chronic kidney disease (CKD) and continues to progress after patients require dialysis. One consequence of secondary HPT is the development of hyperparathyroid bone disease, also known as osteitis fibrosa, which is characterized by increases in bone turnover (bone formation and resorption) and by peritrabecular marrow fibrosis.

Treatment of secondary HPT has been shown to decrease bone turnover and peritrabecular fibrosis in end-stage renal disease (ESRD) patients (Andress et al, 1989; Cannella et al, 1994). Available data suggest that a reduction in parathyroid hormone (PTH) to plasma levels of 150 to 300 pg/mL may be optimal for achieving relatively normal bone turnover (NKF-K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease, 2003).

Calcimimetics, which include cinacalcet, are a novel class of small molecules that act as allosteric modulators of the calcium sensing receptor on the surface of parathyroid cells. Treatment with Sensipar®/Mimpara® (cinacalcet hydrochloride; referred to herein as cinacalcet) increases the sensitivity of the calcium-sensing receptor to extracellular calcium, leading to a reduction in PTH, calcium, phosphorus, and calcium-phosphorus (Ca x P) product concentrations in ESRD subjects. Because reductions in PTH can lower bone turnover, treatment with cinacalcet was expected to produce decreases in various parameters of bone turnover as measured by bone histomorphometry.

Objectives:

The primary objective of this study was to describe histomorphometric parameters of bone turnover in dialysis subjects with high turnover renal osteodystrophy before and after treatment with cinacalcet either with or without concomitant vitamin D sterols and/or phosphate binders therapy.

Secondary objectives included evaluating:

- the effects of cinacalcet on intact parathyroid hormone (iPTH), bone-specific alkaline phosphatase (BALP), osteocalcin (OC), serum N-telopeptide (NTx), and tartrate resistant acid phosphatase (TRAP)
- the effects of cinacalcet on serum calcium, serum phosphorus, and Ca x P
- the safety and tolerability of cinacalcet including its effect on mineralization lag time, osteoid area/bone area, osteoid width/thickness, and the incidence of adynamic bone disease

Methodology:

This multicenter, single-arm, open-label trial was designed to describe the histomorphometric parameters of bone turnover before and after approximately 1 year of treatment with cinacalcet among subjects managed with dialysis who had bone biopsy evidence of high turnover renal osteodystrophy at baseline. Treatment with cinacalcet was undertaken with or without the concurrent use of vitamin D sterols and/or phosphate binding agents.

The study consisted of 4 consecutive phases which occurred in the following order: a screening phase lasting up to 3 months, a dose-titration phase lasting 20 weeks, a maintenance phase lasting 20 weeks, and an efficacy assessment phase lasting 12 weeks. All enrolled subjects received cinacalcet at a starting dose of 30 mg once daily (QD) beginning on day 1. During the study, dose adjustments were made based on serum iPTH concentrations and serum calcium concentrations, and subject safety information as described in Section 7.7.4.

A baseline bone biopsy was obtained within the 3-month screening period and a follow-up bone biopsy was obtained at end of study (any time between week 48 and 52) or at early termination if subject was on study for at least 6 months. Each subject received 500 mg of tetracycline twice daily for 3 days with the first dose given 20 days before each bone biopsy. In addition, each subject received 300 mg of declomycin (Ledermycin or equivalent) twice daily for 3 days with the first dose given 5 days before each bone biopsy.

The use of concomitant vitamin D analogs was permitted during the study. Changes in vitamin D sterol therapy were permitted (except during the screening period) based upon protocol-specified measurements of serum iPTH, calcium, phosphorus, and Ca x P as described in Section 7.7.5. Changes in doses of calcium supplements/phosphate binders were permitted throughout the study in accordance with the standard clinical practice.

Number of Subjects Planned: 85

Number of Subjects Enrolled: 110

Diagnosis and Main Criteria for Eligibility:

Men or women ≥ 18 years of age with CKD receiving dialysis who, in the investigator's opinion, could complete the study as scheduled were eligible if they met all of the following criteria, including but not limited to:

- 1 serum iPTH concentration of ≥ 300 pg/mL (31.8 pmol/L)
- 1 serum calcium concentration of ≥ 8.4 mg/dL (2.1 mmol/L)
- 1 BALP concentration of > 20.9 ng/mL
- positive histologic confirmation of high bone turnover disease (defined as any of the following: osteoid area < 12%, bone formation rate (BFR) > 613 $\mu m^2/mm^2$/day, and no evidence of fibrosis; osteoid area < 12%, BFR > 97 $\mu m^2/mm^2$/day, and evidence of fibrosis; or osteoid area > 12%, BFR > 97 $\mu m^2/mm^2$/day, with or without evidence of fibrosis)
- treated with dialysis for ≥ 1 month before the date of informed consent

Subjects who had an unstable medical condition, were pregnant or nursing, had a parathyroidectomy within 3 months before the date of informed consent, received vitamin D therapy for less than 30 days before day 1 or required a change in vitamin D brand or dose level within 30 days before day 1 (for those prescribed vitamin D), received therapy with FORTEO™ within 30 days before day 1, ever received therapy with cinacalcet, or ever received bisphosphonates were excluded from the study.

A complete list of subject inclusion/exclusion criteria are provided in Section 7.5.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:

Cinacalcet was synthesized as a hydrochloride salt. Cinacalcet was prepared in light green tablets in 30-, 60-, and 90-mg [redacted] equivalents. Tablets were graduated in size by dose. Possible daily doses of cinacalcet were 30, 60, 90, 120, and 180 mg. Combinations of tablets were used to constitute the doses of 120- and 180-mg [redacted] equivalents. Tablets had to be swallowed whole without biting or chewing. Cinacalcet was to be administered with food or shortly after a meal. Subjects received 1 tablet of cinacalcet at a starting dose of 30 mg daily.

For this study, the manufacturing batch/lot numbers used are provided in Listing 14-3.1 in Appendix 18.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:

No control group was used in this single-arm study.

Duration of Treatment:

The dose-titration, maintenance, and efficacy assessment phases were 12 months in duration.

Study Endpoints:

Efficacy Endpoints:

The primary efficacy endpoint was the change from baseline in BFR.
Secondary efficacy endpoints included:

- change from baseline in osteoblasts perimeter and osteoclasts perimeter
- change from baseline in eroded perimeter and fibrosis area
- percent change from baseline in iPTH, BALP, OC, serum NTx and TRAP
- percent change from baseline in serum calcium, serum phosphorus and Ca x P concentrations

Safety Endpoints:

- change from baseline in mineralization lag time, osteoid area/volume and osteoid width/thickness
- the occurrence of adynamic bone disease as defined by:
  - osteoid area < 12% and
  - BFR < 97 $\mu m^2/mm^2$/day and
  - no evidence of fibrosis
- nature, frequency, severity and relationship to treatment of adverse events; and changes in laboratory parameters

Statistical Methods:

The focus of this study was to estimate the mean change in BFR at 1 year in dialysis subjects with high turnover renal osteodystrophy. All efficacy and bone safety endpoints were analyzed using the efficacy data set (subjects who received at least 1 dose of cinacalcet and had both screening and end of study bone biopsies). Biochemical parameters and baseline bone histomorphometry parameters were further analyzed using the safety data set (subjects receiving at least 1 dose of cinacalcet).

Descriptive statistics were used to summarize efficacy and safety data, which included number of subjects (N), mean, standard deviation (SD), standard error (SE), median, quartiles (Q1, Q3) and (min, max) for continuous variables, and count and percentage for discrete variables. The 95% confidence interval (CI) was provided for the estimate of the primary endpoint. Select variables were presented graphically. The analyses were based on pooled data from all study centers due to the small number of subjects to be enrolled per center. Subject enrollment was summarized by center.

Details of statistical analyses for the study can be found in Section 7.10 and in the statistical analysis plan in Appendix 2.

Summary of Results:

Subject Disposition: A total of 146 subjects underwent the screening biopsy and 110 subjects were enrolled based on confirmed positive findings of high bone turnover as judged by elevated BFR or evidence of tissue fibrosis. Eighty-four subjects completed the study and 77 subjects had screening and follow-up bone biopsies. The mean ± SD and (Q1, Q3) duration of exposure to cinacalcet was 310 ± 102 (307.0, 366.0) days and the average daily cinacalcet dose (mean ± SD [Q1, Q3]) after the titration phase ranged from 74.1 ± 43.6 (30, 90) to 79.4 ± 49.0 (30, 120) mg/day. Twenty-six subjects discontinued the study early and 11 of these subjects discontinued the study due to protocol-specified criteria. Forty-one subjects discontinued treatment with cinacalcet, of these 13 subjects discontinued cinacalcet due to protocol-specified criteria. Two subjects discontinued cinacalcet due to adverse events.

Baseline Demographics and Characteristics: The majority of enrolled subjects were male (70 subjects [64%]) and white (91 subjects [83%]). Subjects were between the ages of 19 and 82 years with a mean (SD) age of 55.2 (14.2) years. The mean (SD) duration of dialysis for all enrolled subjects was 64.2 (62.2) months. At baseline, 59 subjects (54%) were receiving vitamin D and 92 subjects (84%) were receiving a phosphate binder/calcium supplement. For all enrolled subjects, the baseline mean (SD) BFR was 1012 (838) $\mu m^2/mm^2$/day (normal range, 97 to 613 $\mu m^2/mm^2$/day) and the baseline mean (SD) iPTH concentration was 1364 (887) pg/mL.

Efficacy Results: A total of 77 subjects received ≥ 1 dose of cinacalcet and had both a baseline and an end-of-study bone biopsy; these subjects comprise the efficacy analysis data set. Treatment with cinacalcet reduced iPTH, Ca x P, calcium, and phosphorus concentrations.

At end of study (after at least 6 months of cinacalcet treatment) a reduction in BFR was observed. The mean (SE) change in BFR from baseline was -488 (73) $\mu m^2/mm^2$/day with a 95% confidence interval (CI) of (-633, -344). When stratified by baseline iPTH concentrations, subjects with > 800 pg/mL iPTH had a larger decrease in BFR (-631 [62] $\mu m^2/mm^2$/day) compared with those with iPTH levels that were ≤ 800 pg/mL (-192 [98] $\mu m^2/mm^2$/day).

Improvements in secondary bone histomorphometric parameters that characterize the high turnover bone disease of secondary hyperparathyroidism also were observed. The mean (SE) changes in osteoblast perimeter, osteoclast perimeter, and eroded perimeter were -4.3% (1.4%), -2.7% (1.5%), and -3.4% (0.6%), respectively. The number of subjects with 0% fibrosis was increased from 6 subjects (8%) at baseline to 24 subjects (31%) at end of study. Overall, the percent of subjects with normal bone histology increased (from 0% to 26%) by end of study.

The effect of treatment with cinacalcet on biochemical markers of bone turnover from baseline to the end of the efficacy assessment phase was variable, but generally suggested modest, favorable changes in bone formation and bone resorption. At week 52, the mean percent change (SE) from baseline was 6.6% (12.7%) for BALP, -14.0% (14.7%) for NTx, -21.8% (6.2%) for OC, and -3.8% (9.2%) for TRAP.

During the efficacy assessment phase, the mean (SE) iPTH levels decreased by -41.6% (4.4%) from baseline; the mean (SE) percent changes from baseline in serum calcium, serum phosphorus, and Ca x P were smaller: -6.5% (1.1%), -1.1% (2.9%), -6.9% (3.1%), respectively.

[redacted] .

Safety Results: A total of 110 subjects received ≥ 1 dose of cinacalcet; these subjects comprise the safety analysis data set. The average daily dose (mean ± SD [Q1, Q3]) of cinacalcet after the titration phase ranged from 74.1 ± 43.6 (30, 90) to 79.3 ± 49.0 (30, 120) mg/day. Ninety-five subjects (86%) had at least 1 adverse event. Most adverse events reported were mild or moderate in severity. The most common treatment-emergent adverse events were nausea (29 subjects [26%]), vomiting (23 subjects [21%]), diarrhea (22 subjects [20%]), arthralgia (15 subjects [14%]), hypocalcemia (13 subjects [12%]), and dyspnoea and muscle spasms (12 subjects [11%] each). Treatment-related adverse events reported in 47 subjects (43%) were most commonly nausea (16 subjects [15%]), hypocalcemia (12 subjects [11%]), vomiting (10 subjects [9%]), dyspepsia (9 subjects [8%]), and diarrhea (7 subjects [6%]). Three subjects (3%) had treatment-related serious adverse events: 1 subject had hypocalcemia and convulsion, 1 subject had hypocalcemia, and 1 subject had convulsion.

Hypocalcemia, a recognized risk of cinacalcet therapy, was reported as an adverse event for 13 subjects (12%). Treatment-related hypocalcaemia was reported for 12 subjects, of which 2 were serious adverse events. The mean (SD) serum calcium for the safety population was 10.0 (0.7) mg/dL at baseline and 9.2 (0.9) mg/dL at end of study. Subjects who had the adverse event of hypocalcemia had higher iPTH levels and lower serum laboratory calcium values on study compared with subjects who did not have the adverse event of hypocalcemia.

Bone histomorphometric parameters were analyzed as a safety endpoint. Median (SE) mineralization lag time at baseline and at end of study was 18 (17) days and 21 (66) days, respectively. For the majority of subjects, mineralization lag time was between 2.4 and 63 days, which represent the limits of the normal reference range, both at baseline and at end of study. Double-labeled perimeter/bone perimeter was normal at baseline in 27 subjects (35%) and elevated in 50 subjects (65%]). At end of study, 22 subjects (29%) remained normal, 28 subjects (36%) shifted from elevated to normal, and 22 subjects (29%) remained elevated. Osteoid perimeter/bone perimeter was elevated in the majority (55 subjects [71%]) and remained elevated in the majority (31 subjects [40%]) at end of study; shifts from elevated to normal occurred for 23 subjects (30%), shifts from normal to low occurred for 5 subjects (6%) and shifts from normal to elevated occurred for 5 subjects (6%). Osteoid width/thickness was normal at baseline in 53 subjects (69%) and remained normal in the majority of subjects (40 [52%]) at end of study; shifts from elevated to normal occurred for 10 subjects (13%) and shifts from normal to elevated occurred for 13 subjects (17%). Osteoid area/bone area was normal in 41 subjects (53%) and remained normal in the majority of subjects (31 subjects [40%]) at end of study; shifts from normal to elevated occurred in 10 subjects (13%) and shifts from elevated to normal occurred in 20 subjects (26%).

Two of 77 subjects had BFR values below the lower limit of normal on the end-of-study bone biopsy and had other histomorphometric features consistent with adynamic bone. Both subjects developed low serum iPTH levels during the course of the study, [redacted]

Conclusions: A reduction from baseline in the primary endpoint, BFR, was observed in subjects with high turnover renal osteodystrophy after at least 6 months of treatment with cinacalcet. Similar but lesser reductions were observed in other bone histomorphometric parameters that characterize the high turnover bone disease of secondary HPT such as osteoblast perimeter, osteoclast perimeter, eroded bone perimeter, and fibrosis area.

The adverse events reported in this study were similar to those reported in other clinical trials in adult subjects. Nausea, vomiting, and hypocalcaemia were the most commonly reported treatment-related adverse events. Among subjects who had the adverse event of hypocalcemia during the study, higher mean iPTH levels at baseline, certain aspects of the study design, and other protocol related factors may have contributed. Of the 77 subjects with evaluable bone biopsy data at baseline and at follow-up, 2 subjects developed adynamic bone.