2. SYNOPSIS

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

Name of Finished Product: Sensipar® (United States and Canada) or Mimpara® (Europe and Russia)

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: Randomized Trial to Evaluate the Efficacy and Safety of Cinacalcet Treatment in Combination with Low Dose Vitamin D for the Treatment of Subjects with Secondary Hyperparathyroidism (HPT) Recently Initiating Hemodialysis

Investigators and Study Centers: This study was conducted at 82 centers in the United States (18 centers), Europe (37 centers in Belgium [5 centers], France [4 centers], Germany [3 centers], Greece [3 centers], Hungary [4 centers], Italy [5 centers], Norway [2 centers], Spain [7 centers], United Kingdom [4 centers]), Canada (7 centers), Australia (3 centers), and Russia (17 centers). A complete list of investigators participating in the study is provided in Appendix 4.

Publication: Urena P, Kopyt N, Rodriguez M, Bridges I, Dehmel B, Cooper K, Covic A. Efficacy of cinacalcet (Cin) combined with low dose vitamin D (LDVD) in incident hemodialysis (HD) subjects with secondary hyperparathyroidism (SHPT). *J Am Soc Nephrol.* 2011; Abstr.

Study Period: 19 February 2009 (first subject enrolled) to 5 July 2011 (last subject completed end-of-study washout)

Development Phase: 4

Objectives:

Secondary hyperparathyroidism (HPT) develops early in chronic kidney disease (CKD) and continues to progress after patients require dialysis. It is a disorder characterized by hyperplasia of the parathyroid glands and is associated with abnormalities in serum calcium (Ca) and phosphorus (P), and increased concentrations of circulating parathyroid hormone (PTH, unless specified, PTH in this document denotes intact PTH).

Traditional therapies to treat disorders of mineral metabolism and secondary HPT in end-stage renal disease (ESRD) patients include dietary phosphorus restriction, phosphate binders, and vitamin D sterols. 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 cinacalcet (cinacalcet hydrochloride, Sensipar® [United States and Canada], Mimpara®, [Europe and Russia]) increases the sensitivity of the calcium-sensing receptor to extracellular calcium, leading to a reduction in PTH, calcium, phosphorus, and Ca x P, concentrations in ESRD subjects.

Currently, cinacalcet is most frequently used as second-line therapy for secondary HPT. On average, cinacalcet is added to vitamin D and phosphate binders 14 to 19 months after initiation of dialysis in patients receiving hemodialysis. [redacted]

The primary objective of this study was to evaluate the ability of a treatment strategy that included the use of cinacalcet in combination with low-dose vitamin D sterols (if prescribed) to control PTH compared with flexible vitamin D sterols (flexible vitamin D) dosing (if prescribed) per standard treatment guidelines over a 6-month period in subjects recently initiating hemodialysis (within 3 to 12 months of enrollment) with secondary HPT and CKD.

Secondary objectives included:

- evaluating the effect of the treatment strategy on achieving and maintaining treatment targets for PTH, calcium, and phosphorus
- determining the safety and tolerability of cinacalcet in a population of subjects recently initiating dialysis

[redacted]

Methodology:

This was a phase 4, multi-center, randomized, open-label study. Eligible subjects were randomized (1:1) to either the control group: flexible dosing of vitamin D sterols, if prescribed, or the cinacalcet group: cinacalcet and low-dose vitamin D sterols, if prescribed.

Randomization was stratified by PTH concentration (300 to 450 pg/mL, > 450 to 600 pg/mL, > 600 pg/mL) and by vitamin D sterol use / route of administration at enrollment (ie, not on vitamin D, on oral vitamin D, on intravenous [IV] vitamin D).

The study consisted of the following phases:

- a screening phase of up to 14 days to determine eligibility based on PTH and corrected serum calcium
- a 4-week pre-randomization washout phase (of vitamin D, if required)
- a 22-week dose-titration phase
- a 4-week efficacy assessment phase (EAP) at month 6
- a 22-week maintenance phase
- a 4-week EAP at month 12
- a 4-week end-of-study washout phase (of both vitamin D sterols and cinacalcet)

Subjects randomized to the cinacalcet group received cinacalcet at a starting dose of 30 mg once daily. Possible sequential doses of cinacalcet during the titration phase were 30, 60, 90, 120, and 180 mg. Cinacalcet dose adjustments were based upon PTH, serum calcium, and subject safety information.

Number of Subjects Planned: 300 subjects (150 cinacalcet and 150 control)

Number of Subjects Enrolled: 313 subjects were enrolled

Diagnosis and Main Criteria for Eligibility: Men or women ≥ 18 years of age with CKD receiving dialysis for > 3 and ≤ 12 months before enrollment who, in the investigator's opinion, could complete the study as scheduled and who provided written informed consent were eligible if they met the following criteria, including but not limited to:

- mean of 2 PTH concentrations during the screening period (drawn at least 2 days apart) > 300 pg/mL (31.8 pmol/L or bio-intact PTH [biPTH] > 160 pg/mL [17.0 pmol/L]);
- mean of 2 corrected serum calcium concentrations ≥ 8.4 mg/dL (2.1 mmol/L) (drawn on the same day as the PTH determinations).

Subjects were excluded from the study if they met these criteria, including but not limited to:

- mean of 2 PTH determinations during the screening period (drawn at least 2 days apart) > 800 pg/mL (84.9 pmol/L, or biPTH > 430 pg/mL [45.6 pmol/L]) AND received vitamin D upon entering screening;
- parathyroidectomy (partial or full) ≤ 6 months before entering screening;
- anticipated parathyroidectomy (partial or full) within 6 months after randomization;
- had a scheduled date for kidney transplant surgery;
- received cinacalcet since initiating hemodialysis;
- had received vitamin D therapy for less than 30 days before entering screening or required a change in prescribed vitamin D brand or dose within 30 days before entering screening. If subjects were not receiving vitamin D therapy, they had to remain free of vitamin D therapy for the 30 days before entering screening;
- subject was pregnant or was breast feeding;
- had an unstable medical condition within 30 days before screening or otherwise unstable in the judgment of the investigator.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Subjects randomized to cinacalcet (Sensipar® [Australia, United States, and Canada] or Mimpara® [Europe and Russia]) received a starting dose of 30 mg once daily, administered orally. Possible sequential doses of the study medication during the titration phase were 30, 60, 90, 120, and 180 mg daily. The manufacturing batch numbers used during the study were: [redacted],

[redacted]

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: No reference therapy was specified for this study. The control group received vitamin D sterols therapy and phosphate binders (both calcium-containing and non-calcium-containing were permitted) per standard treatment guidelines, if prescribed. The vitamin D and phosphate binder products were not provided by the sponsor of this study.

Duration of Treatment:

Following screening and pre-randomization washout (if required) phases that lasted up to 6 weeks, subjects received treatment for a total of 52 weeks. This was followed by an end-of-study 4-week washout period.

Study Endpoints:

The primary efficacy endpoint was the achievement of a ≥ 30% reduction in mean PTH from baseline to the EAP at month 6 (weeks 22 to 26).

Key secondary efficacy endpoints were:

- achievement of the specified PTH, corrected calcium, and phosphorous treatment targets during the EAP at month 6 (weeks 22 to 26);
- achievement of a ≥ 30% reduction in mean PTH from baseline to the EAP at month 12 (weeks 48 to 52);
- achievement of the specified PTH, corrected calcium, and phosphorous treatment targets during the EAP at month 12 (weeks 48 to 52);
- achievement of a ≥ 30% reduction in mean PTH from baseline to during both EAPs at month 6 (weeks 22 to 26) and month 12 (weeks 48 to 52);
- subject incidence of acute episodes (ie, at least 1 value) of hypercalcemia, hyperphosphatemia, and hypocalcemia during:
  - the EAP at month 6 (weeks 22 to 26),
  - the maintenance phase (22-week period between the EAP at month 6 and the EAP at month 12),
  - the EAP at month 12 (weeks 48 to 52),
  - the treatment phase (the entire period from the titration phase through the EAP at month 12).

Statistical Methods:

The primary analysis of the primary and secondary efficacy endpoints was carried out on the full analysis set, which consisted of all subjects who were randomized into the study and had at least 1 PTH concentration available after study day 1. Analyses of the primary and secondary endpoints were repeated using the efficacy evaluable analysis set at month 6 (EE6) for the assessments of efficacy during the EAP at month 6 and the efficacy evaluable analysis set at month 12 (EE12) for the assessments of efficacy during the EAP at month 12. Safety analyses were performed on the safety analysis set that included all randomized subjects, and for subjects in the cinacalcet arm, who received ≥ 1 cinacalcet dose. For the safety analysis set, subjects were analyzed according to the randomized treatment; however, if a subject received the incorrect treatment over the entire study, they were analyzed according to the treatment received.

For analysis of the primary efficacy endpoint, the number and percentage of subjects who achieved a ≥ 30% reduction in mean PTH at month 6 was summarized by treatment group. A stratified Cochran-Mantel-Haenszel (CMH) test was performed to compare the number of subjects who achieved a ≥ 30% reduction in mean PTH by treatment group and the associated p-value was presented. The odds of a response (achieving target) was presented for each treatment group, along with the odds ratio (cinacalcet/control) and 95% confidence interval. This was presented adjusted for randomization stratum and also, as a sensitivity analysis, unadjusted. Analyses of secondary endpoints were carried out in a manner similar to those of the primary endpoint.

Stratification factors were screening PTH (300 to 450 pg/mL, > 450 to 600 pg/mL, > 600 pg/mL) and vitamin D sterols use/route of administration at enrollment (not on vitamin D, on oral vitamin D, on IV vitamin D). Information on stratification factors was taken from an interactive voice response system (IVRS). The analysis of the primary (ie, ≥ 30% reduction in mean PTH from baseline to the EAP at month) and 3 key secondary efficacy endpoints (ie, ≥ 30% reduction in mean PTH from baseline to the EAP at month 12, and mean PTH ≤ 300 pg/mL during the EAP at months 6 and 12) were repeated by stratum.

Descriptive statistics were used to summarize data for continuous variables at each measurement timepoint during the study. Descriptive statistics included mean, standard deviation [SD], standard error [SE], 95% 2-sided confidence interval (CI) of the mean, median, 25th and 75th percentiles, minimum, and maximum for continuous variables. For categorical variables, the number and percentage of subjects in each category were reported. Efficacy variables measured longitudinally were summarized graphically by plotting the mean and 95% CI for each treatment group against study visit.

Ninety-five percent confidence intervals were presented for the difference between and within treatment groups (change from baseline).

Summary of Results:

Subject Disposition: A total of 309 subjects were randomized (154 who were randomized to cinacalcet and 155 who were randomized to control). Three hundred four subjects (153 cinacalcet, 151 control) subjects had at least 1 after baseline PTH value and were included in the full analysis set. Two hundred forty-six (118 cinacalcet, 128 control) completed the study and 109 subjects in the cinacalcet group completed randomized treatment. The most common reasons for study discontinuation were due to protocol-specified criteria (24 subjects overall [13 cinacalcet, 11 control], including 20 subjects [12 cinacalcet, 8 control] who required renal transplantation), death (15 subjects [8 cinacalcet, 7 control]), full consent withdrawn (6 subjects [2 cinacalcet, 4 control]), adverse event (5 subjects [5 cinacalcet, 0 control]), and administrative decision (5 subjects [2 cinacalcet, 3 control]). Randomization was stratified by screening PTH (154 subjects [50%] had PTH ≥ 300 to 450, 72 [23%] had PTH > 450 to 600, and 83 [27%] had PTH > 600) and use of vitamin D sterols at enrollment (166 subjects [54%] were receiving none, 88 [29%] were receiving oral, and 55 [18%] were receiving IV).

Baseline Demographics:

Sex: 178 (59%) men, 126 (41%) women

Mean (SD) Age: 57.4 (14.1)

Ethnicity/Race: 231 (76%) white; 59 (19%) black or African American; 8 (3%) Asian; 2 (1%) Hispanic or Latino; 1 (< 1%) Aborigine; 3 (1%) other

Efficacy Results:

A summary of the key efficacy results is provided in Table 1. The primary endpoint, a ≥ 30% reduction from baseline in mean PTH concentration, was achieved by 63% of subjects randomized to cinacalcet and 38% of subjects randomized to the control group during the EAP at month 6, which was a statistically significant difference between the treatment groups (p-value < 0.001). Similar results were observed the EAP at month 12; 63% and 48% of subjects randomized to cinacalcet and control, respectively, had a ≥ 30% reduction from baseline in mean PTH concentration (a key secondary endpoint; multiplicity adjusted p-value = 0.0139).

During the EAP at month 6, 57% and 35% of subjects randomized to cinacalcet and control, respectively, had an PTH ≤ 300 pg/mL (a key secondary endpoint; multiplicity adjusted p-value < 0.001). During the EAP at month 12, 52% and 44% of subjects randomized to cinacalcet and control, respectively, had an PTH ≤ 300 pg/mL (a key secondary endpoint; multiplicity adjusted p-value = 0.2386).

Table 1. Summary of Key Efficacy Results

Endpoint	Study Phase	Percentage		p-value[a]
		Cinacalcet	Control	
Achievement of ≥ 30% Reduction From Baseline in Mean PTH Concentration	EAP 6	63%	38%	< 0.001
	EAP 12	63%	48%	0.0139[b]
	EAP 6 and 12	48%	28%	0.0003
Achievement of PTH ≤ 300 pg/mL	EAP 6	57%	35%	< 0.001[b]
	EAP 12	52%	44%	0.2386[b]
	EAP 6 and 12	35%	26%	0.0611
Achievement of PTH ≥ 150 pg/mL and ≤ 300 pg/mL	EAP 6	43%	29%	0.0090
	EAP 12	34%	34%	0.9143
Achievement of Serum Calcium < 10.2 mg/dL	EAP 6	99%	95%	0.0875
	EAP 12	95%	93%	0.4304
	EAP 6 and 12	95%	92%	0.3298
Achievement of Serum Phosphorus < 5.5 mg/dL	EAP 6	65%	56%	0.0910
	EAP 12	53%	53%	0.9520
	EAP 6 and 12	46%	42%	0.4436

Note: EAP = efficacy assessment phase; EAP 6 was from weeks 22 to 26; EAP 12 was from weeks 48 to 52. The full analysis set was used for all endpoints.

[a] Cochran-Mantel-Haenzel p-value stratified by PTH, vitamin D sterols use / route at enrollment.

[b] Dubey and Armitage-Parmar method of adjustment for multiple comparisons.

HT_Regulatory Writing Source Data: Table 14-4.1.1, Table 14-4.2.1, Table 14-4.9.1, Table 14-4.3.1, Table 14-4.4.1, Table 14-4.10.1, Table 14-4.4.7, Table 14-4.4.11, Table 14-4.5.1, Table 14-4.6.1, Table 14-4.11.1, Table 14-4.7.1, Table 14-4.8.1, and Table 14-4.12.1

The absolute values and percent change from baseline to the EAP at month 6 and the EAP at month 12 in PTH and corrected calcium were statistically superior in the cinacalcet group compared with the control group. The least square mean (95% CI) percent change in PTH from baseline to the month-12 EAP was -34.15% (-41.96%, -26.33%) for cinacalcet-treated subjects and -12.41% (-20.32%, -4.49%) for control-treated subjects. The least square mean (95% CI) percent change in calcium from baseline to the month-12 EAP was -2.62% (-3.72%, -1.51%) for cinacalcet-treated subjects and 2.37% (1.25%, 3.49%) for control-treated subjects. Both the mean absolute value and mean percent change in phosphorus from baseline to the month-12 EAP were lower for the cinacalcet group, but these group comparisons did not reach statistical significance. The least square mean (95% CI) percent change in phosphorus from baseline to the month-12 EAP was 3.21% (-1.71%, 8.14%) for cinacalcet-treated subjects and 4.26% (-0.76%, 9.28%) for control-treated subjects.

Across the entire treatment phase, the subject incidence of hypercalcemia (ie, ≥ 1 corrected serum calcium value ≥ 10.2 mg/dL) was lower in the cinacalcet group (24%) than in the control group (37%). Likewise, across the entire treatment phase, the subject incidence of hyperphosphatemia (ie, ≥ 1 serum phosphorus value ≥ 5.5 mg/dL) was lower in the cinacalcet group (80%) than in the control group (85%). In the cinacalcet group, the subject incidence of hypocalcemia (defined as 1 or more corrected serum calcium values < 8.4 and ≤ 7.5 mg/dL) was 77.1% and 33.3% of subjects, respectively. In the control group, corresponding low calcium values were noted in 28.5% and 5.3% of subjects, respectively. In the cinacalcet group, sustained hypocalcemia (2 consecutive corrected calcium values ≤ 7.5 mg/dL) was uncommon (13 subjects [8.7%]).

[redacted]

Safety Results:

Three hundred nine subjects were randomized and evaluable for safety. The mean (range) number of days of exposure to cinacalcet was 308 days (3 to 394 days). Sixty-eight percent of subjects in the cinacalcet group and 86% of subjects in the control group received at least 1 dose of vitamin D sterols during the treatment phase. At least 1 treatment-emergent adverse event was reported in 90% and 85% of subjects who received cinacalcet and control, respectively. The most common adverse events (≥ 10% in either treatment group) were (cinacalcet, control) nausea (19.4%, 9.7%), vomiting (17.4%, 9.1%), diarrhea (16.8%, 12.3%), and hypocalcemia (16.1%, 0.6%). Most subjects had events that were mild to moderate in severity, when subject incidence of adverse events was summarized by highest severity grade. The incidence of adverse events considered by the investigator to be possibly related to cinacalcet was 39%; the most common cinacalcet-related adverse events (> 1 subject in the cinacalcet group) were nausea (14.2%), hypocalcemia (14.2%), vomiting (11.6%), diarrhea (5.2%), muscle spasms (2.6%), abdominal pain upper (1.9%), abdominal pain (1.3%), and blood calcium decreased (1.3%). Adverse events considered by the investigator to be related to vitamin D sterols occurred in 6% and 2% of cinacalcet-treated and control-treated subjects, respectively. The most common vitamin D-related adverse events (> 1 subject in the cinacalcet group) were hypocalcemia (1.3%), hypercalcemia (1.3%), and hyperphosphatemia (1.3%).

Thirteen (8%) subjects in the cinacalcet group withdrew from cinacalcet due to adverse events; the most common adverse events resulting in withdrawal (reported for > 1 subject) were vomiting (5 subjects [3.2%]) and nausea (3 subjects [1.9%]). One subject discontinued cinacalcet due to an adverse event of hypocalcemia. Three (2%) subjects in the cinacalcet group and 1 (1%) in the control group withdrew from vitamin D due to adverse events; the reasons for withdrawal from vitamin D were (cinacalcet, control) hyperphosphatemia (2 [1.3%], 0), gastrointestinal hemorrhage (1 [0.6%], 0), and hypercalcemia (0, 1 [0.6%]). One subject who was in the cinacalcet group withdrew from the study due to a serious adverse event (intestinal obstruction).

The subject incidence of serious adverse events was 72 (46.5%) in the cinacalcet group and 52 (33.8%) in the control group. The most common serious adverse events (subject incidence > 2% in either treatment group) were (cinacalcet, control) by preferred term: arteriovenous fistula thrombosis (4.5%, 1.9%), atrial fibrillation (2.6%, 2.6%), sepsis (3.2%, 1.9%), arteriovenous fistula site complication (2.6%, 0.6%), angina pectoris (3.2%, 0.6%), cellulitis (3.2%, 0.6%), hyperkalemia (2.6%, 0.6%), pulmonary edema (3.2%, 1.3%), and coronary artery disease (0.6%, 2.6%). For the events that occurred more frequently (ie, > 2%) in the cinacalcet group compared with the control group, a case-level review was performed to assess causality. Many of the events in these subjects occurred 30 days or more after stopping cinacalcet either temporarily or permanently. The remaining cases were confounded by prior medical history, concomitant medications, or concurrent illness. There were no serious hypocalcemia adverse events reported for either cinacalcet-treated or control-treated subjects. There were no serious adverse events considered by the investigator to be related to cinacalcet or to vitamin D sterols.

Eight subjects (5.2%) in the cinacalcet group and 7 (4.5%) subjects in the control group died while on study. Deaths most commonly were due to cardiac events, as observed in 5 subjects (2 subjects in the cinacalcet group and 3 subjects in the control group). [redacted] who died of cardiac arrest had an adverse event of hypocalcemia reported 30 days before death; the investigator considered the cardiac arrest event unrelated to cinacalcet and the hypocalcemia event related to cinacalcet. The remaining deaths in the cinacalcet group were due to other causes: sepsis (2 subjects), hyperkalemia (1 subject), cerebrovascular accident (1 subject), grand mal convulsion (1 subject), and renal failure chronic (1 subject). Deaths in the control group were due to the following other causes (1 subject each): gastrointestinal hemorrhage, death (verbatim term was 'death from natural cause'), cerebellar tumor, and respiratory distress. None of the fatal adverse events were considered by the investigator to be related to vitamin D sterols or cinacalcet.

The overall subject incidence of events of interest was greater in the cinacalcet group (85 [55%]) than in the control group (66 [43%]). This difference was primarily driven by the greater incidence of hypocalcemia events of interest in the cinacalcet group (27 [17.4%]) than in the control group (1 [0.6%]). Hypocalcemia adverse events of interest were reported as 2 preferred terms, "hypocalcemia" (16.1% and 0.6% of subjects who received cinacalcet and control, respectively)

and “blood calcium decreased” (1.3% of subjects who received cinacalcet). Events of hypocalcemia were considered treatment-related by the investigator for 89% (24 of 27 subjects) and 0% of subjects, respectively. There were no serious events of hypocalcemia.

No trends indicative of treatment-related effects were evident in hematology variables and serum chemistry.

Conclusions: These results indicate that cinacalcet with low-dose vitamin D provides a more effective treatment approach than flexible doses of vitamin D alone for secondary HPT in incident hemodialysis subjects regardless of baseline disease severity or previous treatment with vitamin D. In the cinacalcet group, nausea, vomiting, hypocalcemia, and muscle spasm were the most commonly reported treatment-related adverse events.