2. SYNOPSIS

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

Name of Finished Product: Sensipar® or Mimpara®

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: **EV**aluation **O**f Cinacalcet HCl Therapy to **L**ower Cardio**V**ascular **E**vents

Investigator(s) and Study Center(s): This study was conducted at 467 centers in 22 countries in North, Central, and South America, Australia, Russia, and Europe. The study centers and principal investigators are listed in Appendix 4.

Publication(s): Chertow GM, Pupim LB, Block GA, et al. Evaluation of cinacalcet therapy to lower cardiovascular events (EVOLVE): Rationale and design overview. Clin J Am Soc Nephrol 2007;2:898-905.

Chertow GM, Correa-Rotter R, Block GA, et al. Baseline characteristics of subjects enrolled in the evaluation of cinacalcet HCl therapy to lower cardiovascular events (EVOLVE) trial. Nephrol Dial Transplant 2012;0:1–8.

The EVOLVE Trial Investigators. Effects of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med 2012 DOI: 10.1056/NEJMoa1205624.

Study Period: 22 August 2006 (first subject enrolled) to 10 April 2012 (last subject completed follow up).

Development Phase: 3

Objectives:

Primary*:* To determine the efficacy of a secondary hyperparathyroidism (HPT) treatment regimen including cinacalcet compared with a treatment regimen not including cinacalcet (placebo) on the composite of time to all-cause mortality or first non-fatal cardiovascular event (myocardial infarction [MI], hospitalization for unstable angina, heart failure [HF], or peripheral vascular event).

Secondary*:* To assess the effects of a secondary HPT treatment regimen including cinacalcet versus a treatment regimen not including cinacalcet, by determining time to:

- All-cause mortality
- Cardiovascular mortality
- Fatal and non-fatal MI
- Fatal and non-fatal hospitalization for unstable angina
- Fatal and non-fatal HF event
- Fatal and non-fatal peripheral vascular event
- Fatal and non-fatal stroke
- Bone fracture
- Parathyroidectomy

Safety and tolerability of cinacalcet were also secondary objectives. Tertiary objectives are presented in Section 6.3.

Methodology: This multicenter study utilized a randomized, double-blind, placebo-controlled design. The study consisted of a screening period (up to 30 days) followed by 2 consecutive phases: a dose-titration phase lasting 20 weeks with study visits every 2 weeks and a follow-up phase (up to approximately 4 years) with study visits every 8 weeks. Subjects who qualified for the study were randomized at a 1:1 ratio to cinacalcet (active) or placebo (control). Randomization was stratified by diabetes (yes/no) and country. Subjects received cinacalcet or placebo orally at a starting dose of 30 mg once daily and were eligible for a dose titration once every 4 weeks during the dose-titration phase and once every 8 weeks during the follow-up phase. Possible sequential doses during the titration phase were 30, 60, 90, 120, and 180 mg of

cinacalcet or placebo. Dose escalation was based upon intact parathyroid hormone (iPTH) values, serum calcium values, and subject safety information.

Number of Subjects Planned: 3800 (1:1 cinacalcet:placebo)

Number of Subjects Enrolled: 3883 (1948 cinacalcet, 1935 placebo)

Diagnosis and Main Criteria for Eligibility: Subjects were eligible for the study if they were men or women ≥ 18 years of age at screening; treated with maintenance hemodialysis 3 times a week for ≥ 3 months before randomization; had a iPTH concentration obtained from the central laboratory ≥ 300 pg/mL (31.8 pmol/L); had a serum calcium concentration obtained from the central laboratory ≥ 8.4 mg/dL (2.1 mmol/L); had a serum calcium times serum phosphorous product (Ca x P) concentration obtained from the central laboratory ≥ 45 mg^2/dL^2 (3.63 $mmol^2/L^2$). Subjects were not included if they had received cinacalcet or parathyroidectomy in the 12 weeks before the date of informed consent or were anticipated to undergo a parathyroidectomy within 6 months after randomization or had a scheduled date for kidney transplant from a known living donor. A complete list of inclusion/exclusion criteria are provided in Section 7.5.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Cinacalcet tablets were provided in dose strengths of 30, 60, and 90 mg, graduated in size from smallest to largest. Combinations of these tablets comprised the 120 and 180 mg doses. Tablets were to be swallowed whole without biting or chewing. Investigational product was to be administered with food or shortly after a meal. Cinacalcet 30 mg, 60 mg, and 90 mg tablets were distributed from 8, 6, and 2 batches, respectively; unique batch numbers are provided in Listing 14-3.1.1.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Placebo tablets were provided in 30, 60, and 90 mg dose strengths to match cinacalcet. Placebo tablets were distributed from 12 batches; unique batch numbers are provided in Listing 14-3.1.1.

Duration of Treatment: The study consisted of a screening period (up to 30 days) followed by 2 consecutive phases: a dose-titration phase lasting 20 weeks with study visits every 2 weeks and a follow-up phase (up to approximately 4 years) with study visits every 8 weeks. The median (min, max) duration of randomized treatment was 21.17 (0.0, 64.1) months in the cinacalcet group and 17.48 (0.0, 63.6) months in the placebo group.

Study Endpoints:

Primary Efficacy Endpoint
Time to composite event comprising all-cause mortality and non-fatal cardiovascular events (MI, hospitalization for unstable angina, HF, or peripheral vascular event).

Secondary Efficacy Endpoints
Time to: all-cause mortality; cardiovascular mortality; fatal and non-fatal MI; fatal and non-fatal hospitalization for unstable angina; fatal and non-fatal HF event; fatal and non-fatal peripheral vascular event; fatal and non-fatal stroke; bone fracture; parathyroidectomy

Safety Endpoints
Nature, frequency, severity, and relationship to treatment of adverse events, and changes in laboratory parameters

Tertiary endpoints are presented in Section 6.3.

Statistical Methods:

One primary composite endpoint (all-cause mortality and non-fatal cardiovascular events [MI, hospitalization for unstable angina, HF, or peripheral vascular event]) was evaluated in this study.

The 2 treatment groups were statistically compared at each of the 3 interim and final analyses using a 2-sided log-rank test stratified by country and history of diabetes at baseline. The significance level at the final test equaled 0.044.

Secondary endpoint analyses of death, MI, hospitalization for unstable angina, HF and peripheral vascular event were conducted since the purpose of these analyses was to show how each component contributed to the results of the primary composite endpoint. For the remaining secondary endpoints (time to event for cardiovascular mortality, fatal and non-fatal stroke, bone

fracture, or parathyroidectomy) analyses utilized a closed testing procedure to control the overall family-wise error rate. These endpoints were to be tested only if the primary endpoint reached statistical significance. Secondary endpoints were analyzed in the same manner as the primary endpoint. Secondary endpoints of cardiovascular mortality, stroke, bone fracture and parathyroidectomy were to be formally tested using the Hochberg method only if the primary composite endpoint was statistically significant. No adjustment for multiple comparisons of the analyses of the individual components of the primary composite endpoint, listed as secondary endpoints, were made since the purpose of these analyses was to show how each component contributed to the results of the primary composite endpoint.

The principal analyses of time to event endpoints (primary, secondary and tertiary endpoints) employed the intent-to-treat (ITT) method and included all randomized subjects according to their randomly assigned treatment group. For the primary endpoint of time to the primary composite event, Kaplan-Meier estimates of the event-free survival time were computed and graphically displayed. The difference between treatment groups was analyzed using a 2-sided log-rank test stratified by country and history of diabetes at baseline. The treatment effect was evaluated in a Cox proportional hazards regression model stratified by country and history of diabetes. As a secondary analysis of the primary endpoint, baseline covariates were evaluated one at a time to investigate the impact of each covariate on the treatment effect. The hazard ratio (HR) and its 95% confidence interval (CI) for cinacalcet versus placebo were estimated.

Safety endpoints were analyzed using the safety analysis set, which included all randomized subjects who received $\geq$ 1 dose of investigational product; subjects in this analysis set were analyzed according the randomized treatment unless they received the wrong treatment the entire time on study. All non-serious adverse events occurring after the first dose of investigational product and through 1 week (7 days) after the last dose of investigational product were reported. All serious adverse events occurring from the date of signature of informed consent through 7 days after the last dose of investigational product were reported unless the event was deemed by the investigator to be related to investigational product, in which case reporting could take place up to and > 7 days following the subject's discontinuation of investigational product. All deaths occurring on study, within 30 days of the last dose of investigational product, or up to the last formal on-study follow-up period, whichever occurred later, were reported. The subject incidence of each adverse event was tabulated by system organ class (SOC), preferred term, severity, seriousness, and relationship to treatment. The following adverse events, as well as current identified or potential risks of cinacalcet, were summarized separately: hypocalcemia, seizure/convulsion, hypersensitivity, hypotension and worsening heart failure, myocardial ischemia, ventricular arrhythmia, acute pancreatitis, fracture, nervous system disorders, and potential drug-induced hepatic disorders. Clinical laboratory parameters and vital signs were summarized using descriptive statistics and/or shift tables.

Summary of Results:

Subject Disposition: The study was conducted globally at 467 study centers: 163 centers in the United States (36.8% of subjects enrolled), 178 in Europe (30.6% of subjects enrolled), 63 in Latin America (17.7% of subjects enrolled), 20 in Russia (7.3% of subjects enrolled), 20 in Australia (3.8% of subjects enrolled) and 23 in Canada (3.8% of subjects enrolled).

A total of 5755 subjects were screened and 1872 were determined to be ineligible to participate; therefore, 3883 subjects were enrolled in the study. A total of 1948 subjects were randomized to cinacalcet and 1935 subjects were randomized to placebo. The median (min, max) duration of exposure was 21.17 (0, 64.1) months in the cinacalcet group and 17.48 (0.0, 63.6) months in the placebo group. The observation period was approximately 264 more subject years for the cinacalcet group compared with the placebo group.

A total of 1300 (66.7%) subjects in the cinacalcet group and 1365 (70.5%%) subjects in the placebo group permanently discontinued investigational product; 430 (22.1%) subjects in the cinacalcet group and 388 (20.1%) subjects in the placebo group discontinued because they met the protocol-specified criteria of parathyroidectomy, kidney transplant, low iPTH, calcium levels < 7.5 mg/dL or symptoms of hypocalcemia. A total of 308 (15.8%) subjects in the cinacalcet group and 229 (11.8%) subjects in the placebo group had investigational product permanently discontinued because of adverse events.

Baseline Demographics:

Sex: 1578 (40.6%) women; 2305 (59.4%) men

Age: Mean (SD) 54.4 (14.4) years

Ethnicity/Race: 2240 (57.7%) white, 837 (21.6%) black, 806 (20.8%) other races, including Hispanic or Latino

Efficacy Results: The study did not meet statistical significance on the primary composite endpoint in the ITT analysis, a 2-sided log-rank test (HR 0.93; 95% CI 0.85, 1.02; p = 0.112).

A total of 1890 primary composite endpoint events occurred: 938 (48.2%) events among the 1948 subjects randomized to the cinacalcet group and 952 (49.2%) among the 1935 subjects randomized to the placebo group. Annualized event rates were 14.0% (95% CI 13.2, 14.9) in the cinacalcet group and 14.8% (95% CI 13.9, 15.7) in the placebo group.

Secondary univariate and multivariate analyses of the primary composite endpoint were performed to evaluate potential covariates that could affect the estimates of the event-free survival time and to calculate adjusted treatment effects. Results from the multivariate analysis (multivariate best fit model) showed that cinacalcet resulted in a reduction in risk of a primary composite endpoint event (HR 0.88; 95% CI 0.79, 0.97; nominal p = 0.008). Of the baseline characteristics evaluated, age was the most important covariate affecting the treatment effect on the primary composite endpoint.

Sensitivity analyses showed an effect on the primary composite endpoint for censoring at the time of parathyroidectomy, time of kidney transplant, and lag censoring (subjects who were off investigational product for > 6 months had data censored at 6 months after stopping investigational product). Hazard ratios (cinacalcet/placebo) and nominal p-values for these parameters are presented below.

- Censoring at time of parathyroidectomy: HR 0.90 (95% CI 0.82, 0.99); p = 0.031
- Censoring at time of kidney transplant: HR 0.90 (95% CI 0.82, 0.99); p = 0.029
- Lag censoring: HR 0.85 (95% CI 0.76, 0.95); p = 0.003

Since the primary endpoint was not statistically significant, reported p-values should be considered nominal.

Secondary Endpoints:

- Time to cardiovascular mortality: HR 0.92 (95% CI 0.80, 1.07); p = 0.277
- Time to fatal and nonfatal stroke: HR 1.07 (95% CI 0.82, 1.40); p = 0.607
- Time to bone fracture: HR 0.89 (95% CI 0.75, 1.07); p = 0.218
- Time to parathyroidectomy: HR 0.44 (95% CI 0.36, 0.54); p < 0.0001

Components of the primary composite endpoint:

- Time to all-cause mortality: HR 0.94 (95% CI 0.85, 1.04); p = 0.249
- Time to fatal and nonfatal MI: HR 0.97 (95% CI 0.79, 1.19); p = 0.800
- Time to fatal and nonfatal hospitalization for unstable angina: HR 0.82 (95% CI 0.58, 1.18); p = 0.283
- Time to fatal and nonfatal heart failure events: HR 0.82 (95% CI 0.68, 0.99); p = 0.034
- Time to fatal and nonfatal peripheral vascular events: HR 0.87 (95% CI 0.72, 1.07); p = 0.190

As a tertiary endpoint, the percentage of subjects achieving NKF-K/DOQI (2003) metabolism and disease recommended iPTH targets was consistently greater in the cinacalcet group compared with the placebo group during the treatment period. Consistent results were observed for the

percentage of subjects achieving recommended corrected serum calcium levels and serum calcium times serum phosphorus product (Ca x P) levels during the study.

Safety Results: Since the observation period differs between the treatment groups (ie, approximately 264 more subject years of observation for the cinacalcet group), the exposure-adjusted rate (per 100 subject-years) is presented for all single event results.

Treatment-emergent adverse events were reported for 1806 (93.2%) subjects in the cinacalcet group and 1748 (90.9%) subjects in the placebo group. The exposure-adjusted event rates (per 100 subject-years) were 273.2 for the cinacalcet group and 217.8 for placebo group.

The most frequent adverse events (exposure-adjusted subject incidence > 10 per 100 subject-years in either group) were nausea (18.3 cinacalcet, 9.1 placebo), vomiting (15.4 cinacalcet, 8.0 placebo), and diarrhea (12.0 cinacalcet, 11.5 placebo). The exposure-adjusted incidence rates for hypocalcemia (a known risk of cinacalcet) reported as an adverse event were 6.0 (cinacalcet) and 0.7 (placebo). The system organ classes (SOCs) with the highest exposure-adjusted incidence rate of adverse events in both treatment groups were gastrointestinal disorder (67.5 cinacalcet, 44.6 placebo) and cardiac disorders (18.8 cinacalcet, 20.6 placebo).

Adverse events were reported as possibly related to investigational product for 890 (45.9%) subjects in the cinacalcet group and 363 (18.9%) subjects in the placebo group; the exposure-adjusted incidence rates (per 100 subject-years) were 35.3 and 11.3 for cinacalcet and placebo, respectively. The most common treatment-related adverse events (exposure-adjusted subject incidence > 5 per 100 subject-years in either group) were nausea (10.6 cinacalcet, 2.9 placebo) and vomiting (7.1 cinacalcet, 1.2 placebo).

A total of 1338 (69.0%) subjects in the cinacalcet group and 1351 (70.3%) subjects in the placebo group reported a serious adverse event during the study. The exposure-adjusted incidence rates (per 100 subject-years) of serious adverse events were similar between treatment groups: 53.3 and 56.9 for cinacalcet and placebo, respectively. The most common serious adverse events (exposure-adjusted subject incidence > 3 per 100 subject-years in either group) were sepsis (3.1 cinacalcet, 3.0 placebo) and pneumonia (3.0 cinacalcet, 4.9 placebo).

A total of 673 (34.7%) subjects in the cinacalcet group and 689 (35.8%) subjects in the placebo group had a fatal adverse event reported during the study. The exposure-adjusted incidence rates (per 100 subject-years) for fatal adverse events were 14.8 in the cinacalcet group and 16.6 in the placebo group. The most common fatal adverse events (exposure-adjusted subject incidence ≥ 1 per 100 subject-years in either group) reported by investigators were sepsis (1.6 cinacalcet, 1.3 placebo), cardiac arrest (1.3 cinacalcet, 1.3 placebo), MI (1.2 cinacalcet, 1.2 placebo) and death (0.9 cinacalcet, 1.0 placebo).

A total of 419 (21.6%) subjects in the cinacalcet group and 365 (19.0%) subjects in the placebo group had investigational product withdrawn because of adverse events. The exposure-adjusted incidence rates (per 100 subject-years) were similar between treatment groups (10.6 cinacalcet, 10.0 placebo). The most common adverse events (exposure-adjusted subject incidence > 1 per 100 subject-years in either group) leading to withdrawal of investigational product were nausea (1.8 cinacalcet, 0.4 placebo), vomiting (1.5 cinacalcet, 0.2 placebo) and hyperparathyroidism (0.3 cinacalcet, 1.1 placebo). Exposure-adjusted subject incidences (per 100 subject-years) of events of hypocalcemia leading to withdrawal of investigational product were 0.3 in the cinacalcet group and < 0.1 in the placebo group.

Adverse events of special interest, as defined in the Risk Management Plan for cinacalcet, include the previously known and labeled risks (hypocalcemia, convulsions/seizures, hypotension and/or worsening HF, and hypersensitivity reactions, including rash, angioedema, and urticaria) and potential risks (myocardial ischemia, ventricular arrhythmias, fractures, acute pancreatitis, possible drug-related hepatic disorders, and nervous system disorder events [excluding seizures]). The subject incidences of the above events of interest were assessed based on a predefined strategy for searching the clinical trial database. The exposure-adjusted incidence rates (per 100 subject-years) for the labeled identified risks (cinacalcet, placebo) were 1.2 and 0.8 for convulsions, 6.7 and 0.9 for hypocalcemia, 4.9 and 4.6 for hypersensitivity, 6.5 and 6.5 for hypotension, and 5.6 and 7.9 for cardiac failure. The exposure-adjusted incidence rates

(per 100 subject-years) for the potential risks (cinacalcet, placebo) were 0.5 and 0.5 for acute pancreatitis, 1.1 and 1.4 for drug-related hepatic disorders, 3.6 and 4.9 for fractures, 7.1 and 7.2 for ischemic heart disease, 24.3 and 20.5 for nervous system disorders, and 0.4 and 0.6 for ventricular arrhythmias.

Over time, median calcium values decreased consistently in the cinacalcet group, but generally these changes were ≤ 1.0 mg/dL. These median decreases in the cinacalcet group represented a 4% to 10% decrease from baseline. In the placebo group, either no change from baseline was observed or small increases were observed throughout the study. In general, there were no unexpected findings in clinical laboratory parameters, vital signs, or electrocardiograms.

Adverse events in the SOC "Neoplasms Benign, Malignant and Unspecified" were reported for 140 (7.2%) subjects in the cinacalcet group and 118 (6.1%) subjects in the placebo group; exposure-adjusted incidence rates (per 100 subject-years) were 3.6 and 3.3, respectively. Serious adverse events in this SOC were reported for 82 (4.2%) subjects in the cinacalcet group and 76 (4.0%) subjects in the placebo group; exposure-adjusted incidence rates were 2.1 and 2.1, respectively. Fatal events in this SOC were reported for 26 (1.3%) subjects in the cinacalcet group and 24 (1.2%) subjects in the placebo group; exposure-adjusted incidence rates were 0.6 and 0.6, respectively. Neoplastic events as defined by Standard MedDRA Query (SMQ) "Malignant or Unspecified Tumor" (which excluded events reported as benign) were reported for 115 (5.9%) subjects in the cinacalcet group and 90 (4.7%) subjects in the placebo group, corresponding to exposure-adjusted incidence rates (per 100 subject-years) of 2.9 and 2.5, respectively. Serious neoplastic events as defined by SMQ "Malignant or Unspecified Tumor" were reported for 78 (4.0%) subjects in the cinacalcet group and 65 (3.4%) subjects in the placebo group, corresponding to exposure-adjusted incidence rates (per 100 subject-years) of 2.0 and 1.8, respectively. Fatal neoplastic events as defined by SMQ "Malignant or Unspecified Tumor" were reported for 25 (1.3%) subjects in the cinacalcet group and 23 (1.2%) subjects in the placebo group, corresponding to exposure-adjusted incidence rates (per 100 subject-years) of 0.6 and 0.6, respectively.

Conclusions: The EVOLVE trial tested the hypothesis that a treatment regimen for secondary HPT including cinacalcet reduces the risk of mortality and cardiovascular morbidity compared to a treatment regimen without cinacalcet in subjects with chronic kidney disease receiving maintenance hemodialysis. The study did not meet statistical significance on the primary composite endpoint in the ITT analysis (HR 0.93; 95% CI 0.85, 1.02; p = 0.112).

After adjusting for baseline characteristics, the HR for the primary composite endpoint was 0.88 (95% CI 0.79 to 0.97). Results from sensitivity analyses suggest that imbalance in age, poor long-term compliance with treatment and use of cinacalcet in the placebo group may have limited the study's ability to demonstrate a potential clinically important benefit.

Since the primary endpoint was not statistically significant, secondary endpoints were not tested for statistical significance. Cinacalcet reduced the rate of parathyroidectomy by more than half when compared with placebo (HR 0.44 [95% CI 0.36, 0.54]; nominal p < 0.0001).

The rates and characteristics of adverse events and serious adverse events reported in the study were generally consistent with the known safety profile of cinacalcet.