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: ADVANCE: A Randomized Study to Evaluate the Effects of Cinacalcet Plus Low Dose Vitamin D on Vascular Calcification in Subjects with Chronic Kidney Disease (CKD) Receiving Hemodialysis

Investigator(s) and Study Center(s): This study was conducted at 100 sites in the United States (43 centers), Europe (37 centers in Hungary [6 centers], Italy [5 centers], Poland [5 centers], Spain [6 centers], France [4 centers], Germany [4 centers], Switzerland [3 centers], Finland [2 centers], Portugal [2 centers]), Canada (10 centers), Australia (8 centers), and Russia (2 centers). The principal investigators are listed in Appendix 4.

Publication(s): Floege J, Raggi P, Block GA, et al. Study Design and Subject Baseline Characteristics in the ADVANCE Study: Effects of Cinacalcet on Vascular Calcification in Haemodialysis Patients. *Nephrol Dial Transplant.* 2010 Jan 27.

Study Period: 27 October 2006 (first subject enrolled) to 15 May 2009 (last subject completed follow-up phase)

Development Phase: 4

Introduction and Objectives: Traditional therapeutic interventions for secondary hyperparathyroidism (HPT) include large oral doses of calcium as a phosphate-binding agent and the administration of pharmacological doses of vitamin D sterols. These therapies are associated with increases in serum calcium-phosphorus product (Ca x P), calcium, and phosphorus levels, which have been implicated in the development of vascular calcification in patients with CKD. The calcimimetic cinacalcet is a novel therapy that increases the sensitivity of parathyroid gland calcium-sensing receptor to extracellular calcium, leading to a reduction in parathyroid hormone (PTH). Completed phase 3 clinical trials in patients with end stage renal disease (ESRD) and secondary HPT have demonstrated that treatment with cinacalcet also reduces serum Ca x P, calcium, and phosphorus levels, and, therefore, improves the imbalances in calcium and phosphate metabolism that are associated with increased vascular calcification. Previous studies also have demonstrated that when treating subjects with secondary HPT with cinacalcet and low dose vitamin D, control of PTH and Ca x P is enhanced as compared with standard therapy.

The primary objective of this study was to evaluate whether a treatment regimen including cinacalcet with low dose vitamin D attenuated the progression of coronary artery calcification (CAC) at week 52 compared with a regimen of flexible vitamin D dosing in the absence of cinacalcet in hemodialysis subjects. The secondary objectives of this study included evaluation of the effect of cinacalcet with low dose vitamin D in comparison to flexible vitamin D dosing on:

- attenuation of the progression of aortic calcification
- attenuation of the progression of aortic valve calcification
- proportion of subjects achieving > 15% progression of CAC
- absolute and percent changes in PTH, corrected calcium, phosphorus, and Ca x P
- safety and tolerability of cinacalcet

Methodology: This phase 4, multicenter, randomized, open-label study evaluated the impact of

cinacalcet and low dose vitamin D on the progression of vascular calcification in subjects with secondary HPT receiving hemodialysis. The study consisted of a screening phase of up to 45 days, a dose titration phase of 20 weeks, and a follow-up phase of 32 weeks. Subjects were randomized 1:1 to a cinacalcet treatment or control treatment group. The cinacalcet treatment group received cinacalcet at a starting dose of 30 mg and a low dose of vitamin D if previously prescribed. The control group received their previously prescribed therapy for secondary HPT during the study (use of non-calcium based phosphate binders was not permitted). Randomization was stratified with respect to CAC score (≥ 30 to 399, ≥ 400 to 999, and ≥ 1000).

Cinacalcet doses were titrated every 4 weeks based on intact parathyroid hormone (iPTH) and serum calcium levels, as well as on safety assessments. Possible sequential doses were 30, 60, 90, 120, and 180 mg. Dose reductions were allowed at any time during the study to maintain iPTH targets and appropriate serum calcium and phosphorus levels.

Subjects in both the cinacalcet and control treatment groups were to maintain a low dose vitamin D regimen (oral or intravenous) as prescribed. If at the time of randomization, subjects were on a lower dose of vitamin D than recommended by standard treatment guidelines or on no dose of vitamin D, they entered the study on the lower or no dose of vitamin D.

Number of Subjects Planned: A total of 330 subjects were planned to be randomized into the study (165 cinacalcet, 165 control).

Number of Subjects Enrolled: 360 enrolled

Sex: 207 (58%) men; 153 (43%) women
Age: 61.5 (12.7) years
Ethnicity (Race): 236 (66%) white; 85 (24%) black; 25 (7%) Hispanic; 10 (3%) Asian; 1 (< 1%) American Indian; 2 (1%) Pacific Islander; 1 (< 1%) other

Diagnosis and Main Criteria for Eligibility: Subjects eligible for this study were adults (≥ 18 years of age) receiving hemodialysis for ≥ 3 months before study day 1. Eligible subjects were to have iPTH levels > 300 pg/mL (31.8 pmol/L) or bio-intact parathyroid hormone (biPTH) levels >160 pg/mL (17.0 pmol/L). Subjects receiving active vitamin D therapy who had a corrected serum Ca x P of > 50 mg^2/dL^2 (3.9 $mmol^2/L^2$) were eligible if they had an iPTH level ≥ 150 pg/mL and ≤300 pg/mL (15.9 to 31.8 pmol/L) or biPTH level 80 to 160 pg/mL (8.5 to 170 pmol/L). In addition, subjects were required to have a serum calcium level (corrected for albumin) of ≥ 8.4 mg/dL (2.1 mmol/L) and a screening CAC score of ≥ 30.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Subjects randomized to cinacalcet (Sensipar® [Australia, US, Canada] or Mimpara® [Europe]) 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]

Duration of Treatment: The planned treatment period was a 20-week dose titration period followed by a 32 week follow-up period.

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

were not provided by the sponsor of this study.

Study Endpoints

Primary Efficacy Endpoint:
- percent change from baseline in CAC score at week 52

Secondary Efficacy Endpoints:
- absolute change from baseline in CAC score at week 52
- absolute change and percent change from baseline in aortic calcification score at week 52
- absolute change and percent change from baseline in aortic valve calcification score at week 52
- proportion of subjects achieving > 15% progression of CAC at week 52 (versus baseline)
- absolute and percent change from baseline to end of study (weeks 44 to 52) in PTH, calcium, phosphorus, and Ca x P

Safety Endpoint:
- the nature, frequency, severity and relationship to treatment of adverse events throughout the study

Statistical Methods: The percent change from baseline in CAC score at 52 weeks (primary endpoint) was compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test on ranks, stratified by screening CAC score (≥ 30 to 399, ≥ 400 to 999, and ≥ 1000). An additional supportive analysis using generalized linear models (GLM) was performed to estimate the treatment effect, stratified by screening CAC score. The absolute change from baseline to week 52 in CAC score and the absolute change and percent change from baseline to week 52 in aortic and aortic valve calcification were analyzed using the same methods as those used for the primary endpoint. [redacted] The proportion of subjects achieving a > 15% progression of CAC were compared between treatment groups using the CMH test, stratified by CAC score strata at randomization. In addition, a supportive analysis using a logistic regression model was performed with baseline CAC score as a covariate. The odds ratio of achieving a > 15% progression of CAC adjusted for baseline CAC score was presented with its 95% confidence interval (CI). Absolute and percent change from baseline to end of study (weeks 44 to 52) in PTH, calcium, phosphorus, and Ca x P were compared between treatment groups using a generalized CMH test on ranks, stratified by screening CAC score. Serum calcium, phosphorus, PTH, and Ca x P (absolute values, absolute change and percent change from baseline) were summarized using descriptive statistics at each time-point by treatment group. Descriptive statistics were provided for all efficacy endpoints by treatment group at each measurement time point. Adverse events occurring during the treatment period were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 11.0 (or higher). The subject incidence of all adverse events was compared between the 2 treatment groups. Safety laboratory variables were summarized.

Summary of Results:

Subject Disposition: A total of 360 subjects were randomized (180 subjects in each of the 2 treatment groups). Of the 360 subjects randomized, 2 subjects (1 in each group) did not undergo study day 1 procedures and, therefore, were not included in the analyses. One hundred forty (78%) subjects in the cinacalcet group and 140 (78%) subjects in the control group completed the study. One hundred twenty seven (71%) subjects in the cinacalcet group completed randomized treatment. Randomization was stratified by CAC score; 134 subjects had a CAC score ≥ 30 to 399, 94 subjects had a CAC score ≥ 400 to 999, and 132 subjects had a CAC score ≥ 1000.

Efficacy Results: For all calcification endpoints evaluated, there were consistent trends between treatment groups in favor of cinacalcet treatment with regard to attenuated progression of cardiovascular calcification.

The Agatston scoring methodology was used for primary endpoint analyses. The median (Q1,

Q3) percent change in total Agatston CAC score from baseline to week 52 was 24% (-1%, 63%) in the cinacalcet group and 31% (8%, 81%) in the control group (generalized CMH p-value = 0.073). In an additional analysis with volume scores, the corresponding median (Q1, Q3) percent change in volume CAC scores were 22% (2%, 52%) and 30% (10%, 78; p-value = 0.009). An additional analysis showed the median treatment difference (95% CI) from control of the percent change in total Agatston CAC score from baseline to week 52 was -10.3% (-22.6%, 0.8%). For volume scores, the median treatment difference (95% CI) was -13.3% (-23.8%, -3.3%). A difference in percent change from baseline favoring cinacalcet treatment was also observed in a supportive analysis based on a GLM, with an 8% geometric mean difference from control in the progression of total Agatston CAC score (geometric mean ratio [cinacalcet:control] = 0.92, 95% CI = 0.82 to 1.03). The corresponding changes in volume scores was a 10% geometric mean difference from control (geometric mean ratio [cinacalcet:control] = 0.90, 95% CI = 0.82 to 0.99).

The median (Q1, Q3) absolute change in total Agatston CAC score from baseline to week 52 was 93.90 (-4.80, 300.10) in the cinacalcet group and 148.90 (23.45, 385.15) in the control group (generalized CMH p-value = 0.152). A similar trend favoring cinacalcet treatment was observed in a supportive analysis based on a GLM (mean difference from control group = -106.85, 95% CI = -220.41, 6.70).

The proportion of subjects demonstrating a >15% progression in total Agatston CAC score from baseline to week 52 also was lower for the cinacalcet treatment group (55% compared with 65%; CMH p-value = 0.094; odds ratio = 0.62, 95% CI = 0.36 to 1.08) though statistical significance was not achieved. A supportive analysis using logistic regression adjusted for log-transformed baseline total Agatston CAC score showed that the cinacalcet treatment group had a 36% reduction in odds of achieving >15% progression (adjusted odds ratio = 0.64, 95% CI = 0.37 to 1.11).

The median (Q1, Q3) percent change in aortic calcification from baseline to week 52 was lower for the cinacalcet treatment group (20% [7%, 47%] compared with 33% [5%, 69%], generalized CMH p-value = 0.073, 0 values at baseline were excluded as defined in Statistical Analysis Plan). Supportive analyses using a GLM and excluding subjects with a 0 value at baseline showed a 15% geometric mean difference from control (geometric mean ratio = 0.85, 95% CI = 0.72, 1.01, p-value = 0.070). [redacted] The median (Q1, Q3) absolute change in aortic calcification score from baseline to week 52 was 196 (0, 1104) in the cinacalcet group and 349 (18, 1118) in the control group (generalized CMH p-value = 0.338). For aortic calcification, analysis of cubic root-transformed data in a generalized linear model resulted in a mean treatment difference (95% CI) from control of -0.48 (-1.00, 0.05) cubic root Agatston units (p value = 0.073). For the aortic valve calcification score, the median (Q1, Q3) absolute change from baseline to week 52 was 0 (0, 15.5) and 0 (0, 34.1) in the cinacalcet and control groups, respectively (generalized CMH p-value = 0.258). Analysis of cubic root-transformed data using a GLM showed a mean difference (95% CI) from control of -0.31 (-0.72, 0.10) cubic root Agatston units (p value = 0.136). [redacted]

The absolute and percent change from baseline to end of study (weeks 44 to 52) in mean iPTH, corrected calcium, phosphorus and Ca x P in the cinacalcet group all were statistically superior to the control group.

Safety Results: Three hundred sixty subjects (180 cinacalcet, 180 controls) were randomized and were evaluable for safety. Most subjects (87% cinacalcet, 87% control) reported at least 1 adverse event. The most common adverse events (≥ 10% in either treatment group) were (cinacalcet, control): nausea (18%, 8%), diarrhea (17%, 14%), vomiting (13%, 12%), cough (10%, 13%), pain in extremity (4%, 13%), headache (7%, 12%), dyspnea (7%, 11%). Adverse events with a difference in incidence between treatment groups ≥ 5% included nausea, pain in extremity,

headache as well as hypocalcaemia (8%, 1%), arthralgia (3%, 9%), and depression (1%, 6%). The most common cinacalcet treatment-related adverse events were nausea (11%), hypocalcemia (7%), diarrhea (4%) vomiting (4%), abdominal discomfort (3%), abdominal pain upper (2%), muscle spasms (2%), and paresthesia (2%). The active vitamin D treatment-related adverse events were (cinacalcet, control) blood parathyroid hormone decreased (0%, 1%), hypercalcemia (1%, 3%), hyperphosphatemia (0%, 1%), arthralgia (0%, 1%), pruritus (0%, 1%) aniexty (1%, 0%) and vascular calcification (1%, 0%).

The incidences of withdrawals due to adverse events were 4% in the cinacalcet group and 2% in the control group. Nausea and diarrhea were the most common adverse event resulting in withdrawal from the study (cinacalcet: 1%; control: 0%). The incidences of serious adverse events were 49% and 46% in the cinacalcet and control groups, respectively, and the incidences of treatment-related serious adverse events were 1% and 0%, respectively. The incidence of fatal adverse events was 7% in both treatment groups; none of the fatal adverse events were considered by the investigators to be related to investigational product.

The overall incidence of subjects having reported an adverse event that was considered as a hypocalcemia event of interest based on prespecified search criteria was greater in the cinacalcet group: 16 (9%) subjects in the cinacalcet group and 5 (3%) subjects in the control group. Hypocalcemia was noted as an adverse event for 8% and 1% of subjects in the cinacalcet and control groups, respectively; at least 1 adverse event of hypocalcemia was considered treatment-related by the investigator for 7% and 0% of subjects, respectively. In comparison, the incidences of hypercalcemia were 1% in the cinacalcet group and 4% in the control group.

Mean (SE) corrected serum calcium concentrations at baseline were 9.38 (0.05) and 9.39 (0.04) mg/dL in the cinacalcet and control groups, respectively. In the cinacalcet group, mean corrected serum calcium concentrations decreased to the minimum of 8.55 (0.06) mg/dL by week 6; mean corrected serum calcium concentrations slightly increased during weeks 10, 14 and 18. At week 28, corrected serum calcium concentrations were 8.99 (0.08) mg/dL and remained near the latter value throughout the rest of the study. In the control group, mean corrected serum calcium concentrations were stable throughout the study, with values ranging from 9.35 (0.06) to 9.55 (0.06) mg/dL. Overall, 77%, 57%, and 28% of subjects in the cinacalcet group experienced a single low serum calcium concentration value of < 8.4, < 8.0, and < 7.5 mg/dL, respectively; in the control group, single low calcium values were noted in 28%, 12% and 2% of subjects, respectively.

Mean (SE) serum phosphorus concentrations at baseline were 5.97 (0.14) mg/dL and 5.60 (0.13) mg/dL in the cinacalcet and control groups, respectively. In the cinacalcet group, mean serum phosphorus concentrations decreased to a minimum of 4.79 (0.12) mg/dL at week 36 and were 5.27 (0.14) mg/dL at week 52. In the control group, mean serum phosphorus concentrations decreased slightly to a minimum of 5.17 (0.12) mg/dL at week 10; at week 52 the concentration was 5.20 (0.15) mg/dL. Hyperphosphatemia was not observed in the cinacalcet group and the incidence was 1% for the control group.

Vital signs showed no clinically important change from baseline to weeks 28 and 52. The use of concomitant medications by subjects in both treatment groups was overall generally well balanced and dialysate calcium concentration was similar between treatment groups.

Conclusions: This phase 4, randomized, open-label study did not reach statistical significance for the primary endpoint of percent change from baseline in total CAC score at week 52. An additional analysis using volumetric scoring, however, showed a more pronounced effect in favor of cinacalcet for the primary endpoint. This study showed trends that favored cinacalcet treatment with low dose vitamin D in attenuating the progression of vascular calcification in subjects with secondary HPT receiving dialysis. The overall subject incidence of adverse events and serious adverse events was well balanced between treatment groups and clinical laboratory results were within expected values.