Name of Sponsor: Amgen Development Europe, 240 Cambridge Science Park, Milton Road, Cambridge CB4 0WD, United Kingdom

Name of Finished Product: Cinacalcet hydrochloride (cinacalcet HCl)

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

Title of Study: Study to investigate cinacalcet treatment in haemodialysis patients with secondary hyperparathyroidism

Investigators and Study Centers: This study was conducted at 85 sites in Germany and 28 sites in Spain. The study centres and principal investigators are listed in Appendix 4.

Publication: Schaefer RM, Bover J, Kleophas W, et al. The SENSOR study: a study to evaluate the efficacy of administering cinacalcet (Mimpara®/Sensipar®) with the first meal after dialysis [abstract]. *Nephrol Dial Transplant.* 2006;21(suppl 4):iv288. Abstract MO003.

Study Period: The first subject was enrolled on 05 October 2004, and the last subject completed all dose-optimisation phase assessments on 10 November 2005. By the time the first subject completed the dose optimisation phase, cinacalcet had become commercially available in each of the participating countries and thus, in accordance with the protocol, no subject entered the planned follow-up phase of the study. Subjects received cinacalcet for up to 21 weeks.

Development Phase: 3b

Introduction and Objectives:

Primary

To demonstrate that the efficacy of cinacalcet when coadministered with the first meal after dialysis is comparable (non-inferior) to the efficacy of cinacalcet when administered during the dialysis study visit.

Secondary

To evaluate the safety of cinacalcet when coadministered with the first major meal after dialysis.

To evaluate a predefined strategy to manage nausea/vomiting during the study.

Methodology: This was a multicentre, randomised, open-label study, comprising 3 phases, a screening phase, a 21-week dose optimisation phase, and a maximum 60-week follow-up phase. The study was terminated on completion of the dose optimisation phase, in accordance with the protocol. Eligible subjects received cinacalcet (30 mg) once daily on entering the study, being randomised in a 1:1 ratio to receive the drug either with the first meal after dialysis or during the dialysis study visit on dialysis days. Cinacalcet was to be taken by individual subjects at approximately the same time on both dialysis and non-dialysis days. Randomisation was stratified according to screening parathyroid hormone (PTH) values and vitamin D usage at baseline, the proportion of subjects enrolled with a baseline intact PTH (iPTH) value > 800 pg/mL being capped at 25% in each country. Subjects were treated with cinacalcet with the aim of controlling iPTH and serum calcium and phosphorus values and the product of serum calcium and phosphorus concentrations (Ca x P) within Kidney Disease Outcomes Quality Initiative target ranges. Two treatment algorithms for the titration of cinacalcet doses and the adjustment of

concomitant vitamin D doses and phosphate binders were evaluated, one for subjects not prescribed vitamin D at baseline, the other for subjects who were receiving vitamin D at baseline. The study also incorporated a management plan for nausea and/or vomiting.

Number of Subjects Planned: 800 (1:1 cinacalcet with first meal after dialysis:cinacalcet during dialysis visit, on dialysis days)

Number of Subjects Enrolled: 673 (337 cinacalcet with first meal after dialysis, 336 cinacalcet during dialysis visit, on dialysis days)

A lower than anticipated dropout rate (21% instead of the estimated 35%) allowed the required number of evaluable subjects to be achieved with a smaller than planned study population, and subject recruitment was thus prematurely terminated.

Sex: 267 (40%) female; 394 (60%) male

Age: Mean (range) 57.0 (18.0 to 87.0) years

Ethnicity (Race): 646 (98%) white, 4 (1%) black, 11 (2%) other

Diagnosis and Main Criteria for Eligibility: Male or female patients ≥ 18 years of age with CKD, requiring dialysis (haemodialysis, haemodiafiltration, haemofiltration) for at least 1 month; iPTH determination within 14 days before randomisation ≥ 300 pg/mL (biologically intact PTH ≥ 150 pg/mL); serum calcium determination (corrected for albumin) within 14 days before randomisation ≥ 8.4 mg/dL (2.1 mmol/L).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Cinacalcet, orally administered in tablet form (30, 60, 90 mg free-base equivalents); starting dose 30 mg/day; possible sequential once daily doses 30, 60, 90, 120, 180 mg; possible subsequent twice daily doses 90, 120, 180 mg; possible three times weekly (TIW) doses 30 mg. Batch numbers of cinacalcet used were 038A023885, 038D030340 (each 30 mg), 038A023886, 038D032346 (each 60 mg), 038A023887, 038D032347 (each 90 mg).

Duration of Treatment: Subjects received cinacalcet for up to 21 weeks.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Not applicable; all subjects received cinacalcet.

Study Endpoints

Efficacy Endpoints:

Mean values of laboratory assessments obtained at weeks 11 and 13 were used to assess achievement of the efficacy endpoints in the 2 treatment groups.

Primary

The proportion of subjects with a mean iPTH ≤ 300 pg/mL

Secondary

The proportion of subjects with:

- a mean Ca x P value < 55 mg^2/dL^2 and iPTH ≤ 300 pg/mL
- a mean iPTH ≥ 150 pg/mL and ≤ 300 pg/mL

- a mean Ca x P value < 55 mg^2/dL^2
- a mean calcium value between ≥ 8.4 and < 9.5 mg/dL
- a mean phosphorus value between ≥ 3.5 and < 5.5 mg/dL

Safety Endpoints:

The proportion of subjects who terminate the study because of nausea or vomiting during the dose optimisation phase.

The safety and tolerability of cinacalcet during the dose optimisation and follow-up phases.

Exploratory Endpoints:

The proportion of subjects with a baseline iPTH > 800 pg/mL that achieve an iPTH ≤ 300 pg/mL at week 21 after twice daily administration of cinacalcet but who did not achieve the target at week 14.

The proportion of subjects with an iPTH ≤ 300 pg/mL at week 21.

The proportion of subjects with mean calcium between ≥ 8.4 and < 9.5 mg/dL, mean phosphorus between ≥ 3.5 and < 5.5 mg/dL, and mean Ca x P < 55 mg^2/dL^2 at week 21.

Mean iPTH, calcium, phosphorus, and Ca x P in the follow-up phase.

Statistical Methods: As appropriate for a non-inferiority study, the primary analysis of the primary endpoint was performed on the full analysis set, while a secondary analysis was performed on the per protocol analysis set. The proportions of subjects with a mean iPTH ≤ 300 pg/mL at weeks 11 and 13, adjusted for baseline iPTH and vitamin D use, were compared between treatments by calculating the weighted average of the stratum differences in the proportions, with weights proportional to the inverse of the variance of the stratum. Analyses of the secondary endpoints (full analysis set) consisted of descriptive summaries presenting the percentages of subjects achieving each endpoint in each treatment group and differences between the percentages, together with 95% confidence intervals (CIs) for the differences. Among subjects in the safety analysis set, the incidence of all adverse events within body systems was summarised by treatment group and preferred term using descriptive statistics.

Summary of Results:

Subject Disposition: A total of 673 subjects, initially to receive 30 mg once daily, were enrolled in this study, of whom 337 were randomised to receive cinacalcet with the first meal after dialysis and 336 were randomised to receive cinacalcet during the dialysis study visit on dialysis days. Eighty-one percent of subjects who administered cinacalcet with their first major meal after dialysis and 76% of those who administered cinacalcet during their dialysis study visit completed the dose optimisation phase.

Efficacy Results: Among subjects in the full analysis set, 57% of subjects randomised to receive cinacalcet with the first meal after dialysis had a mean iPTH value ≤ 300 pg/mL at weeks 11 and 13 compared with 54% of subjects randomised to receive cinacalcet during the dialysis visit. The difference between the cinacalcet with meal group and the cinacalcet during dialysis visit group was 3% (95% CI: -4%, 10%).

Among subjects in the per protocol analysis set, 62% of subjects who received cinacalcet with the first meal after dialysis had a mean iPTH value ≤ 300 pg/mL at weeks 11 and 13 compared with

57% of subjects who received cinacalcet during the dialysis visit. The difference between the cinacalcet with meal group and the cinacalcet during dialysis visit group was 5% (95% CI: -3%, 12%).

Forty-three percent of subjects randomised to receive cinacalcet with the first meal after dialysis had a mean iPTH ≤ 300 pg/mL and mean Ca x P < 55 mg^2/dL^2 at weeks 11 and 13, compared with 46% of subjects randomised to receive cinacalcet during the dialysis visit. The difference between the cinacalcet with meal and cinacalcet during dialysis visit groups was -3% (95% CI: -10%, 4%).

Thirty-eight percent of subjects randomised to receive cinacalcet with the first meal after dialysis had a mean iPTH ≥ 150 pg/mL and ≤ 300 pg/mL at weeks 11 and 13, compared with 35% of subjects randomised to receive cinacalcet during the dialysis visit. The difference between the cinacalcet with meal and cinacalcet during dialysis visit groups was 4% (95% CI: -4%, 11%).

Seventy-three percent of subjects randomised to receive cinacalcet with the first meal after dialysis had a mean Ca x P value < 55 mg^2/dL^2 at weeks 11 and 13, compared with 78% of subjects randomised to receive cinacalcet during the dialysis visit. The difference between the cinacalcet with meal and cinacalcet during dialysis visit groups was -5% (95% CI: -11%, 2%).

Forty-three percent of subjects randomised to receive cinacalcet with the first meal after dialysis had a mean serum calcium value ≥ 8.4 and < 9.5 mg/dL at weeks 11 and 13, compared with 44% of subjects randomised to receive cinacalcet during the dialysis visit. The difference between the cinacalcet with meal and cinacalcet during dialysis visit groups was -1% (95% CI: -8%, 7%).

Forty-five percent of subjects randomised to receive cinacalcet with the first meal after dialysis had a mean serum phosphorus value ≥ 3.5 and < 5.5 mg/dL at weeks 11 and 13, compared with 49% of subjects randomised to receive cinacalcet during the dialysis visit. The difference between the cinacalcet with meal and cinacalcet during dialysis visit groups was -4% (95% CI: -12%, 4%).

Fifty percent (3/6) of subjects with a baseline iPTH value > 800 pg/mL randomised to receive cinacalcet with the first meal after dialysis who failed to achieve an iPTH value ≤ 300 pg/mL at week 14 with once daily dosing achieved this target at week 21 after switching to twice daily dosing, compared with 25% (3/12) of subjects randomised to receive cinacalcet during the dialysis visit.

Fifty-eight percent of subjects randomised to receive cinacalcet with the first meal after dialysis had an iPTH value ≤ 300 pg/mL at week 21, compared with 60% of subjects randomised to receive cinacalcet during the dialysis visit. The difference between the cinacalcet with meal and cinacalcet during dialysis visit groups was -2% (95% CI: -9%, 5%).

Mean iPTH, Ca x P, and serum calcium and phosphorus values at scheduled time points throughout the dose optimisation phase of the study were comparable among subjects randomised to receive cinacalcet with the first meal after dialysis and subjects randomised to receive cinacalcet during the dialysis visit, and a fall occurred in each following the commencement of dosing with cinacalcet. The approximate extent of the decrease in each between baseline and the mean value for weeks 11 and 13 in each treatment group was 50% for iPTH, 20% for Ca x P, 9.5% for serum calcium, and 11% for serum phosphorus.

Safety Results: Approximately 80% of subjects in each treatment group reported 1 or more adverse events, the most frequent among which (cinacalcet with first meal after dialysis group, cinacalcet during dialysis visit group) were nausea (28%, 33%), vomiting (19%, 25%), muscle spasms (16%, 14%), and diarrhoea (15%, 12%). Vomiting was the only adverse event reported with a difference in incidence between the 2 treatment groups ≥ 5%.

Among adverse events considered by the investigator to have been treatment-related, reported by 40% to 44% of subjects in each treatment group, the most frequent (≥ 5% subject incidence in either treatment group) (cinacalcet with meal group, cinacalcet during dialysis visit group) were nausea (20%, 25%), vomiting (12%, 19%), upper abdominal pain (4%, 7%), and hypocalcaemia (5%, 3%). Serious adverse events were reported by approximately 18% of subjects in each treatment group, and judged by the investigator to have been treatment-related in 1% of subjects in each group.

Approximately 7% of subjects in each treatment group discontinued the study because of adverse events, most frequently vomiting and nausea (each 1 to 2% of subjects in each group). Fewer subjects who received cinacalcet with the first meal after dialysis than who received cinacalcet during the dialysis visit discontinued the study because of nausea and/or vomiting (5/336 [1.5%] subjects vs 12/334 [3.6%] subjects, respectively).

Hypocalcaemia (serum calcium < 8.4 mg/dL at some stage in the study) was reported by approximately 77% of subjects in each treatment group and controlled by adjustment of phosphate binder, vitamin D sterol, and cinacalcet doses according to the treatment algorithms. No subject discontinued the study because of hypocalcaemia, and cinacalcet administration was temporarily interrupted in only 1 subject (in the cinacalcet during dialysis visit group).

Fourteen deaths occurred on study (2% of subjects in each group), the causes of each of which were consistent with those commonly observed in the patient population studied, and none of which was considered by the investigator to have been related to cinacalcet.