2. SYNOPSIS

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

Name of Finished Product: Cinacalcet hydrochloride (Sensipar®, Mimpara®)

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

Title of Study: An Open-label, Randomized, Single-dose, 3-period, 3-treatment Crossover Study to Assess the Comparative Bioavailability of 5 mg Cinacalcet Capsules to the 30 mg Commercial Formulation Cinacalcet Tablets in Healthy Adult Volunteers

Investigator and Study Center: This single-center study was conducted by [redacted], MD at [redacted], [redacted]).

Publication: None

Study Period: The first subject enrolled in the study on 28 June 2008, and the last subject completed the study on 05 August 2008.

Development Phase: 1

Introduction and Objectives:
Cinacalcet is an organic small molecule that is synthesized and administered as hydrochloride salt of the dextrorotatory isomer, which is formulated as a tablet for oral administration. Tablets are manufactured in strengths of 30, 60, and 90 mg of [redacted] equivalents. Cinacalcet is currently approved in multiple countries for administration at doses of 30 mg to 180 mg once daily to treat secondary hyperparathyroidism (HPT) in adults with chronic kidney disease (CKD) receiving dialysis and at doses of 30 mg twice daily to 90 mg four times daily to reduce hypercalcemia in adults with parathyroid carcinoma or adults with primary HPT for whom parathyroidectomy is not a treatment option or a subset thereof. [redacted].

The primary objective of this study was to assess the comparative bioavailability, based on area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0\text{-}inf}$), AUC from time 0 to the time of the last quantifiable concentration ($AUC_{0\text{-}t}$), and the maximum observed plasma concentration (C_{max}), between six of the 5-mg capsules of cinacalcet swallowed whole with applesauce, contents of six of the 5-mg capsules sprinkled over and consumed with applesauce, and a single 30-mg commercial formulation tablet of cinacalcet swallowed whole with applesauce in healthy adult volunteers under fasted conditions. The secondary objectives of this study were to assess the safety and tolerability (eg, subject incidence of treatment-emergent adverse events, clinically significant changes in laboratory tests, electrocardiograms [ECGs], and vital signs) and additional pharmacokinetic parameters (time to C_{max} [t_{max}] and terminal elimination half-life [$t_{1/2}$]) of cinacalcet in healthy adult volunteers under fasted conditions.

Methodology:
This randomized, single-center, open-label, 3-treatment, 3-period, 6-sequence, crossover study assessed the comparative bioavailability of 5-mg cinacalcet capsules and 30-mg commercial formulation cinacalcet tablets in healthy adult volunteers. Subjects were enrolled and randomized in a 1:1:1:1:1:1 ratio to 1 of 6 treatment sequences: ABC, CAB, BCA, CBA, BAC, or ACB, where the 3 treatments, A, B, and C, were six of the 5-mg capsules swallowed whole with applesauce, a single 30-mg tablet swallowed whole with applesauce, and contents of six of the 5-mg capsules sprinkled over and consumed with applesauce, respectively. Following an overnight fast of ≥ 10 hours, treatments A, B, and C were administered with 4 oz of applesauce and 240 mL of

water. Cinacalcet treatment administration in each period was separated by a washout period of at least 14 days.

Number of Subjects Planned: Forty-two subjects were planned for this study.

Number of Subjects Enrolled: Forty-two subjects were enrolled in this study.

Sex: 24 (57%) women, 18 (43%) men

Mean (Standard Deviation) Age: 30 (7) years (range: 20 to 45 years)

Ethnicity (Race): 52% white/Caucasian, 14% black/African American, 29% Hispanic/Latino, 2% American Indian/Alaskan native, 2% native Hawaiian/other Native Pacific Islander

Diagnosis and Main Criteria for Eligibility: Eligible subjects for this study were healthy men and women between the ages of 18 and 45 years, inclusive, at the time of randomization whose baseline serum calcium levels were ≥ 9.0 mg/dL (2.25 mmol/L). Use of the following agents was not allowed unless prior approval from the investigator and Amgen was obtained:

- prescription and nonprescription drugs within 14 days or 5 half-lives, whichever was longer, before the first dose of study medication
- herbal supplements (eg, St. John's wort), enzyme inducers, hormonal methods of contraception, and hormone replacement therapy within 28 days or 5 half-lives, whichever is longer, before the first dose of study medication
- grapefruit or grapefruit-containing products within 7 days before the first dose of study medication
- investigational drug or device within 30 days or 5 half lives of the investigational drug, whichever is longer, before the first dose of study medication

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

After an overnight fast of ≥ 10 hours, Treatment A, B, or C was administered with 4 oz of applesauce and 240 mL of water, as described below. No food was allowed for ≥ 4 hours postdose. Water was allowed as desired except for 1 hour before and after drug administration.

Treatment A: A 30-mg (6 x 5 mg capsules) oral dose of cinacalcet swallowed whole with 240 mL of water after consumption of 4 oz of applesauce. The applesauce was consumed within 1 minute and dosing occurred within 1 minute of finishing the applesauce.

Treatment B: A single 30-mg (1 x 30 mg tablet) oral dose of cinacalcet swallowed whole with 240 mL of water after consumption of 4 oz of applesauce. The applesauce was consumed within 1 minute and dosing occurred within 1 minute of finishing the applesauce.

Treatment C: A 30-mg (6 x 5 mg capsules) oral dose of cinacalcet with the contents of the capsules sprinkled over 4 oz of applesauce and consumed within 1 minute with 240 mL of water.

For Treatments A and C, cinacalcet was provided as white, opaque, size-two, hard gelatin capsules of 5 mg [redacted] equivalents; the fill lot number used was [redacted]. For Treatment B, cinacalcet was provided as light-green, film-coated tablets of 30 mg [redacted] equivalents (commercial formulation); the fill lot number used was [redacted].

Duration of Treatment: Each subject received treatment on 3 separate days (with a washout period of at least 14 days between each treatment). The study duration for each subject from screening to end of study was approximately 64 days.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: None

Study Endpoints

The primary endpoints were the $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} of each treatment type (six 5-mg capsules swallowed whole with applesauce, six 5-mg capsules sprinkled over and consumed with applesauce, and the single 30-mg commercial formulation tablet swallowed whole with applesauce) in healthy adult volunteers under fasted conditions.

The secondary endpoints included safety and tolerability as measured by the subject incidence of treatment-emergent adverse events, clinically significant changes in laboratory tests, ECGs, and vital signs; and additional pharmacokinetic parameters (t_{max} and $t_{1/2}$) under fasted conditions.

Statistical Methods:

Descriptive statistics, including mean, standard deviation (SD), median, minimum, and maximum were provided for continuous data, and categorical data were summarized using frequency counts and percentages. Graphs of individual and mean (SD) cinacalcet plasma concentration-time profiles by treatment were provided.

The derived pharmacokinetic parameters were statistically analyzed using a crossover analysis of variance model. $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} were log-transformed before the analysis was conducted. The effects due to sequence, period, and treatment were evaluated as fixed effects in a mixed effect model, and subject within sequence was treated as a random effect. The 90% confidence intervals (CIs) for the estimate of comparative bioavailability (ie, the mean difference between the 3 treatments (A/B, C/B, C/A) for log-transformed $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max}) were calculated and expressed as the original-scale ratio/percent.

The number and percentage of subjects reporting any treatment-emergent adverse event and each adverse event were tabulated by system organ class and by preferred term or high-level term within system organ class according to the Medical Dictionary for Regulatory Authorities (MedDRA) coding dictionary. Adverse event, clinical laboratory, ECG, and vital sign data were listed for each subject. Select clinical laboratory data were summarized over time.

Summary of Results:

Subject Disposition: Forty-two subjects were randomized and received ≥ 1 dose of cinacalcet in this study. Forty (95%) subjects completed the study; 2 subjects were withdrawn from the study as a result of noncompliance (before completing period 3 assessments).

Pharmacokinetics Results: The 90% CI for the Treatment C/B ratio (6 x 5 mg sprinkle/30 mg tablet) of geometric least squares (LS) means was within the equivalence range of 0.80 to 1.25 (and included 1) for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}; this indicates that the 6 x 5 mg sprinkle treatments and the 30 mg tablet resulted in comparable systemic exposure. Geometric LS mean $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ values for Treatment A (6 x 5 mg capsule) were 11% lower than values for Treatment B (30 mg tablet) and Treatment C (6 x 5 mg sprinkle), and the geometric LS mean C_{max} value for Treatment A was 14% to 17% lower than for Treatments B and C. The 90% CIs for the Treatment A/B ratio (6 x 5 mg capsule/30 mg tablet) and Treatment C/A ratio (6 x 5 mg sprinkle/6 x 5 mg capsule) of geometric LS means for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ did not include 1, but they were within 0.80 to 1.25; this indicates that the AUC values are equivalent between Treatments A and B and between Treatments A and C. However, the 90% CIs for the corresponding C_{max} ratios were slightly outside of 0.80 to 1.25.

Geometric Least Squares Means, Point Estimates, and 90% Confidence Intervals for the Ratio for Geometric Least Squares Means for Pharmacokinetic Parameter Estimates Following Administration of 30 mg Cinacalcet Given as Three Different Cinacalcet Formulations to Healthy Adult Volunteers

Parameter	Geometric Least Squares Mean [a]			Point Estimate [b] (90%CI)		
	A (N = 42)	B (N = 42)	C (N = 40)	A/B	C/B	C/A
AUC_{0-t} (ng*hr/mL)	41.6	46.8	46.6	0.889 (0.836, 0.946)	0.997 (0.935, 1.062)	1.121 (1.052, 1.194)
AUC_{0-inf} (ng*hr/mL)	45.2	50.7	50.7[a]	0.891 (0.839, 0.947)	1.000 (0.940, 1.065)	1.123 (1.054, 1.195)
C_{max} (ng/mL)	4.3	5.0	5.2	0.863 (0.796, 0.935)	1.037 (0.955, 1.126)	1.202 (1.107, 1.304)

[a] N = 38
[b]Point estimate and 90% confidence intervals (CI) are for the respective ratio of log-transformed $AUC_{0\,t}$, $AUC_{0\,inf}$ and C_{max} values converted back to the original scale
A = 6 x 5 mg capsule; B = 1 x 30 mg tablet; C = 6 x 5 mg sprinkle
AUC_{0-t} = area under plasma cinacalcet concentration-time curve from 0 to the last quantifiable concentration
AUC_{0-inf} = area under the plasma cinacalcet concentration-time curve from time 0 to infinity
C_{max} = maximum observed plasma cinacalcet concentration
Source: documentum\Docbases\usddms\R&D Candidates\Development\Calcimimetics - 3501\Study 20070293\PKDM\Final Analysis\Unmodified Data\ t_09_001_pkparam_mix1.rtf; t_09_002_pkparam_mix2.rtf; t_09_003_pkparam_mix3.rtf

Safety Results: Overall, 21 subjects (50%) had ≥ 1 treatment emergent adverse event (defined as an adverse event that began or became more severe after the first dose of the investigational product in study period 1) during the study. Twelve subjects (29%) had adverse events during their Treatment A period, 9 subjects (21%) had adverse events during their Treatment B period, and 10 subjects (25%) had adverse events during their Treatment C period. The most common adverse events (> 5% total subject incidence) were (total; Treatment A, Treatment B, Treatment C) hypocalcemia (26%; 12%, 7%, 15%), abdominal pain (12%; 12%, 0%, 0%), headache (12%; 5%, 5%, 8%), and diarrhea (7%; 7%, 0%, 0%). All adverse events were mild to moderate in severity.

Adverse events considered by the investigator to be related to treatment occurred in 19 subjects (45%) during the study. The most common treatment-related adverse events (> 5% total subject incidence) were (total; Treatment A, Treatment B, Treatment C) hypocalcemia (26%; 12%, 7%, 15%), abdominal pain (12%; 12%, 0%, 0%), headache (12%; 2%, 5%, 5%), and diarrhea (7%; 7%, 0%, 0%). No serious adverse events were reported, no subjects withdrew due to adverse events, and no deaths occurred on study.

Eleven subjects had transient decreases in albumin-adjusted serum calcium concentration to below the lower limit of normal (2.225 mmol/L, per the laboratory normal range); these were the subjects for whom adverse events of hypocalcemia were reported and who consequently received oral calcium supplements. The low calcium concentrations for these subjects ranged from 2.07 to 2.20 mmol/L. No other clinically significant trends were observed for any of the other laboratory parameters (serum chemistry, hematology, and urinalysis) or vital signs.

Conclusions: This study demonstrated that the extent of systemic cinacalcet exposure was comparable across all 3 treatments (A, B, and C), with equivalent AUC values across the 3 treatments. Peak exposure, as assessed by C_{max} values, was equivalent between Treatments B and C. However, C_{max} was slightly outside the equivalence criteria for the comparisons between Treatments A and C and between Treatments A and B.

Overall, cinacalcet was well tolerated. Treatment-related adverse events were similar to what have been reported previously for cinacalcet. Although abdominal pain and diarrhea were only noted during Treatment A, the small number of subjects reporting adverse events does not permit meaningful conclusions regarding safety differences between the 3 treatment arms.