SYNOPSIS

Name of Sponsor: Amgen Development Europe

Product or Therapeutic Area: Cinacalcet HCl

Indication: The reduction of hypercalcaemia in patients with primary hyperparathyroidism (pHPT) for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated.

Title of Study: PRIMARA: A Prospective Descriptive Observational Study to Review Mimpara® (Cinacalcet) Use in Patients With Primary Hyperparathyroidism in Clinical Practice.

Investigator(s) and Study Center(s): This study was conducted at 60 centers in Europe. The list of investigators and enrollment by site are provided in Table 14-1.1.

Publication(s): None

Study Period: 19 October 2009 to 14 December 2011

Development Phase: Observational

Introduction and Objectives: Primary HPT is characterised by increased secretion of parathyroid hormone (PTH) leading to hypercalcaemia. The disease is often asymptomatic, but complications can be progressive and/or severe, ranging from vague, non-specific complaints to life-threatening hypercalcaemia. Significant complications associated with pHPT (likely as a result of persistently elevated serum calcium and PTH levels) include bone loss, gastrointestinal disturbances, kidney stones, muscle weakness, depression, and neuropsychiatric disturbance. Parathyroidectomy is the only definitive treatment for pHPT, but surgery can be unsuccessful or may be contraindicated (eg, because of comorbidity).

Calcimimetics, a novel class of organic small molecules, act as allosteric modulators of the calcium-sensing receptor (CaR). By targeting the CaR on the surface of parathyroid gland cells, calcimimetics provide a means of regulating PTH secretion by amplifying the sensitivity of the receptor to extracellular calcium, thereby reducing PTH secretion (Nemeth et al, 2004; Nemeth and Bennett, 1998). Cinacalcet is a first-in-class calcimimetic. Worldwide, cinacalcet has received marketing authorization in a total of 55 countries and is indicated for the treatment of secondary HPT in patients with chronic kidney disease receiving dialysis (all regions), for the treatment of hypercalcaemia in patients with parathyroid carcinoma (all regions except Brazil), and for the treatment of pHPT in patients for whom parathyroidectomy is not a treatment option or a subset thereof, depending on the region. The focus of Study 20070363 was to gather information on the manner in which cinacalcet is used in clinical practice for treatment of pHPT.

The objectives of the study were:

- To describe treatment patterns in subjects prescribed cinacalcet for pHPT in clinical practice.
- To describe serum calcium and other relevant laboratory parameters in subjects with pHPT in clinical practice in whom treatment with cinacalcet has recently been initiated.
- To describe bone mass and remodelling in subjects prescribed cinacalcet for primary HPT in clinical practice.
- To describe the subject population receiving cinacalcet for pHPT in clinical practice.
- To summarise the incidence of adverse drug reactions to cinacalcet in subjects prescribed cinacalcet for pHPT in clinical practice.
Study Hypothesis: No formal hypothesis was tested in this descriptive observational study. Outcome measures were estimated at various time points after the initiation of cinacalcet.

Study Design/Methodology: This was a multicentre, descriptive observational study of adult subjects with pHPT receiving cinacalcet in clinical practice in several European sites. Subjects were scheduled to be enrolled within 1 month of initiating cinacalcet treatment, and data were collected prospectively for up to 1 year from initiation. All data collected at nominal baseline (pre-cinacalcet) and throughout the 12-month observational period were abstracted from medical records to electronic case report forms (eCRFs). Every effort was made to continue collecting data for subjects who discontinued cinacalcet before the end of the 12-month observational period.

Centers were selected based on documented experience with, and focus on, the treatment of pHPT and experience in using cinacalcet. Eligible subjects at participating centers initiating cinacalcet were enrolled in a sequential manner. A log was maintained of all subjects receiving cinacalcet, but not enrolled and the reason for exclusion.

Study Endpoints/Outcomes:

- Cinacalcet treatment pattern:
  - Cinacalcet daily dose (mg/day) and frequency at initiation, at 3, 6, and 12 months after initiation, and at end of treatment.
  - Mean daily cinacalcet dose (mg/day) over the entire study.
  - Occurrence of a change in cinacalcet dose or frequency of administration during the first 3 months after initiation, > 3 to 6 months after initiation, and > 6 months after initiation.
  - Duration of exposure to cinacalcet.

- Serum calcium and other relevant laboratory parameters:
  - Achievement of a reduction from baseline (pre-cinacalcet) of serum calcium ≥ 1 mg/dL at 3, 6, and 12 months after the initiation of cinacalcet.
  - Incidence of a serum calcium concentration ≤ 10.3 mg/dL at 3, 6, and 12 months after the initiation of cinacalcet.
  - Absolute values and change from baseline in biochemical parameters (serum calcium, albumin, plasma intact parathyroid hormone [iPTH], phosphorus, creatinine, 25-OH-vitamin D, urinary calcium/creatinine ratio) at 3, 6, and 12 months after the initiation of cinacalcet.

- Bone mass and remodelling:
  - Absolute value and percent change in bone mineral density by anatomic site from baseline to the end of the observational period as assessed by dual X-ray energy absorptiometry.
  - Absolute values and change from baseline in total alkaline phosphatase, bone-specific alkaline phosphatase, osteocalcin, type I collagen N-telopeptides, and type I collagen C-telopeptides at 3, 6, and 12 months after the initiation of cinacalcet.

- Subject population receiving cinacalcet:
  - Receipt of cinacalcet for each of the following reasons: failed surgery (ie, parathyroidectomy), surgery contraindicated, surgery not considered appropriate by physician, acute or chronic use for the reduction of hypercalcaemia before surgery, surgery declined, other.
• Adverse drug reactions (ADRs):
  – Incidence of ADRs; (adverse events considered by the investigator to be causally associated with the administration of cinacalcet).

• Additional Outcomes
  – Incidence of parathyroidectomy
  – Incidence of kidney stones
  – Incidence of fracture
  – Exposure to relevant medications
  – Deaths

Statistical Methods: Analyses are descriptive in nature. For continuous outcome measures descriptive statistics, eg, mean, standard deviation, standard error (SE), 95% confidence interval (CI) for mean, median, 25th and 75th percentiles, and minimum and maximum values, are presented. For categorical outcome measures the number and percentage of subjects in each category are reported together with 95% CIs. Variables measured longitudinally, eg, calcium, iPTH, are also summarised graphically by plotting the mean ± SE against time. The Full Analysis Set (FAS) included all enrolled subjects who fulfilled the study inclusion/exclusion criteria. The FAS was the primary analysis set for all analysis and unless otherwise stated results are shown for this analysis set. Some analyses were repeated on the “FAS with Censoring” where data after cinacalcet discontinuation were not included.

A complete description of the statistical methods is provided in the Statistical Analysis Plan (SAP) (Appendix 7).

Summary of Results:

Number of Subjects Included in Study: A total of 305 subjects were enrolled in the study, of which 303 were included in the FAS. Six subjects (2.0%) were entered into the study in violation of the protocol by either having cinacalcet initiated more than 1 month prior to study entry or after enrolment (Table 14-3.1).

Subject Disposition: A total of 282/305 (92.5%) subjects completed the 12-month observation period (Table 14-1.3). Eighty-six subjects (28.2%) discontinued cinacalcet during the study; the main reasons were parathyroidectomy (13.1%), nausea and/or vomiting (2.0%) and other (7.9%). The latter category mainly comprised ADRs (17 of 24 subjects), which are discussed below with all ADRs (Listing 14-1.10, Listing 14-6.16 and Listing 14-6.18).

Subject Characteristics: The majority of subjects were female (241/303, 79.5%), and all subjects for whom race was available were white/Caucasian (199/303, 65.7%) (Table 14-2.1.1). The median (min, max) age of subjects at the initiation of cinacalcet was 70 (23, 92) years and 64% (194/303) of subjects were ≥ 65 years of age.

Medical history is presented in Table 14-2.2.1 (pHPT) and Table 14-2.4.1 (comorbidities). Median (Q1, Q3) time since pHPT diagnosis was 0.55 (0.10, 2.42) years and diagnosis was symptomatic (ie, based on symptoms) in 44.2% of subjects. Of those with symptomatic diagnosis, the most common symptoms were bone pain (43.3%) and kidney stones (37.3%). The primary aetiology of pHPT was predominantly parathyroid adenoma (73.9%) and parathyroid hyperplasia (16.2%). Forty five subjects (14.9%) had a history of parathyroidectomy. A total of 49/303 (16.2%) subjects had a history of renal disease.

Baseline laboratory data (most recent value within 3 months prior to cinacalcet initiation) are presented in Tables 14-2.6.1 and Table 14-2.7.1. Serum total calcium was recorded for most subjects with mean (SD) of 11.34 (1.26) mg/dL (n=275). Albumin-corrected serum calcium was available for fewer subjects (n=198); mean (SD) was 11.42 (1.03) mg/dL. Median (Q1, Q3) iPTH was 152.7 (105.0, 263.0) pg/mL and mean (SD) phosphorus was 2.60 (0.80) mg/dL.
Study Outcomes:

Subject Population Receiving Cinacalcet: Reasons for which subjects were prescribed cinacalcet are presented in Table 14-1.5.2. The majority of subjects received cinacalcet because surgery was not considered appropriate by their physician (107/303, 35.3%) or surgery was declined by the subject (86/303, 28.4%). Other reasons for receiving cinacalcet included acute or chronic use for treatment of hypercalcaemia prior to surgery (43/303, 14.2%), failed surgery (33/303, 10.9%), and surgery contraindicated (33/303, 10.9%). Of the 107 subjects for whom surgery was not considered appropriate by their physician, the main reason was that the parathyroid gland/adenoma could not be localized (45/107, 42.1%).

Subjects who received cinacalcet because surgery was contraindicated or was not considered appropriate, or who had declined surgery, tended to be older than subjects who failed surgery or were prescribed cinacalcet prior to surgery (median age: 76.0, 71.0, 70.5, 62.0 and 64.0 years, respectively) (Table 14-2.1.3).

Cinacalcet Treatment Pattern: Table 14-5.1.1 presents dose and frequency of cinacalcet dosing during the study. At initiation, the mean (SE) daily dose was 43.9 (0.9) mg (median 30.0 mg) with the majority of subjects starting with a dose of 30 mg once a day (53.8%) or 30 mg twice a day (43.6%). Mean (SE) daily dose at 3, 6 and 12 months after cinacalcet initiation was 48.7 (1.9) mg, 48.9 (2.0) mg, and 51.3 (2.1) mg based on 255, 233, and 219 subjects, respectively. Median daily dose was 30.0 mg at all three timepoints. The mean (SE) daily dose at end of treatment (last dose received) was 53.1 (2.0) mg; 55.4% (168/303) of subjects were taking cinacalcet once daily and 38.9% (118/303) of subjects were taking cinacalcet twice daily at the end of treatment. Cinacalcet was withheld in 2.4% of subjects at month 3 and 1.3% at month 6.

Table 14-5.2.1 presents the occurrence of changes to cinacalcet daily doses and frequency of administration after cinacalcet initiation. Within the first 3 months after initiation, 99/303 (32.7%) subjects had a change in their daily dose of cinacalcet. Between 3 and 6 months and after 6 months of initiating cinacalcet treatment, 106/255 (41.6%) and 107/233 (45.9%) subjects, respectively, had a change in dose. Frequency of cinacalcet administration changed for 76/303 (25.1%) subjects within the first 3 months. Between 3 and 6 months, 77/255 (30.2%) subjects had a change in dose administration frequency and 82/233 (35.2%) subjects had a change after 6 months of initiating cinacalcet treatment. For the 148 subjects with at least 1 change in dose or frequency of administration during the study, the reasons for changes were: hypercalcaemia (52.7%), cinacalcet reinitiated (22.3%), nausea and/or vomiting (18.9%), hypocalcaemia (12.2%), high PTH (10.1%), and other (31.8%), (Table 14-5.3.1).

Table 14-5.4.1 presents the duration of exposure to cinacalcet on study (time from first dose to non-zero last dose). Mean (SD) duration of exposure was 295.9 (127.1) days. Approximately 6% of subjects received cinacalcet for less than 1 month with an additional 10.2% receiving cinacalcet for between 1 and 3 months. Two hundred and twenty two subjects (73.3%) received cinacalcet for more than 9 months.

Mean (SD) daily dose during the study was 49.6 (27.5) mg including periods of withheld dose and 50.4 (27.2) mg excluding periods of withheld dose (Table 14-5.5.1).

Serum Calcium and Other Relevant Laboratory Parameters:

Reduction from Baseline (Pre-cinacalcet) of Serum Calcium ≥ 1 mg/dL

Table 14-4.1.1 presents the percentage of subjects achieving a reduction from baseline (pre-cinacalcet) in albumin-corrected serum calcium ≥ 1 mg/dL during the study. This reduction was observed in 101/180 (56.1%) subjects with data available at 3 months, 95/152 (62.5%) subjects with data available at 6 months, and 70/117 (59.8%) subjects with data available at 12 months after cinacalcet initiation. Data for this outcome was missing for 41%, 50% and 61% of subjects at the respective timepoints, primarily because data were not available for subjects still in the study. Results were similar in the “FAS with Censoring” analysis set where data after cinacalcet discontinuation were excluded (57.3%, 64.5% and 62.0% respectively) (Table 14-4.1.2). Owing to the high proportion of missing data, this outcome was also calculated using total calcium or serum ionised calcium instead of albumin-corrected calcium (since albumin...
was missing in many cases when total calcium was available) (Table 14-4.9.1). The percentage of subjects achieving a reduction in total serum calcium ≥ 1 mg/dL was similar: 63.7%, 62.2% and 69.0% at 3, 6 and 12 months after cinacalcet initiation. Missing data rates were lower for this analysis: 16%, 27% and 38% of subjects at the respective timepoints.

**Incidence of a Serum Calcium Concentration ≤ 10.3 mg/dL**

Table 14.4.4.1 presents the percentage of subjects with albumin-corrected serum calcium concentration ≤ 10.3 mg/dL during the study. The percentage of subjects with albumin-corrected serum calcium concentration ≤ 10.3 mg/dL was 9.9% (22/223) at baseline (pre-cinacalcet) and increased to 62.7% (138/220) at 3 months, 69.4% (134/193) at 6 months and 70.9% (105/148) at 12 months after cinacalcet initiation. Data for this outcome was missing for 26% to 51% of subjects at a timepoint. Results from the “FAS with Censoring” analysis set were similar to those observed in for the FAS (Table 14-4.4.2). When this outcome was assessed using total calcium or serum ionised calcium instead of albumin-corrected calcium, the percentages of subjects achieving a calcium concentration ≤ 10.3 mg/dL increased from 9.2% (26/282) at baseline to 67.5% (185/274) at 3 months, 66.8% (161/241) at 6 months and 74.1% (146/197) at 12 months after cinacalcet initiation (Table 14.4.10.1). Missing data rates were lower for this analysis, ranging from 7% to 35% of subjects at a timepoint.

**Absolute Values and Change from Baseline in Serum Calcium and Other Relevant Laboratory Parameters**

Albumin-corrected calcium over time is presented for the FAS in Table 14.7.4.1. Mean (SE) albumin-corrected calcium decreased from 11.42 (0.07) mg/dL at baseline (n = 198) to 10.12 (0.08) at 3 months (n = 200), representing a mean (SE) decrease of 1.28 (0.08) mg/dL over this period. Mean (SE) values at 6 months (n = 165) and 12 months (n = 137) were 10.04 (0.07) and 10.05 (0.07) mg/dL, respectively; mean (SE) decreases from baseline were 1.40 (0.11) mg/dL at 6 months and 1.43 (0.12) mg/dL at 12 months. The mean percentage reduction from baseline in albumin-corrected calcium was approximately 11% to 12% for the 3 timepoints. Results from the “FAS with Censoring” analysis set were similar to those observed in the FAS (Table 14-7.4.2).

Similar reductions were observed in total calcium concentrations over time (Table 14-7.2.1). Mean (SE) total calcium decreased from 11.34 (0.08) mg/dL at baseline (n = 275) to 9.92 (0.07) mg/dL at 3 months (n = 268), 10.02 (0.06) mg/dL at 6 months (n = 233), and 9.86 (0.06) mg/dL at 12 months (n = 192). The mean percentage reduction from baseline in total calcium was approximately 11% to 12% for the 3 timepoints.

Other relevant laboratory parameters were evaluated at baseline and months 3, 6, and 12 post cinacalcet administration:

- Median (Q1, Q3) baseline serum/plasma iPTH was 16.20 (11.14, 27.91) pmol/L (Table 14-7.6.1). By month 3, the median (Q1, Q3) serum/plasma iPTH was 13.85 (8.90, 23.66) pmol/L, which represented a median (Q1, Q3) decrease from baseline of 2.00 (-8.60, 1.91) pmol/L. At months 6 and 12, median (Q1, Q3) values were 13.95 (8.49, 20.80) pmol/L and 12.52 (7.97, 21.65) pmol/L, respectively; the median (Q1, Q3) decreases from baseline at these timepoints were 2.40 (-8.24, 1.75) pmol/L and 2.48 (-10.00, 1.52) pmol/L, respectively. The median percentage reduction from baseline in serum/plasma iPTH was approximately 13% to 18% for the 3 timepoints.

- Mean (SE) baseline serum phosphorus was 2.60 (0.05) mg/dL (Table 14-7.9.1). By month 3, the mean (SE) serum phosphorus was 2.97 (0.04) mg/dL, which represented a mean (SE) increase from baseline of 0.38 (0.06) mg/dL. At months 6 and 12, mean (SE) values were 2.98 (0.05) mg/dL and 2.98 (0.05) mg/dL, respectively; the mean (SE) increases from baseline at these timepoints were 0.38 (0.07) mg/dL and 0.38 (1.09) mg/dL, respectively.

- Mean (SE) baseline serum albumin was 42.1 (0.3) g/L (Table 14-7.10.1). By month 3, the mean (SE) serum albumin was 41.8 (0.3) g/L. At months 6 and 12, mean (SE) values were 41.7 (0.4) g/L and 41.0 (0.5) g/L, respectively; the mean (SE) decreases from baseline at these timepoints were 0.5 (0.3) g/L and 0.7 (0.5) g/L, respectively.
• Median (Q1, Q3) baseline serum 25-OH Vitamin D was 41.4 (29.0, 62.3) nmol/L (Table 14-7.11.1). By month 3, the median (Q1, Q3) serum 25-OH Vitamin D was 49.3 (34.9, 71.1) nmol/L, which represented a median (Q1, Q3) increase from baseline of 3.3 (-9.0, 16.4) nmol/L. At months 6 and 12, median (Q1, Q3) values were 43.9 (29.0, 68.3) nmol/L and 52.3 (33.4, 73.6) nmol/L; the median (Q1, Q3) changes from baseline at these timepoints were -1.8 (-13.0, 15.3) nmol/L and 6.1 (-6.6, 28.1) nmol/L, respectively.

• Mean (SE) baseline serum creatinine was 82.6 (2.2) µmol/L (Table 14-7.12.1). By month 3, mean (SE) serum creatinine was 83.6 (2.2) µmol/L, which represented a mean (SE) increase from baseline of 0.9 (1.3) µmol/L. At months 6 and 12, mean (SE) values were 80.5 (2.0) µmol/L and 85.7 (2.5) µmol/L; the mean (SE) increases from baseline at these timepoints were 0.6 (1.4) µmol/L and 1.3 (1.7) µmol/L, respectively.

• Median (Q1, Q3) baseline urine calcium:creatinine ratio was 0.75 (0.37, 1.13) (Table 14-7.13.1). By month 3, median (Q1, Q3) urine calcium:creatinine ratio was 0.79 (0.41, 1.17), which represented a median (Q1, Q3) decrease from baseline of 0.02 (-0.21, 0.14). At months 6 and 12, median (Q1, Q3) values were 0.68 (0.42, 0.96) and 0.73 (0.43, 1.15); the median (Q1, Q3) decreases from baseline at these timepoints were 0.02 (-0.27, 0.15) and 0.05 (-0.28, 0.17), respectively.

Bone Mass and Remodelling:

Bone Mineral Density

Bone mineral density assessed by dual-energy X-ray absorptiometry (DXA) is summarized by anatomic site and densitometer in Table 14-4.7.1. Few subjects had bone mineral density data available at both baseline and month 12 (maximum of 19 subjects for lumbar spine with Hologic densitometer: mean [SD] percent change was -2.57 [9.56] g/cm² for these subjects).

T and Z-scores are summarized by anatomic site in Table 14-4.8.1. Mean (SD) baseline T-scores were -2.08 (1.13), -1.43 (1.22) and -1.93 (1.33) for femoral neck, proximal femur and lumbar spine respectively (based on n = 65, 35 and 88 subjects). There was little data for femoral trochanter and distal radius. Mean (SD) baseline Z-scores were -0.38 (0.79), -0.16 (0.97) and -0.18 (1.25) for femoral neck, proximal femur and lumbar spine, respectively (based on n = 56, 31 and 76 subjects). Mean (SD) changes in T-Score from baseline to month 12 were small: -0.04 (0.32), -0.15 (0.44) and -0.19 (0.52) for femoral neck, proximal femur and lumbar spine, respectively (based on n = 17, 11 and 23 subjects). Changes in Z-Score from baseline to month 12 were also small.

Other Markers of Bone Remodelling

Change from baseline to months 3, 6, and 12 were evaluated for other markers of bone remodelling:

• Median (Q1, Q3) baseline (n = 213) total alkaline phosphatase was 88.0 (72.0, 123.0) U/L (Table 14-7.14.1). By month 3 (n = 174), median (Q1, Q3) total alkaline phosphatase was 93.5 (74.0, 126.0) U/L, which represented a median (Q1, Q3) increase from baseline of 2.0 (-9.6, 15.0) U/L. At months 6 (n = 141) and 12 (n = 116), median (Q1, Q3) values were 91.8 (70.0, 118.0) U/L and 87.5 (71.5, 113.0) U/L; the median (Q1, Q3) increases from baseline at these timepoints were 5.0 (-13.0, 24.0) U/L and 1.0 (-21.0, 18.0) U/L, respectively.

• Median (Q1, Q3) baseline (n = 50) bone-specific alkaline phosphatase was 19.85 (12.60, 27.00) µg/L (Table 14-7.15.1). By month 3 (n = 38), median (Q1, Q3) bone-specific alkaline phosphatase was 19.33 (13.00, 30.30) µg/L, which represented a median (Q1, Q3) increase from baseline of 1.30 (-2.80, 6.50) µg/L. At months 6 (n = 37) and 12 (n = 31), median (Q1, Q3) values were 20.82 (14.60, 40.20) µg/L and 15.70 (12.00, 29.00) µg/L; the median (Q1, Q3) increases from baseline at these timepoints were 4.55 (-3.65, 16.10) µg/L and 1.97 (-6.00, 6.00) µg/L, respectively.
Median (Q1, Q3) baseline (n = 87) serum osteocalcin was 30.0 (20.0, 43.6) µg/L (Table 14-7.17.1). By month 3 (n = 82), median (Q1, Q3) serum osteocalcin was 31.1 (15.9, 48.5) µg/L, which represented a median (Q1, Q3) increase from baseline of 0.7 (-6.0, 8.4) µg/L. At months 6 (n = 77) and 12 (n = 53), median (Q1, Q3) values were 32.4 (21.0, 42.2) µg/L and 31.5 (19.0, 48.0) µg/L; the median (Q1, Q3) changes from baseline at these timepoints were 1.6 (-4.4, 9.4) µg/L and -0.1 (-8.4, 15.1) µg/L, respectively.

Median (Q1, Q3) baseline (n = 51) serum Type I collagen C-telopeptides was 609.0 (380.0, 940.0) ng/L (Table 14-7.21.1). By month 3 (n = 48), median (Q1, Q3) serum Type 1 collagen C-telopeptides was 637.0 (398.3, 1161.5) ng/L, which represented a median (Q1, Q3) increase from baseline of 116.8 (-19.0, 475.0) ng/L. At months 6 (n = 43) and 12 (n = 28), median (Q1, Q3) values were 604.6 (290.0, 901.7) ng/L and 556.0 (334.3, 832.0) ng/L; the median (Q1, Q3) changes from baseline at these timepoints were 140.0 (-20.4, 416.2) ng/L and 57.0 (-295.0, 380.0) ng/L, respectively.

Additional Study Outcomes

Incidence of Parathyroidectomy

Subject incidence of parathyroidectomy was assessed from initiation of cinacalcet to end of study. A total of 45/303 (14.9%) subjects underwent parathyroidectomy during the study (Table 14-8.2.1). One subject underwent 2 parathyroidectomies: a minimal invasive procedure followed by an open neck procedure a week later.

Incidence of Kidney Stones and Fracture

Subject incidence of both kidney stones and fracture was assessed from initiation of cinacalcet to end of study. A total of 6/303 (2.0%) subjects were diagnosed with kidney stones (Table 14-8.3.1) and 7/303 (2.3%) subjects experienced a clinical fracture during the study (Table 14-8.4.1).

Exposure to Relevant Medications

Prescribed medications considered relevant to the treatment of pHPT are summarised in Table 14-5.6.1. Bisphosphonates were the most commonly prescribed medication during the study (53/303, 17.5% of subjects) and the use of these medications during the study increased over baseline (28/303, 9.2% of subjects).

Deaths

A total of 5/303 (1.7%) subjects died during the study (defined as the day of cinacalcet initiation to end of study, inclusive) (Table 14-8.1.1 and Listing 14-8.1.3); none of the deaths were reported by investigators as related to cinacalcet treatment. Brief summaries of these cases are provided below:

- Subject 36354004005, an 80-year-old female with a medical history of cardiovascular disease, hypertension and renal disease, died of cardiac failure on day 232 of cinacalcet treatment.
- Subject 36354004007, a 79-year-old female with a medical history of cardiovascular disease, hypertension, renal disease, and cognitive impairment, died of cardiopulmonary failure on day 252 of cinacalcet treatment.
- Subject 36325008008, a 77-year-old female with a medical history of gastritis, died of gastrointestinal hemorrhage on day 76 of cinacalcet treatment.
- Subject 36321004001, an 81-year-old female with a medical history of cardiovascular disease, hypertension, renal disease, diabetes, and cognitive impairment, died of a cerebrovascular accident on day 54 of cinacalcet use.
- Subject 36358004001, an 81-year-old female with a medical history of cardiovascular disease died suddenly on day 339 of the study; cinacalcet treatment was discontinued on day 29.
Adverse Drug Reactions: Adverse drug reactions (ADRs) were reported in 81/303 (26.7%) subjects (Table 14-6.1). Two subjects (0.7%) had serious ADRs and ADRs leading to discontinuation were reported in 23 (7.6%) subjects.

All Adverse Drug Reactions

Adverse drug reactions by system organ class (SOC) and preferred term are presented in Table 14-6-2. Nausea was the most frequently reported ADR and was reported in 41/303 (13.5%) subjects. Vomiting was reported in 11 (3.6%) subjects, and abdominal pain and diarrhea each were reported in 6 (2.0%) subjects. Hypocalcaemia and paraesthesia were reported in 5 (1.7%) subjects. There were no reported ADRs of seizure, hypersensitivity reaction, hypotension, or worsening heart failure, which are known risks associated with cinacalcet treatment.

Adverse Drug Reactions by Severity

Adverse drug reactions are presented by severity in Table 14-6-8; these data are summarized by highest severity grade. Most subjects experienced ADRs that were mild to moderate in severity. No subjects experienced life-threatening or fatal ADRs.

Serious Adverse Drug Reactions

Three serious ADRs were reported in 2 subjects; these events were hypocalcaemia and muscle spasms in 1 subject, and circulatory collapse in 1 subject (Table 14-6.3). Complete narratives are provided in Appendix 5 and summaries of these cases are provided below:

- Subject 36342002006, an 81-year-old female, developed hypocalcaemia and cramps in lower extremities approximately 3 weeks after initiating cinacalcet for pHPT. The subject was hospitalised on the same day. Laboratory test results revealed a total calcium level of 1.94 mmol/L (baseline calcium was 2.75 mmol/L). Cinacalcet was discontinued, after which calcium levels normalized and the subject no longer experienced cramping of the lower extremities.

- Subject 36326009003, a 70 year-old female, with a history of alcohol dependence, anxiety, depression, asthma, and osteoporosis initiated cinacalcet therapy (30 mg twice daily) on 22 June 2010 for pHPT. The subject experienced diarrhea, vertigo, tachycardia, muscle weakness, and dyspnea after approximately 12 days of cinacalcet treatment. Due to these symptoms, it was reported that “the subject started to drink alcohol again”. The subject was subsequently hospitalised for these symptoms, described as “collapse” by the investigator. There was no syncope or loss of consciousness according to the investigator. Baseline blood pressure was 130/70 mmHg; on admission, blood pressure was 115/70 mmHg and heart rate was 100 bpm. Vomiting and diarrhea resolved after discontinuation of both cinacalcet and alcohol. Tachycardia resolved after diltiazem was discontinued and verapamil was started. The subject was also being treated with diazepam and zoledronic acid. The event of collapse was reported to have resolved on day 21. No laboratory values were reported at the time of the event.

Company Comment: The subject’s vital signs reported at the time of the event did not indicate hypotension or true circulatory compromise. The verbatim term provided by the investigator was “collapse”, which coded in MedDRA to the preferred term of “circulatory collapse”. Causality assessment of these events is confounded by the alcohol dependency, possible alcohol withdrawal, benzodiazepine use and medication changes. Zoledronic acid was considered co-suspect by the investigator.

Adverse Drug Reactions Leading to Discontinuation

Adverse drug reactions leading to discontinuation were reported in 23/303 (7.6%) subjects (Table 14-6.4), of which the most frequently reported were nausea (7 subjects, 2.3%), vomiting (5 subjects, 1.7%), and paraesthesia (3 subjects, 1.0%). Decreased appetite, hypocalcaemia, headache, and tremor each occurred in 2 subjects. All other ADRs leading to discontinuation were each reported in 1 subject only.
Adverse Drug Reactions of Special Interest

Adverse drug reactions of special interest are summarized separately in Table 14-6.6 and include the important identified and potential risks of cinacalcet, as described in the product’s Risk Management Plan (RMP). The identified (expected and currently listed in the product labeling) risks of cinacalcet include hypocalcaemia, convulsion, hypersensitivity, and hypotension or worsening heart failure; the potential risks are events that are not identified, but are under heightened pharmacovigilance including fracture, acute pancreatitis, cardiac ischemia, ventricular arrhythmia, nervous system disorders, and potential drug induced hepatic disorders. These events were identified using a Standard MedDRA Query (SMQ) or the sponsor’s standard search strategy.

The most frequently reported ADRs were in the special interest category of nervous system disorders and included paraesthesia (5/303, 1.7%), dizziness (3/303, 1.0%), headache (3/303, 1.0%), tremor (3/303, 1.0%), and syncope (1/303, 0.3%). Hypocalcaemia was reported in 5 (1.7%) subjects. Grade 2 liver enzyme increases (ALT, aspartate aminotransferase [AST], and gamma-glutamyltransferase [GGT]) were reported in one subject (36325008001); although the values were not reported, the AST/ALT increases reportedly occurred after cinacalcet administration. It is unclear if GGT was elevated prior to or following cinacalcet administration (Listing 14-6.15). There was no clinically relevant change in alkaline phosphatase (data on file) and bilirubin levels were not collected. The clinical significance of these changes is not clear from the information reported.

A broad search strategy was performed to identify events reported with the preferred term hypocalcaemia, as well as symptoms that may be associated with hypocalcaemia (Table 14-6.7). Adverse drug reactions in this special interest category comprised hypocalcaemia (5/303, 1.7%), paraesthesia (5/303, 1.7%), and muscle spasms (2/303, 0.7%); arrhythmia and oral hypoesthesia were reported in 1 subject each (0.3%).

Bias/Limitations: Although this study was prospectively designed as observational, it shares similar limitations to other observational analyses, eg, lack of a controlled setting and the limited ability to control for variables.

Reasons for non-enrollment of potential subjects were collected to help assess the impact of selection bias. For the 77 subjects considered for participation, but who did not participate, non-participation was primarily the result of failure to meet the eligibility criteria (mainly due to use of cinacalcet for more than 1 month before enrolment) (Table 14-1.2).

Centres were selected for participation in the study based on documented experience and a focus on treating subjects with pHPT, as well as experience using cinacalcet. It is possible that the centres included in the study may not be representative of those within the participating countries. Key baseline characteristics and outcomes were therefore also summarised by type of centre (university hospital, general hospital, private practice). Baseline laboratory parameters did not differ markedly for university hospital and general hospital centres (Tables 14-2.6.5, 14-2.7.5) and there were no consistent trends across timepoints for calcium outcomes (Tables 14-4.1.7, 14-4.4.7). Sample size was too small for private practice centres to make comparisons.

A potential bias is that availability of data such as bone mineral density, which is not routinely collected, may be linked to severity of disease (eg, subjects with more severe disease may be monitored more frequently). This was not found to be the case (Tables 14-2.5.3, 14-2.10.5, 14-8.4.5), although the sample size was small for the group with available bone mineral density data (n=27).

A potential issue with data interpretation is the inclusion of data post-parathyroidectomy in the main analysis (FAS). However, of the 45 subjects who underwent parathyroidectomy during the study, 43 discontinued cinacalcet prior to surgery and therefore the “FAS with Censoring” analysis, which excludes data after cinacalcet discontinuation, will also exclude data after parathyroidectomy for the majority of these subjects (43/45) (Listing 14-8.2.4). Results for the calcium outcomes were similar in analyses based on the FAS and the “FAS with Censoring”.
Conclusions:

- The population in this study was representative of the general population with pHPT where medical therapy can be highly considered. In the majority of subjects, cinacalcet was prescribed because 1) they had failed surgery, 2) surgery was considered inappropriate by the physician, 3) surgery was contraindicated, or 4) surgery was declined by the subject.

- Despite the initial tendency to use suboptimal doses, clinically relevant reductions in hypercalcaemia and PTH were observed after initiation of cinacalcet, as was partial correction of hyperphosphataemia during the course of the study. These are important observations in this cohort of predominantly non-operable pHPT subjects.

- The interpretation of bone remodeling and bone mass changes is limited by the small number of subjects for whom T and Z scores were reported; however, small mean changes from baseline to month 12 were demonstrated with both scores in this small subject subgroup.

- There were no unexpected safety concerns.

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