Synopsis

<table>
<tr><td>Abbott Laboratories</td><td rowspan="3">Individual Study Table Referring to Part of Dossier:
Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug: Paricalcitol</td></tr>
<tr><td>Name of Active Ingredient:
Paricalcitol</td></tr>
<tr><td colspan="3">Title of Study: The IMPACT SHPT Study: Study to Evaluate the Improved Management of iPTH with Paricalcitol-centered Therapy vs. Cinacalcet Therapy with Low-dose Vitamin D in Hemodialysis Patients with Secondary Hyperparathyroidism</td></tr>
<tr><td colspan="3">Investigator: Prof. Dr. Markus Ketteler, MD, Division of Nephrology, Klinikum Coburg GmbH, Ketschendorfer Strasse 33, D-96450 Coburg, Germany</td></tr>
<tr><td colspan="3">Study Sites: A total of 29 sites in the United States (US), 1 site in Russia, and 44 sites outside the US and Russia enrolled subjects in this study.</td></tr>
<tr><td colspan="3">Publications: 2 manuscripts</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject's First Visit: 07 November 2009
Last Subject's Last Visit: 27 May 2011</td><td>Phase of Development: 4</td></tr>
<tr><td colspan="3">Objective:
The primary objective was to evaluate the superiority of paricalcitol as compared with cinacalcet with supplemental low-dose vitamin D therapy, as assessed by the proportion of subjects that achieved a mean intact parathyroid hormone (iPTH) value between 150 pg/mL and 300 pg/mL during Weeks 21 to 28.
Secondary objectives of this study were to evaluate the following in each treatment group:
1. The proportion of subjects achieving at least 30% reduction from Baseline in iPTH, as assessed by the mean iPTH obtained in Weeks 21 to 28.
2. The proportion of subjects achieving at least 50% reduction from Baseline in iPTH, as assessed by the mean iPTH obtained in Weeks 21 to 28.
3. The change from Baseline in iPTH, calcium, and calcium-phosphorus product (Ca×P), as assessed by the mean values obtained in Weeks 21 to 28.
4. The proportion of subjects with calcium < 8.4 mg/dL (2.09 mmol/L), as assessed by the mean calcium obtained in Weeks 21 to 28.
5. The proportion of subjects with calcium > 10.5 mg/dL (2.61 mmol/L), as assessed by the mean calcium obtained in Weeks 21 to 28.</td></tr>
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Methodology:

This was a Phase 4, prospective, randomized, open-label, 28-week, multicenter clinical trial to assess the superiority of paricalcitol titrated to target iPTH over cinacalcet combined with low-dose vitamin D in subjects with chronic kidney disease (CKD) Stage 5 on hemodialysis who have SHPT as defined by a Screening iPTH between 130 pg/mL and 700 pg/mL (inclusive) and a calcium level of ≤ 10 mg/dL (2.49 mmol/L). The study was designed to enroll approximately 248 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects was enrolled, there was a possibility that additional subjects in Screening would not be enrolled. Subjects were randomized in a 1:1 ratio to 1 of 2 treatment arms within a stratum for intravenous (IV) sites (124 subjects) and oral sites (124 subjects): paricalcitol arm or cinacalcet arm. Subjects in the paricalcitol arm received paricalcitol capsules (non-Russian and non-US subjects) or injection (US and Russian subjects) plus supplemental cinacalcet for hypercalcemia. Subjects in the cinacalcet arm received cinacalcet plus low-dose vitamin D. The low-dose vitamin D was IV doxercalciferol (1.0 µg 3 times weekly) for US sites and daily oral alfacalcidol (0.25 µg/day) for non-US sites, including Russia.

The doses selected for this study were based on dosing published in the package insert for paricalcitol injection and for cinacalcet use in dialysis patients. The starting dose for paricalcitol injection is based on the patient's weight (US label); the starting dose for paricalcitol capsules is calculated by the patient's iPTH divided by 60 (European label). The low doses of vitamin D (doxercalciferol [US sites] and alfacalcidol [non-US sites, including Russia]) were based on the suggested dose equivalencies published in the recent literature when used in combination with cinacalcet treatment. Subjects in the paricalcitol arm were allowed to receive cinacalcet as supplemental medication if serum calcium was ≥ 10.5 mg/dL (2.61 mmol/L) on 2 consecutive blood draws in the presence of iPTH ≥ 150 pg/mL

The study was divided into 2 periods plus a 30-Day (approximate) Post-Treatment Follow-up: Screening and Pre-Treatment Washout Period (up to 7 weeks total) and a 28-Week Treatment Period. The 30-Day Post-Treatment Follow-up was an observational phase for safety after discontinuation of study drug dosing.

Number of Subjects (Planned and Analyzed): 248 planned, half in each of the 2 strata; 129 subjects were randomized into the IV stratum, and data from 126 were analyzed for efficacy; 143 subjects were randomized into the oral stratum, and data from 142 were analyzed for efficacy.

Diagnosis and Main Criteria for Inclusion:

Patients with CKD Stage 5 undergoing hemodialysis and with elevated iPTH who were at least 18 years of age were selected as the target population for this study. Potential subjects who had a history of allergic reaction or significant sensitivity to paricalcitol or vitamin D analogs or to cinacalcet were excluded in order to avoid confounding factors related to the active disease process. Subjects who were not naïve to VDRA or cinacalcet had to have the following values at Screening to enter the Pre-Treatment Washout Period: iPTH between 130 pg/mL and 700 pg/mL inclusive, serum total alkaline phosphatase ≥ 40 U/L, calcium ≤ 10.0 mg/dL, and Ca×P ≤ 75 mg^2/dL^2 (US) and ≤ 70 mg^2/dL^2 (non-US). Subjects who were naïve to VDRA or cinacalcet had to have the following values at randomization to enter the Treatment Period: iPTH between 300 pg/mL and 800 pg/mL inclusive, calcium between 8.4 mg/dL and 10.0 mg/dL inclusive, and phosphorus ≤ 6.5 mg/dL.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: Paricalcitol injection in 2-mL vials of 5 µg/mL for distribution at [redacted] sites and in 1-mL ampoules of 5 µg/mL for distribution at [redacted] sites and paricalcitol capsules, 1 µg, for distribution at [redacted] Paricalcitol injection was administered as 0.07 µg/kg 3 times weekly (TIW) with titration every 2 weeks at [redacted] and [redacted] sites. Paricalcitol capsules were administered at a microgram dose determined by iPTH/60 TIW at [redacted], [redacted] sites. Cinacalcet was administered at a dose of 30 mg QD to subjects with calcium ≥ 10.5 mg/dL on 2 occasions after Week 2. Lot numbers are shown below for paricalcitol.

Location	Formulation	Route of Administration	Bulk Lot Numbers
[redacted]	5 µg/mL (2-mL vials)	IV	09-023674
[redacted]	5 µg/mL (1-mL ampoules)	IV	09-021870 10-001267
[redacted]	1-µg capsules	Oral	08-018121 10-002403

Duration of Treatment: 28 weeks

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: Reference therapy for paricalcitol was cinacalcet 30 mg QD with titration every 2 weeks. Doxercalciferol injection 1 µg TIW was provided in [redacted] sites when indicated and oral alfalcalcidol 0.25 µg QD was provided when indicated in capsules of 0.25 µg at [redacted] sites and at [redacted] sites. Lot numbers are shown below for cinacalcet.

Location	Formulation	Route of Administration	Bulk Lot Numbers
[redacted]	30-mg tablets	Oral	09-023112 09-023114 09-023113 09-023115
[redacted]	30-mg tablets	Oral	09-023553

Additional Therapy: lot numbers are shown below for doxercalciferol and alfacalcidol.

Doxercalciferol

[redacted]	4 µg/2 mL (2-mL vials)	IV	09-023231 10-002363

Alfacalcidol

[redacted]	0.25-µg capsules	Oral	09-253552 10-002433

Redacted information - 08Jun2012

Criteria for Evaluation

Efficacy: The primary efficacy variable was the proportion of subjects who achieved a mean iPTH value between 150 to 300 pg/mL during Weeks 21 to 28 of the Treatment Period. Secondary efficacy variables were the proportion of subjects who achieved at least a 30% reduction from baseline in iPTH based on the mean iPTH obtained in Weeks 21 to 28 of the Treatment Period and the proportion of subjects who achieved at least a 50% reduction from baseline in iPTH based on the mean iPTH obtained in Weeks 21 to 28 of the Treatment Period. Additional efficacy variables were the cumulative cost of paricalcitol and cinacalcet treatment over the Treatment Period, the number of study drug doses held during the Treatment Period, and the proportion of subjects who prematurely terminated the study.

Safety: Safety was assessed by the incidence of adverse events, the proportion of subjects who prematurely terminated from the study, the changes from Baseline to final observation in complete chemistry and hematology measurements obtained in the Treatment Period, the changes from Baseline to final observation in vital signs obtained in the Treatment Period, repeated measures of changes from Baseline in iPTH, calcium, phosphorus, and Ca×P over all study visits, the proportion of subjects with calcium < 8.4 mg/dL (2.09 mmol/L) based on the mean calcium obtained in the Treatment Period, and the proportion of subjects with calcium > 10.5 mg/dL (2.61 mmol/L) based on the mean calcium obtained in the Treatment Period.

Statistical Methods:

Efficacy: The primary efficacy analysis was a comparison between treatment groups in the proportion of subjects that achieve a mean iPTH value between 150 to 300 pg/mL during Weeks 21 to 28 using Fisher's exact test. Subjects who did not have at least 2 iPTH values during Weeks 21 to 28 were excluded from the primary analysis. A sensitivity analysis was performed that excluded subjects who did not have at least 1 iPTH value during Weeks 21 to 28.

To investigate the impact of cinacalcet on paricalcitol-treated subjects in the achievement of the primary efficacy endpoint, a post hoc sensitivity analysis of the primary efficacy endpoint was performed in which these subjects were removed from the analysis. The comparison between treatment groups within each stratum was performed using Fisher's exact test.

The following were secondary efficacy analyses:

1. Comparison between treatment groups in the percentage of subjects who achieved at least a 30% reduction from Baseline in iPTH on the basis of the mean iPTH value obtained during Weeks 21 to 28 by using Fisher's exact test.
2. Comparison between treatment groups in the percentage of subjects who achieved at least a 50% reduction from Baseline in iPTH on the basis of the mean iPTH values obtained during Weeks 21 to 28 by using Fisher's exact test.
3. A combined analysis using Cochran-Mantel-Haenszel (CMH) test, controlling for IV site and oral site randomization strata, to evaluate treatment group differences overall in the percentage of subjects achieving the primary efficacy endpoint. The overall percentage of subjects who achieve the primary efficacy endpoint by treatment group (i.e., for paricalcitol and for cinacalcet as primary therapies) was presented.

Subjects who did not have at least 1 iPTH value during Weeks 21 to 28 were excluded from these secondary efficacy analyses.

Statistical Methods, continued

Efficacy, continued:

The following were other efficacy analyses:

1. The cumulative cost of paricalcitol and cinacalcet treatment over 28 weeks of treatment.
2. The number of study drug doses held during the Treatment Period.
3. The comparison between treatment groups in patient-reported outcomes.

Safety:

Analyses of adverse events included only treatment-emergent events (i.e., those that first occur or worsen after the first dose of study drug). Each adverse event was mapped to a primary Medical Dictionary for Regulatory Activities (MedDRA®) system organ class and preferred term according to the MedDRA adverse event-coding dictionary. The treatment group comparability in the percentage of subjects experiencing adverse events was evaluated by using Fisher's exact test.

Because a numerically higher incidence of cardiovascular adverse events (cardiac disorders system organ class) was observed in the paricalcitol arms of both strata, an analysis of major adverse cardiovascular events (MACE) was performed using terms identified in a MACE company MedDRA query (CMQ) defined by Abbott. The comparison of MACE between treatment groups within each stratum was performed using Fisher's exact test.

The following analyses were performed to evaluate hypocalcemia and hypercalcemia:

A comparison between treatment groups in the percentage of subjects with calcium < 8.4 mg/dL (2.09 mmol/L) based on the mean calcium obtained in Weeks 21 to 28 of the Treatment Period by using Fisher's exact test.

A comparison between treatment groups in the proportion of subjects with calcium > 10.5 mg/dL (2.61 mmol/L) based on the mean calcium obtained in Weeks 21 to 28 of the Treatment Period by using Fisher's exact test.

Limited chemistry measurements (iPTH, albumin, calcium, phosphorus, and Ca×P) were collected at scheduled visits during the Treatment Period. For each limited chemistry variable, a mixed-effects model repeated-measures (MMRM) analysis using all the longitudinal observations across the visits was used to evaluate treatment group differences in the change from Baseline to each postbaseline visit. The model included the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline measurements and baseline-by-visit interaction. The covariance structure was unstructured. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Type III sum-of-squares for the least squares means was used. Analyses were implemented by using SAS PROC MIXED.

Change from baseline to final observations on vital sign variables was evaluated by using a 1-way ANCOVA model with treatment group as the factor and Baseline as a covariate.

In addition, an MMRM analysis of vital signs data was performed similar to the longitudinal data analyses described above for limited chemistry variables.

Summary/Conclusions

Efficacy Results: In the primary analysis of the primary efficacy endpoint, which was based on at least 2 values, in the IV stratum, a greater percentage of subjects who received paricalcitol achieved a mean iPTH between 150 and 300 pg/mL during Weeks 21 to 28 than subjects who received cinacalcet (57.7% versus 32.7%, $P = 0.016$ by Fisher's exact test). In the oral stratum, although a greater percentage of subjects who received paricalcitol (54.4%) achieved a mean iPTH between 150 and 300 pg/mL during Weeks 21 to 28 than subjects who received cinacalcet (43.4%), the difference was not statistically significant ($P = 0.260$). Results were similar in a sensitivity analysis, which was based on at least 1 value.

In a secondary efficacy analysis using a CMH test, which controlled for the site strata, paricalcitol was statistically significantly superior to cinacalcet in the proportion of subjects achieving the primary efficacy endpoint ($P = 0.010$). Overall, 55.96% of paricalcitol subjects and 38.24% of cinacalcet subjects achieved the primary efficacy endpoint of a mean iPTH value between 150 and 300 pg/mL. In other secondary efficacy analyses, the effect of paricalcitol on reducing iPTH in the IV stratum was demonstrated by the statistically significantly greater percentage of subjects in the paricalcitol group who achieved at least a 30% or 50% reduction from Baseline in iPTH compared with cinacalcet (84.6% and 65.4% in the paricalcitol group versus 49.0% and 22.4%, respectively, in the cinacalcet group; $P < 0.001$). As in the primary analysis, results of these secondary analyses in the oral stratum were not statistically significantly different between treatment groups.

The primary efficacy endpoint was analyzed for subgroups of gender, race, age, diabetic status, baseline iPTH, and time on chronic dialysis. In the IV stratum, a greater percentage of subjects in the paricalcitol group than in the cinacalcet group achieved a mean iPTH value between 150 and 300 pg/mL during Weeks 21 to 28 for all subgroups, and the difference between treatment groups was statistically significant for all subgroups. In the oral stratum, the difference between treatment groups was not statistically significant for any subgroup.

In repeated-measures analysis of select chemistry variables, there was no difference between treatment groups in mean changes in albumin and no consistent trend in the differences between treatment groups in mean changes in inorganic phosphorus. At both the IV and oral strata, the paricalcitol group showed mean increases in corrected calcium and Ca×P compared with mean decreases in these variables in the cinacalcet group and the difference between treatment groups was statistically significant at nearly all time points ($P < 0.001$ for all time points for corrected calcium and at all time point except Week 28 for Ca×P). Also in both strata, the paricalcitol group showed statistically significantly greater mean decreases in iPTH compared with smaller mean decreases in the cinacalcet group at nearly all time points.

In order to investigate the impact of cinacalcet on paricalcitol-treated subjects in the achievement of the primary efficacy endpoint, a post hoc sensitivity analysis of the primary efficacy endpoint was performed in which subjects in the paricalcitol group who received cinacalcet to control hypercalcemia were removed from the analysis. The results of this analysis were similar to those for the primary analysis, in which a greater percentage of subjects who received paricalcitol achieved a mean iPTH between 150 and 300 pg/mL during Weeks 21 to 28 than subjects who received cinacalcet in both strata, and the difference between treatments groups was statistically significant for the IV stratum only.

Safety Results: In IV stratum, a higher percentage of subjects in the cinacalcet group experienced at least 1 adverse event compared with subjects in the paricalcitol group (84.4% with cinacalcet versus 80.6% with paricalcitol). In oral stratum, a higher percentage of subjects in the paricalcitol group experienced at least 1 adverse event compared with subjects in the cinacalcet group (83.3% with paricalcitol versus 77.1% with cinacalcet). The difference between groups was not statistically significant in either stratum. In the IV stratum, a statistically significantly higher percentage of subjects in the cinacalcet group (10/64, 15.6%) than in the paricalcitol group (2/62, 3.2%) experienced an adverse event leading to discontinuation of randomized study drug ($P = 0.030$). The most common adverse event leading to discontinuation with cinacalcet treatment was nausea, which led to study drug discontinuation for 2 subjects (3.1%) in the IV stratum and 3 subjects (4.3%) in the oral stratum. The difference between treatment groups in the percentage of subjects who experienced severe, serious, or fatal adverse events was not statistically significant in either stratum.

Adverse events were reported for 104 subjects (82.5%) in the IV stratum and for 114 subjects (80.3%) in the oral stratum. In the IV stratum, the most common adverse event reported for subjects receiving paricalcitol was hypotension (12.9%), followed by abdominal pain, diarrhea, nausea, and hypertension (11.3% each). The most common adverse event reported for subjects receiving cinacalcet was hypocalcemia (14.1%), followed by diarrhea, nausea, and vomiting (12.5% each). In the oral stratum, the most common adverse event reported for subjects receiving paricalcitol was hypercalcemia (18.1%), followed by vomiting (13.9%) and diarrhea (12.5%). The most common adverse event reported for subjects receiving cinacalcet was hypocalcemia (25.7%), followed by nausea and vomiting (10.0% each).

In the IV stratum, a statistically significantly greater percentage of subjects receiving paricalcitol than those receiving cinacalcet experienced abdominal pain (11.3% versus 1.6%, $P = 0.031$), hypercalcemia (8.1% versus 0%, $P = 0.026$), and events in the general disorders and administration site conditions system organ class (30.6% versus 12.5%, $P = 0.017$). Also in the IV stratum, a statistically significantly greater percentage of subjects receiving cinacalcet than those receiving paricalcitol experienced hypocalcemia (14.1% versus 0%, $P = 0.003$). Similarly, in the oral stratum, the percentage of subjects receiving paricalcitol had a statistically significantly greater incidence of hypercalcemia than those receiving cinacalcet (18.1% versus 1.4%, $P = 0.001$), while subjects receiving cinacalcet had a statistically significantly greater incidence of hypocalcemia than those receiving paricalcitol (25.7% versus 4.2%, $P < 0.001$).

The difference between treatment groups in the percentage of subjects who experienced adverse events that the investigator considered possibly or probably related to study drug was not statistically significant in either stratum. In the IV stratum, the majority of subjects in both treatment groups (73 out of 104 who reported an adverse event) experienced only adverse events that were not related to study drug. In the oral stratum, fewer subjects who experienced adverse events experienced only events that were not related to study drug (50 out of 114). In this stratum, more subjects experienced adverse events that were possibly (12 out of 114) or probably (39 out of 114) related to study drug than in the IV stratum (4 out of 104 for possibly related and 21 out of 104 for probably related).

Four subjects, all originally randomized to receive paricalcitol, experienced at least 1 adverse event resulting in death. All adverse events leading to death were considered not related to the study drug, except for the event of myocardial infarction, which was considered probably not related to paricalcitol. Three additional subjects experienced a non–treatment-emergent adverse event that resulted in death.

Safety Results, continued: Fifty subjects (39.7%) in the IV stratum and 37 subjects (26.1%) in the oral stratum experienced at least 1 serious adverse event. The only statistically significant difference in the incidence of serious adverse events was for the system organ class of cardiac disorders for subjects in the IV stratum. Serious adverse events in the cardiac disorders system organ class were reported for 7 subjects in the paricalcitol group (11.3%) and 1 subject in the cinacalcet group (1.6%) ($P = 0.031$).

The system organ class with the most serious adverse event preferred terms was infections and infestations, which were reported for 9.5% of subjects in the IV stratum and 5.6% of subjects in the oral stratum.

Twelve subjects in the IV stratum and 16 subjects in the oral stratum experienced an adverse event that led to discontinuation. Nausea, experienced by 5 subjects overall and all in the cinacalcet treatment group, was the most common adverse event leading to discontinuation. In the IV stratum, a statistically significantly greater percentage of subjects in the cinacalcet group (10/64, 15.6%) than in the paricalcitol group (2/62, 3.2%) experienced adverse events leading to discontinuation ($P = 0.030$). The percentage of subjects who experienced an adverse event leading to discontinuation in the oral stratum was similar in the 2 treatment groups (8/72 subjects [11.1%] in the paricalcitol group and 8/70 subjects [11.4%] in the cinacalcet group). There were no statistically significant differences between treatment groups in the oral stratum

Because of an imbalance in the number of subjects who experienced an adverse event in the cardiac disorders system organ class, a post hoc analysis of MACE was performed. In this analysis, a higher percentage of subjects in the paricalcitol groups in both strata experienced a major adverse cardiovascular event compared with subjects in the cinacalcet groups, but the difference was not statistically significant overall or for any individual preferred term. The greater percentage of MACE in the paricalcitol groups may be explained in part by the greater percentage of subjects with a history of significant cardiovascular disease at study entry, particularly in the IV stratum. More subjects in the paricalcitol group had type 2 diabetes mellitus, particularly in the oral stratum, which may also have contributed to these findings.

There were few differences between treatment groups in mean changes from Baseline to the final value in hematology variables with the exception of WBC count and neutrophils in the oral stratum, where paricalcitol showed mean increases in both variables that were statistically significantly different ($P = 0.016$) from the mean changes with cinacalcet. In chemistry variables, alkaline phosphatase showed mean increases for cinacalcet and mean decreases for paricalcitol that were statistically significantly different ($P < 0.001$). In both strata, paricalcitol resulted in statistically significantly greater mean increases in FGF-23 and statistically significantly greater mean decreases in bone-specific alkaline phosphatase compared with cinacalcet ($P < 0.001$ for all 4 comparisons), but no difference between treatment groups in PTHRP or 25-hydroxy vitamin D.

Hypocalcemia and hypercalcemia were analyzed both as the percentage of subjects meeting predefined cutoffs. In both strata, a statistically significantly greater percentage of subjects in the cinacalcet group than in the paricalcitol group experienced hypocalcemia, defined as < 8.4 mg/dL and based on the mean of at least 2 values during Weeks 21 to 28 ($P < 0.001$ for both strata). Similar results were obtained for the sensitivity analysis based on at least 1 value during Weeks 21 to 28 ($P < 0.001$ for both strata).

Safety Results, continued: Four subjects in the IV stratum, all in the paricalcitol group, and no subject in the oral stratum experienced hypercalcemia, defined as > 10.5 mg/dL and based on the mean of at least 2 values during Weeks 21 to 28. Similar results were obtained for the sensitivity analysis based on at least 1 value during Weeks 21 to 28. In both strata, the difference between treatment groups was not statistically significant for the percentage of subjects with hypercalcemia.

In the IV stratum, a statistically significantly greater percentage of subjects in the cinacalcet group than in the paricalcitol group had 2 consecutive calcium measurements < 8.0 mg/dL (50.8% of cinacalcet subjects) and < 7.5 mg/dL (14.8% of cinacalcet subjects) ($P < 0.001$). No subject in the paricalcitol group had a low calcium measurement. A statistically significantly greater percentage of subjects in the paricalcitol group than in the cinacalcet group had 2 consecutive calcium measurements > 10.5 mg/dL (11.7% of paricalcitol subjects versus 0% of cinacalcet subjects) ($P = 0.006$). No subject in either treatment group had 2 consecutive calcium measurements > 11.0 mg/dL.

In the oral stratum, a statistically significantly greater percentage of subjects in the cinacalcet group than in the paricalcitol group had 2 consecutive calcium measurements < 8.0 mg/dL (64.3% of cinacalcet subjects versus 1.4% of paricalcitol subjects) and < 7.5 mg/dL (31.4% of cinacalcet subjects) ($P < 0.001$ for both analyses). One subject in the paricalcitol group had 2 consecutive calcium measurements < 8.0 mg/dL. A statistically significantly greater percentage of subjects in the paricalcitol group had 2 consecutive calcium measurements > 10.5 mg/dL (25.7% of paricalcitol subjects versus 1.4% of cinacalcet subjects) ($P < 0.001$). Two subjects in the paricalcitol group had 2 consecutive calcium measurements > 11.0 mg/dL, but the difference between treatment groups was not statistically significant.

One subject, who was randomized to receive cinacalcet, discontinued from the study because of an adverse event of hypocalcemia.

There were few and sporadic statistically significant differences between treatment groups in mean changes from Baseline in vital signs by repeated-measures analysis, but there were no clear trends and no clinically meaningful changes. No subject discontinued from the study because of an adverse event related to vital signs.

Conclusions: The results of this study demonstrated the overall superiority of paricalcitol over cinacalcet with low-dose vitamin D in controlling mean iPTH to within 150 and 300 pg/mL in patients with CKD Stage 5 and secondary hyperparathyroidism after 4 weeks of therapy. Differences between the statistical significance of results in the 2 strata may be explained by the lower median daily dose received by subjects in the oral stratum. In both strata, a statistically significantly greater percentage of subjects in the cinacalcet group than in the paricalcitol group experienced hypocalcemia; however, in both strata, the difference between treatment groups was not statistically significant for the percentage of subjects with hypercalcemia. The results suggest that paricalcitol-based therapy with or without supplemental cinacalcet compared with the combination of cinacalcet and low-dose vitamin D provides superior reduction of iPTH to target levels with minimal effects on calcium in patients with SHPT who require hemodialysis.

Adverse events were similar to those observed in other studies with paricalcitol in this patient population and few patients in each stratum required adjunctive cinacalcet therapy for hypercalcemia in the paricalcitol group.

Date of Report: 03Apr2012