



Synopsis

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| Abbott Laboratories | Individual Study Table Referring to Part of Dossier: | (For National Authority Use Only) |
| Name of Study Drug: Paricalcitol | Volume: | |
| Name of Active Ingredient: Paricalcitol | Page: | |
| Title of Study: VITAL Study - Selective <u>VIT</u> amin D Receptor Activator (Paricalcitol) for <u>Al</u> buminuria <u>L</u> owering Study: A Phase 2, Prospective, Randomized, Double-Blind, Placebo-Controlled Multicenter Study to Evaluate the Safety and Efficacy of Paricalcitol Capsules on Reducing Albuminuria in Type 2 Diabetic Nephropathy Subjects Who Are Currently Being Treated with Renin-angiotensin System Inhibitors | | |
| Coordinating Investigator: Dick de Zeeuw, MD, PhD (University Medical Center Groningen, The Netherlands) | | |
| Study Sites: Multicenter 60 sites in the United States (US), Europe, and Taiwan. | | |
| Publications: 1 publication, 1 abstract | | |
| Studied Period (Years): First Subject First Visit: 01 February 2007 Last Subject Last Visit: 09 June 2009 | Phase of Development: 2 | |
| Objective: The objective of this study was to evaluate the safety and efficacy of paricalcitol capsules on albuminuria reduction in chronic kidney disease (CKD) subjects with type 2 diabetic nephropathy receiving optimal angiotensin converting enzyme (ACE) inhibitor and/or angiotensin II receptor blocker (ARB) therapy. | | |
| Methodology: This was a Phase 2, randomized, double-blind, parallel design, placebo-controlled, 24-week, multicenter study to evaluate the efficacy and safety of paricalcitol capsules in the reduction of residual albuminuria in CKD subjects with type 2 diabetic nephropathy who were currently receiving treatment with stable renin angiotensin-aldosterone system (RAAS) therapy. A sufficient number of sites within the US and Europe were to be selected in order to enroll approximately 258 subjects. All subjects were randomized in a 1:1:1 ratio to 1 of 3 treatment groups: Group 1 - placebo; Group 2 - paricalcitol capsules 1 µg once daily (QD); or, Group 3 - paricalcitol capsules 2 µg QD. | | |
| Number of Subjects (Planned and Analyzed): Approximately 258 subjects were planned for enrollment into the study. A total of 281 subjects were enrolled and randomized. | | |
| Diagnosis and Main Criteria for Inclusion: Subjects with CKD and Type 2 diabetic nephropathy who were currently receiving treatment with stable RAAS therapy were included in this study. Main criteria were: received a stable dose of ACE-inhibitor/ARB for ≥ 3 months; had an estimated glomerular filtration rate (eGFR) between 15 and 90 mL/min/1.73 m ² by simplified Modification in Diet in Renal Disease formula; had a urinary albumin to creatinine ratio (UACR) between 100 and 3000 mg/g (11.3 to 339 mg/mmol); and were ≥ 20 years of age. | | |



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| Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: Paricalcitol capsules 1 µg, administered orally; Lot Numbers 06-007393, 05-003351, and 07-011383 |
| Duration of Treatment: The duration of treatment was to be 24 weeks. |
| Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: Placebo for paricalcitol tables, administered orally; Lot Numbers 05-003263 and 07-011386 |
| Criteria for Evaluation Efficacy: The primary efficacy endpoint was the change from baseline to the last on-treatment UACR measurement using UACR levels determined from the first morning void (FMV) urine collections. Secondary efficacy endpoints were: <ul style="list-style-type: none">• The proportion of subjects achieving a ≥ 15% reduction in the last on-treatment FMV UACR levels from baseline• The change from baseline to the last on-treatment measurement in albumin determined from 24-hour urine collections Additional secondary endpoint added prior to finalization of the Statistical Analysis Plan: <ul style="list-style-type: none">• The change from baseline to the last on-treatment measurement in serum intact parathyroid hormone (iPTH) Tertiary efficacy endpoints were: <ul style="list-style-type: none">• Change from baseline to the last on-treatment measurement in:<ul style="list-style-type: none">○ biomarkers (aldosterone, brain natriuretic protein [BNP], high-sensitivity C-reactive protein [hs-CRP], fibrinogen, interleukin-6 [IL-6], plasma renin activity [PRA], tumor necrosis factor-alpha [TNF-α])○ insulin resistance; fasting glucose; glycosylated hemoglobin [HbA_{1c}]; estimated glomerular filtration rate (eGFR); fasting lipid profile parameters (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, triglycerides, very-low-density lipoprotein [VLDL] cholesterol)○ aldosterone, albumin, and creatinine determined from the 24-hour urine collections• Change from baseline to each monthly measurement in FMV UACR, eGFR, and limited chemistry variables• Change from the last on-treatment measurement to the 30-day posttreatment and 60-day posttreatment measurement in UACR determined from the FMV urine collections Exploratory efficacy variables were: <ul style="list-style-type: none">• Change from baseline to last on-treatment observation in:<ul style="list-style-type: none">○ Vitamin D tests (1,25-hydroxyvitamin D₃, 25-hydroxyvitamin D₃)○ eGFR in subsets of subjects with: baseline iPTH ≥ 75 pg/mL; CKD Stage 2, 3, and 4○ eGFR by subgroup (sex, age, history of cardiovascular disease [arterial peripheral vascular disease, coronary artery disease, congestive heart failure, and/or left ventricular hypertrophy]) |



Criteria for Evaluation (Continued)

- FMV UACR by subgroup (sex, race, race by ethnicity, age, baseline FMV UACR category, baseline iPTH, baseline vitamin D₃ normality classification, UACR stratification at randomization, and baseline sodium tertile)

Pharmacokinetic: Plasma paricalcitol concentrations at Treatment Weeks 4, 8, 12, 16, and 20 were determined using a validated liquid chromatography with tandem mass spectrometric (LC-MS/MS) methods.

Safety: Safety endpoints included: the number and percentage of subjects who reported treatment-emergent adverse events (TEAEs) through 30 days posttreatment, serious adverse events (SAEs), and fatal TEAEs; TEAEs leading to premature discontinuation; and events of interest (the number and percentage of subjects with hypercalcemia and who experienced a doubling of serum creatinine, required dialysis, or died); analysis of changes in hematology parameters, clinical chemistry variables, urinalysis parameters, and 24 hour urinalysis variables (electrolytes - calcium [Ca], phosphate [P], sodium; urea nitrogen); changes from last on-treatment observation to 30-day and 60-day posttreatment measurements in: serum Ca, phosphate, and creatinine, eGFR, UACR; and changes in vital signs (baseline to last on-treatment observation; last on-treatment observation to 30-day and 60-day posttreatment measurements)

Statistical Methods

Efficacy:

Primary Efficacy Analysis

The primary efficacy analysis was a comparison between the combined paricalcitol capsules treatment groups (1 µg and 2 µg) and the placebo treatment group in the geometric mean change from baseline to the last on-treatment measurement in FMV UACR using a 1-way analysis of covariance (ANCOVA) model with treatment group as the factor and baseline UACR as a covariate.

Secondary, Tertiary, and Exploratory Efficacy Analyses

Comparisons between treatment groups were made on the combined paricalcitol group versus placebo and for each paricalcitol group versus placebo.

The mean change from baseline to the last on-treatment observation in continuous secondary and tertiary efficacy endpoints (and in exploratory endpoints for eGFR) was analyzed using a 1-way ANCOVA model with treatment group as the factor and the respective baseline value as a covariate.

The proportion of subjects who achieved at least a 15% reduction from baseline to the last on-treatment observation in FMV UACR was analyzed with Fisher's exact test.

The primary efficacy endpoint was further analyzed using a 2-way ANCOVA model that included baseline UACR as the covariate and fixed factors for treatment group, stratification level, and the treatment by stratification level interaction.

A repeated measures analysis was conducted for each limited chemistry variable, eGFR, and FMV UACR at Weeks 4, 8, 12, 16, 20, and 24. The repeated measures analysis was a likelihood-based, mixed-effects, repeated measures analysis using all the longitudinal observations at each post-baseline visit. The model included the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as fixed, continuous effects of baseline measurements and baseline-by-visit interaction, and subject effects.



Statistical Methods (Continued)

Exploratory subgroup analyses (FMV UACR) were conducted using a 2-way ANCOVA model with terms of treatment group, subgroup, treatment-by-subgroup interaction, with the respective baseline variable as a covariate.

Pharmacokinetics: Descriptive statistics for paricalcitol predose plasma concentrations were provided for each scheduled visit with a breakdown by dose level. The predose concentration data were to be explored to see whether variables of importance for explaining pharmacokinetic variability were revealed. Candidate variables were to include weight, age, sex, and race, but other variables could be considered. The explanatory value of the candidate variables was to be explored in an analysis of dose-normalized paricalcitol concentrations using linear mixed effects models, which included an effect for dose.

Safety: The intent-to-treat (ITT) population (same as the all-treated population) was used to evaluate safety (i.e., all randomized subjects who received ≥ 1 dose of study drug) were to be included in the safety evaluation.

Analyses of AEs included only treatment-emergent events (i.e., those that had an onset on or after the day of the first dose of study drug). Analyses did not include AEs that had an onset > 30 days after the last dose of study drug.

Treatment-emergent AEs (TEAE) were mapped according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and MedDRA version 12.0 preferred term (PT). Within each treatment group, AEs were summarized descriptively by counts and percents using the most intense episode (severity) and the most likely relationship to study drug (as indicated by the Investigator). Comparisons of AE incidence rates between each paricalcitol treatment group and the placebo group were performed using Fisher's exact test. In addition, an analysis of subject deaths, subjects experiencing a doubling of serum creatinine levels from baseline, and subjects requiring dialysis was conducted using Fisher's exact test.

Comparisons of mean changes from baseline to the last on-treatment observation for each laboratory variable that was not included in the analysis of efficacy were conducted using 1-way analysis of variance (ANOVA) model with treatment as the factor.

A comparison between treatment groups of the proportion of subjects with ≥ 2 consecutive serum Ca measurements > 10.5 mg/dL (2.63 mmol/L) was conducted using Fisher's exact test.

Comparisons of mean changes from baseline to the last on treatment observation in vital signs were conducted using ANOVA model with treatment as the factor. In addition, a mixed-effects repeated measures analysis was conducted on blood pressure and pulse.

Comparisons of mean changes in blood pressure and pulse from the last on-treatment observation to the 30-day and 60-day Follow-up visits were conducted using ANOVA model with treatment as the factor.



Summary/Conclusions

Efficacy Results: There was no statistically significant difference observed for the mean change from baseline to the last on-treatment observation in FMV UACR between the combined paricalcitol group and the placebo group ($P = 0.071$). A marginally significantly greater reduction in FMV UACR was observed in the paricalcitol 2 μg group compared with the placebo group ($P = 0.053$).

Results for secondary efficacy endpoints included:

- The proportion of subjects who achieved a $\geq 15\%$ reduction from baseline to the last on-treatment FMV UACR was statistically significantly greater for the combined paricalcitol group ($P = 0.038$) and the paricalcitol 2 μg group ($P = 0.038$) compared with the placebo group.
- There was a statistically significantly greater reduction from baseline to the last on-treatment observation in 24-hour albumin levels for the paricalcitol 2 μg group compared with placebo ($P = 0.009$).

For the additional secondary endpoint added prior to finalization of the Statistical Analysis Plan: There were statistically significant differences in the decrease from baseline to last on-treatment observation for serum iPTH in all paricalcitol groups compared with the increase in the placebo group ($P < 0.001$ for all comparisons) and for serum iPTH in the subgroups of subjects with serum iPTH ≥ 65 pg/mL at baseline ($P < 0.001$ for all comparisons).

For tertiary and exploratory endpoints, results included the following:

- No statistically significant differences were observed between the paricalcitol and placebo groups in the mean change from baseline to last on-treatment observation in HDL cholesterol, insulin resistance, fasting glucose, or serum biomarkers, with the exception of BNP which demonstrated a statistically significant difference in favor of the paricalcitol 1 μg group compared with placebo ($P = 0.043$).
- Statistically significant but not clinically meaningful differences in the changes from baseline to final observation were observed for one or more comparisons involving HbA_{1c}, total cholesterol levels, LDL cholesterol levels, VLDL cholesterol levels, and triglycerides. For triglycerides, the paricalcitol 2 μg and combined paricalcitol groups showed mean increases, which reflected shifts to abnormally elevated high values for 4 subjects.
- There were statistically significant differences in the decreases from baseline to the last on-treatment observation in eGFR for the paricalcitol 2 μg ($P = 0.004$) and combined paricalcitol ($P = 0.029$) groups compared with placebo.
- The repeated measures analysis of change from baseline revealed:
 - for FMV UACR, a statistically significantly greater decrease overall in the paricalcitol 2 μg group ($P = 0.014$) and a marginally significantly greater reduction overall in the combined paricalcitol group ($P = 0.052$) compared with the placebo group
 - for serum albumin levels, no statistically significant differences between any of the paricalcitol groups compared with the placebo group overall or at Week 24
- Statistically significant differences using repeated measures analysis for one or more comparisons of the paricalcitol groups and placebo were observed for:
 - Serum corrected Ca levels: greater increases from baseline for all paricalcitol groups overall ($P < 0.001$ for all comparisons) and for the paricalcitol 2 μg and combined paricalcitol



Efficacy Results (Continued)

groups at Week 24 ($P < 0.001$ for each comparison) compared with placebo

- Serum phosphate levels: greater increases from baseline for the paricalcitol 2 mg and combined groups compared with placebo overall ($P < 0.001$ for each comparison) and at Week 24 ($P < 0.001$ and $P = 0.018$, respectively)
- Serum iPTH: greater decreases from baseline for each paricalcitol group versus placebo overall and at Week 24 ($P < 0.001$ for all comparisons)
- Serum creatinine: greater increases from baseline for the paricalcitol 1 μg , 2 μg , and combined paricalcitol groups compared with placebo overall ($P = 0.027$, < 0.001 , and < 0.001 , respectively) and at Week 24 ($P = 0.038$, < 0.001 , and < 0.001 , respectively)
- eGFR: greater decreases from baseline for the paricalcitol 2 μg and combined paricalcitol groups compared with placebo overall ($P < 0.001$ for each comparison) and for the paricalcitol 2 μg at Week 24 ($P = 0.009$). To determine the clinical relevance of the eGFR changes noted in the paricalcitol 2 μg group, additional analyses were conducted with the following results:
 - Changes from baseline to last on-treatment observation revealed no statistically significant differences between the paricalcitol groups and placebo in subjects with baseline iPTH ≥ 75 pg/mL or in subjects with Stage 2 or Stage 4 CKD. However, the difference in mean eGFR in Stage 3 CKD subjects compared with placebo was statistically significant ($P = 0.005$), and the difference in the combined paricalcitol group compared with placebo approached statistical significance ($P = 0.052$).
 - In subgroup analyses, decreases in eGFR compared with small decreases or increases in the placebo group were statistically significant in female subjects in the paricalcitol 2 μg ($P = 0.005$) and combined paricalcitol groups ($P = 0.014$); in subjects ≤ 65 years of age in the paricalcitol 1 μg ($P = 0.014$), 2 μg ($P = 0.004$), and combined paricalcitol ($P = 0.002$) groups; and in subjects without a history of cardiovascular disease in the paricalcitol 1 μg ($P = 0.016$), 2 μg ($P = 0.001$), and combined paricalcitol ($P = 0.001$) groups. In male subjects, the decrease in mean eGFR approached statistical significance in the paricalcitol 2 μg ($P = 0.055$) compared with placebo.
- The differences in mean decreases from baseline to the last on-treatment observation in 1,25-dihydroxyvitamin D₃ were statistically significant for the paricalcitol 1 μg , 2 μg , and combined groups compared with placebo ($P = 0.021$, 0.004, and 0.003, respectively). The differences in mean changes from baseline in 25-hydroxyvitamin D₃ levels was statistically significant only for the combined paricalcitol group compared with placebo ($P = 0.049$).
- The mean change from baseline to last on-treatment observation in FMV UACR levels revealed a statistically significant interaction between treatment (individual randomized paricalcitol groups) and subgroup defined by baseline 24-hour urine sodium tertiles ($P = 0.048$). Statistically significantly greater decreases were noted in the paricalcitol 1 μg group compared with placebo for subjects in the 2nd tertile (121 to 178 mEq/day) at baseline and for the paricalcitol 2 μg group compared with placebo for subjects in the 3rd tertile (> 178 mEq/day) at baseline ($P = 0.047$ and 0.005, respectively).



Pharmacokinetic Results: Mean plasma paricalcitol concentrations by week are presented in the table below for subjects in the randomized paricalcitol groups (1 µg QD and 2 µg QD), as well as for subject who had their dose reduced to 1 µg TIW or 2 µg TIW.

| Paricalcitol Group | Paricalcitol Concentration (ng/mL) at Each Visit | | | | |
|--------------------|--|---------------|---------------|---------------|---------------|
| | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 |
| | Mean ± SD | | | | |
| 1 µg QD | 0.020 ± 0.016 | 0.021 ± 0.018 | 0.019 ± 0.015 | 0.021 ± 0.021 | 0.028 ± 0.053 |
| 2 µg QD | 0.034 ± 0.023 | 0.033 ± 0.025 | 0.035 ± 0.025 | 0.036 ± 0.025 | 0.028 ± 0.020 |
| 1 µg TIW | -- | 0.012 ± 0.014 | 0.014 ± 0.018 | 0.014 ± 0.018 | 0.011 ± 0.017 |
| 2 µg TIW | -- | 0.016 ± 0.023 | 0.023 ± 0.014 | 0.017 ± 0.019 | 0.016 ± 0.015 |

QD = once daily; SD = standard deviation; TIW = 3 times weekly

Some subjects randomized to the placebo group had non-zero paricalcitol concentrations; however, the median concentration of paricalcitol for these subjects was 0 ng/mL across all weeks, and the mean concentrations at all weeks were less than the limit of quantitation for the assay.

A pharmacokinetic and exposure response analysis, using all available paricalcitol concentrations and primary efficacy data after accounting for the time course of placebo effect without imputation for dropouts, showed that there was a statistically significant ($P < 0.05$) relationship between exposure and UACR response for the dosage range of 1 µg daily to 2 µg daily.

Safety Results: There were no statistically significant differences among any of the treatment groups in the number of TEAEs that were either at least possibly related to study drug, severe, serious, or fatal; also, no statistically significant differences were observed among any of the treatment groups in the number of deaths. Three subjects, all from the paricalcitol 2 µg group and with a long-standing history of cardiovascular disease, died during the study; all deaths were assessed by the Investigator as being not related or probably not related to study drug.

Overall, 62% to 66% of subjects in any group reported TEAEs. Most subjects had TEAEs that were mild to moderate in severity. Severe TEAEs reported by ≥ 2 subjects in the paricalcitol groups were acute renal failure, hypotension, cerebrovascular accident, and hypoglycemia; these events were not related to hypercalcemia. Most subjects had TEAEs that were considered by the Investigator as not related or probably not related to study drug. The most frequently reported TEAEs considered possibly or probably related to study drug were hypoparathyroidism and decreased levels of blood parathyroid hormone.

A total of 44 subjects reported treatment-emergent SAEs during the study. The following SAEs were reported by ≥ 2 subjects who received paricalcitol: acute myocardial infarction, coronary artery disease, chest pain, pneumonia, fluid overload, hypoglycemia, cerebrovascular accident, acute renal failure, and hypotension. None of these events were considered by the Investigator to be possibly or probably related to study drug, and none were associated with hypercalcemia.

Seventeen subjects reported TEAEs that led to discontinuation of study drug: 15 subjects who received paricalcitol and 2 subjects who received placebo. This difference was statistically significant ($P = 0.018$). Eleven of the 15 subjects who experienced TEAEs that led to discontinuation were in the paricalcitol 2 µg group; this difference was statistically significant ($P = 0.018$). The following TEAEs that led to discontinuation were reported by at least 2 subjects who took paricalcitol: renal failure acute, blood parathyroid hormone decreased, drug intolerance, dyspnea, and nausea.



Safety Results (Continued)

Five subjects experienced hypercalcemia (defined as at least 2 consecutive Ca values > 10.5 mg/dL): 1 subject, 1 subject, and 3 subjects in the placebo, paricalcitol 1 µg, and paricalcitol 2 µg groups ($P =$ not significant [NS]). Eleven subjects experienced a doubling of serum creatinine, progression to requiring dialysis, and/or death: 2 subjects, 2 subjects, and 7 subjects in the placebo, paricalcitol 1 µg, and paricalcitol 2 µg groups ($P =$ NS for comparison of differences between all paricalcitol groups and placebo). This included 3 subject deaths, all in the paricalcitol 2 µg group in subjects whose diabetes was complicated by a long-standing history of cardiovascular disease.

Overall, mean changes in hematology and clinical chemistry parameter values from baseline to the last on-treatment observation were clinically unremarkable. Mean changes from baseline to the last on-treatment observation for urine urea nitrogen and electrolytes (Ca, phosphate, sodium) showed statistically significant differences from placebo only for Ca, which increased in each paricalcitol group.

At 30 and 60 days posttreatment, changes from the last on-treatment measurement showed that:

- the placebo group had mean decreases in eGFR while the paricalcitol 2 µg and combined paricalcitol groups had increases in mean eGFR. The paricalcitol 1 µg group had a mean increase at 30 days posttreatment and a slight decrease at 60 days posttreatment. The differences in these changes were statistically significant for the paricalcitol 2 µg group compared with the placebo group at 60 days posttreatment ($P \leq 0.01$).
- the placebo group showed decreases while all of the paricalcitol groups had increases in mean UACR. The differences in these changes were significant for the paricalcitol 1 µg and combined paricalcitol groups ($P \leq 0.05$) compared with the placebo group at 30 days posttreatment and for the paricalcitol 1 µg ($P \leq 0.001$), paricalcitol 2 µg ($P \leq 0.05$), and combined paricalcitol ($P \leq 0.01$) groups compared with the placebo group at 60 days posttreatment.
- clinically meaningful differences occurred in the changes in one or more paricalcitol groups compared with placebo at 30 days posttreatment for serum corrected Ca levels ($P \leq 0.01$ for paricalcitol 1 µg; $P \leq 0.001$ for paricalcitol 2 µg and combined paricalcitol), serum creatinine ($P \leq 0.001$ for paricalcitol 2 µg; $P \leq 0.01$ for combined paricalcitol).
- clinically meaningful differences occurred in the changes in one or more paricalcitol groups compared with placebo at 60 days posttreatment for serum corrected Ca levels ($P \leq 0.05$ for paricalcitol 1 µg; $P \leq 0.001$ for paricalcitol 2 µg and combined paricalcitol), serum creatinine ($P \leq 0.01$ for paricalcitol 2 µg and combined paricalcitol), and serum phosphate ($P \leq 0.01$ for each paricalcitol group).

Mean systolic blood pressure (SBP) decreased from baseline to the last on-treatment observation in the paricalcitol groups; the differences compared with placebo were not statistically significant. In a repeated measures analysis of change from baseline, the paricalcitol 2 µg group showed a statistically significantly greater decrease from baseline compared with placebo overall ($P = 0.033$). From the last on-treatment measurement, mean SBP increased in the paricalcitol 2 µg and combined paricalcitol groups at 30 day posttreatment and increased in all paricalcitol groups at 60 days posttreatment; the differences compared with placebo were statistically significant only for the combined paricalcitol group at 60-days posttreatment ($P = 0.036$).

Differences in the changes for mean diastolic blood pressure and pulse between the paricalcitol groups



and the placebo group were not statistically significant in the analysis from baseline to last on-treatment repeated measures analysis over time, or from the last on-treatment observation to 30 days and 60 days posttreatment.

Conclusions: This study showed that 2 µg of paricalcitol administered daily reduces residual albuminuria in subjects with type 2 diabetic nephropathy who were receiving stable doses of RAAS inhibitors, especially in those with the highest salt intake. The albuminuria-lowering effect was associated with early reductions in SBP and eGFR which were sustained over the 24-week treatment period.

Subgroups found to be associated with a reduction in eGFR after treatment with paricalcitol 2 µg daily were female gender, absence of cardiovascular disease at baseline, and CKD Stage 3. eGFR decrements with paricalcitol 2 µg treatment were not observed in subjects who had iPTH \geq 75 pg/mL at baseline (most comparable to the population that would be treated on-label in clinical practice); CKD Stages 2 or 4; or in male subjects or subjects with a history of cardiovascular disease. Given the inconsistencies demonstrated in these subgroups, the change in eGFR may be a poor marker of a real change in GFR, which is further supported by historic clinical studies demonstrating that calcitriol decreases eGFR secondary to an effect on creatinine handling and thus does not have an effect on real GFR.

All effects occurred within 4 to 8 weeks of the initiation of therapy and were stable through the 6-month treatment period, returning toward baseline 60 days posttreatment, indicating reversibility of these effects and suggesting that the 6-month exposure to paricalcitol had no deleterious effects on the kidney function. In addition to its effectiveness on UACR reduction, 2 µg of paricalcitol administered daily had low rates of hypercalcemia compared to placebo (3% versus 1%, respectively; $P = \text{NS}$) and was not associated with any clinically significant new safety signals.

In summary, paricalcitol 2 µg may be a clinically effective adjunctive therapy for the reduction of residual albuminuria in patients with type 2 diabetic nephropathy on stable RAAS inhibition, especially among those with high salt intake. The fact that the group that had the best relative reduction on albuminuria was the high-salt excretion group may be a significant clinically relevant finding given the difficulty of managing salt intake in CKD patients. Current use of paricalcitol 2 µg daily should continue to be restricted to Stage 3 or 4 CKD patients with PTH \geq 500 pg/mL, as indicated in the current product label.

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