Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: Paricalcitol Capsules (ABT-358) (Zemplar®)		
Name of Active Ingredient: Paricalcitol		
Title of Study: The PRIMO Study: Paricalcitol Capsules Benefits in Renal Failure Induced Cardiac Morbidity in Subjects with Chronic Kidney Disease Stage 3/4		
Coordinating Investigator: Ravi Thadhani, MD, MPH Director Clinical Research in Nephrology, Massachusetts General Hospital		
Study Sites: 60 sites (32 United States [US] and 28 Ex-US)		
Publications: 1		
Studied Period (Years): First Subject First Visit: 15 July 2008 Last Subject Last Visit: 22 September 2010	**Phase of Development:** 3	
Objective: The overall objective of this Phase 3 study was to evaluate the effects of paricalcitol capsules on cardiac structure and function over 48 weeks in subjects with Stage 3/4 chronic kidney disease (CKD) who had left ventricular hypertrophy (LVH).		
Methodology: This was a Phase 3, randomized, double-blind, placebo-controlled trial investigating the effects of paricalcitol capsules on changes in cardiac structure and function over 48 weeks in subjects with Stage 3/4 CKD who had LVH. Subjects who met the inclusion criteria and did not meet any of the exclusion criteria were randomized in a 1:1 ratio to each treatment group to receive paricalcitol capsules or placebo. A stratified randomization scheme was used to ensure balance among treatment groups with respect to country, gender, and baseline renin angiotensin-aldosterone system (RAAS) inhibitor use (yes/no). Subjects who completed the 48-Week Treatment Period could continue on in the ongoing Long-term Follow-up Period that will last 18 months, with study visits at 6 months, 12 months and 18 months post Treatment Week 48 Visit. Subjects will not receive study drug, nor will they undergo echocardiogram/MRI procedures during the Long-term Follow-up Period. A sufficient number of US and Ex-US sites were selected in order to enroll approximately 220 subjects (110 per treatment arm) in the double-blind treatment period. It is estimated that approximately 150 of those subjects who complete the double-blind treatment phase will enter the Long-term Follow-up Period.		
Number of Subjects (Planned and Analyzed): 220 planned (110 per treatment arm); 227 enrolled and analyzed (112 in the placebo treatment group and 115 in the paricalcitol treatment group).		

Diagnosis and Main Criteria for Inclusion: Subjects were males or females ≥ 18 years of age with Stage 3/4 CKD who had a diagnosis of LVH confirmed by echocardiogram and cardiac magnetic resonance imaging (MRI).

For entry into the Treatment Period, subjects had to meet the following criteria: Estimated glomerular filtration rate (GFR) between 15 and 60 mL/min/1.73 m^2 by simplified 4-variable Modification of Diet Renal Disease (MDRD) formula, serum intact parathyroid hormone (iPTH) value between 50 and 300 pg/mL, serum calcium level 8.0 to 10.0 mg/dL (2.0 to 2.5 mmol/L), phosphorous level ≤ 5.2 mg/dL (1.68 mmol/L), serum albumin ≥ 3.0 g/dL (30 g/L), negative serum pregnancy test for female subjects of childbearing potential.

For entry into the Treatment Period, the subjects had to meet the following criteria based on Screening echocardiogram: Left ventricular (LV) ejection fraction ≥ 50% and septal wall thickness between 11 and 17 mm for females and between 12 and 18 mm for males.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: Subjects received two 1 mcg capsules of paricalcitol or matching placebo orally once daily (QD) for 48 weeks. If a subject developed serum calcium > 11 mg/dL (2.75 mmol/L), the dose was reduced to one 1 mcg capsule of paricalcitol or matching placebo.

Test Preparation Drug Product	Bulk Lot Number	Source
Paricalcitol capsules 1 mcg gray oval	07-011383 08-018100	[redacted]
Placebo for paricalcitol capsules 1 mcg gray oval	07-011386 08-018081	[redacted]

[redacted]

Duration of Treatment: Subjects were treated with paricalcitol (or matching placebo) for a total of 48 weeks. Total subject participation was approximately 58 weeks (6-week Screening Period, 48-week Treatment Period, and 4-week Post-treatment Follow-up). For subjects who were eligible and consented to participation in the Long-Term Follow-up Period, the total duration of participation will be approximately 130 weeks.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: This was a placebo-controlled study, no reference therapy was used.

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Criteria for Evaluation:

Efficacy:

Primary Variable:

The primary efficacy variable was change from baseline in left ventricular mass index (LVMI) over 48 weeks measured by cardiac MRI. Left ventricular (LV) mass was normalized to the subject's height by the following equation to obtain LVMI:

LVM (g) divided by height $(m)^{2.7}$

Secondary Variables:

The secondary efficacy endpoints of this study were the following:

1. Echocardiographic assessment of diastolic function, assessed through evaluation of changes in diastolic mitral annular relaxation velocity (E') and changes in additional measures of diastolic function (isovolumic relaxation time [IVRT], peak transmitral early diastolic velocity pulse wave [E]/E', mitral (E-wave) deceleration time [DT]).
2. Changes in progression of aortic atherosclerosis, aortic compliance, left ventricular end-systolic volume index, left ventricular end-diastolic volume index, and left ventricular ejection fraction from baseline to Week 24 and Week 48 as assessed by MRI imaging.
3. Changes in biological and inflammatory markers that have been linked to CVD in CKD subjects. Specifically, the markers evaluated included triiodothyronine (T3), interleukin 6 (IL-6), troponin-T, B-type natriuretic peptide (BNP), and high sensitivity C-reactive protein (hsCRP).

Safety:

Safety Variables:

Safety was assessed by the following variables:

1. The incidence of adverse events, including subject deaths.
2. Changes in complete chemistry, hematology, and urinary albumin to creatinine ratio (UACR) measurements.
3. The change from baseline in subject vital signs.
4. The incidence of hypercalcemia, defined as two consecutive serum calcium measurements > 10.5 mg/dL (2.63 mmol/L).

Three data sets were analyzed for this study, as defined below:

Intent-To-Treat (ITT) Population (N = 227): All randomized subjects who took at least one dose of study drug. All analyses were conducted using the ITT Population unless noted otherwise.

Per-Protocol Population (N = 199): A subset of the ITT Population that included all subjects with a duration of study drug exposure of at least 24 weeks (168 days). The Per-Protocol Population was used for secondary efficacy analyses of cardiac MRI and echocardiogram efficacy endpoints.

LVH Population (N = 169): A subset of the ITT Population that included all subjects with baseline LVMI greater than the 25^{th} percentile by gender in cardiac MRI. The LVH Population was used for secondary efficacy analyses of cardiac MRI and echocardiogram efficacy endpoints.

Statistical Methods:

Efficacy:

Primary efficacy analysis: The primary efficacy analysis was a comparison of the treatment effect of paricalcitol versus placebo on changes from baseline in LVMI, as measured by MRI, using a repeated measures model using all longitudinal observations at each visit (i.e., Baseline, Week 24, and Week 48) from the ITT Population. The model adjusted for the continuous variable baseline LVMI as well as the class variables treatment, country, gender, baseline RAAS use (yes/no), and visit. A visit-by-treatment interaction term was also included. Unstructured variance-covariance structures were used as the primary covariance structure in the primary analysis as well as all other repeated measure analyses for secondary efficacy endpoints and safety endpoints. Satterthwaite's approximation was used to estimate denominator degrees of freedom. Type III sum of-squares for the least-squares means was used.

Secondary efficacy analyses: Comparison between the effect of paricalcitol and placebo on changes from baseline in diastolic function variables (left atrial volume, E', IVRT, E/E', and DT), aortic compliance, aortic atherosclerosis, left ventricular end-systolic volume index, left ventricular end-diastolic volume index, left ventricular ejection fraction, iPTH, bone specific alkaline phosphatase, biological and inflammatory markers (T3, IL-6, troponin-T, BNP, and hsCRP), and urine albumin/creatinine ratio using repeated measures analysis and analysis of covariance (ANCOVA) in ITT Population, Per-Protocol Population, LVH Population, or completers. The ANCOVA analysis of primary efficacy endpoints was also consider one of the secondary efficacy analyses.

Comparison between the effect of paricalcitol and placebo on morbidity (incidence of hospitalization, doubling of serum creatinine and initiated dialysis and time to events of hospitalization) using Fisher's exact test and Kaplan-Meier methodology.

Comparison between the effect of paricalcitol and placebo on number of hospitalization and number of days hospitalized using Poisson and negative binomial regression.

Comparison between the effect of paricalcitol and placebo on the composite endpoint of time to events of death, dialysis, or doubling of serum creatinine using Kaplan-Meier methodology.

Comparison between the effect of paricalcitol and placebo on changes from baseline in quality of life measures (i.e., Standard SF-36v2™ Health Survey and the Work Productivity and Activity Impairment - General Health Questionnaire [WPAI-GH]) using analysis of covariance (ANCOVA).

Safety:

The numbers and percentages of subjects with adverse events (AEs) were summarized using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment groups were compared using Fisher's exact test.

Mean changes from clinical laboratory and vital sign variables were analyzed using analysis of variance (ANOVA). The rate of clinically meaningful hypercalcemia (defined as two consecutive serum calcium measurements greater than 10.5 mg/dL) was also compared between treatment groups using Fisher's exact test.

Summary/Conclusions:

Efficacy Results:

This study evaluated the effects of paricalcitol capsules on cardiac structure and function over 48 weeks in subjects with Stage 3/4 CKD who had LVH. The primary efficacy variable was the change from Baseline to Week 48 in LVMI obtained by cardiac MRI. The primary analysis was a comparison of paricalcitol versus placebo on the change in LVMI from baseline to Week 48 using a mixed-effect model of repeated measures (MMRM) for subjects in the ITT Population. The study population was similar across treatment groups.

The paricalcitol group experienced a small mean increase from baseline in LVMI (+0.34 $g/m^{2\,7}$) at Week 48 compared with a small mean decrease in the placebo group (–0.07 $g/m^{2\,7}$), but the difference was not statistically significant. Similar analyses with expanded treatment day intervals also showed no statistically significant differences at Week 48.

The results of LVMI evaluated by repeated measures analysis including baseline systolic blood pressure and UACR as covariates were similar to the results without systolic blood pressure and UACR interaction, respectively. There were no statistically significant interaction effects between treatment by gender, age, race, country, RAAS inhibitor use, systolic blood pressure, body mass index (BMI), UACR, iPTH, or diabetes on the primary efficacy analysis for LVMI.

The results of the repeated measures analysis of change from baseline to each postbaseline visit in the ITT Population indicated no statistically significant differences between treatments for MRI variables.

The results of repeated measures analysis of diastolic function variables showed a statistically significantly greater mean decrease from baseline in left atrial volume for paricalcitol treatment compared with placebo treatment in the ITT Population at Week 48 (–4.94 versus –0.92 mL; $P = 0.002$), and overall ($P = 0.005$). There were no clinically important or statistically significant differences between treatment groups for E', E/E', or IVRT. There were small mean increases in E-wave deceleration time in the paricalcitol group (+0.01 sec at Week 24 and Week 48) compared with no mean changes in the placebo group in the ITT Population, but the differences were not statistically significant ($P = 0.058$ at Week 48 and 0.061 overall).

The results of diastolic function variables evaluated by repeated measures analysis including baseline systolic blood pressure and UACR as covariates were similar to the results without systolic blood pressure and UACR as covariates, respectively.

The biological and inflammatory markers evaluated using repeated measures analysis in the ITT Population showed a small mean change in troponin-T in the paricalcitol group (+0.01 mcg/L) that was statistically significantly different from no change in the placebo group at Week 48, with a statistically significant between-group difference ($P = 0.036$). The overall between-group difference in mean change from baseline was also statistically significant ($P = 0.037$). No statistically significant differences were observed between treatment groups for T3, IL-6, log-transformed BNP, or hsCRP.

Efficacy Results (Continued):

Other laboratory efficacy variables evaluated using repeated measures analysis in the ITT Population showed mean decreases in iPTH in the paricalcitol group that were statistically significantly greater than the mean changes observed in the placebo group at every visit and overall ($P < 0.001$). The mean changes in BSAP in the paricalcitol group were also statistically significantly greater than those observed for placebo at Week 24 (–11.76 versus –2.78 mcg/L; $P < 0.001$), Week 48 (–12.39 versus –2.96 mcg/L; $P < 0.001$), and overall ($P < 0.001$). No statistically significant differences between treatment groups were observed for UACR.

In the analysis of patient-reported outcomes, the SF-36 Health Survey results showed no statistically significant differences between treatment groups for changes from baseline to final evaluation for any domain or summary score. Both treatment groups experienced small mean decreases from baseline in the physical component summary score and small mean increases from Baseline in the mental component summary score. The WPAI-GH results showed no statistically significant differences between treatment groups for changes from baseline to final evaluation for any assessment.

The percentage of subjects hospitalized for any reason during the study was similar between the paricalcitol group (15.7%) and the placebo group (17.0%). The percentage of subjects with hospitalizations attributable to cardiovascular disease was statistically significantly higher in the placebo group (6.3%) than in the paricalcitol group (0.9%; $P = 0.034$). Analysis of the cumulative number of hospitalizations, counting multiple hospitalizations for a subject, showed a statistically significantly higher rate of hospitalizations attributable to cardiovascular disease for placebo treatment compared with paricalcitol treatment. The mean number of days hospitalized was similar between paricalcitol and placebo treatment for any hospitalization (9.2 versus 9.4 days, respectively).

The percentage of subjects who experienced a doubling of serum creatinine or initiated dialysis was 1.8% (2/112) for placebo and 12.2% (14/115) for paricalcitol. The treatment group difference in the survival curves for the time to doubling of serum creatinine or dialysis using the log-rank test was statistically significant ($P = 0.005$).

Safety Results:

Treatment-emergent AEs were reported for 80.0% (92/115) of subjects in the paricalcitol group and 77.7% (87/112) of subjects in the placebo group. AEs that were reported for at least 5% of subjects in the paricalcitol group with at least twice the rate of the placebo group were hypertension (10.4% versus 4.5%), hypercalcemia (8.7% versus 0.9%), diarrhea (7.0% versus 1.8%), dizziness (6.1% versus 1.8%), dyspepsia (5.2% versus 0%), and hypoglycemia (5.2% versus 1.8%).

No treatment-emergent deaths were reported. The percentage of subjects who experienced treatment-emergent serious adverse events (SAEs) was similar between paricalcitol (17.4%) and placebo (17.9%) treatment. SAEs reported for more than 1 subject in the paricalcitol group were hypoglycemia (1 placebo, 2 paricalcitol), renal failure (0 placebo, 2 paricalcitol), and renal failure acute (3 placebo, 2 paricalcitol).

The incidence of AEs resulting in discontinuation of study drug was 2-fold higher in the paricalcitol group (9.6% [11/115]) versus the placebo group (4.5% [5/112]), and the difference can be attributed to high serum calcium levels resulting in discontinuation for 6 subjects in the paricalcitol group and no subjects in the placebo group.

Safety Results (Continued):

The incidence of subjects with AEs considered at least possibly related to study drug was statistically significantly greater ($P < 0.001$) in the paricalcitol group (20.9%) than the placebo group (5.4%), largely due to the higher rate of treatment related hypercalcemia in the paricalcitol group (8.7% versus 0%; $P < 0.01$).

Although mean decreases in hemoglobin were similar between treatment groups (–0.4 g/dL placebo, –0.6 g/dL paricalcitol), there was a higher percentage of subjects in the paricalcitol group with shifts to value below the normal range (17.4% [8/46] placebo, 50% [25/50] paricalcitol). No subjects were discontinued from the study because of anemia or low hemoglobin.

The paricalcitol group had statistically significantly greater mean decreases in BSAP, alkaline phosphatase, and eGFR, and statistically significantly greater mean increases in corrected calcium, corrected calcium-phosphorus product, creatinine, cystatin C, and BUN compared with the placebo group. Likewise, the paricalcitol group had a greater incidence of subjects shifting to values below the normal range for BSAP and alkaline phosphatase, and shifting to values above the normal range for corrected calcium, inorganic phosphate, and creatinine. Calcium values greater than 10.5 mg/dL were recorded for at least 2 consecutive measurements in 22.6% of subjects treated with paricalcitol versus 0.9% of subjects treated with placebo ($P < 0.001$).

No other consistent or clinically important differences, with the exception of eGFR (as measured by creatinine and cystatin C), were observed between treatment groups for clinical laboratory or vital sign evaluations.

Conclusions:

The results of this study showed no statistically significant differences in LVMI over 48 weeks of treatment with paricalcitol capsules when compared with placebo in subjects with Stage 3/4 CKD who had LVH. Overall, the safety, clinical laboratory, and vital sign results were consistent with the known safety profile of paricalcitol in patients with Stage 3/4 CKD.

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