2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-358/Zemplar® (paricalcitol) Capsules		
Name of Active Ingredient: paricalcitol		

Title of Study: A Phase 3, Prospective, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Pharmacokinetics, Safety and Efficacy of Paricalcitol Capsules in Decreasing Serum Intact Parathyroid Hormone Levels in Pediatric Subjects Ages 10 to 16 years with Moderate to Severe Chronic Kidney Disease

Coordinating Investigator: Nicholas Webb, DM FRCP FRCPCH

Study Sites: In the Pharmacokinetic (PK) Portion, Part 1, 5 investigative sites within the US enrolled subjects in the study. In the Safety and Efficacy Portion, Part 2, 22 investigative sites enrolled subjects, 9 sites within the US (including 1 site in Puerto Rico) and 13 sites outside the US (5 sites in Spain, 3 sites in Germany, 2 sites in Portugal, 2 sites in the United Kingdom, and 1 site in Singapore).

Publications: None

Studied Period (Years): First Subject First Visit: 10 February 2010 Last Subject Last Visit: 22 December 2014	**Phase of Development:** 3

Objectives:

Single Dose Pharmacokinetic Portion, Part 1: To determine the safety, tolerability, and pharmacokinetics of a single dose of 3 µg paricalcitol capsules in pediatric subjects ages 10 to 16 years with moderate to severe chronic kidney disease (CKD Stages 3 and 4).

Safety and Efficacy Portion, Part 2: To determine the safety and efficacy of paricalcitol capsules as compared to placebo in decreasing serum intact parathyroid hormone (iPTH) in pediatric subjects ages 10 to 16 years with moderate to severe chronic kidney disease (CKD Stages 3 and 4) with an initial 12 weeks of double-blinded study drug followed by a minimum of 12 weeks of open-label active drug.

Methodology:

Study M10-149 was a Phase 3 study consisting of two parts. The Pharmacokinetic Portion in Part 1 was designed as an open-label, single-dose, non-fasting, multicenter study evaluating the pharmacokinetics of paricalcitol capsules in pediatric subjects with moderate to severe CKD (Stage 3 or Stage 4). The pharmacokinetic blood samples were to be drawn at 0 (prior to dosing), and at 1, 2, 4, 6, 8, 12, 24, 36, and 48 hours postdose.

Methodology (Continued):

The Safety and Efficacy Portion in Part 2 was divided into 2 treatment periods. The first 12 weeks of Part 2 of the study was designed as a randomized, double blind, placebo-controlled multicenter study to evaluate the safety and efficacy of paricalcitol capsules on serum iPTH reduction. To further characterize the safety and efficacy of paricalcitol capsules, subjects who completed the 12-week, double-blind, treatment period of Part 2 were to continue in an open-label period wherein all subjects received paricalcitol capsules. Thirty-six male or female pediatric subjects (ages 10 to 16 years) with Stage 3 or Stage 4 CKD were enrolled in the study. Qualified subjects were randomized in a 1:1 ratio to receive either paricalcitol capsules or placebo. Subjects were to take their oral drug for a minimum of 24 weeks. There were a minimum of 8 scheduled visits for Treatment Day 1, Treatment Weeks 2, 4, 8, 12, 16, 20 and 24/or the end of the trial.

Number of Subjects (Planned and Analyzed): 12 subjects in Part 1 (6 subjects with CKD Stage 3 and 6 subjects with Stage 4 CKD); 36 subjects in Part 2

Diagnosis and Main Criteria for Inclusion:

The entry criteria for both Part 1 and Part 2 of the study were designed to include male or female subjects ages 10 to 16 years, with CKD, Stage 3 (estimated glomerular filtration rate, [eGFR] 30 to 59 mL/min/1.73 m^2) or CKD, Stage 4 (eGFR 15 to 29 mL/min/1.73 m^2, not requiring dialysis).

Main Criteria for Exclusion:

A subject was eligible for study participation if he/she met the following important criteria:

1. Part 2 Subjects who had had a kidney or solid organ transplant ≥ 12 months prior to entry into the Treatment Phase had to have a stable, therapeutic calcineurin inhibitor drug level (at least two stable levels prior to enrollment into Part 2 of the study).
2. Subject had 25-hydroxyvitamin D levels ≥ 30 ng/mL at Screening (Part 2 only).
3. Subject was not expected to begin dialysis for at least 6 months (in the opinion of the investigator).
4. If taking phosphate binders, the subject had to have been on a stable dose (same type and regimen) for at least 4 weeks prior to the Screening Phase.
5. If receiving growth hormone, subject must have been receiving it for > 3 months prior to the Screening Phase and expected to continue to receive it throughout the Treatment Phase.

A subject was to be excluded from the study if he/she met any of the following criteria:

1. Part 1 Subjects: Subject had had an organ transplant except bone marrow transplant recipients. Bone marrow transplant recipients were to have been off of immunosuppressant therapy.
2. Subject had had a small bowel transplant.
3. Subject had had acute kidney failure within 12 weeks of the Screening Phase (defined as an acute rise in serum creatinine).
4. Subject had had symptomatic or significant hypocalcemia requiring active Vitamin D therapy (i.e., calcitriol, paricalcitol, doxercalciferol or alfacalcidol) within 6 months prior to the Screening Phase.
5. Subject had a history of active kidney stones (6 months prior to screening).
6. Within 4 weeks prior to Treatment the subject was taking maintenance calcitonin, bisphosphonates, cinacalcet, glucocorticoids in an equivalent dose of > 5 mg prednisone daily, or other drugs known to affect calcium or bone metabolism.
7. Subject was taking phosphate supplements.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Part 1: All subjects were administered three 1 µg paricalcitol soft gelatin capsules orally for a single dose of 3 µg.

Part 2: Subjects were assigned randomized treatment of either paricalcitol soft gelatin capsules (1 µg strength) or matching placebo soft gelatin capsules. Subjects were to take the capsules orally three times per week (TIW). Subjects were administered bottle containing 30 capsules to last for up to 4 weeks, until the next visit. Starting at Treatment Week 4 of Part 2, doses may have been increased for individual subjects in 1 µg increments every 4 weeks based upon safety observations and blood chemistry evaluations of iPTH, calcium, and phosphorus levels. The dose could be decreased to the previous dose in 1 µg increments as appropriate.

Manufacturing bulk lot numbers of paricalcitol capsules 1 µg for Both Part 1 and Part 2 were 10-002403, 12-007086, and 09-023373.

Duration of Treatment:

Subjects participating in Part 1 were administered a single dose of open-label paricalcitol and were monitored for 48 hours.

Subjects participating in Part 2 were randomly assigned double-blind treatment for 12-weeks. Subjects completing the 12-week double-blind period were to continue in the 12-week open-label period for a total of 24 weeks.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Placebo was the reference therapy in the study. Placebo capsules were taken orally TIW. Manufacturing bulk lot numbers of matching placebo for paricalcitol capsules for the 12-week double-blind period of Part 2 were 10-002443 and 12-007087.

Criteria for Evaluation

Efficacy:

Part 1: Efficacy was not assessed.

Part 2: The primary efficacy endpoint was the proportion of subjects who achieved two consecutive ≥ 30% reductions from baseline in iPTH levels during the 12-week double-blind portion of the study regardless of CKD stage.

Secondary efficacy variables included:

1. The proportion of subjects who attained a final iPTH value within Kidney Dialysis Outcomes Quality Initiatives (KDOQI). iPTH target ranges were evaluated within each CKD stage.
2. The mean change in iPTH from baseline to each post baseline visit (Weeks 2, 4, 8 and 12).
3. The proportion of subjects who attained a final value within the applicable KDOQI target ranges for calcium and for phosphorus. KDOQI recommends serum calcium be maintained within age appropriate normal ranges and serum phosphorus is maintained at or above the age appropriate lower limits and no higher than the age appropriate upper limits.
4. The mean change in first morning void urinary albumin to creatinine ratio (FMV UACR) from baseline to each post baseline visit (Weeks 4, 8 and 12).

Criteria for Evaluation (Continued)

Efficacy (Continued):

5. Subject self-reported health outcomes were assessed at the baseline and the Week 12 visit by using the PedsQL™ 4.0 questionnaire. Two questionnaires were to be completed: one by the subject's parent(s) or caregiver(s) and one by the subject. The caregiver questionnaire results were evaluated independently of the subject questionnaire results.

Pharmacokinetic:

Part 1: maximum observed plasma concentration (C_{max}) and the time to C_{max} (peak time, T_{max}); terminal phase elimination half-life ($t_{1/2}$); area under the plasma concentration-time curve (AUC).

Part 2: Concentration of paricalcitol in serum at each Week (4, 8, 12, 16, 20, and 24). Values for the pharmacokinetic parameters of paricalcitol, including the apparent volume of distribution (V/F) and CL/F were determined using a nonlinear mixed effects model; these results are presented in a separate report.

Safety:

Part 1: Monitoring adverse events (AE), vital signs, physical examinations, ECG, and laboratory assessments.

Part 2: AEs, changes from baseline in blood chemistry, hematology, urinary laboratory analyses; changes from baseline in vital signs and physical examinations; progressive changes in kidney function; occurrences of clinically meaningful hypercalcemia (2 consecutive serum calcium values > 10.2 mg/dL [2.55 mmol/L]).

Statistical Methods

Efficacy:

Part 1: Efficacy was not assessed.

Part 2: For the double-blind period, the primary efficacy analysis was a comparison between the paricalcitol treatment group and placebo treatment group in the proportion of subjects attaining two consecutive ≥ 30% reductions in iPTH from baseline, regardless of CKD stage. The primary efficacy analysis was conducted using Fisher's exact test on the Intent-To-Treat (ITT) Dataset. Secondary efficacy analyses included the proportion of subjects who attained a final iPTH, calcium, phosphorus level within KDOQI target ranges by CKD stage, analyzed using an Exact Cochran-Mantel-Haenszel (CMH) test, adjusting for CKD stage on the ITT Dataset. For the open-label portion of the study, data were summarized descriptively (frequency and percentages of subjects) by randomized treatment group assignment and for the combined groups on the All Treated Dataset for the proportion of subjects achieving two consecutive ≥ 30% reductions in iPTH from baseline and the proportion of subjects who attained a final iPTH, calcium, phosphorus level within KDOQI target ranges, as well as the attainment of iPTH values within KDOQI target range at visits every 4 weeks.

Pharmacokinetic:

Descriptive and summary statistics were used to evaluate PK in Part 1 and Part 2.

Statistical Methods (Continued)

Safety:

Part 1: Descriptive statistics (number and percentage of subjects reporting or observed with event) were used to evaluate AEs. No statistical test was performed for AEs. Summary statistics were provided for laboratory and vital signs. Statistical hypothesis testing was not performed for laboratory tests and vital signs. The Part 1 Safety Analysis Dataset was used for Part 1 safety evaluations.

Part 2: The ITT Dataset was used for the safety evaluation in the double-blind period of Part 2. The All-Treated Dataset was used for the safety evaluation for the open-label period of Part 2. Descriptive statistics (number and percentage of subjects reporting or observed with event) were used to evaluate AEs. Treatment group comparability in the percentage of subjects experiencing adverse events were evaluated using Fisher's exact test. For all the laboratory tests change from baseline to final observations, to minimum and to maximum values during the double-blind portion were analyzed using an analysis of variance (ANOVA) with the fixed effect of treatment group. Type III sum-of-squares for the least-squares means were used. Shift tables cross tabulated the frequency of subjects with baseline values below/within/above the normal range versus final measurement values below/within/above the normal range. The proportions of subjects with hypercalcemia were summarized by treatment group and the treatment group difference compared using Fisher's exact test.

Summary/Conclusions

Efficacy Results:

During the double-blind period of Part 2 in the paricalcitol group 5/18 subjects (27.8%) had 2 consecutive reductions of at least 30% in iPTH from baseline compared with no subjects in the placebo group. The between-group difference was 27.8 (CI: 7.5, 52.8; $p = 0.045$). The difference between treatment groups was statically significant ($p < 0.05$).

The overall, between-group mean change from baseline to the final assessment for iPTH levels was –72.40 mg/dL (CI: –108.05, –36.75; $p < 0.001$). However, the between group differences in iPTH Levels for subjects with Stage 3 CKD were not statistically significant (CI: 2.3, 62.0; $p = 0.090$). Similarly, the between group differences in iPTH levels for subjects with Stage 4 CKD were not statistically significant (CI: 16.4, 60.1; $p = 0.467$).

None of the remaining secondary efficacy analyses had a statistically significant between-group difference. The other secondary efficacy variables were analyzed as follows:

1. 6/18 subjects (33.3%) in the paricalcitol group attained final iPTH within target ranges compared with 2/18 subjects (11.1%) in the placebo group ($p = 0.128$);
2. 15/18 subjects (83.3%) in the paricalcitol group attained final calcium within target ranges compared with 17/18 subjects (94.4%) in the placebo group ($p = 0.327$);
3. 9/18 subjects (50.0%) in the paricalcitol group attained final phosphorus within target ranges compared with 13/18 subjects (72.2%) in the placebo group ($p = 0.194$);
4. The between-group difference between the paricalcitol and placebo treatment groups for FMV UACR was 0.14 (CI: –0.25, 0.53; $p = 0.469$);
5. There were no statistically significant differences at the $p < 0.05$ level between treatment groups for changes from baseline to the final evaluation for the summary score or any individual parameter for the PedsQL™ 4.0 questionnaire for either subject reported health outcomes or parent/caregiver reported health outcomes.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Observations from the open-label period of Part 2 were consistent with observations from the double-blind period.

1. 12/29 subjects (41.4%) attained 2 consecutive ≥ 30% reductions compared with 17/29 subjects (58.6%) who did not;
2. 8/29 subjects (27.6%) attained final iPTH within KDOQI targets compared with 21/29 subjects (72.4%) who did not;
3. 25/29 subjects (86.2%) attained final calcium within KDOQI targets compared with 4/29 subjects (13.8%) who did not;
4. 16/29 subjects (55.2%) attained final phosphorus within KDOQI targets compared with 13/29 subjects (44.8%) who did not;
5. During the 12-week, open-label period, the hormone iPTH decreased from baseline to the post-baseline visit at Weeks 16 and 20, but had increased by Week 24. At Week 16 the change from baseline in iPTH for all participating subjects was –34.4 pg/mL (CI: –64.9, –3.8). At Week 20 the change from baseline in iPTH for all participating subjects was –27.0 pg/mL (CI: –66.0, 12.0). By Week 24 the change from baseline was 10.1 pg/mL (CI: –57.4, 77.6);
6. The results for the subject and caregiver reported health outcomes were consistent with the observations from the 12-week, double-blind period.

Pharmacokinetic Results:

Paricalcitol C_{max}, AUC, T_{max} and $t_{1/2}$ values were similar between Stage 3 and Stage 4 pediatric subjects. Mean C_{max} was 0.13 ng/mL and mean AUC was 2.87 ng•h/mL for combined (Stages 3 and 4) subjects.

Safety Results:

Part 1: A treatment-emergent AE was reported for 2/12 subjects (16.7%), one each from the group with CKF Stage 3 and Stage 4. There were no subjects with SAEs, AEs assessed to be severe, AEs related to study drug, or AEs leading to discontinuation of study drug. No subjects died during Part 1.

Part 2: During the 12-week, double-blind period of Part 2, treatment-emergent AEs were reported for 16/18 subjects (88.9%) in the placebo treatment group and 7/18 subjects (38.9%) in the paricalcitol treatment group; the between-group difference in the number of AEs was statistically significant ($p = 0.005$). Two subjects from the placebo treatment group had AEs assessed as severe and no subjects in the paricalcitol group. SAEs were reported for 2 subjects (11.1%) in the placebo group and no subjects in the paricalcitol group. Two subjects (11.1%) in the placebo treatment group and 1 subject (5.6%) in the paricalcitol treatment group had AEs that led to the discontinuation of study drug. There were no statistically significant differences between treatment groups for mean changes from baseline in hematology, chemistry, urology, and vital sign variables, except for the assessment of iPTH (discussed above as a secondary efficacy endpoint). There were no cases of hypercalcemia during the double-blind period.

Summary/Conclusions (Continued)

Safety Results (Continued):

During the open-label period, treatment-emergent AEs were reported for 12/16 subject (75.0%) in the placebo group and 6/13 subjects (46.2%) in the paricalcitol group. There was no statistical analysis of AEs during the open-label period. One subject from the paricalcitol treatment group had an AE assessed as severe compared with none from the placebo treatment group. SAEs were reported for 1 subject (6.3%) in the placebo treatment group and 1 subject (7.7%) in the paricalcitol treatment group. One subject had hypercalcemia as 2 consecutive calcium values > 10.2 mg/dL; the subject discontinued form the study. The mean changes from baseline in hematology, chemistry, urology, and vitals sign variables, did not appear to represent a consistent trend. No subjects died during the Safety and Efficacy Portion, Part 2.

Conclusions:

Paricalcitol C_{max}, AUC, T_{max} and $t_{1/2}$ values were similar between CKD Stage 3 and Stage 4 pediatric subjects from Part 1.

As per the protocol, the results from the first 6 subjects from the PK Portion, Part 1 supported the use of paricalcitol 1 µg TIW as the initial dose for pediatric subjects 10 to 16 years of age with mild to moderate (Stage 3 or Stage 4) CKD for the 24-week safety and efficacy portion in Part 2 of Study M10-149.

Paricalcitol (initially administered orally at a dose of 1 µg TIW with the ability to increase at 1 µg increments every 4 weeks) was effective in reducing the hormone iPTH in pediatric subjects with mild to moderate (Stage 3 or Stage 4) CKD as evidenced by the statistically significant result for the primary efficacy endpoint of a greater proportion of subjects achieving consecutive ≥ 30% reductions from baseline in iPTH levels during the 12-week double-blind portion of the study regardless of CKD stage and also by the statically significant reduction in iPTH from baseline to the 12-week time point in the paricalcitol treatment group compared with the placebo treatment group. The effect of treatment with paricalcitol was persistent as evidenced by the continued reduction iPTH during the 12-week open-label treatment period.

The remaining secondary endpoints did not demonstrate a statistically significant difference. There was no statistically significant between-group difference in the proportion subjects who attained a final iPTH, calcium, or phosphorus within KDOQI targets and there was no statistically significant between-group difference in mean changes of FMV UACR from baseline to each post-baseline visit at Weeks 4, 8, or 12. In addition neither subjects nor caregivers reported any changes in health outcomes as evidence by the results of the PedsQL™ 4.0 questionnaire; there were no statistically significant differences (at $p < 0.05$) between treatment groups for changes from baseline to the final evaluation for the summary score or any individual parameter from questionnaire or the total score for either caregivers or subjects.

Paricalcitol administered at an initial dose of 1 µg TIW with the ability to increase at 1 µg increments every 4 weeks was well tolerated for 24 weeks within the pediatric population with mild to moderate (Stage 3 or Stage 4) CKD as demonstrated by the mild to moderate severity of most AEs; the low numbers of SAE, discontinuations, and severe AEs; and the few incidence of laboratory assessments out of range.