

2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)	
Name of Study Drug: ABT-358/Zemplar® (paricalcitol) Capsules			Volume:
Name of Active Ingredient: paricalcitol			Page:
Title of Study: A Phase 3, Open-Label, Multicenter Study to Evaluate the Safety of Paricalcitol Capsules in Pediatric Subjects Ages 10 to 16 with Stage 5 Chronic Kidney Disease Receiving Peritoneal Dialysis or Hemodialysis			
Investigator: Nicholas Webb, DM, FRCP, FRCPH			
Study Sites: 9 investigative sites enrolled subjects: 7 sites within the US, 1 site in the United Kingdom, and 1 site in Portugal.			
Publications: None			
Studied Period (Years): First Subject First Visit: 03 October 2011 Last Subject Last Visit: 24 April 2015	Phase of Development: 3		
Objective: To evaluate the safety of paricalcitol capsules for the treatment of secondary hyperparathyroidism in pediatric subjects ages 10 to 16 years with chronic kidney disease (CKD) Stage 5, receiving peritoneal dialysis or hemodialysis through the evaluation of the incidence of hypercalcemia.			
Methodology: The study enrolled 13 subjects to meet scientific and regulatory objectives and as an outpatient trial to minimize the burden to caregivers and pediatric subjects. There was no placebo control group due to the potential health risks associated with 12 weeks of uncontrolled secondary hyperparathyroidism (SHPT) in children with CKD Stage 5. After satisfying washout criteria for Vitamin D receptor (VDR) activators, qualified subjects were to be enrolled and treated for 12 weeks with paricalcitol capsules. Subjects were to take study drug three times weekly (TIW) orally, but no more frequently than every other day. At a minimum, Day 1, Week 2, 4, 8, and 12 visits were required. Additionally, Week 6 and 10 visits may have been conducted at the discretion of the investigator to ensure subject safety and/or make dose adjustments.			
Number of Subjects (Planned and Analyzed): At least 12 subjects planned. 13 subjects were enrolled and analyzed.			

Diagnosis and Main Criteria for Inclusion:

The study was designed to enroll male or female pediatric subjects ages 10 to 16 years with CKD Stage 5 on peritoneal dialysis or hemodialysis who satisfied the entry criteria:

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

1. Subject was receiving peritoneal dialysis or hemodialysis for at least 3 months prior to Screening.
2. Subject was currently being diagnosed and/or treated for secondary hyperparathyroidism.
3. If taking phosphate binders, the subject had been on a stable dose (same type and regimen) for at least 2 weeks prior to Screening.
4. If receiving growth hormone, subject was receiving it for at least 3 months prior to Screening and was expected to remain on a stable dose (same type and regimen) throughout the study.
5. For entry into the Washout Period (for subjects who were currently on a VDR Activator and needed to complete a 2 to 12 week washout), the subject must have met the following laboratory criteria:
 - Corrected calcium value 8.2 mg/dL (2.05 mmol/L) and 10.5 mg/dL (2.63 mmol/L);
 - Phosphorus value 6.5 mg/dL (2.1 mmol/L);
 - intact parathyroid hormone (iPTH) value 130 pg/mL (13.7 pmol/L) and 2000 pg/mL (210.6 pmol/L).
6. For entry into the Dosing Period (for subjects that were naïve to VDR Activators or those who had completed a 2 to 12 week washout), the subject must have met the following laboratory criteria prior to enrollment:
 - Corrected calcium value 8.4 mg/dL (2.10 mmol/L) and 10.2 mg/dL (2.55 mmol/L);
 - Phosphorus value 6.5 mg/dL (2.1 mmol/L);
 - iPTH value > 300 pg/mL (31.6 pmol/L) and 2000 pg/mL (210.6 pmol/L).

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

1. Subject was expected or scheduled to receive a living donor kidney transplant within 3 months of Screening or is a kidney transplant patient requiring full immunosuppressant therapy.
2. Subject was expected to stop peritoneal dialysis or hemodialysis within 4 months of Screening (per investigator discretion).
3. Subject had had a parathyroidectomy within 12 weeks prior to Screening.
4. Subject had chronic gastrointestinal disease, which in the Investigator's opinion may have caused significant gastrointestinal malabsorption, including a small bowel transplant.
5. Subject had a history of active kidney stones within 4 months prior to Screening.
6. Subject had had symptomatic or significant hypocalcemia requiring VDR Activator therapy (i.e., calcitriol, paricalcitol, or doxercalciferol) within 2 months prior to Screening.
7. Subject was taking maintenance calcitonin, bisphosphonates, glucocorticoids in an equivalent dose of > 5 mg prednisone daily, or other drugs known to affect calcium or bone metabolism within 4 to 8 weeks prior to dosing.
8. Subject was receiving cinacalcet at the time of Screening.
9. Subject was taking prescription based phosphate supplements.

<p>Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:</p> <p>All subjects received paricalcitol capsules (1 µg or 2 µg strength), provided as soft gelatin capsules to be taken orally three times weekly (TIW), but never on consecutive days. The starting dose of paricalcitol in µg was calculated according to the following calculation:</p> $[\text{iPTH in p/mL}]/120 = \mu\text{g paricalcitol rounded down to the nearest whole number}$ <p>The paricalcitol dose was to be adjusted in order to maintain an iPTH level between 150 pg/mL (15.8 pmol/L) to 300 pg/mL (31.6 pmol/L), without exceeding 16 µg TIW.</p> <p>Manufacturing bulk lot numbers of paricalcitol capsules 1 µg were 10-002403 and 12-007086.</p> <p>Manufacturing bulk lot numbers of paricalcitol capsules 2 µg were 11-001181, 12-003770, and 12-007251.</p>
<p>Duration of Treatment: 12 weeks</p>
<p>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:</p> <p>None</p>
<p>Criteria for Evaluation</p> <p>Efficacy:</p> <p>Efficacy was not formally assessed in this study. Efficacy of paricalcitol was monitored as follows:</p> <ol style="list-style-type: none">(1) calculating the number of subjects with 2 consecutive iPTH values between 150 and 300 pg/mL and(2) calculating the number of subjects with 2 consecutive iPTH reductions of at least 30% from baseline. <p>Pharmacokinetic:</p> <p>Concentration of paricalcitol in plasma was calculated at each Week (2, 4, 6, 8, 10, and 12). Values for the pharmacokinetic parameters were summarized. Results of population pharmacokinetic analyses will be presented in a separate report.</p> <p>Safety:</p> <p>Safety was assessed by measuring the occurrences of hypercalcemia (2 consecutive serum calcium values > 10.2 mg/dL [2.55 mmol/L]). Additional safety was assessed by monitoring adverse events (AE), changes from baseline in blood chemistry, hematology, urinary laboratory analyses; changes from baseline in vital signs and physical examinations.</p>
<p>Statistical Methods</p> <p>Study M11-612 was a non-randomized, open-label study with a fixed sample size, wherein the sample size was not determined through a statistical power calculation; no statistical hypothesis testing was performed. The All-Treated Data set, which included all 13 subjects, was used for all evaluations.</p> <p>Efficacy:</p> <p>Efficacy was not formally analyzed. Frequency and percentages were provided for the 2 categorical efficacy variables and 95% confidence intervals (CI) were generated for parameter estimates of interest.</p> <p>Pharmacokinetic:</p> <p>Descriptive and summary statistics were used to evaluate pharmacokinetics.</p>

Statistical Methods (Continued)

Safety:

Frequency and percentages were provided for the occurrences of hypercalcemia and 95% confidence intervals (CI) were generated. 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.

Summary/Conclusions

During the study, 13 subjects received at least 1 dose of study drug. The median treatment duration was 83 days (range: 20 to 85 days). Of the 13 subjects, 11 (84.6%) remained on study drug for at least 8 weeks. Two subjects (15.4%) were discontinued: Subject 1498206 withdrew after the parents withdrew consent and Subject 5079601 discontinued because the subject had a kidney transplant. All 13 subjects were included in the analyses.

Efficacy Results:

During the study 5 subjects (38.5%) had 2 consecutive iPTH values between 150 and 300 pg/mL; 8/13 subjects (61.5%) did not, with a (95% CI: 13.9, 68.4). Among the 13 subjects, 8 (61.5%) had 2 consecutive iPTH reductions of at least 30% from baseline; 5/13 subjects (38.5%) did not (95% CI: 31.6, 86.1). Clinical chemistry assessments revealed that mean iPTH was reduced by 437 pg/mL (± 491.83 SD) from a baseline value of 883.6 pg/mL (± 373.81 pg/mL, SD).

Subjects reported a trend towards improvement in health outcomes as evidenced by the increase in scores on each of 6 parameters and the total score on the PedsQL™ 4.0 Questionnaire, as well as an increase in scores on 6 of 7 parameters and the total score on the PedsQL™ 3.0 Questionnaire End Stage Renal Disease Module. In contrast, parents/caregivers reported an overall trend towards worsening in health outcomes as evidenced by the decrease in scores on 5 of 6 parameters and the total score on the PedsQL™ 4.0 Questionnaire, as well as an decreases in scores on 3 of 7 parameters and the total score on the PedsQL™ 3.0 Questionnaire End Stage Renal Disease Module.

Pharmacokinetic Results:

The mean concentrations for paricalcitol for each week assessed were: Week 2: 0.08 ± 0.05 ng/mL; Week 4: 0.16 ± 0.19 ng/mL; Week 6: 0.16 ± 0.19 ng/mL; Week 8: 0.09 ± 0.12 ng/mL; Week 10: 0.16 ± 0.19 ng/mL; Week 12: 0.08 ± 0.08 ng/mL.

Summary/Conclusions (Continued)

Safety Results:

There were 2/13 subjects (15.3%) with hypercalcemia, defined as at least 2 consecutive calcium values > 10.2 mg/dL (2.55 mmol/L) during the study (95% CI: 1.9% – 45.4%).

Treatment-emergent AEs were reported for 11/13 subjects (84.6%) during the study. The AEs reported for more than one subject each were nausea, (2 subjects [15.4%]); pyrexia (2 subjects [15.4%]); and cough (2 subjects [15.4%]). One subject had AEs assessed as moderate; other AEs were reported as mild. Two subjects had serious adverse events (SAE; one case each of peritoneal dialysis complication and fluid overload); in each case the SAE was deemed unrelated to study drug by the investigator and resolved during the treatment period and the subject continued in the trial. Two AEs were considered by investigators to be possibly related to treatment (one case each of blood calcium increased and hyperphosphatemia); in each case the AE resolved during the treatment period and the subject continued in the trial. No subjects died during the study. No subject reported a pregnancy during the study.

There were no clinically significant mean changes from baseline in hematology, chemistry, urology, and vital sign variables. In addition few subjects had shifts from the baseline value to values outside the reference ranges for hematology, chemistry, or biochemical bone markers.

Conclusions:

Overall, 12-weeks of treatment with paricalcitol in pediatric subjects 12 – 17 years of age with CKD Stage 5 was observed to reduce iPTH without a significant number of hypercalcemia events and without new clinically concerning safety observations for paricalcitol.