



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of Dossier: Volume: Page:	(For National Authority Use Only)
Name of Study Drug: Paricalcitol (ABT-358) (Zemplar®)		
Name of Active Ingredient: Paricalcitol		
Title of Study: A Phase 3b, Randomized, Active-Controlled, Single-Blind, Multicenter Study to Evaluate the Safety and Efficacy of Paricalcitol Injection in Reducing Serum Intact Parathyroid Hormone Levels in Chronic Kidney Disease Stage 5 Subjects Receiving Hemodialysis		
Coordinating Investigator: Professor Jiaqi Qian [REDACTED] [REDACTED] China		
Study Sites: 11 sites in China		
Publications: None		
Studied Period (Years): First Subject First Visit: 27 November 2009 Last Subject Last Visit: 29 October 2010	Phase of Development: 3b	
Objectives: The primary purpose of this study was to evaluate the safety and efficacy of paricalcitol injection in reducing elevated serum iPTH levels in CKD Stage 5 subjects receiving HD in the Chinese population when using two different dosing regimens. The study sample size was determined to ensure the statistical power of performing the primary efficacy analysis of the study that was to evaluate the non-inferiority of the dosing regimen of paricalcitol injection with initial dose at 0.04 µg/kg as used in the United States (US) package insert against the dosing regimens of paricalcitol injection with initial dose based on iPTH/80 (the dosing regimen that is used in paricalcitol injection European Union [EU] package insert) in achieving at least two consecutive ≥ 30% decreases from baseline in iPTH in CKD Stage 5 HD subjects during 12 weeks of therapy. Secondary objectives of this study were to compare the two paricalcitol injection dosing regimens in the following efficacy or safety endpoints. <ol style="list-style-type: none">1. The proportion of subjects achieving a final iPTH value between 150 and 300 pg/mL.2. The change from baseline to the final observation in iPTH, calcium, and calcium-phosphorus product.3. The change from baseline to the final observation in vital signs.4. The proportion of subjects with two consecutive calcium measurements > 11.0 mg/dL (2.75 mmol/L).		



Methodology:

Study M06-823 was a Phase 3b, randomized, active-controlled, single-blind, multicenter study to evaluate the safety and efficacy of paricalcitol injection with two different dosing regimens (the approved dosing regimen based on the US package insert and dosing based on a the EU package insert (formula of $iPTH/80$) in CKD Stage 5 subjects with SHPT receiving HD. Approximately 214 subjects were to be randomized in a 1:1 ratio to one of two treatment groups: Group 1 - dosing based on the EU PI dosing instructions (starting dose based on the formula of $iPTH/80$, where $iPTH$ is the baseline value in pg/mL) and Group 2 - dosing determined by US paricalcitol injection package insert dosing instructions (starting dose $0.04 \mu g/kg$). A sufficient number of sites were recruited in order to randomize approximately 214 subjects.

The study was divided into five or four phases according to whether the subject was receiving VDR activators or not, respectively. If the subjects were receiving VDR activators, they participated in the following five phases: Washout Phase, Screening Phase, Pretreatment Phase, Treatment Phase, and Follow-up Phase. If the subjects had not received VDR activators for at least 2 weeks prior to the Screening Visit, they participated in the following four phases: Screening Phase, Pretreatment Phase, Treatment Phase, and Follow-up Phase.

Number of Subjects (Planned and Analyzed):

214 planned (107 in Group 1 and 107 in Group 2), 216 analyzed (108 in Group 1 and 108 in Group 2)

Diagnosis and Main Criteria for Inclusion:

Subjects were Chinese males or females ≥ 20 years old who were diagnosed with CKD Stage 5 and on maintenance hemodialysis TIW for at least 2 months prior to the Screening Visit and expected to remain on hemodialysis for the duration of the study. For entry into the Treatment Phase, the subject must have had $iPTH \geq 300 \text{ pg/mL}$, serum calcium measurement $< 10.2 \text{ mg/dL}$ (2.55 mmol/L), and $\text{Ca} \times \text{P} < 65 \text{ mg}^2/\text{dL}^2$.

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

The Paricalcitol Injection ($5 \mu g/mL$) dose was based on a formula of $iPTH/80$ (where $iPTH$ is the baseline value in pg/mL) or determined by US paricalcitol injection package insert dosing instructions (starting dose $0.04 \mu g/kg$). Paricalcitol injection was administered by intravenous or intracatheter bolus dose, 3 times per week and no more frequently than every other day.

The bulk lot number used in this study was 09-021870.

Duration of Treatment:

Subjects were to be treated with paricalcitol injection for a total of 12 weeks.

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

None



Criteria for Evaluation

Efficacy:

The primary efficacy endpoint was the achievement of two consecutive $\geq 30\%$ decreases from baseline iPTH levels.

The secondary efficacy endpoint was the proportion of subjects achieving a final iPTH value between 150 and 300 pg/mL.

Pharmacokinetic:

Pharmacokinetics were not evaluated in this study.

Safety:

Safety was assessed by the following variables:

- The incidence of adverse event and serious adverse events.
- The proportion of subjects with two consecutive calcium measurements > 11.0 mg/dL (2.75 mmol/L).
- Changes from baseline to final observation in complete chemistry and hematology measurements.
- Changes from baseline to final observation in vital signs.
- Repeated measures of change from baseline in iPTH, albumin, calcium, phosphorus and calcium phosphorus product to each post-baseline visit.
- Repeated measures of change from baseline in vital signs to each post-baseline visit.

Statistical Methods

Efficacy:

The primary efficacy analysis was to evaluate non-inferiority in the proportion of subjects achieving at least two consecutive $\geq 30\%$ decreases from baseline in iPTH between Group 1, the group of subjects receiving paricalcitol injection based on the EU package insert (starting dose based on formula $iPTH/80$) in comparison to Group 2, the group of subjects receiving paricalcitol injection based on the US package insert (starting dose $0.04 \mu\text{g}/\text{kg}$). Non-inferiority was tested by comparing the lower bound of a one-sided 97.5% confidence interval (using a normal approximation) for the between treatment group difference (Group 1 – Group 2) in the proportion of subjects achieving at least two consecutive $\geq 30\%$ decreases from baseline in iPTH with the non-inferiority margin, which is defined as -20% .

The secondary efficacy analysis was a comparison between treatment groups in the proportion of subjects that achieve a final iPTH in the interval 150 to 300 pg/mL using Fisher's exact test.



Statistical Methods (Continued):**Safety:**

The treatment group differences in safety endpoints were assessed by the following analyses:

- The incidence of adverse events and serious adverse events were analyzed by Fisher's exact test.
- The proportion of subjects with two consecutive calcium measurements > 11.0 mg/dL (2.75 mmol/L) were analyzed by Fisher's exact test.
- Changes from baseline to final observation in complete chemistry and hematology measurements were analyzed by ANOVA.
- Changes from baseline to final observation in vital signs were analyzed by ANOVA.
- Longitudinal measures of change from baseline in iPTH, albumin, calcium, phosphorous and calcium phosphorus product to each post-baseline visit were evaluated by repeated measures analysis.
- Longitudinal measures of change from baseline in vital signs to each post-baseline visit were evaluated by repeated measures analysis.

Summary/Conclusions**Efficacy Results:**

This study evaluated the efficacy of paricalcitol injection in reducing elevated serum iPTH levels in CKD Stage 5 subjects receiving hemodialysis when using 2 different dosing regimens for 12 weeks of treatment. The study population was similar across treatment groups.

The proportion of subjects achieving 2 consecutive decreases of at least 30% from baseline iPTH values was 88.6% in the group dosed by the EU PI and 55.9% in the group dosed by the US PI for the Per-Protocol population. Similar results were seen in the ITT population.

The proportion of subjects with final iPTH values between 150 and 300 pg/mL was similar between treatment groups. The proportion of subjects with final iPTH values in the KDIGO target range (130 to 585 pg/mL) was also similar between treatment groups. Only 1 subject experienced hypercalcemia (defined as 2 consecutive calcium measurements > 11.0 mg/dL) during the treatment period, so analyses in subjects without hypercalcemia showed similar results.

Statistically significantly greater decreases from baseline to final iPTH measurement were observed for the group dosed by the EU PI when compared with the group dosed by the US PI.

An exploratory analysis showed that higher doses of study drug administered had no statistically significant effect on the change from baseline to final measurement in hemoglobin.



Safety Results:

Overall, the safety evaluation revealed no clinically important differences between the group dosed by the EU PI and the group dosed by the US PI. The incidence of treatment-related AEs (i.e., considered possibly or probably related to study drug by the investigator) was similar between treatment groups (3.7% in the group dosed by the EU PI, 2.8% in the group dosed by the US PI). Pruritus was the only preferred term reported as possibly or probably related to study drug for more than 1 subject (2 in the group dosed by the EU PI, 0 in the group dosed by the US PI). There were no deaths, SAEs, or discontinuations due to AEs that were considered related to study drug.

Treatment-emergent AEs, regardless of relationship to study drug, were reported for 50 of the 216 subjects (23.1%): 29/108 (26.9%) in the group dosed by the EU PI and 21/108 (19.4%) in the group dosed by the US PI. Adverse events reported for at least 1.0% of subjects overall were upper respiratory tract infection (6.5%), diarrhea (1.9%), hypertension (1.9%), pyrexia (1.4%), hypoglycemia (1.4%), dizziness (1.4%), insomnia (1.4%), and pruritus (1.4%). There were no statistically significant differences between treatment groups for these events. The majority of AEs were assessed as mild or moderate by the investigator. Only 1 subject had a severe AE (cerebral hemorrhage).

One death, which was considered not related to study drug, was reported for a ■■■-year-old ■■■ in the group dosed by the US PI. This subject had a history of hypertension and diabetes and experienced a fatal cerebral hemorrhage. Other SAEs that were not considered treatment related were deafness neurosensory and myocardial ischemia, each reported for 1 subject in the group dosed by the US PI. Two additional subjects in the group dosed by the US PI had AEs that led to discontinuation of study drug (eyelid edema, lip edema, peripheral edema, abdominal discomfort, insomnia, and hypertension [not related to study drug] for 1 subject; and pyrexia [probably not related to study drug] for 1 subject).

There were statistically significantly greater mean increases in corrected calcium in the group dosed by the EU PI compared with the group dosed by the US PI during the first 8 weeks of treatment, and a statistically significantly greater mean increase in corrected calcium-phosphorus product in the group dosed by the EU PI compared with the group dosed by the US PI at Week 2. No other consistent or clinically important differences were observed between treatment groups for clinical laboratory or vital sign evaluations.

Conclusions:

The results of this study show the non-inferiority of paricalcitol injection dosed by the EU PI when compared with dosing by the US PI in reducing elevated serum iPTH levels in subjects with CKD receiving hemodialysis. Furthermore, this study showed the superiority of paricalcitol injection dosed by the EU PI. Overall, the safety, clinical laboratory, and vital sign evaluations showed no clinically important differences between treatment groups.