# 2.0 Synopsis

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| **AbbVie Corporation** | **Individual Study Table Referring to Part of Dossier:** | **(For National Authority Use Only)** |
| **Name of Study Drug:** Paricalcitol injection (ABT 358) | **Volume:** | |
| **Name of Active Ingredient**: Paricalcitol injection (ABT 358) | **Page:** | |

**Title of Study:** Comparison of Efficacy and Safety of Paricalcitol Injection with Maxacalcitol Injection in Adult Japanese Chronic Kidney Disease Subjects Receiving Hemodialysis with Secondary Hyperparathyroidism

**Investigator:** Jun Niwayama and others

**Study Site:** [redacted] Clinic Hospital and others

**Publications:** N/A

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|---|---|
| **Studied Period (Years):**<br>First Subject First Visit: 9 May 2011<br>Last Subject Last Visit: 17 April 2012 | **Phase of Development:** 3 |

**Objective:** The primary objective of the study was to demonstrate noninferiority of paricalcitol injection to maxacalcitol injection in the composite endpoint, which is the proportion of subjects who had iPTH in the target range of 60 to 180 pg/mL based on the average iPTH obtained in the last 3 visits and with no hypercalcemia during treatment phase. If noninferiority was demonstrated, a superiority analysis also was to be performed on the composite endpoint.

**Methodology:** Study M11-517 was a double-blind, double-dummy, parallel-group, non-inferiority study comparing paricalcitol injection with maxacalcitol injection on iPTH control in subjects with CKD with SHPT who are undergoing hemodialysis. The study consisted of a 1- to 2-week washout period for subjects who were receiving vitamin D therapy and any other prohibited medication immediately before signing the informed consent, followed by Screening for all subjects. Eligible subjects were registered and randomly allocated to 1 of 2 treatment groups (paricalcitol or maxacalcitol). Dynamic allocation of subjects on the basis of Screening iPTH level was employed to ensure equal distribution of subjects with iPTH < 500 pg/mL and those with ≥ 500 pg/mL into the 2 treatment groups.

Subjects received both the Drug P and Drug M, as this was a double-dummy study

| | **Drug P (Vials)** | | **Drug M (Ampoules)** | |
|---|---|---|---|---|
| **Group** | **Paricalcitol** | **Paricalcitol Placebo** | **Maxacalcitol** | **Maxacalcitol Placebo** |
| Paricalcitol | X | | | X |
| Maxacalcitol | | X | X | |

**Methodology (Continued):**

The initial dose was 2 µg for paricalcitol and 5 µg (iPTH < 500 pg/mL at Screening) or 10 µg (iPTH ≥ 500 pg/mL at Screening) for maxacalcitol, as follows. A maximum of 5 dose increases were possible. Therefore, the maximum dose of paricalcitol was 7 µg, and the maximum dose of maxacalcitol was 20 µg, as stipulated in its approved package insert.

| Group | Initial Dose | Titration Dose |
|---|---|---|
| Paricalcitol | 2 µg (1 mL) | ± 1 µg (0.5 mL) |
| Maxacalcitol | 5 µg (1 mL) or 10 µg (2 mL) | ± 2.5 µg (0.5 mL) |

The initial dose continued for 2 weeks, and the subsequent dose was adjusted (temporarily stop dose, decrease, maintain, increase, or resume) on the basis of the dose adjustment criteria shown below. The timing for dose adjustment was as follows.

| Ca (adjusted)[a], P levels | iPTH Level | Dose Adjustment |
|---|---|---|
| Ca > 11.0 mg/dL or<br>2 consecutive Ca ≥ 10.5 mg/dL | Any | Temporarily stop dosing.<br>Resume dosing at 0.5 mL of Drug P and Drug M after iPTH > 180 pg/mL, Ca < 10.2 mg/dL, and phosphorus < 7.0 mg/dL. |
| Any | < 60 pg/mL | |
| Ca ≥ 10.5 mg/dL or 2 consecutive phosphorus ≥ 7.0 mg/dL | ≥ 60 pg/mL | Decrease doses by 0.5 mL of both Drug P and Drug M.<br>If the doses decrease to 0 mL, resume dosing at 0.5 mL of both drugs after iPTH > 180 pg/mL, Ca < 10.2 mg/dL, and phosphorus < 7.0 mg/dL. |
| Ca < 10.5 mg/dL and 2 consecutive phosphorus are not ≥ 7.0 mg/dL | 60 to < 120 pg/mL | Decrease doses by 0.5 mL of both Drug P and Drug M.<br>If the doses decrease to 0 mL, resume dosing at 0.5 mL of both drugs after iPTH > 180 pg/mL, Ca < 10.2 mg/dL, and phosphorus < 7.0 mg/dL. |
| | ≥ 120 to ≤ 180 pg/mL | 1) Decrease doses of Drug P and Drug M by 0.5 mL if iPTH level has decreased compared with the previous week.<br>If the doses decrease to 0 mL, resume dosing at 0.5 mL of both drugs after iPTH > 180 pg/mL, Ca < 10.2 mg/dL, and phosphorus < 7.0 mg/dL.<br>*or*<br>2) Maintain current doses of both drugs if iPTH level has not decreased compared with the previous week. |
| Ca < 0.5 mg/dL and phosphorus ≥ 7.0 mg/dL (not consecutive) | > 180 pg/mL | Maintain current doses. |
| Ca < 10.5 mg/dL and phosphorus < 7.0 mg/dL | > 180 pg/mL | Increase doses of Drug P and Drug M by 0.5 mL. |

**Methodology (Continued):**

Ca = calcium; iPTH = intact parathyroid hormone

a. Payne's formula: Adjusted Ca = serum Ca + (4 – serum albumin), when serum albumin is ≥ 4 g/dL.

Note: Dosing was to be decreased or held immediately at the first opportunity of the week and was to be increased at the first dialysis session of the next week. Doses were to be increased no more frequently than every other week and a dose decrease was allowed every week. A decrease in iPTH from the previous week was interpreted by the sites to mean a clinically meaningful decrease.

**Number of Subjects (Planned and Analyzed):** 252 subjects (126 in each treatment group, paricalcitol and maxacalcitol) were planned and a total of 255 subjects (127 subjects to the paricalcitol group and 128 subjects to the maxacalcitol group) were randomized. All 255 subjects were included in FAS and Safety Analysis Set, and 237 subjects (119 subjects to the paricalcitol group and 118 subjects to the maxacalcitol group) were included in primary efficacy population, PPS.

**Diagnosis and Main Criteria for Inclusion:** The study population consisted of male or female subjects with CKD receiving hemodialysis and with SHPT who met the inclusion criteria and none of the exclusion criteria described.

[Main inclusion criteria]

1. Patients with CKD who are receiving hemodialysis are the target population.
2. There is a possibility that delaying the initiation of the dose may affect the efficacy evaluation.
3. To represent CKD subjects with SHPT receiving hemodialysis, an iPTH value of ≥ 300 pg/mL has been set as a criterion. Adjusted calcium of ≥ 8.4 to < 10.2 mg/dL has been set by reference to the Japanese SHPT guideline (the target range of 8.4 to 10.0 mg/dL) and Kidney Disease Outcomes Quality Initiative (KDOQI) guideline (change of treatment should be considered at the level of adjusted calcium > 10.2 mg/dL). The target range of phosphorus is 3.5 to 6.0 mg/dL and change of treatment should be considered when phosphorus rises above 7.0 mg/dL according to the Japanese SHPT guideline. Meanwhile, a survey by the Japanese Dialysis Society in 2005 showed that 32.4% of patients had phosphorus levels > 6.0 mg/dL in actual medical practice. Given this situation, phosphorus of ≤ 6.5 mg/dL has been determined.
4. There is limited experience with the use of paricalcitol in patients younger than 20 years of age.

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

| Label | Identification | Packaging | Bulk Lot Numbers |
|---|---|---|---|
| Drug P | Paricalcitol injection | 1 vial (1 mL) contains 2 µg of paricalcitol | 95-625-DK |
| | Paricalcitol placebo | 1 mL of placebo | 95-260-DK |

**Duration of Treatment:** 12 weeks

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

| Label | Identification | Packaging | Bulk Lot Numbers |
|---|---|---|---|
| Drug M | Maxacalcitol injection | 1 ampoule (1 mL) contains 5 µg of maxacalcitol | 10F050A |
| | Maxacalcitol placebo | 1 mL of placebo | 10S01 |

**Criteria for Evaluation:**

**Efficacy:**

The primary efficacy endpoint was the proportion of subjects with iPTH in the target range of 60 to 180 pg/mL, based on the average iPTH obtained in the last 3 weeks and with no hypercalcemia during treatment phase.

The secondary efficacy endpoints were follows:

- The proportion of subjects with ≥ 50% reduction in iPTH from Baseline to the average iPTH obtained in the last 3 weeks without hypercalcemia during treatment phase.
- The proportion of subjects within target range of 60 to 180 pg/mL based on the average iPTH obtained in the last 3 weeks.
- The proportion of subjects with a ≥ 50% reduction in iPTH from Baseline to the average iPTH obtained in the last 3 weeks.
- Frequency of iPTH control defined as ≥ 50% reduction in iPTH from Baseline.
- Frequency of iPTH control defined as in the target range of 60 to 180 pg/mL.

**Pharmacokinetic:** Pre-dose paricalcitol concentrations were to be measured (at the end of dose interval). Population mixed effects modeling techniques were to be used to estimate population central values for paricalcitol and maxacalcitol clearance (CL) and volume of distribution (V). Conditional post-hoc estimates of CL and V for individual subjects was to be determined. Additional parameters were to be estimated if useful in the interpretation of the data. Relationships between exposure (concentration) and clinical observations (primary efficacy variable or other efficacy and safety variables) were to be explored. The results of pharmacokinetics were shown in other reports.

**Safety:** Safety was evaluated on the basis of adverse events, including abnormalities of hematology and biochemistry tests, vital signs, 12-lead ECG, and physical examinations. In particular, the following variables were assessed:

- The incident rate of hypercalcemia (at least 1 adjusted calcium > 11.0 mg/dL or at least 2 consecutive adjusted calcium ≥ 10.5 mg/dL).
- The incident rate of hyperphosphatemia (at least 2 consecutive phosphorus ≥ 7.0 mg/dL).
- Mean changes of calcium (adjusted), phosphorus, and Ca × P from Baseline.

**Statistical Methods:**

**Efficacy:**

Primary Efficacy Analysis: The primary efficacy analysis was to test the non-inferiority of paricalcitol compared with maxacalcitol in a composite endpoint defined as the proportion of subjects who achieve iPTH in the target range of 60 to 180 pg/mL based on the average iPTH obtained in the last 3 weeks and with no hypercalcemia during treatment phase. The non-inferiority test was carried out through the generation of a lower limit for a 1-sided 97.5% confidence interval (CI) for the between–treatment group difference (paricalcitol–maxacalcitol) in the proportion of subjects achieving the composite endpoint using a normal approximation. If the lower limit of the observed 1-sided 97.5% CI was greater than –5%, then non inferiority was demonstrated. Superiority was shown if the lower limit of the 95% CI exceeds 0%. The PPS was used for this analysis.

**Statistical Methods (Continiued):**

Secondary Efficacy Analyses:

1. Evaluation of the primary efficacy endpoint as specified above but using the ITT population FAS.
2. Comparison between treatment groups in the proportion of subjects with ≥ 50% reduction in iPTH from baseline based on the average iPTH obtained in the last 3 weeks and with no hypercalcemia during treatment phase.
3. Comparison between treatment groups in the proportion of subjects who achieve iPTH in the target range of 60 to 180 pg/mL based on the average iPTH obtained in the last 3 weeks.

Comparison between treatment groups in the proportion of subjects with ≥ 50% reduction in iPTH from Baseline based on the average iPTH obtained in the last 3 weeks.

**Safety:**

Adverse events

Analyses of adverse events include only "treatment-emergent" events (i.e., those that first occur or worsen after the first dose of study drug). Each adverse event as collected was mapped to a primary Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and a preferred term (PT) according to the MedDRA adverse event coding dictionary. Adverse events were summarized by treatment group and overall as described below:

1. An overview of the number and percentage of subjects with treatment-emergent adverse events.
2. A summary of the number and percentage of subjects with treatment-emergent adverse events by MedDRA SOC and PT.
3. A summary of the number and percentage of subjects with treatment-emergent serious adverse events by MedDRA SOC and PT.
4. A summary of the number and percentage of subjects with treatment-emergent adverse events leading to discontinuation by MedDRA SOC and PT.
5. A summary of the number and percentage of subjects with possibly or probably drug-related treatment-emergent adverse events by MedDRA SOC and PT.
6. A summary of the number and percentage of subjects with treatment-emergent nonserious adverse events by MedDRA SOC and PT.
7. A summary of the number and percentage of subjects with treatment-emergent adverse events by MedDRA SOC, PT, and maximum relationship to study drug (i.e., highest relationship rating of probably related, possibly related, probably not related, or not related for an event that is reported more than once during the analysis period by a subject).
8. A summary of the number and percentage of subjects with treatment-emergent adverse events by MedDRA SOC, PT, and maximum severity (i.e., highest severity rating of severe, moderate, or mild for an event that is reported more than once during the analysis period by a subject).

The treatment group comparability in the percentage of subjects experiencing adverse events in items 1 through 6 above was evaluated using Fisher's exact test.

Hypercalcemia

A comparison between treatment groups in the proportion of subjects with at least 1 calcium > 11.0 mg/dL or 2 consecutive calcium values ≥ 10.5 mg/dL was performed using Fisher's exact test.

**Statistical Methods (Continiued):**

Hyperphosphatemia

A comparison between treatment groups in the proportion of subjects with 2 consecutive phosphorus values ≥ 7.0 mg/dL was performed using Fisher's exact test.

Laboratory parameters

For all laboratory parameters listed in the protocol, changes (and percentage change for iPTH) from Baseline to final observations in the Treatment Period was analyzed using an ANOVA with the fixed effect of treatment group. Type III sum-of-squares for the least squares means was used.

Where it was applicable to categorize a laboratory assessment by normal, high, or low according to the normal range provided by the central laboratory, the normal, high, or low status at the final observation was summarized in relation to the normal, high, or low status at Baseline by treatment group using the number and percentage within each cross classification category.

Limited chemistry measurement (iPTH, calcium, phosphorus, and albumin) were collected at scheduled visits during the treatment period. For each limited chemistry variable, a mixed-effects repeated-measures (MERM) analysis using all the longitudinal observations across the visits was used to evaluate treatment group differences in the change from Baseline to each postbaseline visit. The model included the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline measurements and baseline-by-visit interaction. The covariance structure was unstructured, unless it caused convergence issues for some variables. In such a situation, the following structures were considered, and the structure converging to the best fit as determined by Akaike's information criteria was used: spatial power, heterogeneous Toeplitz, heterogeneous compound symmetry, and heterogeneous AR(1). The Kenward-Roger method was used to estimate the denominator degrees of freedom. Type III sum-of-squares for the least squares means was also used. Analyses were implemented using SAS PROC MIXED.

The least squares mean change from Baseline to each postbaseline visit for iPTH, calcium, and phosphorus, albumin as generated by the repeated-measures analysis, was plotted by treatment group.

Change from Baseline to final observations for vital sign variables was evaluated using a 1-way ANOVA model with treatment group as the factor. In addition, a MERM analysis of vital sign data was performed using the same model as that used for the longitudinal data analyses described above for limited chemistry variables.

**Summary/Conclusions**

**Efficacy Results:**

The primary efficacy endpoint (proportion of subjects with iPTH in target range of 60 to 180 pg/mL based on the average iPTH obtained in the last 3 weeks and with no hypercalcemia during the treatment period) in PPS was 27.7% in paricalcitol group and 30.5% in maxacalcitol group. The paricalcitol group did not demonstrate noninferiority since the lower limit of the observed 1-sided 97.5% CI was –15.16% and this was greater than the –5% noninferioirty margin.

**Safety Results:**

The frequency of reported adverse events in the paricalcitol group (93.7%) was similar to that in the maxacalcitol group (96.9%). The frequencies of "at least possibly drug related" adverse events, "at least probably not drug related" adverse events, severe adverse events, hypercalcemia, and hyperphosphatemia

**Safety Results (Continiued):**

were also similar in both groups. The frequencies of serious adverse events and adverse events leading to discontinuation in the maxacalcitol group (11.7% and 7.0%) were slightly higher than in the paricalcitol group (7.9% and 3.9%), but the differences were not statistically. No deaths were reported in this study. Adverse events were reported for 119 subjects (93.7%) in the paricalcitol group and for 124 subjects (96.9%) in the maxacalcitol group. A statistically significantly greater percentage of subjects receiving paricalcitol than those receiving maxacalcitol experienced excoriation (7.1% versus 1.6%, P = 0.034). Half of subjects in both group experienced adverse events considered possibly or probably related to study drug (paricalcitol group, 46.5%; maxacalcitol group, 50.0%). The most common adverse event considered possibly or probably related to study drug in both group was hypercalcaemia (38.6% in the paricalcitol group and 42.2% in the maxacalcitol group) and hyperphosphataemia (7.9% and 5.5%, respectively). Severe sinus bradycardia was reported in 1 subject in the paricalcitol group, and severe renal disorder in pregnancy (renal transplantation due to primary disease as "renal disorder in pregnancy") was reported in 1 subject in maxacalcitol group. These severe adverse events also met the criteria for serious adverse events.

No subject died during the study. Ten subjects (7.9%) in the paricalcitol group and 15 subjects (11.7%) in the maxacalcitol group experienced at least 1 serious adverse event. None of the serious adverse events was statistically significantly different in incidence between treatment groups. Serious adverse events reported for at least 2 subjects overall were shunt stenosis, nausea, and shunt occlusion. Serious nausea and shunt occlusion were reported only in the maxacalcitol group. Five subjects (3.9%) in the paricalcitol group and 9 subjects (7.0%) in the maxacalcitol group experienced at least 1 adverse events leading to discontinuation of study drug. None of the adverse events leading to discontinuation of study drug was statistically significantly different in incidence between treatment groups. Adverse events leading to discontinuation of study drug reported for at least 2 subjects overall were nausea and hypocalcaemia.

Mean changes from Baseline in hematology variables were not statistically significantly different between treatment groups. Mean changes from Baseline in most chemistry variables generally were not statistically significantly different between treatment groups. Alkaline phosphatase and BSAP, however, showed larger decreases for the maxacalcitol group than for the paricalcitol group that were statistically significantly different ($P < 0.001$, $P = 0.003$, respectively). For iPTH, subjects in the paricalcitol group showed gradual decreases through Week 7, which stablized afterward. Subjects in the maxacalcitol group showed a relatively rapid decrease by Week 4, which stablized afterward. The changes from Baseline for corrected calcium, phosphorus, Ca × P, and iPTH at the final visit were not statistically significantly different between treatment groups. Forty-seven subjects (37.0%) in the paricalcitol group and 51 subjects (39.8%) in the maxacalcitol group experienced hypercalcemia defined as at least 1 corrected calcium value > 11.0 mg/dL or at least 2 corrected calcium values ≥ 10.5 mg/dL. Seventeen subjects (13.4%) in the paricalcitol group and 14 subjects (10.9%) in the maxacalcitol group experienced hyperphosphatemia defined as at least 2 consecutive phosphorus values ≥ 7.0 mg/dL. These differences between treatment groups were not statistically significant.

Overall, the safety profile for paricalcitol and maxacalcitol was similar, and paricalcitol was generally well tolerated.

**Conclusions:**

The noninferiority of paricalcitol injection compared with maxacalcitol injection was not demonstrated in this study. The safety profiles for paricalcitol and maxacalcitol were similar, and paricalcitol was generally well tolerated.