



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of Dossier: Volume: Page:	(For National Authority Use Only)
Name of Study Drug: ABT-358/Paricalcitol		
Name of Active Ingredient: ABT-358/Paricalcitol		
Title of Study: Late Phase II Study of Paricalcitol Injection Dose-response study of paricalcitol injection in chronic kidney disease subjects receiving hemodialysis with secondary hyperparathyroidism (Examination of initial dose and incremental dose)		
Investigator: Nobuo Hashimoto and others, total 29 personnel		
Study Sites: 29 sites in Japan		
Publications: None		
Study Period: First Subject First Visit: 31 Mar 2008 Last Subject Last Visit: 18 Mar 2009		Phase of Development: 2
Objective: To examine the dose response (initial dose and incremental dose) of paricalcitol injection in chronic kidney disease (CKD) subjects receiving hemodialysis (HD) with secondary hyperparathyroidism (SHPT) in order to select an appropriate dosing regimen for phase III study.		
Methodology: This was a multicenter, randomized, open-label trial in patients with chronic kidney disease on hemodialysis who had complicated secondary SHPT to investigate the initial dose and the dose adjustment range of Paricalcitol injection. A dose-adjustment regimen with an open-label design was applied for this trial, with four Paricalcitol injection groups (the initial dose and dose adjustment range were $2 \pm 1 \mu\text{g}$, $2 \pm 2 \mu\text{g}$, $4 \pm 1 \mu\text{g}$ and $4 \pm 2 \mu\text{g}$, respectively) and a maxacalcitol group (the initial dose and dose adjustment range were $5 \mu\text{g} \pm 2.5 \mu\text{g}$ or $10 \mu\text{g} \pm 2.5 \mu\text{g}$) as a reference group. Although this was a dose-response study of Paricalcitol injection, the maxacalcitol group was used as a reference group to evaluate the effect of Paricalcitol with another vitamin D formulation in iPTH suppression. Prior to any study procedures the informed consent was obtained from the subject. Subjects who have been receiving vitamin D or cinacalcet were to have a washout period for 1 to 2 weeks before screening. Subjects who met the inclusion criteria were randomized equally to one of the treatment groups. In randomization, iPTH values at the screening ($< 500 \text{ pg/mL}$ or $\geq 500 \text{ pg/mL}$) were used as a dynamic allocation factor. Study drugs were administered 3 times weekly (every other day) from the venous end of the hemodialysis circuit just before completion of the dialysis session. The initial doses were continued for 2 weeks, followed by dose adjustments (increase, maintenance, decrease, suspension, or resumption) by $1 \mu\text{g}$ or $2 \mu\text{g}$ unit for the Paricalcitol groups and by $2.5 \mu\text{g}$ unit for the maxacalcitol group based on iPTH, calcium (adjusted) and phosphorus values every 2 weeks. Subjects in Paricalcitol groups were		



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Methodology (Continued): to be suspended from the treatment when the iPTH value decreased to < 60 pg/mL in accordance with the “Guidelines for the management of secondary hyperparathyroidism in chronic dialysis patients”. On the other hand, the dose adjustment criteria based on iPTH values for the maxacalcitol group were set according to the package insert of maxacalcitol (suspended when iPTH decreased to ≤ 150 pg/mL). The study was not designed to perform statistical comparisons of the safety and efficacy between the Paricalcitol and maxacalcitol groups.		
Number of Subjects (Planned and Analyzed): Planned : 150 subjects (120 subjects for paricalcitol group and 30 subjects for maxacalcitol group) Analyzed: 152 subjects (122 subjects for paricalcitol group and 30 subjects for maxacalcitol group) and 153 subjects (123 subjects for paricalcitol group and 30 subjects for maxacalcitol group) were included in the efficacy analysis and safety analysis, respectively.		
Diagnosis and Main Criteria for Inclusion: Male or female chronic kidney disease subjects receiving hemodialysis with secondary hyperparathyroidism who met the inclusion criteria and did not meet any of the exclusion criteria described below. <u>Inclusion Criteria</u> 1. Patients diagnosed with chronic kidney disease receiving hemodialysis three times a week for at least 3 months prior to obtaining the informed consent and scheduled to be receiving the same hemodialysis during the study period. 2. Patients had been using dialysate with constant concentration of calcium for 4 weeks prior to obtaining informed consent and phosphate binder with constant dose regimen for 2 weeks prior to obtaining informed consent. 3. Subject must have satisfied the following levels of iPTH, calcium (adjusted) and phosphorus by the screening test. <ul style="list-style-type: none">● iPTH: ≥ 300 pg/mL● Calcium (adjusted): ≥8.4-< 10.2 mg/dL● Phosphorus: ≤ 6.5 mg/dL 4. ≥ 20 years of age (on obtaining informed consent) <u>Exclusion Criteria</u> 1. Subjects with a history of allergic reaction or significant sensitivity to vitamin D or vitamin D related compounds. 2. Subjects who received a parathyroidectomy or ethanol infusion within one year prior to obtaining the informed consent. 3. Subjects with a progressive malignancy or clinically significant hepatic diseases (e.g., three times or more of the upper limit of normal range of serum glutamic-oxaloacetic transaminase [AST] and serum glutamic-pyruvic transaminase [ALT]).		



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<p>4. Subjects with severe cerebral/cardiovascular diseases (e.g., cardiovascular diseases designated to New York Heart Association [NYHA] Class III and IV (██████████), life-threatening arrhythmia, cerebrovascular disease, cardiac failure, cardiac infarction, angina pectoris).</p> <p>5. Subjects with severe hypertension (mean resting supine systolic and diastolic blood pressures before dialysis at 6 dialysis sessions prior to obtaining the informed consent: ≥ 180 mmHg and ≥ 110 mmHg, respectively).</p> <p>6. Subjects with uncontrolled diabetes mellitus (e.g., mean HbA1c $\geq 8\%$ for three months prior to obtaining IC).</p> <p>7. Subjects with a history of drug or alcohol abuse within 6 months prior to obtaining the informed consent.</p> <p>8. Subjects who are taking calcitonin, maintenance intravenous or oral glucocorticoids, cinacalcet, bisphosphonates, SERM, vitamin D compounds (other than study drug), or other drugs that may affect calcium or bone metabolism (other than estrogen or progestin, vitamin K2).</p> <p>9. Subjects who will need to take chronic dose (≥ 2 consecutive weeks) of cytochrome P450 (CYP3A) inhibitors (e.g., clarithromycin, grapefruit products) or inducers (e.g., carbamazepine, rifampycin).</p> <p>10. Patients who are taking aluminum containing products (2 weeks prior to IC).</p> <p>11. Patients who have experience of administration of paricalcitol in the past.</p> <p>12. Subjects who have participated in clinical trials of other investigational drugs or medical devices within 3 months prior to obtaining the informed consent.</p> <p>13. Female subjects who are pregnant, possibly pregnant, wish to become pregnant, or breastfeeding during the study period.</p> <p>14. For any reason, subjects who are judged to be inappropriate as a subject for this study by the investigator or sub-investigator.</p>		
Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: Test Product: Paricalcitol Injection Vial: 2 μ g/mL Dose: 4 treatments (initial dose and dose adjustment : 2 \pm 1 μ g, 2 \pm 2 μ g, 4 \pm 1 μ g, 4 \pm 2 μ g, respectively) Mode of Administration: Three times per week (no more frequently than every other day; e.g. Mon, Wed, Fri or Tue, Thu, Sat) at immediately before the completion of hemodialysis through intravenous-catheter of dialysis. Lot Number: 60-333-DK, Package Number: RV3A		
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: Reference Therapy: Maxacalcitol Injection Ampule: 5 μ g/mL Dose: Initial dose and dose adjustment : 5 or 10 \pm 2.5 μ g Mode of Administration: Three times per week (no more frequently than every other day; e.g. Mon, Wed, Fri or Tue, Thu, Sat) at immediately before the completion of hemodialysis through intravenous-catheter of dialysis. Lot Number: A7J04, Package Number: RV3B		
Duration of Treatment: 12 weeks		



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Criteria for Evaluation		
Efficacy: Primary Endpoint: The proportion of subjects with $\geq 50\%$ decrease from baseline in iPTH at the final visit. Secondary Endpoints: <ul style="list-style-type: none">● The mean change of iPTH from baseline at the final visit● The proportion of subjects with iPTH measurement ≤ 180 pg/mL at the final visit● The proportion of subjects with two or more $\geq 50\%$ decrease from baseline in iPTH during the treatment phase● The time course change of iPTH level during the treatment phase● The duration of two consecutive iPTH $\geq 50\%$ decrease● The duration of two consecutive iPTH ≤ 180 pg/mL		
Safety: Safety was evaluated based on adverse events including abnormalities of hematology & biochemistry tests, vital signs, ECG, physical examinations. In particular the following items were focused. <ul style="list-style-type: none">● The incident rate of hypercalcemia (at least one adjusted calcium > 11.5 mg/dL or at least two consecutive adjusted calcium ≥ 11.0 mg/dL)● The incident rate of hyperphosphatemia (at least two consecutive phosphorus ≥ 7.0 mg/dL)● Mean changes of calcium (adjusted), phosphorus and Ca\timesP from baseline		
Statistical Methods No statistical hypothesis testing was performed.		
Efficacy: The primary efficacy endpoint was evaluated in both FAS and PPS population of each group. The secondary efficacy endpoints were evaluated in FAS population of each group. Baseline of iPTH was defined as the measurement at Screening.		
Safety: Safety was evaluated based on adverse events including abnormalities of hematology & biochemistry tests, vital signs, ECG, physical examinations. In particular the following items were focused. The incident rate of hypercalcemia (at least one adjusted calcium > 11.5 mg/dL or at least two consecutive adjusted calcium ≥ 11.0 mg/dL), and the incident rate of hyperphosphatemia (at least two consecutive phosphorus ≥ 7.0 mg/dL)The number and proportion of subjects experiencing treatment emergent adverse event was counted by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Drug Regulatory Affairs (MedDRA) in FAS of each group. A summary of adverse events by severity and causal relationship to study drug was presented. The narrative of all serious adverse events observed was described regardless of its causal relationship to the study drug. Continuous variables were summarized		



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<p>by treatment group with the number of observations, mean, mean change, standard deviation, first quartile, median, third quartile, minimum and maximum. Discrete variables were summarized by frequency and proportion. The change and percent change in Ca (adjusted), P and Ca×P were summarized by treatment group with the number of observations, mean, mean change, standard deviation, first quartile, median, third quartile, minimum and maximum. Baseline of calcium (adjusted), phosphorus and Ca×P were defined as the measurement at Screening and baseline of other clinical laboratories were defined as the last measurement before the first dose (Week 1).</p>		
<p>Summary/Conclusions</p> <p>Efficacy Results:</p> <ul style="list-style-type: none">● In tabulation of the FAS, the proportion of subjects with $\geq 50\%$ decrease from baseline in iPTH at the final visit, the primary endpoint, 53.3%, 41.9%, 38.7% and 56.7% for the $2 \pm 1 \mu\text{g}$, $2 \pm 2 \mu\text{g}$, $4 \pm 1 \mu\text{g}$ and $4 \pm 2 \mu\text{g}$ groups, respectively. Higher proportion of the subjects achieved primary end point in $2 \pm 1 \mu\text{g}$ and $4 \pm 2 \mu\text{g}$ group. The proportion of subjects with primary end points was 43.3% for the maxacalcitol group. The tabulation results for the PPS were also similar.● Regarding the mean change of iPTH from baseline at the final visit, the iPTH values at the final visit was -233.2 pg/mL, -260.8 pg/mL, -178.2 pg/mL and -211.7 pg/mL for the $2 \pm 1 \mu\text{g}$, $2 \pm 2 \mu\text{g}$, $4 \pm 1 \mu\text{g}$ and $4 \pm 2 \mu\text{g}$ groups, respectively, showing a decrease of iPTH from baseline at the final visit in all of the Paricalcitol groups. The mean decrease of iPTH from baseline was -236.6 pg/mL for the maxacalcitol group.● The proportion of subjects with iPTH measurement $\leq 180 \text{ pg/mL}$ at the final visit was 36.7%, 32.3%, 32.3% and 36.7% for the $2 \pm 1 \mu\text{g}$, $2 \pm 2 \mu\text{g}$, $4 \pm 1 \mu\text{g}$ and $4 \pm 2 \mu\text{g}$ groups, respectively, being almost similar for all groups. The proportion of subjects with iPTH measurement $\leq 180 \text{ pg/mL}$ at the final visit was 33.3% for the maxacalcitol group.● In tabulation of the FAS, the proportions of subjects with two or more $\geq 50\%$ decrease from baseline in iPTH during the treatment phase was 90.0%, 100%, 90.3% and 90.0% for the $2 \pm 1 \mu\text{g}$, $2 \pm 2 \mu\text{g}$, $4 \pm 1 \mu\text{g}$ and $4 \pm 2 \mu\text{g}$ groups, respectively. Most of the subjects who received Paricalcitol exhibited two or more $\geq 50\%$ decrease from baseline in iPTH during the treatment phase. In addition, 93.3% of subjects in the maxacalcitol group showed two or more $\geq 50\%$ decrease from baseline in iPTH during the treatment phase.● In the Paricalcitol groups included in the FAS, the mean iPTH values increased from baseline to Week 1, followed by a decrease over time. Except $2 \pm 1 \mu\text{g}$ group, iPTH was gradually increased on or after Week 4 to Week 8. In $2 \pm 1 \mu\text{g}$ group, iPTH level on or after Week 7 was stable and was almost less than 50% compared to the baseline (from Week 7 to Week 13, iPTH was 223.3 to 274.3 pg/mL). In the maxacalcitol group, the mean iPTH showed little change from baseline to Week 1. The iPTH value decreased from Week 1 to Week 3, and the mean iPTH became generally increased after Week 4.● The mean duration of two consecutive iPTH $\geq 50\%$ decrease was 23.8 days, 27.7 days, 29.0 days and 25.2 days for the $2 \pm 1 \mu\text{g}$, $2 \pm 2 \mu\text{g}$, $4 \pm 1 \mu\text{g}$ and $4 \pm 2 \mu\text{g}$ groups, respectively, being almost similar in all the groups. The mean duration of two consecutive iPTH $\geq 50\%$ decrease was 10.9 days for the maxacalcitol group.		



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<ul style="list-style-type: none">The mean duration of two consecutive iPTH \leq 180 pg/mL was 22.0 days, 26.1 days, 19.7 days, and 17.2 days for the $2 \pm 1 \mu\text{g}$, $2 \pm 2 \mu\text{g}$, $4 \pm 1 \mu\text{g}$ and $4 \pm 2 \mu\text{g}$ groups, respectively, being almost similar for all the groups. The mean duration of two consecutive iPTH \geq 50% decrease was 3.1 days for the maxacalcitol group.		
Safety Results: <ul style="list-style-type: none">The incident rate of adverse events were 100%, 93.5%, 96.8% and 93.5% for the $2 \pm 1 \mu\text{g}$, $2 \pm 2 \mu\text{g}$, $4 \pm 1 \mu\text{g}$ and $4 \pm 2 \mu\text{g}$ groups, respectively, and 95.9% in total, being almost similar across the groups. The incidence rate of adverse event in maxacalcitol group was 96.7%. Adverse events with an incident rate of \geq 5% in the total Paricalcitol groups by preferred term were hypercalcemia (60.2%), nasopharyngitis (30.1%), hyperphosphatemia (27.6%), hypertension (8.9%), diarrhoea (7.3%), constipation (6.5%) and headache (6.5%).The incident rate of adverse events thought to be at least “possibly related” to the study drug was 50.0%, 71.0%, 74.2% and 77.4% for the $2 \pm 1 \mu\text{g}$, $2 \pm 2 \mu\text{g}$, $4 \pm 1 \mu\text{g}$ and $4 \pm 2 \mu\text{g}$ groups, respectively, and 68.3% for the total Paricalcitol groups, and the incident rate was lower in the $2 \pm 1 \mu\text{g}$ group by \geq 20% than in the other three groups. The incident rate of adverse events thought to be at least “probably not related” to the study drug was 66.7%, 77.4%, 80.6% and 80.6% for the $2 \pm 1 \mu\text{g}$, $2 \pm 2 \mu\text{g}$, $4 \pm 1 \mu\text{g}$ and $4 \pm 2 \mu\text{g}$ groups, respectively, and 76.4% in total. The incident rate of adverse events thought to be at least “possibly related” and at least “probably not related” to the study drug in maxacalcitol group were both 60.0%.Severe adverse events occurred in one subject each in the $2 \pm 2 \mu\text{g}$ and $4 \pm 1 \mu\text{g}$ groups. The incident rate of moderate adverse events was lower in the $2 \pm 1 \mu\text{g}$ group than in the other three groups.No deaths were observed.The incident rate of serious adverse events was 3.3% (1/30 subjects), 6.5% (2/31 subjects), 9.7% (3/31 subjects) and 6.5% (2/31 subjects) for the $2 \pm 1 \mu\text{g}$, $2 \pm 2 \mu\text{g}$, $4 \pm 1 \mu\text{g}$ and $4 \pm 2 \mu\text{g}$ groups, respectively, and 6.5% (8/123 subjects) in total. In the maxacalcitol group, serious adverse events occurred in 6.7% (2/30 subjects). All these serious adverse events were judged as “not related” to the study drug. Serious adverse events which were severe in severity were spinal osteoarthritis in one subject in the $2 \pm 2 \mu\text{g}$ group, and muscular weakness and iliac artery occlusion in one subject in the $4 \pm 1 \mu\text{g}$ group. One subject in the $2 \pm 2 \mu\text{g}$ group discontinued the trial due to spinal osteoarthritis. Except for a serious adverse event in one subject, all serious events resolved within the trial period.An adverse event leading to discontinuation (spinal osteoarthritis) occurred in one subject in the $2 \pm 2 \mu\text{g}$ group. This adverse event was judged as “not related” to the study drug and severe in severity, and it resolved in 120 days after the onset.The incident rate of hypercalcemia was 30.0%, 48.4%, 45.2% and 58.1% for the $2 \pm 1 \mu\text{g}$, $2 \pm 2 \mu\text{g}$, $4 \pm 1 \mu\text{g}$ and $4 \pm 2 \mu\text{g}$ groups, respectively, being lowest in the $2 \pm 1 \mu\text{g}$ group. The incident rate of hypercalcemia in the maxacalcitol group was 30.0%.		



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<ul style="list-style-type: none">● The incident rate of hyperphosphatemia was 10.0%, 9.7%, 9.7% and 19.4% for the $2 \pm 1 \mu\text{g}$, $2 \pm 2 \mu\text{g}$, $4 \pm 1 \mu\text{g}$ and $4 \pm 2 \mu\text{g}$ groups, respectively, being similar except for the $4 \pm 2 \mu\text{g}$ group for which the incidence was high. The incident rate of hyperphosphatemia in the maxacalcitol group was 13.3%.● For the $2 \pm 1 \mu\text{g}$ group, mean changes of calcium (adjusted) from baseline were less than 1 mg/dL at all measurement weeks. In addition, the change over time of calcium (adjusted) in the $2 \pm 1 \mu\text{g}$ group showed a mild increase compared to the other groups, being less than 10 mg/dL at all measurement week.● The mean change of P for $2 \pm 1 \mu\text{g}$ group was slightly larger than the other paricalcitol groups, which was less than 0.5 mg/dL. Regarding the mean change of phosphorus from baseline, measured values for the $2 \pm 1 \mu\text{g}$ and $4 \pm 1 \mu\text{g}$ groups were less than 5.5 mg/dL at all measurement weeks.● Mean changes of $\text{Ca} \times \text{P}$ from baseline were greater for the $4 \pm 2 \mu\text{g}$ group than for the other groups at most of the measurement weeks, and tended to be smaller for the $2 \pm 1 \mu\text{g}$ and $4 \pm 1 \mu\text{g}$ groups than for the other groups. Measured values of $\text{Ca} \times \text{P}$ for the $2 \pm 1 \mu\text{g}$ group were less than $55 \text{ mg}^2/\text{dL}^2$ at all measurement weeks.● Laboratory values and vital signs showing a marked change from baseline were Al-P, BSAP and neutral fat. Decreases in Al-P and BSAP were greatest for the $2 \pm 1 \mu\text{g}$ group while decreases in neutral fat were greater for $2 \pm 1 \mu\text{g}$ group and $4 \pm 1 \mu\text{g}$ group than for the other groups.		
Conclusions: The initial dose and the dose adjustment range for Paricalcitol injection were investigated in patients with chronic kidney disease on hemodialysis who had SHPT. Based on the efficacy and safety results, it was concluded that the initial dose of $2 \mu\text{g}$ and the dose adjustment range of $\pm 1 \mu\text{g}$ were the recommended dose of Paricalcitol.		