



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: Phase II Study of Paricalcitol Injection - Extension long-term safety study of paricalcitol injection in chronic kidney disease subjects receiving hemodialysis with secondary hyperparathyroidism		
Investigator: Nobuo Hashimoto and others, total 29 personnel		
Study Sites: 29 sites in Japan		
Publications: None		
Study Period: First Subject First Visit: 9 July 2008 Last Subject Last Visit: 4 December 2009		Phase of Development: 2
Objective: To evaluate the long-term safety and efficacy of paricalcitol injection in chronic kidney disease (CKD) subjects receiving hemodialysis (HD) with secondary hyperparathyroidism (SHPT)		
Methodology: <p>This was a multicenter, open-label, extension study from phase IIb study (M10-309). Subjects allocated to paricalcitol groups in the phase IIb study (dose-response study) and completed it with good tolerability to paricalcitol injection were enrolled, and the long-term safety and efficacy of paricalcitol injection was evaluated.</p> <p>Visit week was calculated from Study M10-309, thus the start week in this study was Week 13. Informed consent was obtained in subjects who were treated with paricalcitol with good tolerability at Week 11 in Study M10-309. At Week 13, subjects were treated with paricalcitol. The dosage at Week 13 was determined based on the Ca (adjusted), P, and iPTH at Week 12. On or after Week 14, the dosage was determined based on the Ca (adjusted), P, and iPTH at previous week. Dose adjustment included temporarily stopping, dose reduction, maintain, dose escalation, and re-dose. The treatment period was 40 weeks (overall 52 weeks from Study M10-309). The study drug will be administered three times a week (no more frequently than every other day) immediately before the completion of hemodialysis through intravenous-catheter of dialysis.</p> <p>During the study, efficacy and safety evaluation were performed. All adverse events reported from the time of study drug administration until 30 days, following discontinuation of study drug administration had elapsed were collected, whether elicited or spontaneously reported by the subject. In addition, serious adverse events were collected from the time the subject signed the study-specific informed consent.</p>		



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Dose adjustment (Protocol version 1.0 to 2.1)				
Ca (adjusted), P levels		iPTH	Dose adjustment	
Ca >11.5 mg/dL or 2 consecutive Ca ≥11.0 mg/dL		—	stop	Resume dosing at 1 or 2 µg after iPTH ≥ 180 pg/mL, Ca < 10.2 mg/dL and P < 7.0 mg/dL
—		<60 pg/mL		
Ca ≥11.0 mg/dL or 2 consecutive P ≥7.0 mg/dL		≥60 pg/mL	decrease	Decrease dose by 1 or 2 µg. (If the dose reaches 0 µg: Resume dosing at 1 or 2 µg after iPTH ≥ 180 pg/mL, Ca < 10.2 mg/dL and P < 7.0 mg/dL)
Ca <11.0 mg/dL and P ≥7.0 mg/dL		≥60 pg/mL	maintain	Maintain the current dose
Ca <11.0 mg/dL and P <7.0 mg/dL		≥60 ~ ≤180 pg/mL		
Dose adjustment (Protocol version 3.0)				
Ca (adjusted), P levels		iPTH	Dose adjustment	
Ca >11.5 mg/dL or 2 consecutive Ca ≥11.0 mg/dL		—	stop	Resume dosing after iPTH ≥ 180 pg/mL, Ca < 10.2 mg/dL and P < 7.0 mg/dL, from 1 µg if iPTH ≥180 to <500 pg/mL, 2 µg if iPTH ≥500 pg/mL
—		<60 pg/mL		
Ca ≥11.0 mg/dL or 2 consecutive P ≥7.0 mg/dL		≥60 pg/mL	decrease	Decrease dose by 2 µg. (If the dose reaches 0 µg: Resume dosing iPTH ≥ 180 pg/mL, Ca < 10.2 mg/dL and P < 7.0 mg/dL, from 1 µg if iPTH ≥180 to <500 pg/mL, 2 µg if iPTH ≥500 pg/mL)
Ca <11.0 mg/dL and P ≥7.0 mg/dL, or P <7.0 mg/dL		≥60~<120 pg/mL		
Ca <11.0 mg/dL and P ≥7.0 mg/dL, or P <7.0 mg/dL		≥120~≤180 pg/mL	Decrease (1 µg) or Maintain	Decrease by 1 µg if iPTH decreased. If the dose reaches 0 µg: Resume dosing iPTH ≥ 180 pg/mL, Ca < 10.2 mg/dL and P < 7.0 mg/dL, from 1 µg if iPTH ≥180 to <500 pg/mL, 2 µg if iPTH ≥500 pg/mL. Maintain the current dose if iPTH increased or stable.
Ca <11.0 mg/dL and P ≥7.0 mg/dL		>180 pg/mL	maintain	Maintain the current dose



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Ca \geq 10.5 ~ <11.0 mg/dL and P <7.0 mg/dL			
Ca <10.5 mg/dL and P <7.0 mg/dL	>180~<500 pg/mL	increase	Increase dose by 1 μ g
	\geq 500 pg/mL	increase	Increase dose by 2 μ g
Number of Subjects (Planned and Analyzed):			
Planned: 100 subjects or more			
Analyzed: 104 subjects and 106 subjects 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. Subjects who completed the dose-response study (M10-309).			
2. Subjects who were allocated to paricalcitol groups in the dose-response study.			
3. Subjects who showed well tolerance to paricalcitol injection in the dose-response study.			
<u>Exclusion Criteria</u>			
1. Subjects who have a plan or a high possibility to receive parathyroidectomy or ethanol infusion during the study.			
2. Subjects who showed 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]) during the period of the dose-response study.			
3. Subjects who showed 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) during the period of the dose-response study.			
4. Subjects who showed severe hypertension (mean resting supine systolic and diastolic blood pressures of 6 measurements during the treatment phase of the dose-response study are \geq 180 mmHg and \geq 110 mmHg, respectively) during the period of the dose-response study.			
5. Subjects who showed uncontrolled diabetes mellitus (e.g., HbA1c \geq 8%, the average during M10-309) during the period of the dose-response study.			
6. Subjects who will need to take 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) during study period.			



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Diagnosis and Main Criteria for Inclusion (Continued): 7. Subjects who will need to take chronic dose (≥ 2 consecutive weeks) cytochrome P450 (CYP3A) inhibitors (e.g., clarithromycin, grapefruit products) or inducers (e.g., carbamazepine, rifampin). 8. Subjects who have a plan or a high possibility that the study drug cannot be administered for 2 or more consecutive weeks due to subject's personal reason (e.g., travel). 9. Female subjects who are pregnant, possibly pregnant, wish to become pregnant, or breastfeeding during the study period. 10. For any reason, subjects who are judged to be inappropriate as a subject for this study by the investigator or sub-investigator.			
Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: Test Product: Paricalcitol Injection Vial: 2 $\mu\text{g/mL}$ Dose: The dose at Week 13 will be determined based on iPTH, adjusted Ca and P at Week 12 according to the dose adjustment. The subsequent dose will be adjusted every 2 weeks based on the iPTH, Ca and P levels. 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: RV5A			
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: None			
Duration of Treatment: 40 weeks			
Criteria for Evaluation Efficacy: The clinical efficacy was evaluated according to the following variables. <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 $\geq 50\%$ decrease from baseline in iPTH 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● The proportion of subjects whose abnormal alkaline phosphatase or BSAP at baseline is normalized at the final visit			



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<p>Safety:</p> <p>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.</p> <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×P from baseline 		
<p>Statistical Methods</p> <p>The objective of this clinical study is to examine the long-term safety of paricalcitol injection in chronic kidney disease subjects receiving hemodialysis with secondary hyperparathyroidism. In addition, this clinical study is performed by open-label manner in subjects who completed the dose-response study and were allocated to paricalcitol groups in the dose-response study, and showed well tolerance to paricalcitol injection in the dose-response study. Therefore, the safety and efficacy in this study will be evaluated including the results of the dose-response study.</p> <p>Efficacy:</p> <p>Since the primary objective of this clinical study is to evaluate the long-term safety of paricalcitol injection, efficacy endpoints are not divided to primary and secondary endpoint. The data obtained at screening in the dose-response study will be adopted as a baseline.</p> <p>Safety:</p> <p>The number and proportion of subjects experiencing treatment emergent adverse event will be counted by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Drug Regulatory Affairs (MedDRA ver.11.0) in FAS. A summary of adverse events by severity and causal relationship to study drug will be presented. The narrative of all serious adverse events observed will be described regardless of its causal relationship to the study drug. The number and proportion of subjects experiencing hypercalcemia (at least one adjusted calcium > 11.5 mg/dL or at least two consecutive adjusted calcium 11.0 mg/dL) will be analyzed regardless of assessment of the investigator or sub-investigators. In addition, the number and proportion of subjects experiencing hyperphosphatemia (at least two consecutive phosphorus 7.0 mg/dL) will be analyzed regardless of assessment of the investigator or sub-investigator. Continuous variables will be summarized by the number of observations, mean, mean change, standard deviation, first quartile, median, third quartile, minimum and maximum. Discrete variables will be summarized by frequency and proportion. The change and percent change in Ca (adjusted), P and Ca×P will be summarized by 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 will be defined as the measurement at Screening and baseline of other clinical laboratories will be defined as the last measurement before the first dose (Week 1).</p>		



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Summary/Conclusions Efficacy Results: <ul style="list-style-type: none">● The mean change of iPTH at the final visit from baseline was 226.4 pg/mL, showing a decrease at the final visit from baseline. The mean iPTH in each phase increased from baseline to Week 1 (before study drug administration), followed by a decrease over time to Week 8. Furthermore, the mean iPTH increased from Week 9 to Week 17 (328.4 pg/mL). Then the value slightly decreased from Week 19, and remained in the range of 245 – 300 pg/mL from Week 21 onwards.● The proportion of subjects with iPTH measurement ≤ 180 pg/mL at the final visit was 40.4%. The proportion of subjects with iPTH measurement at the final visit decreased by $\geq 50\%$ from the baseline was 55.8%, and the proportion of subjects who showed two consecutive iPTH $\geq 50\%$ decrease during the treatment phase was 99.0%.● The mean duration of two consecutive iPTH $\geq 50\%$ decrease was 44.0 days, and the mean duration of two consecutive iPTH ≤ 180 pg/mL was 28.3 days.● Of the subjects with abnormality in AI-P or BSAP, AI-P returned to the normal (within the normal range) in 50.0% (9/18 subjects) and BSAP in 65.7% (23/35 subjects) at the final visit. <p>These results demonstrated the long-term efficacy of Paricalcitol injection in patients with chronic kidney disease on hemodialysis who had SHPT.</p>		



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Safety Results: <ul style="list-style-type: none">● The incident rate of adverse events in the Safety Set was 100% (106/106 subjects). There were a total of 63 adverse events with an incident rate of $\geq 3\%$ by preferred term. Adverse events with high incidence ($\geq 10\%$) were hypercalcemia (72.6%), nasopharyngitis (66.0%), hyperphosphatemia (61.3%), diarrhoea (21.7%), constipation (18.9%), contusion (18.9%) hypertension (17.9%), pruritus (17.0%), headache (16.0%), arthralgia (15.1%), back pain and haemorrhage subcutaneous (13.2% each), procedural hypotension (11.3%), and fall and hypercalcaemia (10.4% each).● The incident rate of adverse events for which a causal relationship to the study drug could not be ruled out (at least “probably not related”) was 91.5%. Adverse events thought to be “probably not related” to the study drug with an incident rate of $\geq 3\%$ were hypercalcaemia (71.7%), hyperphosphataemia (46.2%), hypertension (9.4%), pruritus (5.7%), diarrhoea and muscle spasms (3.8% each). At least probably not drug related adverse events with at least 3 % of increase of incidence in Study M10-312 compared to Study M10-309 were hyperphosphataemia (21.7% in Study M10-309 and 46.2% in Study M10-312) and hypertension (2.8% and 9.4%). Considering with the study duration (12 weeks of Study M10-309 and 48 weeks of Study M10-312), these differences were not deem to be clinically important.● Severe adverse events occurred in 5.7% (6 subjects). Of these, severe adverse events for which a causal relationship to the study drug could not be ruled out occurred in 2.8% (3 subjects) (Subject [REDACTED], arteriosclerosis obliterans; [REDACTED], sudden death; [REDACTED], interstitial lung disease). All the severe adverse events for which a causal relationship to the study drug could not be ruled out were serious.● In this trial, death was reported in three subjects. Of these, two subjects died during the safety evaluation period.● The incident rate of serious adverse events during the study period was 22.6% (24/106 subjects). Of the serious adverse events by preferred term, events which occurred in two or more subjects were shunt occlusion (3 subjects, 2.8%), and myocardial infarction, pneumonia, shunt occlusion, and arteriosclerosis obliterans (2 subjects, 1.9% each). Eight serious adverse events for which a causal relationship to the study drug could not be ruled out occurred in six subjects (“probably related”: arteriosclerosis obliterans; “probably not related”: cerebral infarction; cardiac failure, angina pectoris and myocardial infarction; arteriosclerosis obliterans; sudden death; interstitial lung disease).● Adverse events leading to discontinuation occurred in only two subjects (1.9%).● The incident rate of hypercalcemia was 57.5%. The proportion of the subjects who developed hypercalcemia was high during Week 6 - 13 with its peak of 20.8% in Week 8 - 9. In Week 14 and thereafter that are the study period of Study M10-312, the proportion of the subject who developed hypercalcemia remained less than 7%.● The incident rate of hyperphosphatemia was 35.8%. The proportion of the subjects who developed hyperphosphatemia remained at 10% or less throughout the study period.		



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<ul style="list-style-type: none">● The mean change of calcium (adjusted) from baseline increased over time from Week 1 (0.05 mg/dL), and remained within the range of 0.50 - 1.02 mg/dL from Week 4 of administration onwards. The mean change at Week 53 was 0.75 mg/dL. The percent change of calcium (adjusted) from baseline also increased over time from Week 1 (0.47%), and remained within the range of 5.47—11.07% of increase from Week 4 of treatment onwards.● The mean change of phosphorus from baseline increased from Week 1 to Week 53. The mean change at Week 53 was 0.69 mg/dL. The mean percent changes showed the same trend, and the mean percent change of phosphorus from baseline at Week 25 onwards remained over 10% of increase except Week 31.● The mean change of Ca × P from baseline increased from Week 1 (0.61 mg²/dL²), and remained within the range of 5.79 - 10.64 mg²/dL² from Week 4 of treatment onwards, being 10.64 mg²/dL² at Week 53.● There were no clinically relevant changes in laboratory values or vital signs of the Safety Set throughout the study period.		
Conclusions: The safety and efficacy of long-term administration of Paricalcitol injection in patients with chronic kidney disease on hemodialysis who had SHPT were investigated. The results of this trial indicated that there were no problems in the safety of long-term administration of Paricalcitol injection. The efficacy of the long-term administration was also demonstrated.		