2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Paricalcitol	**Volume:**	
Name of Active Ingredient: Paricalcitol	**Page:**	
Title of Study: The PRIMO II Study: Paricalcitol Injection Benefits in Renal Failure Induced Cardiac Morbidity in Subjects with Chronic Kidney Disease Stage 5		
Coordinating Investigator: [redacted] Redacted information - 9Jun2014		
Study Sites: This study was conducted at 10 sites in the United States, Europe, and Taiwan.		
Publications: none		
Studied Period (Years): First Subject First Visit: 28 January 2009 Last Subject Last Visit: 22 May 2009	**Phase of Development:** 3	
Objectives: The overall objective of this Phase 3 study was to evaluate the effects of paricalcitol injection on cardiac structure and function over 48 weeks in subjects with Stage 5 chronic kidney disease (CKD) receiving hemodialysis who had left ventricular hypertrophy (LVH). <u>Primary Objective</u> To investigate the effects of paricalcitol injection on progression or regression of LVH in subjects with Stage 5 CKD receiving hemodialysis compared to placebo, as assessed by comparing changes in left ventricular mass index (LVMI) over 48 weeks measured by sequential cardiac magnetic resonance imaging (MRI).		

Objectives (Continued):

:Secondary Objectives

1. Echocardiographic assessment of diastolic function was to be assessed by evaluating changes in diastolic mitral annular relaxation velocity (E') and changes in additional measures of diastolic function (IVRT, E/E', DT).
2. Changes in progression of aortic atherosclerosis, aortic compliance, left ventricular end-systolic volume index, left ventricular end-diastolic volume index, and left ventricular ejection fraction from baseline to Week 24 and Week 48 were to be assessed by MRI.
3. Changes in biological and inflammatory markers that have been linked to cardiovascular disease in CKD subjects. Specifically, the markers to be evaluated were to include plasma triiodothyronine (T3), interleukin-6 (IL-6), troponin-T, B-type natriuretic peptide (BNP) and high sensitivity C-reactive protein (hsCRP).

Methodology:

This Phase 3, randomized, double-blind, placebo-controlled trial was designed to investigate the effects of paricalcitol injection on changes in cardiac structure and function over 48 weeks in subjects with Stage 5 CKD receiving hemodialysis who had LVH. A subject's total participation in the study was approximately 58 weeks. A total of 75 US and ex-US sites were selected in order to enroll approximately 220 subjects (110 per treatment group).

The study was conducted in 3 periods as discussed below, a Screening Period, Treatment Period, and a Follow-up Period.

Screening Period

The Screening Period consisted of 3 visits and occurred within 6 weeks prior to the subject randomization and enrollment into the Treatment Period of the study. The procedures performed at the first visit were to obtain informed consent, discontinue any use of active vitamin D therapy (as applicable), call into an Interactive Voice Response System (IVRS) for assignment of a screening number, record serious adverse events (SAEs), record concomitant medications, obtain vital signs, collect laboratory specimens for limited chemistry (including intact parathyroid hormone [iPTH]) and serum pregnancy test (for female subjects of childbearing potential), and schedule the screening echocardiogram.

The screening echocardiogram was to be conducted on a non-dialysis day after verification that the subject met all of the laboratory criteria. The report from the [redacted] was used to determine a potential subject's eligibility for the study. Echocardiograms that were not technically adequate could be repeated once.

Redacted information - 9Jun2014

Methodology (Continued):

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Screening Period (Continued)

If the subject met all inclusion and none of the exclusion criteria, and all screening lab and echocardiogram requirements had been met, a cardiac MRI was obtained in order for the subject to be randomized into the Treatment Period. The cardiac MRI was to occur within the 6 week Screening Period on a non-dialysis day. The cardiac MRI was performed at [redacted] which confirmed that it was technically adequate. Cardiac MRIs that were not technically adequate could be repeated once within the 6 week screening period. If a technically adequate cardiac MRI could not be obtained, the subject was not randomized into the study.

Treatment Period

There were 10 scheduled visits during the Treatment Period occurring at Treatment Day 1 and Weeks 4, 8, 12, 18, 24, 30, 36, 42, and 48. Aside from Treatment Day 1, all treatment visits occurred at the end of the treatment week during the same day of the week. There was to be a ± 5 day window period maintained around the study visits.

Subjects who qualified for the study had their Treatment Day 1 procedures performed prior to their dialysis session. The sites called into the IVRS on Treatment Day 1 to obtain the randomization number and the assignment of the study drug kit number(s) for the subject. Following randomization, subjects received the study drug (paricalcitol injection or matching placebo) intravenously 3 times per week (TIW) during dialysis and continued in the Treatment Period for the next 48 weeks. The starting dose of paricalcitol injection (or equivalent volume of placebo) was 4 μg TIW (total of 12 μg/week). Subsequent doses were adjusted based on clinical laboratory parameters, specifically serum calcium (Ca). Dose of study drug was decreased or discontinued at any time during the study if, in the judgment of the Investigator, there was a risk to subject safety. Dose of study drug was not to be increased during the study.

Methodology (Continued):

Treatment Period

The first visit, Treatment Day 1, captured baseline laboratory values that included collection of blood samples (under fasting conditions) for complete chemistry (including iPTH and lipid profile [cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL)]), serum pregnancy test for females, hematology, DNA/RNA samples (if separate consent was given), plasma protein binding samples, and serum biological/inflammatory markers. Treatment Day 1 procedures also included obtaining vital signs, recording of all adverse events (AEs) (serious and non-serious) and concomitant medications, obtaining medical history, conducting a physical exam, and completing a Standard SF-36v2™ Health Survey and a Work Productivity and Activity Impairment – General Health Questionnaire (WPAI GH). Study drug was also administered on Treatment Day 1 during dialysis. A subject's dose of RAAS inhibitors, such as angiotensin converting enzyme inhibitors (ACEis) and/or angiotensin II receptor blockers (ARBs) therapy and/or aldosterone blockers were to be kept stable or maintained at an equivalent dose one month prior to the Screening Period through the end of the study. If a subject was started on or they received an increased dose of RAAS inhibitor therapy during the course of the study, they were to be removed from the study. Interruption of RAAS inhibitors was permitted for up to 6 weeks during the course of the study if the Investigator deemed it to be medically necessary; however, interruption > 6 weeks was to result in the subject's discontinuation from the study. Following an interruption of RAAS inhibitor therapy, the subject was to be returned to the previous regimen of RAAS inhibitor therapy that was previously prescribed. If the subject's blood pressure was > 130/80 mmHg, non-RAAS inhibitors anti-hypertensive medication were to be added at the discretion of the Investigator to obtain acceptable blood pressure control based on current guidelines.

Procedures performed at Treatment Weeks 4, 8, 12, 18, 30, 36, and 42 included obtaining vital signs, collection of blood samples for limited chemistry (including iPTH), recording of all AEs (serious and non-serious) and concomitant medications, and performing study drug accountability. During Treatment Weeks 4, 8, 12, 18, 30, 36, and 42 visits, a call into IVRS was made to receive the assignment of the study drug kit number(s) for the subject. Study drug was administered during dialysis.

Procedures performed at Treatment Weeks 24 and 48 or Early Termination visits included collection of cardiac MRI and echocardiogram. The cardiac MRI and the echocardiogram occurred ± 1 week from Week 24 and Week 48 (or at the time of early discontinuation) on a non-dialysis day. If a subject discontinued within 6 weeks of their last cardiac MRI or echocardiogram, a discontinuation cardiac MRI/echocardiogram was not performed. Additional procedures to be performed at Treatment Week 24 and Treatment Week 48/Early Termination visits included obtaining vital signs, collection of blood samples (under fasting conditions) for complete chemistry (including iPTH and lipid profile), hematology, biological/inflammatory markers, RNA samples, completion of a Standard SF-36v2™ Health Survey questionnaire and a WPAI-GH, recording of all AEs (serious and non-serious) and concomitant medications, and performing study drug accountability.

Methodology (Continued):

Follow-up Period

For subjects who successfully completed the Treatment Period or prematurely discontinued from the study, the Follow-up Period consisted of a phone call to the subject 30 days after the last treatment visit was completed. Procedures performed during this period included recording of all AEs (serious and non-serious) and concomitant medications.

Ambulatory Blood Pressure Exploratory Sub-Study:

As part of this study there was an exploratory substudy to assess ambulatory blood pressure; however, no subjects were enrolled into the substudy.

Number of Subjects (Planned and Analyzed):

Planned: 220 subjects; Analyzed: 12

Diagnosis and Main Criteria for Inclusion:

To be eligible for participation, subjects had to be Stage 5 CKD receiving chronic hemodialysis three times per week for ≥ 3 months and ≤ 12 months from date of Randomization (Day 1); for entry into the Treatment Period, the subject had to satisfy the criteria based on the Screening laboratory values for serum iPTH value between 100 and 350 pg/mL, serum calcium level between 8.4 and 10.5 mg/dL (2.1 - 2.6 mmol/L), and phosphate < 7 mg/d, serum albumin ≥ 3.0 g/dL (30 g/L); for entry into the Treatment Period, the subject had to satisfy the criteria based on the Screening echocardiogram for females, left ventricular (LV) ejection fraction ≥ 50% and septal wall thickness between 11 to 17 mm; and for males, LV ejection fraction ≥ 50% and septal wall thickness between 12 and 18 mm.

To be eligible for participation, subjects must not have met any of the exclusion criteria including active vitamin D therapy (e.g., calcitriol, paricalcitol, doxercalciferol, alfacalcidol), subjects on vitamin D therapy for a total duration greater than 3 months since the start of dialysis; subject had clinically significant coronary artery disease within 3 months prior to the Screening Period; subject had major cardiac valve abnormality linked with LVH and/or diastolic dysfunction; subject had asymmetric septal hypertrophy; and subject had a severe cerebrovascular accident within the last 3 months (e.g., hemorrhagic) prior to screening.

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

Paricalcitol Injection: Solution for IV for injection (5 mcg/mL in 2-mL vials)

Bulk Lot Number: 08-017983 and MMID Number D0600235

Paricalcitol Injection: Solution for IV for injection (5 mcg/mL in 1-mL ampules)

Bulk Lot Number: 07-013870 and MMID D0500076.

Blinded supplies (vials): Lot Number: 08-018705 - Expiry date - 30 April 2010.

Blinded supplies (ampules): Lot Number: 07-014822 - Expiry date - 31 May 2009.

Duration of Treatment:

48 weeks

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

Placebo for Paricalcitol: Solution for IV injection (2 mL vials)

Bulk Lot Number: 08-018014 - MMID D0600236

Placebo for Paricalcitol: Solution for IV injection (1 mL ampules)

Bulk Lot Number: 07-013871and MMID D0500075

Blinded supplies (vials): Lot Number: 08-018705 - Expiry date - 30 April 2010.

Blinded supplies (ampules): Lot Number: 07-014822 - Expiry date - 31 May 2009.

Criteria for Evaluation

Efficacy:

Primary efficacy variable:

The primary efficacy variable was to be change from baseline in LVMI over 48 weeks measured by cardiac MRI. Left ventricular mass was to be normalized to the subject's height by the following equation to obtain LVMI: LVM (g) divided by height (m).

Secondary efficacy variables were to be:

- Echocardiographic assessment of diastolic function, assessed through evaluation of changes in diastolic mitral annular relaxation velocity (E') and changes in additional measures of diastolic function (IVRT, E/E', DT).
- Changes in progression of aortic atherosclerosis, aortic compliance, left ventricular end systolic volume index, left ventricular end-diastolic volume index, and left ventricular ejection fraction from baseline to Week 24 and Week 48 as assessed by MRI.
- Changes in biological and inflammatory markers that have been linked to CVD in CKD subjects. Specifically, the markers to be evaluated were to include T3, IL-6, troponin-T, BNP and hsCRP.
- Changes in laboratory measurements: iPTH and bone-specific alkaline phosphatase.
- Number of hospitalizations: any hospitalization, as well as cardiac and noncardiac-related hospitalizations; and the respective length of stays.
- Time to first hospitalization (any hospitalization), first cardiac-related hospitalization, and non-cardiac-related hospitalization.
- Overall, cardiac, and non-cardiac-related mortality rates.
- Changes in the global domains and sub-domains of Standard SF-36v2 Health Survey questionnaire from baseline to Week 24 and Week 48.
- Changes in work productivity from baseline to Week 24 and Week 48 as measured by WPAI-GH.

Criteria for Evaluation Continued):

Safety:

Safety assessment was of treatment-emergent adverse events (TEAEs) including severity and relationship of study drug, change in chemistry and hematology measurements, and change from baseline in vital signs.

TEAEs were defined as any event that worsened after first administration of study drug, and any event with an onset date that was after the first dose of study drug until 30 days following administration of study drug. SAEs were collected from the time the subject signed the informed consent.

Statistical Methods

Data were summarized using descriptive statistics. No formal statistical analyses were conducted.

Efficacy:

The study was prematurely terminated due to low enrollment. Analysis of efficacy was not done because with the premature termination of the study, it was not possible to evaluate the effects of paricalcitol injection on progression or regression of LVH in subjects with Stage 5 CKD receiving hemodialysis compared to placebo, as assessed by comparing changes in LVMI over 48 weeks measured by sequential cardiac MRI. Efficacy analyses on the secondary efficacy end points were also not performed since only 12 subjects were enrolled in the study.

Safety:

The number and percentage of the subjects who reported at least one TEAE and for each of the events were summarized by treatment group. Adverse events were also summarized descriptively with counts and percentages by severity (using the most severe episode) and relationship to study drug as indicated by the Investigator (using the most likely relationship to study drug).

Clinical laboratory data were summarized with mean change from Baseline to the minimum, maximum, and final values during paricalcitol blinded treatment. Vital signs were analyzed similarly. Serum Ca measurements used in the analyses were corrected to an albumin level of 4.0 g/dL.

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 status at the final observation was compared with that at the baseline and the "shifts" (i.e., changed from baseline category) were summarized by treatment group.

Summary/Conclusions

Efficacy Results:

The study was prematurely terminated due to low enrollment. Analysis of efficacy was not done because with the premature termination of the study, it was not possible to evaluate the effects of paricalcitol injection on progression or regression of LVH in subjects with Stage 5 CKD receiving hemodialysis compared to placebo, as assessed by comparing changes in left ventricular mass index (LVMI) over 48 weeks measured by sequential cardiac MRI. Efficacy analyses on the secondary efficacy end points were also not performed since only 12 subjects were enrolled in the study.

Safety Results:

Three subjects from each treatment group experienced at least one TEAE. As assessed by the investigator, none were possibly or probably related to study drug and all were mild or moderate in severity. No deaths were reported during the study. No severe AEs, serious AEs, or AEs leading to discontinuation were reported during the study. Mean changes from Baseline in laboratory and vital signs evaluations were clinically unremarkable. Shifts from normal to high and normal to low were infrequent.

Conclusions:

Study M10-221 was a Phase 3, randomized, double-blind, placebo-controlled, multi-center study to investigate the effects of paricalcitol injection on changes in cardiac structure and function over 48 weeks in subjects with Stage 5 CKD receiving hemodialysis who had LVH. The primary efficacy variable was to be change from baseline in LVMI over 48 weeks measured by cardiac MRI. Based on poor enrollment Abbott prematurely terminated the study. At the time of study termination, a total of 12 subjects were randomized and received study drug. Since the study was prematurely terminated, efficacy was not evaluated for this study.

Paricalcitol was safe and well tolerated in this study. No deaths, SAEs, or AEs leading to discontinuation occurred. Mean changes from Baseline in laboratory and vital signs evaluations were clinically unremarkable. Shifts from normal to high and normal to low were infrequent.