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:

A Phase 4, Single-center, Open-label, Randomized, Active-controlled, Cross-over Pilot Study to Evaluate the Effects of Two Vitamin D Analogs, Zemplar® Injection and Hectorol® Injection, on Intestinal Absorption of Calcium in CKD Stage 5 Subjects on Hemodialysis

Investigator:

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Study Site:

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[redacted]
NE

Publications: None

Studied Period (Years):	**Phase of Development:** 4
First Subject First Visit: 8 Jun 2006 Last Subject Last Visit: 26 Jan 2008	

Objective:

The objective of this pilot study was to evaluate the effects of Zemplar® Injection and Hectorol® Injection on intestinal calcium absorption in chronic kidney disease (CKD) Stage 5 subjects on hemodialysis (HD).

Methodology:

This was a single-center, open-label, randomized, active-controlled, cross-over pilot study to evaluate the effects of Zemplar® Injection and Hectorol Injection on intestinal absorption of calcium. Subjects received one of two sequences of study drug (Sequence I - 6 mcg Zemplar Injection every other day [QOD] for 6 doses followed by 3.6 mcg Hectorol Injection QOD for 6 doses, and Sequence II being the reverse, 3.6 mcg Hectorol Injection QOD for 6 doses followed by 6 mcg Zemplar Injection QOD for 6 doses). In either sequence, subjects were to receive both study drug A (6 mcg Zemplar Injection QOD for 6 doses) and study drug B (3.6 mcg Hectorol Injection QOD for 6 doses) at different treatment periods. Dosing of study drug was to occur at the end of each dialysis session.

Adult male and female subjects on HD were to be selected to participate in the study according to the subject selection criteria. Forty-two (42) subjects were to be enrolled in anticipation that 36 subjects completed both treatment periods of the study.

Subjects who satisfied all inclusion criteria and none of the exclusion criteria were eligible to enroll in this study and were assigned randomly in equal numbers to Sequence Group I or II.

The sequences of treatments were such that each subject was to have received both study drugs upon completion of the study. A wash-out interval of 14 days was to separate the last day of Treatment Period 1 (Study Day 14) and the first day of Treatment Period 2 (Study Day 29).

The calcium absorption study was to be performed on Study Day −1 and on the day following the day of the last dose of each treatment period (Study Days 14 and 42). Subjects were to be confined to the study site at approximately 7:30 am. The test calcium source was to be ingested in the morning, midway through a low calcium test breakfast. A blood sample was to be drawn both before (for Study Days 14 and 42 only) and 5 hours after ingestion of the low calcium test breakfast for measurement of serum calcium specific activity. The subject was to abstain from all food after the test breakfast until the 5 hour blood sample was drawn.

In the event of a hypoglycemic episode during the calcium absorption study, sites were instructed to follow Section 5.2.3.4 of the study protocol.

Number of Subjects (Planned and Analyzed):

Planned: 42 subjects

Randomized: 41 subjects

Completed: 37 subjects

Diagnosis and Main Criteria for Inclusion:

Subjects were adult males and females ≥ 20 years of age with CKD Stage 5 who were on maintenance (chronic) HD three times a week for at least 2 months prior to the Screening Visit and expected to remain on HD for the duration of the study.

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

Test Product: Paricalcitol (Zemplar®)

Test Dose/Strength/Concentration: 5 mcg/mL in 2-mL vials of solution

Mode of Administration: IV injection

Lot Numbers: 05-003488, 06-007063, and 06-009548

Duration of Treatment:

The study consisted of two treatment periods each 14 days in duration with a 14-day washout period between the two treatment periods.

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

Reference Therapy: Doxercalciferol (Hectorol®)

Test Dose/Strength/Concentration: 2 mcg/mL in 2-mL ampules of solution

Mode of Administration: IV injection

Lot Numbers: 06-003775, 06-008492, and 07-010710

Criteria for Evaluation

Efficacy:

The efficacy variable was the within subject difference in calcium absorption fractions between treatment regimens.

Safety:

Safety was assessed by monitoring adverse events (AEs), vital signs, physical examinations, and laboratory data.

Statistical Methods

Efficacy:

The mean within subject difference in calcium absorption fractions between treatment regimens were analyzed using analysis of variance (ANOVA), appropriate for a two-period cross-over trial. The ANOVA model included effects for sequence, subject-within-sequence, period and treatment regimen. The Per-Protocol population, i.e., all randomized subjects who completed both Treatment Periods and did not have any major protocol violations as defined in the study protocol, was to be used for the primary efficacy assessment. In addition, a secondary efficacy assessment was to be performed for the mean within subject difference in calcium absorption fractions between treatment regimens utilizing all randomized subjects who completed both Treatment Periods.

Descriptive summary statistics (e.g., mean, standard deviation, minimum value, median value and maximum values) were to be provided for the calcium absorption fractions obtained at treatment Study Day 14 and 42 by randomized treatment sequence and treatment period.

In addition, a descriptive summary was to be performed using means, standard error, and ranges (minimum and maximum values) for the pre-treatment calcium absorption fraction obtained prior to the first dose of Treatment Period 1 by randomized treatment sequence. An ANOVA F-test was to be used to evaluate the equality of means between treatment sequence groups.

Safety:

The Intent-to-treat (ITT) population was to be used to evaluate safety, i.e., all randomized subjects who received at least one dose of study drug were to be included in the safety evaluation.

Adverse Events

Analyses of AEs were to include only "treatment-emergent" events, i.e., those that have an onset on or after the day of the first dose of study medication. Analyses were not to include AEs with an onset greater than 30 days after the last dose of study medication. Adverse events occurring between the day of the first dose of Period 1 and prior to the first dose of Period 2 were to be attributed to Period 1; AEs occurring between the day of the first dose of Period 2 and within 30 days after the last dose of study drug were to be attributed to Period 2.

Treatment-emergent AEs were to be mapped by system organ class (SOC) and Medical Dictionary for Regulatory Activities (MedDRA®) preferred term (PT) according to the MedDRA AE coding dictionary. Within each treatment group, AEs were to be summarized descriptively by counts and percents using the most intense episode (severity) and also using the most likely relationship to study drug (as indicated by the Investigator). A summary was also to be generated that lists subject treatment numbers associated with each MedDRA term within each treatment group.

For subjects who completed both treatment periods, a table was to be generated to evaluate the association of the occurrence of at least one AE between period and sequence by the method of Mainland-Gart; a Fisher's Exact test was to be used to formally evaluate the association.

Chemistry and Hematology Assessments

A descriptive summary was to be performed using means, standard error, and ranges (minimum and maximum values) for the last chemistry and hematology assessments obtained on or before the first dose of Treatment Period 1. This analysis was to be performed by randomized treatment sequence and was to include all subjects who received at least one dose of study drug and had respective chemistry and hematology measurements. An ANOVA F-test was to be used to evaluate the equality of means between treatment sequence groups.

Limited Chemistry Assessments

An analysis was to be performed using limited chemistry assessments (normalized calcium, phosphorus, Ca×P and albumin) obtained at Treatment Days 1, 14, 29, and 42. If more than one measurement exists for a subject on a particular treatment day, the most extreme value (largest value) was to be utilized for that day's limited chemistry assessment. Baseline for Treatment Periods 1 and 2 was to be defined as the last value obtained on or before Day 1 and Day 29 visits, respectively; the Day 29 visit was to have the further restriction of being no more than two days prior to the first dose of Period 2. The Day 14 and Day 42 visits were to be defined as the limited chemistry assessment obtained closest to each respective treatment day within ± 3 days. If two visit values were equally close to the nominal visit, the last measurement was to be selected for analysis.

Descriptive summary statistics were to be provided by treatment regimen and treatment period using means, standard deviations, and ranges (minimum and maximum values) for the Day 14 and Day 42 assessments and were to include the Baseline and the change from Baseline within each period. The mean within subject difference in the response for the change from Baseline within each period was to be analyzed by sequence group with the t test for normally distributed data and the sign rank test for non-normally distributed data. The normality assumption was to be evaluated by the Wilks-Shapiro test statistic.

iPTH Assessments

A descriptive summary was to be performed using means, standard error, and ranges (minimum and maximum values) for the last iPTH assessment obtained on or before the first dose of Treatment Period 1. This analysis was to be performed by randomized treatment sequence and was to include all subjects who received at least one dose of study drug and have an iPTH measurement. An ANOVA F−test was to be used to evaluate the equality of means between treatment sequence groups.

An analysis was to be performed using iPTH assessments obtained at Treatment Days 1, 14, 29, and 42. If more than one measurement existed for a subject on a particular treatment day, the most extreme value (largest value) was to be used for that day's assessment. Baseline for Treatment Periods 1 and 2 was to be defined as the last iPTH value obtained on or before the Day 1 and Day 29 visits, respectively; the Day 29 visit was to have the further restriction of being no more than two days prior to the first dose of Period 2. The Day 14 and Day 42 visits were to be defined as the iPTH assessment obtained closest to each respective treatment day within ± 3 days; if two visit values were equally close to the nominal visit, the last measurement was to be selected for analysis.

Descriptive summary statistics was to be provided by treatment regimen and treatment period using means, standard deviations, and ranges (minimum and maximum values) for the Day 14 and Day 42 assessments and were to include the Baseline and the change from Baseline values. The mean within subject difference in the response for the change from Baseline within each period was to be analyzed by sequence group with the t test for normally distributed data and the sign rank test for non-normally distributed data. The normality assumption was to be evaluated by the Wilks-Shapiro test statistic.

Pre-treatment Vitamin D [1,25(OH)2D, 25(OH)D, 25(OH)D2 and 25(OH)D3] Assessments

A descriptive summary was to be performed using means, standard error, and ranges (minimum and maximum values) for pre-treatment vitamin D assessments obtained prior to the first dose of Treatment Period 1. This analysis was to be performed by randomized treatment sequence and was to include all subjects who received at least one dose of study drug. An ANOVA F-test was to be used to evaluate the equality of means between treatment sequence groups.

Summary/Conclusions

Efficacy Results:

No significant differences in demographics (except for gender; more females were randomized to Sequence Group II and more males in Sequence Group I), medical history, presenting Baseline disease conditions, and prior and concomitant medications were observed between treatment groups.

Calcium absorption test results were similar between the two treatment regimens. No statistically significant differences between Zemplar Injection and Hectorol Injection on intestinal calcium absorption in CKD Stage 5 subjects on HD were observed. However, the PTH response was not the same in both groups. In Period 1, Zemplar treated subjects had a reduction in PTH from 863.0 to 778.1 pg/ml (p=0.033) while Hectorol treated subjects did not have a significant change in PTH from Baseline (from 784.6 to 744.7 pg/ml; p=0.507). In Period 2, Zemplar treated subjects had a reduction in PTH from 775.9 to 384.2 pg/ml (p=0.005) while Hectorol treated subjects did not have a significant change in PTH from Baseline (from 855.5 to 787.3 pg/ml; p=0.319). These data suggest that the doses of the two drugs were not comparable.

Safety Results:

Zemplar Injection at 6 mcg for up to 6 doses QOD was generally safe and well tolerated, comparable to the safety profile exhibited by 3.6 mcg Hectorol Injection QOD for up to 6 doses, in this two period open-label crossover study. No significant differences between treatment regimens were observed in AEs, laboratory data, vital signs, or physical findings during the study.

- A total of 27 (65.9%) subjects experienced any treatment-emergent AE.
- No AEs were considered at least possibly related to study drug and no discontinuations due to AEs or deaths occurred during the study. One subject died prior to randomization into the study.
- No statistically significant association of the occurrence of AEs between treatment and Sequence Groups were observed using the Mainland-Gart test ($P = 0.622$).
- Overall, six subjects reported SAEs during the study, none of which were considered by the Investigator to have a causal relationship to study drug.
- No statistically significant differences between treatment regimens were observed for final iPTH or chemistry variables (calcium, phosphorus, CaxP, or albumin).
- No clinically meaningful differences between treatment regimens for vital signs or physical findings were observed.

Conclusions:

No significant differences were observed in the effects of Zemplar Injection vs. Hectorol Injection on intestinal calcium absorption. However, because Zemplar effectively suppressed PTH, while Hectorol did not, it appears that comparable doses were not tested. Short-term treatment of Zemplar Injection in dialysis patients effectively suppresses PTH levels without stimulating intestinal calcium absorption. Despite more effective PTH reduction, Zemplar did not result in greater intestinal calcium absorption than Hectorol.