2.0   Synopsis
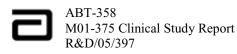
Abbott Laboratories	Individual Study Table Referring to Item of the Submission:	(For National Authority Use Only)
Name of Study Drug: Zemplar Injection	**Volume:**	
Name of Active Ingredient: Paricalcitol	**Page:**	

Title of Study: A Phase 4, Double-Blind, Double-Dummy, Single-Center, Randomized, Active-Controlled, Cross-Over, Pilot Study to Evaluate the Effects of Two Vitamin-D Compounds, Zemplar® Injection and Calcijex® on Intestinal Absorption of Calcium
Investigator: Richard Lund, M.D.
Study Site: Creighton University, Omaha, Nebraska
Publications: None

Studied Period (Years): Date First Subject Dosed: 22 September 2004 Date Last Subject Completed Dosing: 28 April 2005	**Phase of Development:** 4

Objective: The objective of this Phase 4, single-center, double-blind, double-dummy, randomized, active-controlled, pilot study was to investigate the effects of Zemplar and Calcijex on intestinal calcium absorption in hemodialysis (HD) subjects.
Methodology: This was a single-center, double-blind, double-dummy, randomized, active-controlled, crossover, pilot study to evaluate the effects of Zemplar and Calcijex on intestinal absorption of calcium. Subjects received 1 of 2 sequences of study drug administered intravenously: Drug A (6 mcg Zemplar Injection every other day [QOD]* for 6 doses) and Drug B (2 mcg Calcijex Injection QOD for 6 doses) at different treatment periods under non-fasting conditions. Additionally, all subjects received matching placebo for the counter-treatment. Dosing of both active drug and placebo occurred at the end of each dialysis session. Adult male and female subjects on HD were selected to participate in the study according to the subject selection criteria. Thirty (30) subjects were to be enrolled in anticipation that 24 subjects would complete both periods of the crossover. Subjects who satisfied inclusion/exclusion criteria after 1 week of washout were eligible to enter into the Treatment Phase. The sequences of treatments were such that each subject received both study drugs upon completion of the study. A washout interval of 8 days separated the last dose of Period 1 (Study Day 13) and the first dose of Period 2 (Study Day 22). *QOD - every other day, but not more frequent than three times per week.

Methodology (Continued):

The intestinal calcium absorption study was to be done on the day following the last dose of each treatment period (Study Days 14 and 35). Subjects were confined to the study site at approximately 7:30 a.m. The test calcium source was ingested in the morning, midway through a low-calcium test breakfast. A blood sample was drawn at 5 hours after ingestion of the low-calcium test breakfast for measurement of serum calcium specific activity. The subject abstained from all food after the test breakfast until the 5-hour blood sample was drawn.

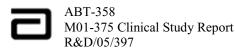**Number of Subjects (Planned and Analyzed):**

Planned: 30 subjects

Enrolled: 29 subjects (14 into sequence A [6 mcg Zemplar Injection QOD for 6 doses in Period 1 and 2 mcg Calcijex Injection QOD for 6 doses in Period 2] and 15 into sequence B [2 mcg Calcijex Injection QOD for 6 doses in Period 1 and 6 mcg Zemplar Injection QOD for 6 doses in Period 2])

Analyzed: 29 subjects were evaluated for safety (14 into sequence A and 15 into sequence B) 18 subjects were evaluated for the primary efficacy assessment (Per-Protocol Population; 9 into sequence A and 9 into sequence B)

Diagnosis and Main Criteria for Inclusion:

Subject was ≥ 20 years of age, diagnosed with chronic kidney disease (CKD) Stage 5, also known as end-stage renal disease, and must have been on maintenance HD 3 times a week for at least 2 months prior to the Screening Phase and expected to remain on HD for the duration of the study. If female, subject was either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), or was of childbearing potential and practicing one of the protocol specified methods of birth control, was not breastfeeding and had a negative serum pregnancy test prior to the Treatment Phase. Subject had an intact PTH (iPTH) value > 200 pg/mL, serum calcium level < 10.2 mg/dL, phosphorus level < 6.5 mg/dL, and Ca×P product ≤ 65 mg^2/dL^2 at Screening Visit.

Subject was to be excluded from the study if he/she met any of the following criteria:

1. Subject had a history of an allergic reaction or significant sensitivity to vitamin D or vitamin D-related compounds.

2. Subject had chronic gastrointestinal disease, which in the Investigator's opinion, may have resulted in clinically significant gastrointestinal malabsorption.

3. Liver function defects defined as > 2 times the upper limit of normal for liver enzymes or > 1.5 times the upper limit of normal for coagulation levels.

4. Subject was taking maintenance calcitonin, glucocorticoids in an equivalent dose > 5 mg prednisone, or other drugs that may have affected calcium or bone metabolism, other than females on stable (same dose and product for 3 months) estrogen and/or progestin therapy.

5. For any reason, subject was considered by the Investigator to be an unsuitable candidate to receive pharmacological doses of vitamin D.

6. Subject had received any investigational drug within 4 weeks prior to the Treatment Phase.

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

Test product: Zemplar solution for IV injection

Dose: 6 mcg (5 mcg/mL in 2-mL vials)

Mode of administration: IV injection

Lot numbers: 04-660-DK, 09-177-4P, 16-215-4P, 21-249-4P

Placebo (2-mL vials), identical in appearance to Zemplar.

Mode of administration: IV injection

Lot numbers: 04-661-DK, 93-385-DK, 16-217-4P, 21-250-4P

Duration of Treatment: 35 days

Reference Therapy, Dose and Mode of Administration, Lot Number:

Test product: Calcijex solution for IV injection

Dose: 2 mcg (1 mcg/mL in 1-mL ampules)

Mode of administration: IV injection

Lot numbers: 04-094-DK, 09-179-4P, 16-220-4P, 21-251-4P

Placebo (1-mL ampules), identical in appearance to Calcijex.

Mode of administration: IV injection

Lot numbers: 04-663-DK, 16-221-4P, 21-252-4P
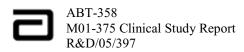
Criteria for Evaluation:

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

Safety: Safety was assessed through adverse event monitoring, clinical chemistry and hematology assessments, physical examinations and vital sign measurements.

Statistical Methods:

Efficacy: The mean within subject difference in intestinal calcium absorption fractions between treatment groups was analyzed using ANOVA appropriate for a 2-period crossover 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) that had results for both calcium absorption tests and did not have any major protocol violations was used for the primary efficacy assessment. In addition, a secondary efficacy assessment was performed for the mean within subject difference in calcium absorption rates between treatment groups utilizing all randomized subjects who completed both Treatment Periods and had results for both calcium absorption tests.

Safety: Analyses of adverse events included only "treatment-emergent" events (*i.e.*, those that had an onset on or after the day of the first dose of study medication). Analyses did not include adverse events with an onset > 30 days after the last dose of study medication.

Safety (continued): Treatment emergent adverse events were mapped by body system and Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) term according to the COSTART V adverse event coding dictionary. Adverse events with a given severity or relationship to study drug (as indicated by the investigator) were summarized descriptively by treatment group using counts and percentages. If a COSTART description occurred more than once for a subject, while the subject was taking a particular therapy, the most intense severity was summarized for the assessment regarding severity. Similarly, if a COSTART description occurred more than once for a subject, while the subject was taking a particular therapy, the most likely relationship to study drug was summarized for the assessment regarding the relationship to study drug. A summary was also generated that listed subject treatment numbers associated with each COSTART term within each treatment group.

For subjects who completed both treatment periods, a table was generated to evaluate the association of the occurrence of at least 1 adverse event between periods and sequence by the method of Mainland-Gart; a Fisher's Exact test was used to formally evaluate the association.

In addition, treatment-emergent serious adverse events were mapped by body system and COSTART term according to the COSTART V adverse event-coding dictionary and summarized by treatment group using counts and percentages.

For subjects completing both treatment periods and having respective chemistry and hematology assessments for both treatment periods, the mean within subject difference between treatment groups for chemistry and hematology determinations obtained at treatment Study Day 14 and 35 were analyzed using the 2-period crossover ANOVA model similar to the efficacy analysis described above and utilized values obtained closest to each respective treatment day.

Limited chemistry and iPTH, vital signs, medical history, physical examination, and concurrent medications were summarized descriptively by treatment regimen.
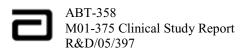
Summary/Conclusions:

Efficacy Results:

The efficacy variable was the within subject difference in the intestinal calcium absorption fractions between treatment regimens performed on the Per-Protocol Population (primary efficacy assessment) and using all randomized subjects who completed both Treatment Periods and had both calcium absorption tests (secondary efficacy assessment).

A statistically significant difference was observed between the treatment regimens for both the primary and secondary efficacy assessment. In both cases, the mean calcium absorption fraction was lower for Zemplar Injection compared to Calcijex Injection.

Safety Results:

Treatment-emergent adverse events were experienced by 13/27 (48%) subjects during dosing with Zemplar Injection and by 13/28 (46%) subjects during dosing with Calcijex Injection. The most commonly reported (≥ 2 subjects) treatment-emergent adverse events experienced during dosing with Zemplar Injection were vomiting, lymphadenopathy, and hypoglycemia (2 subjects each). The most commonly reported treatment-emergent adverse events experienced during dosing with Calcijex Injection were infection (4 subjects) and left heart failure (2 subjects).

Safety Results (Continued):

During dosing with Zemplar Injection, a greater proportion of subjects reported treatment-emergent adverse events of vomiting, lymphadenopathy, and hypoglycemia (7% each) compared to subjects during dosing with Calcijex Injection (0% each). During dosing with Calcijex Injection, a greater proportion of subjects reported treatment-emergent adverse events of infection (14%) compared to subjects during dosing with Zemplar Injection (4%).

All adverse events were considered by the Investigator to be mild or moderate in severity, except for 2 serious adverse events (lung edema and left heart failure), which were considered severe and were experienced by 1 subject 27 days after the last dose of Zemplar Injection. All adverse events were considered by the Investigator to be not related or probably not related to study drug, except for 1 adverse event of taste loss (Zemplar Injection) that was considered to be probably related to study drug.

No statistically significant difference was observed between the treatments in the overall adverse event incidence rates for all subjects completing both treatment periods.

No subjects died or were prematurely discontinued from the study due to adverse events. Overall, 7 subjects reported serious adverse events during the study, none of which were considered by the Investigator to have a causal relationship to study drug. The incidence of serious adverse events was similar between the treatment regimens.

No statistically significant differences were observed between Zemplar Injection and Calcijex Injection for the final iPTH assessment or for any of the chemistry variables, except for potassium.

Evaluations of other laboratory analyses, vital signs, and physical examinations revealed no clinically meaningful treatment group differences.

Conclusions:

The objective of this Phase 4, single-center, double-blind, double-dummy, randomized, active-controlled, pilot study was to investigate the effects of Zemplar Injection and Calcijex Injection on intestinal calcium absorption in HD subjects. The efficacy variable was the within subject difference in the calcium absorption fractions between treatment regimens performed on the Per-Protocol Population (primary efficacy assessment) and using all randomized subjects who competed both Treatment Periods and had both calcium absorption fractions (secondary efficacy assessment).

Results of this study suggest that Zemplar has less of an effect on intestinal calcium absorption than Calcijex when administered at doses equivalent to those used for PTH suppression. A statistically significant difference was observed between the treatment regimens for both the primary and secondary efficacy assessment. In both cases, the mean calcium absorption fraction was lower for Zemplar Injection compared to Calcijex Injection.

The treatment regimens administered in the study were generally safe and well tolerated. No new or unexpected patterns of adverse event occurrences were identified with the administration of either Zemplar Injection or Calcijex Injection.