# 2.0 Synopsis

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| **Abbott Laboratories** | **Individual Study Table Referring to Part of Dossier:** | **(For National Authority Use Only)** |
| **Name of Study Drug:**<br>Zemplar® Injection<br>Calicjex® | **Volume:** | |
| **Name of Active Ingredient:**<br>Paricalcitol<br>Calcitriol | **Page:** | |

**Title of Study:** A Phase 4, Prospective, Randomized, Active-controlled, Double-blind, Double-dummy, Multicenter Study to Evaluate the Survival Benefits of Zemplar® Relative to Calcijex® in Subjects with Stage 5 Chronic Kidney Disease on Hemodialysis

**Rationale for Abbreviated Clinical Study Report:** Based on the review of unblinded data, the Data Monitoring Committee (DMC) did not find any safety reasons to stop the study; however, based on low enrollment and the primary study endpoint (mortality), the DMC determined that it was unlikely that a sufficient number of subjects could be enrolled to meet the primary study endpoint and, thus, it was unethical to continue the study. Abbott prematurely terminated the study based on the recommendation of the DMC. Study results are reported using an abbreviated clinical study report format.

**Investigator:** Multicenter; 33 Investigators

**Study Sites:** 33 study sites in the United States

**Publications:** None

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| **Studied Period (Years):**<br>First Subject First Visit: 14 Jul 2003<br>Last Subject Last Visit: 16 Jul 2006 | **Phase of Development:** 4 |

**Objectives:** The primary objective of this study was to evaluate the survival benefit associated with Zemplar therapy as compared to Calcijex for the treatment of secondary hyperparathyroidism (SHPT) in subjects with Stage 5 chronic kidney disease (CKD) on hemodialysis (HD) as measured by time to death.

Secondary objectives were to evaluate:

- the survival endpoint of death attributable to cardiovascular disease
- the impact of treatment on morbidity as assessed by:

  The number of hospitalizations due to any cause.

  The number of hospitalizations attributable to cardiovascular disease.

  The number of days spent hospitalized due to any cause.

  The number of days spent hospitalized that were attributable to cardiovascular disease.

**Methodology:** This was a phase 4, prospective, randomized, active-controlled, double-blind, double-dummy, multicenter study in subjects with Stage 5 CKD on HD. The study was performed in three phases – a Screening Phase, a Treatment Phase of up to 24 months (including an End of Study Visit), and a Follow-Up Phase. Each month consisted of 4 weeks/28 calendar days.

Approximately 2200 subjects aged ≥ 20 years were to be assigned randomly, in an equal ratio (1:1), to either Zemplar or Calcijex, both to be administered no more frequently than every other day after HD. Placebo was administered to all subjects in addition to active study drug treatment. For the Zemplar treatment group, placebo was to represent Calcijex and for the Calcijex treatment group, placebo was to represent Zemplar. Subjects were to remain on treatment for 24 months.

Study visits were to occur monthly for the first 12 months and quarterly during the second year of treatment. Calcium, phosphorus, calcium-phosphorus product (Ca×P), and albumin levels were to be monitored monthly, while intact parathyroid hormone (iPTH) levels were monitored at each quarterly study visit.

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

**Planned**: 2200 subjects

**Enrolled**: 122 Zemplar and 127 Calcijex

**Analyzed**: 120 Zemplar and 124 Calcijex (efficacy and safety)

**Diagnosis and Main Criteria for Inclusion:** Subject was ≥ 20 years of age; diagnosed with Stage 5 CKD; received chronic dialysis three times weekly for at least 50 days prior to the Screening Visit; was currently on HD; was expected to remain on HD. If not currently receiving vitamin D therapy, they had an iPTH value ≥ 400 pg/mL as measured at the Screening Visit, or if currently receiving intravenous (IV) and/or oral vitamin D therapy (at least 3 μg Zemplar, 1 μg Calcijex, or 1.5 μg Rocaltrol or equivalent), they had an iPTH value ≥ 400 pg/mL or whole PTH value ≥ 200 pg/mL at any measurement during dialysis, before or during vitamin D therapy. If female, subject was either not of childbearing potential or surgically sterile; if female and of childbearing potential, the subject must have been practicing one of the Abbott specified methods of birth control; if female, subject was not breast feeding; if female, subject must have had a negative serum pregnancy test prior to the Treatment Phase. Subject or their legal representative had voluntarily signed and dated an informed consent form.

Subject was to be excluded from the study if he/she was on maintenance chronic dialysis three times a week > 500 days prior to the Screening Phase, on oral and/or IV vitamin D therapy > 6 months (cumulative) before the date of Screening while on chronic dialysis, or had a history of an allergic reaction or significant sensitivity to vitamin D or vitamin D related compounds.

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

Test product: Zemplar 5 μg/mL vial (10 μg in 2 mL).

Dose: The initial dose for subjects not currently receiving IV vitamin D therapy was 3.0-6.0 μg of Zemplar. Dosing was possible in increments of 3.0 μg, 4.5 μg, or 6.0 μg. As the treatment group was not known, the initial dose was based on the Disease Outcomes Quality Initiative (DOQI) Guidelines, individual patient situation, and individual dialysis clinic dosing procedures.

Active study medication and placebo were administered to every subject (double-dummy design). Appropriate volumes of liquid were withdrawn from both a vial of Zemplar and an ampule of placebo to correspond with the subject's current dose increment.

Subjects currently receiving IV vitamin D therapy were assigned their initial dose based on their current levels of medication.

- Subjects receiving ≥ 6.0 μg of Zemplar or the equivalent were to start treatment at Dose Level 5 (6.0 μg of Zemplar).
- Subjects receiving ≥ 4.5 μg and < 6.0 μg of Zemplar or the equivalent were to start treatment at Dose Level 4 (4.5 μg of Zemplar).
- Subjects receiving < 4.5 μg of Zemplar or the equivalent were to start treatment at Dose Level 3 (3.0 μg of Zemplar).

Mode of administration: IV injection

Lot numbers: Zemplar – 16-215-4P, 21-249-4P, 25-265-4P
Placebo – 16-217-4P, 21-250-4P, 25-266-4P

**Duration of Treatment:** Duration of treatment was to have been up to 24 months (96 weeks/672 days). Mean days from first dose to last dose was 352.8 for the Zemplar treatment group and 338.8 days for the Calcijex treatment group.

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

Test product: Calcijex 1 μg/mL ampule (1 μg in 1 mL).

Dose: The initial dose for subjects not currently receiving IV vitamin D therapy was 1.0-2.0 μg of Calcijex. Dosing was possible in increments of 1.0 μg, 1.5 μg, or 2.0 μg for Calcijex. As the treatment group was not known, the initial dose was based on the DOQI Guidelines, individual patient situation, and individual dialysis clinic dosing procedures.

Active study medication and placebo were administered to every subject (double-dummy design). Appropriate volumes of liquid were withdrawn from both a vial of placebo and an ampule of Calcijex to correspond with the subject's current dose increment.

Subjects currently receiving IV vitamin D therapy were assigned their initial dose based on their current levels of medication.

- Subjects receiving ≥ 2.0 μg of Calcijex or the equivalent were to start treatment at Dose Level 5 (2.0 μg of Calcijex).
- Subjects receiving ≥ 1.5 μg and < 2.0 μg of Calcijex or the equivalent were to start treatment at Dose Level 4 (1.5 μg of Calcijex).
- Subjects receiving < 1.5 μg of Calcijex or the equivalent were to start treatment at Dose Level 3 (1.0 μg of Calcijex).

Mode of administration: IV injection

Lot numbers: Calcijex – 16-220-4P, 21-251-4P, 25-267-4P
Placebo – 16-221-4P, 21-252-4P, 25-268-4P

**Criteria for Evaluation**

**Efficacy:** Efficacy was not evaluated for this abbreviated report.

**Safety:** The primary study endpoint was time to death.

A secondary study endpoint was the survival endpoint of death attributable to cardiovascular disease.

Additional secondary study endpoints were:

- To evaluate morbidity as assessed by the number of hospitalizations for any cause.
- The number of hospitalizations attributable to cardiovascular disease.
- The number of days hospitalized for any cause.
- The number of days hospitalized that were attributable to cardiovascular disease.

Safety was further assessed through adverse event (AE) monitoring, clinical laboratory evaluations, and vital signs assessment.

**Statistical Methods:** The primary study analysis was a comparison of the survival distributions (time to death) between the Zemplar and Calcijex treatment groups using the log rank statistic. The survival distribution (time to death) was estimated for each treatment group using Kaplan-Meier methodology. A log rank statistic was used to test the null hypothesis that the survival rates for the Zemplar and the Calcijex treatment groups were the same.

A summarization of the number of days subjects were exposed to study drug was generated by treatment group.

Treatment-emergent AEs were summarized by body system and Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) term according to the COSTART V AE coding dictionary. Treatment-emergent AEs were summarized 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). Additionally, a summary was generated listing subject treatment numbers associated with each COSTART term. Comparisons of the percentages of subjects experiencing a treatment-emergent AE between Zemplar and Calcijex treatment groups were performed using Fisher's Exact tests.

Additionally, serious adverse events (SAEs) were summarized by counts and percents using the most intense episode and Fisher's Exact test was used to make comparisons between treatment groups.

At a given visit, the change and/or percent change from Baseline for each laboratory parameter was compared between Zemplar and Calcijex using a one-way analysis of variance (ANOVA) with treatment as the factor. Also at a given visit, the change and/or percent change from Baseline was compared between Zemplar and Calcijex using an analysis of covariance (ANCOVA) using the Baseline measurement for the parameter as the second factor.

Shifts from Baseline categories to categories assessed at scheduled post-Baseline visits and at the final visit for laboratory parameters were summarized by treatment group.

Analyses of the change from Baseline in vital sign parameters for each scheduled post-Baseline visit were analyzed using an ANOVA with treatment as the factor. Also at a given visit, the change from Baseline was compared between Zemplar and Calcijex using an ANCOVA using the Baseline measurement for the parameter as the second factor.

**Summary/Conclusions:**

**Safety Results:** A statistically significant difference was not detected in survival distributions between the Zemplar and the Calcijex treatment groups. Zemplar and Calcijex, as administered in this study, were generally safe and well-tolerated as evaluated by the proportions of subjects who experienced treatment-emergent AEs, treatment-emergent SAEs including death, other significant treatment-emergent AEs, and laboratory and vital signs assessment:

- Treatment-emergent AEs were experienced by similar proportions of subjects in the Zemplar and Calcijex treatment groups (90% and 83%, respectively).
- The most commonly (≥ 10% of subjects) reported treatment-emergent AEs in both treatment groups were pain and infection.
- Three treatment-emergent AEs were observed to be statistically significantly different between treatment groups:
  - A statistically significantly greater proportion of subjects in the Zemplar treatment group experienced cholecystitis and pneumonia compared with subjects in the Calcijex treatment group.
  - A statistically significantly greater proportion of subjects in the Calcijex treatment group experienced gastroenteritis compared with subjects in the Zemplar treatment group.
- Most subjects reported treatment-emergent AEs that were mild or moderate in severity. Severe treatment-emergent AEs were experienced by similar numbers and proportions of subjects: 45 subjects (38%) in the Zemplar treatment group and 42 subjects (34%) in the Calcijex treatment group.
- The majority of treatment-emergent AEs were considered by the Investigator to be not related or probably not related to study drug. Twelve subjects in the Zemplar treatment group and ten subjects in the Calcijex treatment group reported treatment-emergent AEs with a possible or probable relationship to study drug.
- Ten subjects in the Zemplar treatment group and 11 subjects in the Calcijex treatment group died during the study. No deaths were considered possibly or probably related to study drug.
- No statistically significant differences were observed between the Zemplar and Calcijex treatment groups in the proportion of subjects with treatment-emergent SAEs.
- Sixteen subjects in the Zemplar treatment group and 10 subjects in the Calcijex treatment group terminated prematurely from study drug due to an AE. The majority of these events were considered by the Investigator to be not related or probably not related to study drug.
- The proportion of subjects reporting specific treatment-emergent SAEs resulting in hospitalization was similar between the treatment groups: 62 (52%) subjects in the Zemplar group vs. 58 (47%) subjects in the Calcijex group.
- Evaluations of safety laboratory analyses and vital signs revealed no clinically meaningful pattern of treatment group differences.

No new safety signals were identified with the administration of either Zemplar or Calcijex.

**Conclusions:** No statistically significant difference was detected in survival distributions between the Zemplar and the Calcijex treatment groups.

Zemplar and Calcijex as administered in this study were safe and well-tolerated.

No statistically significant differences were observed between the Zemplar and Calcijex treatment groups in the proportion of subjects who developed hypercalcemia, hyperphosphatemia, or elevated Ca×P.

No new safety signals were identified with the administration of either Zemplar or Calcijex.