



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Item of the Submission: Volume: Page:	(For National Authority Use Only)
Name of Study Drug: Zemplar Injection		
Name of Active Ingredient: Paricalcitol		
Title of Study: A Phase IV Randomized, Active-Controlled, Double-Blind, Multi-Center Study to Compare Two Methods of Dosing Zemplar® Injection in Stage V Chronic Kidney Disease Subjects on Hemodialysis		
Investigator: Multi-center; 20 Investigators		
Study Site: 20 study sites in Greece		
Publications: None		
Studied Period (Years): Date First Subject Dosed: 03 August 2004 Date Last Subject Completed Dosing: 14 January 2006	Phase of Development: 4	
Objective: <p>The primary objective of this study was to show non-inferiority in the proportion of the study subjects achieving at least 2 consecutive $\geq 30\%$ decreases from baseline iPTH (as measured by the second-generation PTH assay) between 2 treatment groups: a group receiving mcg dosing of Zemplar Injection based on the formula iPTH/80 and a group receiving mcg dosing of Zemplar Injection based on the US package insert (starting dose at 0.04 mcg/kg).</p> <p>The secondary objective of this study was to evaluate the incidence rate of hypercalcemia between treatment groups.</p>		
Methodology: <p>This was a double-blind, randomized, multi-center, 12 week study to determine if Zemplar Injection dosing based on iPTH/80 was not inferior in reducing PTH to current approved dosing based on the US package insert.</p> <p>A sufficient number of subjects with ESRD were enrolled at multiple sites in order to randomize approximately 190 subjects. The study consisted of a Screening Visit, a Pre-Treatment Phase, a Treatment Phase, an End of Study Visit, and a Follow-Up Contact.</p> <p>Subjects with an iPTH level ≥ 300 pg/mL, who had not received any vitamin D treatment for the past 2 weeks and were on a stable dose of phosphate binder, completed Pre-Treatment Week 1 and then were eligible to enter the Treatment Phase after meeting all inclusion and exclusion criteria. Subjects with an iPTH level < 300 pg/mL, who had received vitamin D therapy within the 2 weeks prior to screening, and/or were not on a stable phosphate binder regimen, were eligible for the Pre-Treatment Phase. The purpose of the Pre-Treatment Phase was to "wash-out" any remaining vitamin D compounds and their carry-over effects and to identify a maintenance dose of phosphate binder therapy.</p>		



Methodology (Cont.):

After entering the Pre-Treatment Phase, subjects were to undergo HD 3 times a week by the procedure routinely in use at their HD center. The calcium concentration in the dialysate was to be maintained at a constant level (2.5 mEq/L [1.25 mmol/L]) during the Pre-Treatment and Treatment Phases.

Subjects who entered the Treatment Phase were assigned randomly, in an equal ratio (1:1), to 1 of 2 treatment groups: Group 1 – initial dose by iPTH/80 and dose adjustments based on weekly iPTH/80 as well as, calcium and Ca×P levels, and Group 2 – initial dose (starting at 0.04 mcg/kg) by weight and the dose adjustment based on the US package insert. A unique subject number was assigned to each subject at randomization. Subjects received their study drug three times weekly during HD for a total of 12 weeks, no more frequently than every other day. The dose may have been increased up to a per dose maximum of 18 mcg of Zemplar Injection for both Groups 1 and 2. Decisions to maintain, increase, or decrease the dose were based on limited chemistry results that were drawn once a week. Safety and efficacy were determined through adverse event monitoring and clinical laboratory evaluations during the 12-week Treatment Phase and extending through the End of Study Visit.

After the End of Study Visit, subjects were contacted via telephone for the Follow-Up Contact. This contact should have been made 30 days after the subjects' last dose of study drug for the purpose of recording any adverse events and concurrent medications since their last dose of study drug.

Subjects completing this study were to have been eligible to enroll in an extension protocol to continue treatment with Zemplar Injection for management of their SHPT. However, the conduction of the extension study was not necessary since Zemplar Injection had market approval in Greece by the time the first subject would have been eligible for the extension study.

Number of Subjects (Planned and Analyzed):

Planned:	190 subjects
Enrolled:	201 subjects
Analyzed:	200 subjects

Diagnosis and Main Criteria for Inclusion:

Subject was ≥ 20 years of age, was diagnosed with ESRD, and must have been on maintenance HD 3 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. Subject had a serum iPTH level as determined by the second-generation assay, of ≥ 300 pg/mL. 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 1 of the protocol specified methods of birth control, was not breastfeeding and had a negative serum pregnancy test prior to the Treatment Phase.



Diagnosis and Main Criteria for Inclusion (Cont.):

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. Corrected serum calcium level for 2 of the last 3 measurements > 10.5 mg/dL (2.6 mmol/L).
 3. Serum phosphorus level for 2 of the last 3 measurements > 6.5 mg/dL (2.1 mmol/L).
 4. Ca \times P for 2 of the last 3 measurements > 60 mg²/dL².
 5. Subject had chronic gastrointestinal (GI) disease, which in the Investigator's opinion, may have resulted in clinically significant GI malabsorption.
 6. Liver function defects defined as > 2 times the upper limit of normal for liver enzyme or > 1.5 times the upper limit of normal coagulation levels.
 7. Subject had taken aluminum-containing phosphate binders for greater than 3 consecutive weeks in the last 3 months prior to the Screening Visit. If use of aluminum-containing phosphate binders became necessary during the study, the medications may have been administered for 1 consecutive period of time not exceeding 3 weeks.
 8. Subject was known to have had a parathyroidectomy.
 9. Subject had a current malignancy (with the exception of basal or squamous cell carcinoma of the skin) or clinically significant liver disease, in the opinion of the Investigator.
 10. Subject was known to be HIV positive.
 11. Subject had evidence of poor compliance with diet, medication or HD that may have interfered, in the Investigator's opinion, with adherence to the protocol.
 12. Subject was taking maintenance calcitonin, glucocorticoids, 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.
 13. For any reason, subject was considered by the Investigator to be an unsuitable candidate to receive pharmacological doses of vitamin D.
 14. Subject had received any investigational drug within 4 weeks prior to the Treatment Phase.
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<p>Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:</p> <p>Test product: Zemplar solution for IV injection (2 mL single-dose flip top vial [5 mcg/mL])</p> <p>Dose: Study medication was provided for each subject as modules containing 2 types of identical vials labeled as type A and type B. One type of vial contained active study medication and the other contained placebo. At every HD session, the subject was to receive 1 injection from each vial type for a total of 2 injections.</p> <p>The equivalent microgram amount for initial injections from type A vials were to be calculated according to the formula ($iPTH/80 = \text{equivalent dose [mcg]}$). The first treatment dose level for vial A was based on the subject's iPTH level from the last Pre-Treatment week. The equivalent microgram amount for initial injections from type B vials was to be calculated according to the US package insert (starting at 0.04 mcg/kg). The first treatment dose level for vial B (mcg/kg) was calculated using the subject's physician-prescribed dry weight at the Treatment Phase Week 1/Baseline Visit.</p> <p>The need for dose adjustments was assessed weekly based on the protocol-specified criteria for vials of type A and B, respectively.</p> <p>Mode of administration: IV injection</p> <p>Lot numbers: 17-523-S2, 22-807-S2, 24-869-S2, 24-882-S2, 29-100-S2, 32-183-S2</p>
<p>Duration of Treatment: 12 weeks</p>
<p>Reference Therapy, Dose and Mode of Administration, Lot Number:</p> <p>None</p>
<p>Criteria for Evaluation:</p> <p>Efficacy: The primary study endpoint was the proportion of study subjects achieving at least 2 consecutive $\geq 30\%$ decreases from baseline iPTH within the 2 treatment groups. The secondary study endpoint evaluated the incidence rates for hypercalcemia between the 2 treatment groups.</p>
<p>Safety: Safety was assessed through adverse event monitoring, clinical chemistry and hematology assessments, physical examinations and vital sign measurements.</p>
<p>Statistical Methods:</p> <p>Efficacy:</p> <p>Primary Study Analysis</p> <p>The primary study analysis was designed to demonstrate non-inferiority in the proportion of subjects achieving at least 2 consecutive $\geq 30\%$ decreases from baseline in serum intact PTH (iPTH) between 2 treatment groups; a group receiving mcg dosing of Zemplar Injection based on the formula $iPTH/80$ (Group 1 [$iPTH/80$], the Test expected proportion) and a group receiving mcg dosing of Zemplar Injection based on the US package insert (Group 2 [0.04 mcg/kg], the Standard proportion). Non-inferiority was demonstrated through the generation of a lower limit for a one-sided 97.5% confidence interval for the between treatment group difference (Group 1-Group 2) in the proportion of subjects achieving at least 2 consecutive $\geq 30\%$ decreases from baseline in iPTH using a normal approximation. If the lower limit of the observed one-sided 97.5% confidence interval was greater than -20%, then non-inferiority was demonstrated. Subjects who did not have at least 2 on-treatment iPTH assessments were excluded from the analysis.</p>



Efficacy (Cont.):**Secondary Study Analyses**

A comparison of the proportion of subjects in each treatment group achieving clinically meaningful hypercalcemia was to be performed using Fisher's exact test.

Exploratory Analyses

Matched pairs of iPTH and bio-iPTH values were obtained for each subject over each week of treatment and for the final visit. Least Squares Linear regression models were used to evaluate the relationship between iPTH and bio-iPTH levels at each weekly visit and for the final visit. The regression model included iPTH as the dependent variable and bio-iPTH as the independent variable; treatment group was not included as a factor in the model because all subjects received paricalcitol. Pearson's correlation coefficient was used to assess the strength of the linear relationship between iPTH and bio-iPTH. A 95% confidence interval was generated for Pearson's correlation coefficient and for the intercept and slope regression coefficients.

Safety:

The all treated subject population, *i.e.*, all randomized subjects who received at least one dose of study medication, was used to evaluate safety.

Adverse Events

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 drug. Analyses did not include those that have an onset greater than 30 days after the last dose of study drug.

Treatment-emergent adverse events were mapped by body system and Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) term according to the COSTART V adverse event-coding dictionary. Treatment-emergent adverse events were summarized by frequencies and percentages 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 proportions of subjects experiencing an adverse event between treatment groups were performed using Fisher's exact test.

Additionally, serious adverse events (SAEs) were summarized by frequencies and percentages and Fisher's exact test was used to make comparisons between treatment groups.

Chemistry and Hematology Assessments

The mean change from baseline to the final measurement for each variable was compared between treatment groups using a one-way ANOVA with treatment as the factor. In addition, an ANCOVA was performed to evaluate the sensitivity of the ANOVA model that included treatment as the factor and the baseline measurement for the parameter as a covariate. Subjects who did not have a baseline measurement or did not have a final post baseline measurement within 3 days following the last dose of study medication were not included in these analyses.

Longitudinal Analyses of Laboratory Data

The primary chemistry variables were collected at weekly visits. Hematology and secondary chemistry were collected at baseline and at the final visit. Analyses of changes and/or percent changes from baseline were analyzed for each scheduled post-baseline visit and for the final visit.



Safety (Cont.):

Both "observed value" and "last value carried forward" methods were used for analyses at scheduled post-baseline visits. At a given visit, the change and/or percent change from baseline for each parameter was compared between treatment groups using a 1-way ANOVA with treatment as the factor. Also at a given visit, the change and/or percent change from baseline was compared between treatment groups using an analysis of covariance (ANCOVA) that included treatment as the factor and the baseline measurement for the parameter as a covariate. The ANCOVA analysis was performed to evaluate the sensitivity of the ANOVA model.

Analyses of Laboratory Data Using High and Low Criteria

Chemistry and hematology assessments were categorized as being Normal, High, Low, or Missing relative to the normal range provided. Shifts from baseline categories to the final assessment categories for each treatment group were summarized descriptively by treatment group using frequencies and percentages.

Analyses of Vital Sign Data

Descriptive summary statistics (*i.e.*, mean, standard error, minimum and maximum values) were provided for baseline vital sign measurements by treatment group. Baseline was defined as the last vital sign measurement obtained on or before the first dose of study medication. An ANOVA model was used to evaluate the equality of baseline means between treatment groups.

The mean change from baseline to the final measurement for each vital sign variable was compared between treatment groups using an ANOVA model with treatment as the factor. In addition, an ANCOVA model was used to evaluate the sensitivity of the ANOVA model that included treatment as the factor and the baseline measurement for the parameter as a covariate. Subjects who did not have a baseline vital sign measurement or have a final post baseline vital sign measurement within 3 days of the last dose of study medication were not included in these analyses.

Summary/Conclusions:**Efficacy Results:**

In the Per-Protocol Population (primary efficacy assessment) and Intent-to-Treat Population (secondary efficacy assessment), the proportion of subjects achieving at least 2 consecutive $\geq 30\%$ decreases from baseline iPTH in Group 1 (iPTH/80) was shown to be non-inferior to that of Group 2 (0.04 mcg/kg).

In the All Treated Subject Population, the ANCOVA did not detect a statistically significant difference between Group 1 (iPTH/80) and Group 2 (0.04 mcg/kg) in the mean percent change from baseline to final in iPTH. In addition, the mean percent change was not statistically significant based on the ANOVA model.

The ANCOVA detected a statistically significant difference between Group 1 (iPTH/80) and Group 2 (0.04 mcg/kg) in the mean percent change from baseline to final in bio-iPTH. Group 1 (iPTH/80) had a mean percent decrease from baseline of -36.5% pg/mL and Group 2 (0.04 mcg/kg) had a mean percent decrease from baseline of -23.0% pg/mL. In addition, the ANOVA model also detected a statistically significant difference in the mean percent change from baseline to final in bio-iPTH.



Efficacy Results (Cont.):

There was a statistically significant difference in the time to achieve the second decrease of at least 30% in iPTH between the treatment groups. The median days for Group 1 (iPTH/80) was 24 days compared to 45 days for Group 2 (0.04 mcg/kg).

There is a strong linear association between iPTH and bio-iPTH at baseline, each weekly visit, and at the final visit. The correlation coefficient at each of these time points is approximately 0.9.

Safety Results:

No statistically significant difference was observed between the treatment groups in the overall adverse event incidence rates or for the incidence of any specific adverse events. Fewer subjects in Group 2 (0.04 mcg/kg) reported treatment-emergent adverse events compared to Group 1 (iPTH/80).

Treatment-emergent adverse events (*i.e.* with onset after treatment began) were experienced by 46 (47.4%) subjects in Group 1 (iPTH/80) and 37 (35.9%) subjects in Group 2 (0.04 mcg/kg). The most commonly reported (≥ 4 subjects) treatment-emergent adverse events in Group 2 (0.04 mcg/kg) were hyperphosphatemia (10 subjects), pruritus, infection (5 subjects each), headache, pain, and hypervolemia (4 subjects each). The most commonly reported (≥ 4 subjects) treatment-emergent adverse events in Group 1 (iPTH/80) were hyperphosphatemia and hypertension (5 subjects each).

The majority of adverse events were considered by the Investigator to be mild or moderate in intensity; however, 9 subjects (4 in Group 1 [iPTH/80] and 5 in Group 2 [0.04 mcg/kg]) experienced treatment-emergent adverse events that were considered by the Investigator to be severe. Most adverse events were considered by the Investigator to be not related or probably not related to study drug. Eight (8) subjects in Group 1 (iPTH/80) and 5 subjects in Group 2 (0.04 mcg/kg) had treatment-emergent adverse events that were considered to be possibly or probably related to study drug.

Five (5) subjects (4 in Group 1 [iPTH/80] and 1 in Group 2 [0.04 mcg/kg]) died during the study; however, each of these deaths was considered by the Investigator to be probably not related or not related to study drug. Additionally, 1 subject (1222 in Group 1 [iPTH/80]) died prior to receiving study drug. Treatment-emergent SAEs were reported by 20 subjects (11 in Group 1 [iPTH/80] and 9 in Group 2 [0.04 mcg/kg]) during the Treatment and Follow-Up Phases, including 5 of the 6 deaths. None of these SAEs were considered by the Investigator to have a causal relationship to study drug.

Neither treatment group experienced clinically meaningful hypercalcemia defined as 2 consecutive calcium values greater than 11.0 mg/dL. The upper bound of the 95% confidence interval for the rate of clinically meaningful hypercalcemia is less than 4% in each treatment group.

Statistically significant treatment differences in mean change from baseline to the final visit were observed for corrected Ca \times P and serum phosphorus using an ANCOVA model with treatment as a factor and baseline as the covariate. Group 1 (iPTH/80) had mean increases from baseline of 10.49 mg²/dL² and 0.97 mg/dL in Ca \times P and Phosphorus, respectively. Group 2 (0.04 mcg/kg) had mean increases from baseline of 5.88 mg²/dL² and 0.53 mg/dL in Ca \times P and Phosphorus, respectively. The mean difference for the change from baseline to the final visit for corrected calcium was not significantly different between the 2 treatment groups.

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



Conclusions:

The primary objective of this randomized, active-controlled, double-blind, multicenter study was to show non-inferiority in the proportion of study subjects achieving at least 2 consecutive $\geq 30\%$ decreases from baseline iPTH between 2 treatment groups: a group receiving mcg dosing of Zemplar Injection based on the formula $iPTH/80$ and a group receiving mcg dosing of Zemplar Injection based on the US package insert with a starting dose of 0.04 mcg/kg.

In the Per-Protocol Population (primary efficacy assessment) and Intent-to-Treat Population (secondary efficacy assessment), the proportion of subjects achieving at least 2 consecutive $\geq 30\%$ decreases from baseline iPTH in Group 1 ($iPTH/80$) was shown to be non-inferior to that of Group 2 (0.04 mcg/kg).

In the All Treated Subject Population, the percent reduction of iPTH from baseline to final visit was greater for Group 1 ($iPTH/80$) compared to Group 2 (0.04 mcg/kg), however, it did not reach statistical significance. At Weeks 2, 3, 4, 6, and 7 there was a statistically significant difference between treatment groups for the percent change from baseline to each visit. In addition, there was a statistically significant difference in the time to achieve the second decrease of at least 30% in iPTH between the treatment groups. The median days for Group 1 ($iPTH/80$) was 24 days compared to 45 days for Group 2 (0.04 mcg/kg).

The ANCOVA detected a statistically significant difference between Group 1 ($iPTH/80$) and Group 2 (0.04 mcg/kg) in the mean percent change from baseline to final in bio-iPTH. The mean percent change from baseline to each weekly visit was statistically significantly different between treatment groups for Weeks 2 through 10 even though the average weekly dose of study drug was essentially the same between the 2 treatment groups by Week 5.

There is a strong linear association between iPTH and bio-iPTH at baseline, each weekly visit, and at the final visit. The correlation coefficient at each of these time points is approximately 0.9.

The treatments 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 methodology for determining the starting dose of Zemplar Injection.

Neither treatment group experienced clinically meaningful hypercalcemia, defined as 2 consecutive calcium values greater than 11.0 mg/dL. The upper bound of the 95% confidence interval for the rate of clinically meaningful hypercalcemia is less than 4% in each treatment group.

Statistically significant treatment differences in mean change from baseline to the final visit were observed for corrected Ca \times P and serum phosphorus using an ANCOVA model with treatment as a factor and baseline as the covariate. Group 1 ($iPTH/80$) had mean increases from baseline of 10.49 mg²/dL² and 0.97 mg/dL in Ca \times P and Phosphorus, respectively. Group 2 (0.04 mcg/kg) had mean increases from baseline of 5.88 mg²/dL² and 0.53 mg/dL in Ca \times P and Phosphorus, respectively. The mean difference for the change from baseline to the final visit for corrected calcium was not significantly different between the 2 treatment groups.

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

No statistically significant difference was observed between the treatment groups in the overall adverse event incidence rates or for the incidence of any specific adverse events. Fewer subjects in Group 2 (0.04 mcg/kg) reported treatment-emergent adverse events compared to Group 1 ($iPTH/80$).
