2.0 Synopsis

<table>
<thead>
<tr>
<th>Abbott Laboratories</th>
<th>Individual Study Table Referring to Item of the Submission: (For National Authority Use Only)</th>
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<tbody>
<tr>
<td>Name of Study Drug:</td>
<td>Zemplar Injection</td>
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<tr>
<td>Name of Active Ingredient:</td>
<td>Paricalcitol</td>
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<tr>
<td>Title of Study:</td>
<td>A Phase 4, Double-Blind, Placebo-Controlled, Multi-Center Study to Determine the Safety and Effectiveness of Zemplar® (Paricalcitol Injection) in Decreasing Serum Intact Parathyroid Hormone Levels in Pediatric End Stage Renal Disease Subjects on Hemodialysis</td>
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<tr>
<td>Investigator(s):</td>
<td>Multi-center; coordinating investigator. Removed for privacy reasons</td>
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<tr>
<td>Study Site(s):</td>
<td>14 study sites in the U.S. were selected and 11 sites enrolled subjects</td>
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<tr>
<td>Publications:</td>
<td>None</td>
</tr>
</tbody>
</table>
| Studied Period (Years): | Initiation Date: 28 January 2002  
                          | Completion Date: 03 January 2003                                                                 |
| Phase of Development: | 4                                                                                                |

Objective(s): The objective of this study was to characterize the efficacy and safety of Zemplar as compared to placebo in lowering iPTH levels in pediatric subjects with end-stage renal disease (ESRD) undergoing hemodialysis (HD).

Methodology:
This was a Phase 4, double-blind, placebo-controlled, multi-center study in pediatric ESRD subjects with secondary hyperparathyroidism (2° HPT) who were undergoing HD. A sufficient number of subjects were entered into the Pre-treatment Phase in order to obtain approximately 28 subjects (approximately one-quarter of the subjects under the age of 10 years) with a baseline iPTH measurement and 2 on-treatment iPTH measurements. Subjects were randomized (1:1) to receive either Zemplar or placebo.

The study was divided into 4 phases: Screening Phase, Pre-treatment Phase, Treatment Phase, and Follow-Up Phase.

Potential subjects underwent screening procedures in order to determine eligibility for the Pre-treatment Phase. During the Screening Phase, subjects or the subject's parent or legal guardian reviewed and signed the informed consent prior to the conduct of any study-specific screening procedures. A limited chemistry evaluation was performed for calcium, phosphorus, calcium-phosphorus product (Ca×P), iPTH, and albumin. Subjects with serum calcium (Ca) ≤ 10.5 mg/dL and Ca×P ≤ 70 and iPTH ≥ 100 pg/mL were eligible to enter the Pre-treatment Phase. If screening results were not consistent with the subject's history, a second blood sample could have been collected and the subject could have been rescreened 1 time.
Methodology: (continued)
The Pre-treatment Phase was defined as the 2- to 6-week period prior to the start of study drug administration. The purpose of the Pre-treatment Phase was to "wash out" any remaining vitamin D compounds and their carry-over effects from the subject's system and to establish baseline values. The length of the Pre-treatment Phase was dependent on the time it took the subject to achieve the appropriate lab criteria for entry into the Treatment Phase (Ca $\leq$ 10.5 mg/dL, Ca x P $\leq$ 70, and iPTH $\geq$ 300 pg/mL).

Subjects satisfying all inclusion/exclusion criteria were eligible for entry into the Treatment Phase. Qualified subjects were randomized in a 1:1 ratio to receive either Zemplar or placebo. Study drug was administered as a bolus dose 3 x weekly (no more frequently than every other day) at any time during HD. The initial dose of study drug was based on the degree of 2° HPT, as determined by the last iPTH value (< 500 pg/mL = 0.04 mcg/kg; $\geq$ 500 pg/mL = 0.08 mcg/kg) obtained at the final week of the Pre-treatment Phase (baseline iPTH), and the physician's prescribed-dry weight from that same week. Decisions to maintain, increase, or decrease the dose were based on limited chemistry results collected weekly. The initial dose level was maintained for Treatment Weeks 1 and 2. Dose decreases could have occurred weekly and dose increases could have occurred no more frequently than every other week, starting at Treatment Week 3. To limit exposure to inappropriately high levels of iPTH, subjects were to be withdrawn from the study if they had 2 consecutive iPTH values $> 700$ pg/mL after 4 weeks of treatment and if this level represented an increase from baseline, regardless of their phosphorus level. Safety was monitored through adverse event monitoring, the change from baseline in laboratory assessments, and the change from baseline in vital signs.

After the Treatment Phase, subjects entered the Follow-Up Phase. Subjects returned for study procedures at the Follow-Up Visit (approximately 2-7 days after the last dose of study drug) and were not to restart any vitamin D treatment until after the Follow-Up Visit was complete.

<table>
<thead>
<tr>
<th>Number of Subjects (Planned and Analyzed):</th>
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<tr>
<td><strong>Planned:</strong> 28 subjects (14 per treatment group) with a baseline and 2 on-treatment iPTH measurements.</td>
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<tr>
<td><strong>Analyzed:</strong></td>
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<tr>
<td>Evaluated for Primary Efficacy (Intent-to-Treat)</td>
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<tr>
<td>Evaluated for Safety and Other Efficacy (All Treated)</td>
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**Diagnosis and Main Criteria for Inclusion:**

A subject was selected for study participation if he/she met the following criteria:

- Subject had signed an IRB-approved informed consent form, or had one signed by a parent or legal guardian, prior to screening and the occurrence of any study related procedures.
- Subject was at least 2 years of age and no more than 20 years of age at their last birthday.
- Subject had ESRD and had been undergoing maintenance HD for at least 1 month prior to the Screening Phase.
- Subject was undergoing maintenance HD 3 x weekly and was expected to remain on HD for the duration of the study.
- If taking growth hormone, subject must have been receiving it for ≥ 3 months prior to the Screening Phase.
- For entry into the Pre-treatment Phase the subject must have had:
  - iPTH level of ≥ 100 pg/mL
  - corrected calcium level: ≤ 10.5 mg/dL
  - Ca×P level: ≤ 70
- For entry into the Treatment Phase the subject must have had:
  - iPTH level of ≥ 300 pg/mL
  - corrected calcium level: ≤ 10.5 mg/dL
  - Ca×P level: ≤ 70

The last iPTH, calcium and Ca×P values were obtained at the final week of the Pre-treatment Phase.

- Pubescent female subjects or female subjects ≥ 10 years of age, who were of childbearing potential, must have had a negative serum pregnancy test at Pre-treatment Week 1, must have been non-nursing and must have been using one of the following methods of contraception upon enrollment and must have continued to use one of these methods for the duration of the study:
  - total abstinence
  - hormonal contraceptive
  - barrier method
  - intrauterine device
  - surgical sterilization (bilateral tubal ligation or hysterectomy)
  - monogamous relationship with a vasectomized partner
### Diagnosis and Main Criteria for Inclusion: (continued)

Subjects were excluded for the following reasons:

- Subject had a history of an allergic reaction or significant sensitivity to drugs similar to the study drug.
- Subject had received partial parathyroidectomy within 1 year prior to the Screening Phase.
- Subject had acute renal failure within 3 months of the Screening Phase.
- Subject had taken aluminum-containing phosphate binders for > 3 weeks in the last 3 months prior to the Screening Phase, or required such medications for > 3 weeks during the study.
- Subject had a current malignancy, or clinically significant liver disease, in the opinion of the Investigator.
- Subject had a history of drug or alcohol abuse within 6 months prior to the Screening Phase.
- Subject was known to be human immunodeficiency virus (HIV) positive.
- 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.
- Subject had received any investigational drug within 30 days prior to the Screening Phase.
- Subject was taking maintenance calcitonin, glucocorticoids, or other drugs that may have affected calcium or bone metabolism.
- For any reason, subject was considered by the Investigator to be an unsuitable candidate to receive Zemplar injection.

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

Test product: Zemplar injection.

Dose: Initial dose was based on the degree of 2° HPT, as determined by the last iPTH value ($< 500 \text{ pg/mL} = 0.04 \text{ mcg/kg}; \geq 500 \text{ pg/mL} = 0.08 \text{ mcg/kg}$) obtained at the final week of the Pre-treatment Phase (baseline iPTH), and the physician's prescribed-dry weight from that same week.

Mode of administration: intravenous injection.

Lot numbers: 79-303-DK and 88-019-DK (resupply).

### Duration of Treatment:

Up to 12 weeks

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

Placebo, identical in appearance to Zemplar.

Dose: the quantity (mL) of placebo dosed was similar to that of the Zemplar group.

Mode of administration: intravenous injection.

Lot Numbers: 79-081-DK and 88-020-DK (resupply).
**Criteria for Evaluation:**

**Efficacy:** The primary efficacy endpoint was the achievement of 2 consecutive $\geq 30\%$ decreases from baseline in iPTH. The secondary efficacy endpoint was the proportion of subjects in each group who achieved 2 consecutive iPTH values below 300 pg/mL.

**Safety:** Safety was assessed through adverse event monitoring, the change from baseline in chemistry and hematology laboratory variables, and the change from baseline in a subject's vital signs. The incidence of hypercalcemia (corrected serum calcium $> 11.2$ mg/dL) was a secondary safety endpoint.

**Statistical Methods:**

**Efficacy:** The efficacy endpoint was the achievement of 2 consecutive $\geq 30\%$ decreases from baseline in iPTH; missing values were excluded. Baseline was defined as the last value obtained during the final week of Pre-treatment. Each subject either achieved the efficacy endpoint at some point during the trial or failed to achieve the efficacy endpoint throughout the trial (dichotomous outcome).

The primary efficacy endpoint was evaluated with statistical hypothesis testing utilizing subjects in the Intent-to-Treat population (full analysis set). A Fisher's exact test was used to test for a difference between treatment groups in the proportion of subject's achieving the efficacy endpoint.

The proportion of subjects in each treatment group who achieved 2 consecutive iPTH values below 300 pg/mL, a secondary efficacy endpoint, was evaluated with descriptive summary statistics.

**Safety:** The statistical safety summary was based on the incidence rates of adverse events, and the change from baseline in laboratory assessments and vital signs.

The proportion of subjects in each treatment group who achieved a corrected serum calcium level $> 11.2$ mg/dL, a secondary safety endpoint, was evaluated with descriptive summary statistics.

Adverse events were summarized by counts and percents using the most severe 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. An overall summary of adverse events was generated to show the numbers of subjects reporting adverse events, as well as an overall display of adverse events in descending order of incidence.
Summary/Conclusions:

**Efficacy Results:** A greater proportion of subjects in the Zemplar group (9/15, 60%) had 2 consecutive ≥ 30% decreases from baseline in iPTH compared with subjects in the placebo group (3/14, 21%). Although this difference was not statistically significant (p = 0.060), the 39% difference between the 2 treatment groups was considered clinically meaningful; a 95% confidence interval for the difference is given by -1% to 63%.

A statistically significantly (p = 0.021) greater proportion of subjects in the Zemplar group (9/15, 60%) had 2 consecutive ≥ 30% decreases from baseline in iPTH compared with subjects in the placebo group (2/14, 14%) when baseline was defined, per protocol, as the last iPTH value collected prior to or on the first day of treatment. A similar result was obtained when baseline was defined as the average of the last iPTH value collected prior to treatment and on the first day of treatment.

For subjects with a baseline iPTH level < 500 pg/mL, 1 of 4 (25%) subjects in the Zemplar group and 1 of 5 (20%) subjects in the placebo group had 2 consecutive ≥ 30% decreases from baseline in iPTH. For subjects with baseline iPTH levels ≥ 500 - ≤ 1000 pg/mL and > 1000 pg/mL, greater proportions of subjects in the Zemplar group (4/6, 67% and 4/5, 80%, respectively) had 2 consecutive ≥ 30% decreases from baseline in iPTH compared to subjects in the placebo group (1/5, 20% and 1/4, 25%, respectively).

Statistically significantly greater proportions of subjects in the Zemplar group had 3 consecutive ≥ 30% decreases from baseline in iPTH (p = 0.050) and 4 consecutive ≥ 30% decreases from baseline in iPTH (p = 0.035) compared with subjects in the placebo group.

There was a statistically significant (p = 0.027) difference between the treatment groups in mean change from baseline to the Final Visit in iPTH using ANOVA with treatment as the factor. The Zemplar group experienced a mean decrease (-164.13 pg/mL) from baseline to the Final Visit in iPTH while the placebo group experienced a mean increase (238.36 pg/mL); these changes within the treatment groups were not statistically significant.

The secondary efficacy endpoint was the proportion of subjects in each treatment group who achieved 2 consecutive iPTH values below 300 pg/mL. Few subjects in either treatment group achieved this endpoint (3/15, 20% Zemplar and 2/14, 14% placebo).
**Safety Results:** No statistically significant differences were observed between the Zemplar and placebo treatment groups for the overall incidence of adverse events or for any specific adverse event reported. Treatment-emergent adverse events were experienced by 10 of 15 (67%) of Zemplar subjects and 6 of 14 (43%) of placebo subjects. The majority of the adverse events reported in either treatment group were mild in severity (10/17, 59% Zemplar and 9/15, 60% placebo) and considered by the Investigator to be not related to study drug administration (14/17, 82% Zemplar and 11/15, 73% placebo). Among all Zemplar subjects, treatment-emergent adverse events reported by ≥ 2 subjects included peripheral vascular disorder (4 subjects), infection, infection bacterial, and rash (2 subjects each). Among all placebo subjects, treatment-emergent adverse events reported by ≥ 2 subjects included hemorrhage (2 subjects). No other treatment-emergent adverse events were reported by more than 1 subject in either treatment group.

No subjects died or prematurely terminated from the study due to adverse events. Overall, 10 subjects reported serious adverse events during the Pre-treatment, Treatment, and Follow-Up Phases of the study. All of the serious adverse events reported during any of the phases of the study were considered by the investigator to be not related to study drug.

No subjects in either the Zemplar group or placebo group developed hypercalcemia (defined as at least 1 calcium value > 11.2 mg/dL) during the study.

Although not statistically significant between the treatment groups, Zemplar-treated subjects had a decrease in alkaline phosphatase and a relatively small increase in bone specific alkaline phosphatase compared to increases observed among placebo-treated subjects. These differences may suggest a beneficial effect on bone disease associated with 2° HPT.

A statistically significant (p = 0.034) difference was observed between treatment groups in the mean change from baseline to the Final Visit in cholesterol; however, this difference was not considered clinically meaningful.

Evaluations of other laboratory analyses, vital signs and physical examinations revealed no clinically meaningful changes as a result of Zemplar treatment.

**Conclusions:**

Zemplar injection is safe and well tolerated for the treatment of 2° HPT in pediatric ESRD subjects. No statistically significant differences were observed between the Zemplar and placebo treatment groups for the overall incidence of adverse events or for any specific adverse events reported. No subjects in either the Zemplar group or placebo group developed hypercalcemia (defined as at least one calcium value > 11.2 mg/dL) during the study.
Conclusions: (continued)

A 39% difference in the efficacy response was seen in the Zemplar group compared to the placebo group and, although not statistically significant (p = 0.060), this result represents a clinically meaningful difference in response rates. In addition, 2 analyses were performed that redefined baseline value as the last iPTH value collected prior to or on the first day of treatment or as the average of the last iPTH value collected prior to treatment and on the first day of treatment. This resulted in statistically significant and clinically meaningful results (p = 0.021 in each respective analyses). Furthermore, the durability of the efficacy response was evaluated to demonstrate duration of effect by examining efficacy endpoints of 3 consecutive 30% decreases from baseline and 4 consecutive 30% decreases from baseline. These analyses resulted in statistically significant p-values of 0.050 and 0.035, respectively. The results of these post hoc efficacy analyses are supportive evidence of a statistically significant efficacy response between the Zemplar and placebo groups.

Date of the Report: 04 August 2003