U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-819 /SE5-014 (Pediatric Exclusivity)
Drug Name:	Zemplar (paricalcitol) injection
Indication(s):	Prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure
Applicant:	Abbott Laboratories
Date(s):	Submission: September 30, 2003 PDUFA: March 30, 2004
Review Priority:	Priority
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Keywords: Clinical study, NDA review, Pediatric exclusivity

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The proportion of patients who achieved 2 consecutive ≥30% decreases from baseline in PTH was 60% (9/15) vs. 21% (3/14), Zemplar vs. placebo (p=0.06). The total sample size of 29 patients provided 80% power to detect 80% vs. 20% response rates, a 60% difference between Zemplar and placebo. Thus, the result is not robust with such a small sample size. However, the sponsor stated although the difference was not statistically significant, the 39% difference between the 2 treatment groups was considered clinically meaningful.

1.2 Brief Overview of Clinical Studies

The objective of this pediatric study was to investigate the efficacy and safety of Zemplar as compared to placebo in lowering iPTH levels in pediatric patients with end stage renal disease (ESRD) undergoing hemodialysis (HD). The 12-week study examined a total of 29 pediatric patients 5-19 years of age (¼ patients <10 years) with chronic kidney disease Stage 5 (ESRD) in response to the formal Written Request issued on February 22, 2001. Eleven centers enrolled patients in the U.S. The primary efficacy comparison was the percentage of patients with 2 consecutive ≥30% decreases from baseline iPTH between Zemplar and placebo.

2. INTRODUCTION

2.1 Overview

Zemplar (paricalcitol injection), a synthetic vitamin D analog of calcitriol, was approved on April 17, 1998 for the prevention and treatment of secondary hyperparathyroidism (HPT) associated with chronic renal failure. The purpose of this double-blind, placebo-controlled study was to evaluate the safety and efficacy of Zemplar's for 2^{ndary} HPT in pediatric ESRD patients on HD and generate dosing information for pediatric use.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study Design and Endpoints

This was a multicenter, randomized, double-blind study to evaluate the safety and efficacy of Zemplar compared to placebo in lowering iPTH levels in pediatric patients with ESRD undergoing HD.

The primary efficacy variable was at least a ≥30% decrease from baseline in iPTH for 2 consecutive iPTH assessments.

Demographic and Baseline Characteristics

Eleven investigative sites in the US randomized 29 patients; 15 patients received Zemplar and 14 patients received placebo. 40% of patients in the Zemplar group and 29% of patients in the placebo group were < 13 years of age. 13% (2/15) of zemplar patients and 36% of (5/14) placebo patients were female. 47% of Zemplar patients and 57% of placebo patients were white.

Statistical Methodologies

The primary efficacy analysis was a comparison between the Zemplar and placebo treatment groups of the proportion of patients achieving at least 2 consecutive decreases from baseline in iPTH of at least 30% using the intent-to-treat population. This comparison was performed using the Fisher's exact test.

Results and Conclusions

Patient Disposition

Patient disposition is displayed in Table 1.

Table 1 Patient disposition by treatment group

	Zemplar (n=15)	Placebo (n=14)
Increased iPTH	4 (27%)	10 (71%)
Missed 3 consecutive doses of study drug	0 (0%)	1 (7%)
Other	1 (7%)	1 (7%)
Total withdrawal	5 (33%)	12 (86%)
Completers	10 (67%)	2 (14%)

A greater proportion of patients in the placebo group (71%) compared with the Zemplar group (27%) prematurely terminated from the study due to the protocol-specified withdrawal criterion of 2 consecutive iPTH values >700 pg/ml and greater than baseline after 4 weeks of treatment.

Primary analysis of efficacy

Table 2 presents the primary efficacy analysis results. Figures 1 and 2 in the appendix display the iPTH outcomes by patient.

Table 2 Proportion of patients with 2 consecutive ≥30% decreases from baseline in iPTH - ITT

Responders	Zemplar (n=15)	Placebo (n=14)	p-value
#	9 (60%)	3 (21%)	0.06

Secondary analysis of efficacy

The proportion of patients in each treatment group achieving at least 2 consecutive iPTH values below 300 pg/ml was 3 (20%) for the Zemplar group and 2 (14%) for the placebo group (Fig. 6).

The mean change and mean percent change from baseline of iPTH are summarized by treatment group in Table 3.

Table 3 Mean change and mean percent change from baseline to endpoint in iPTH - ITT

	Zemplar (n=15)	Placebo (n=14)
Mean baseline (SD)	841 (418)	740 (357)

Mean final (SD)	**677 (403)**	**979 (449)**
Mean change from baseline (SD)	**-164 (568)**	**238 (315)**
Mean % change from baseline (SD)	**2.3% (73.5)**	**43.6% (73.5)**

The mean dose of Zemplar was 4.6 (2.7) mcg with range of 0.8 mcg to 9.6 mcg.

3.2 Evaluation of Safety

The insufficient number of patients prohibits meaningful comparisons of calcium. In addition, a greater proportion of patients in the placebo group (86%) compared with the Zemplar group (33%) prematurely terminated from the study. Figures 7 to 9 display the Ca level for the two treatment groups.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Figures 3 to 5 in appendix display patient's iPTH by subgroups.

5. LABELING COMMENTS

6. SUMMARY AND CONCLUSIONS

The pediatric study demonstrated a 39% difference (60% vs. 21%) in response rates between Zemplar and placebo in the primary efficacy variable, 2 consecutive ≥30% decreases from baseline in iPTH (p=0.06).

APPENDICES

Figure 1 Individual patient iPTH change from baseline (circle) to endpoint (square) by treatment and response (Yes, or No) of the 2 consecutive 30% reduction from baseline - ITT

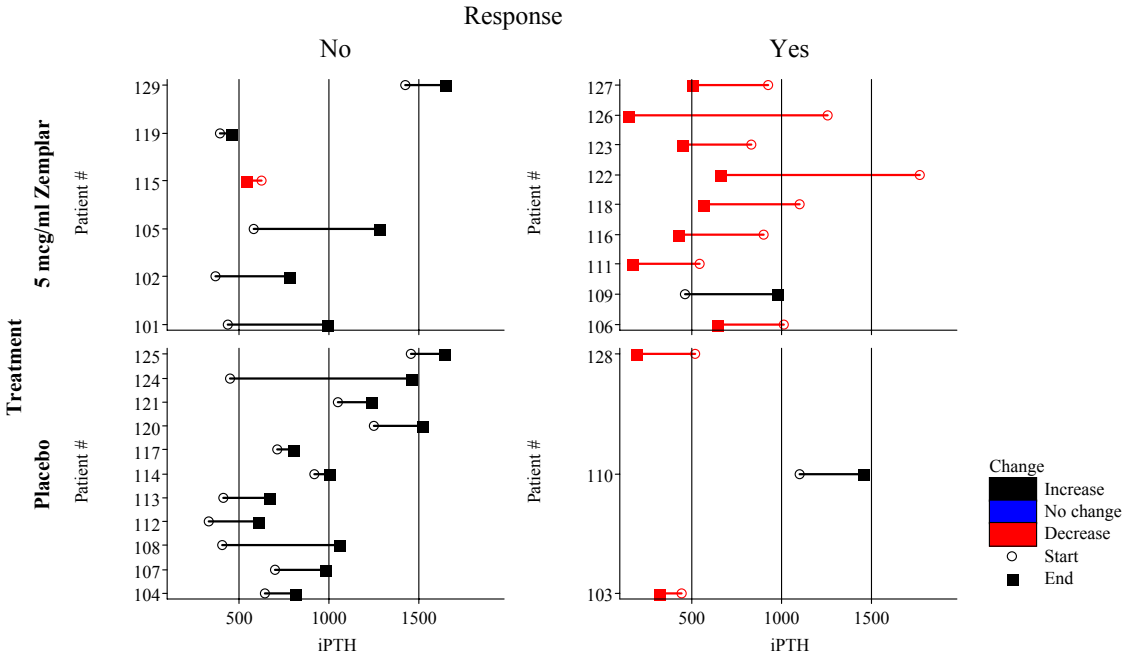
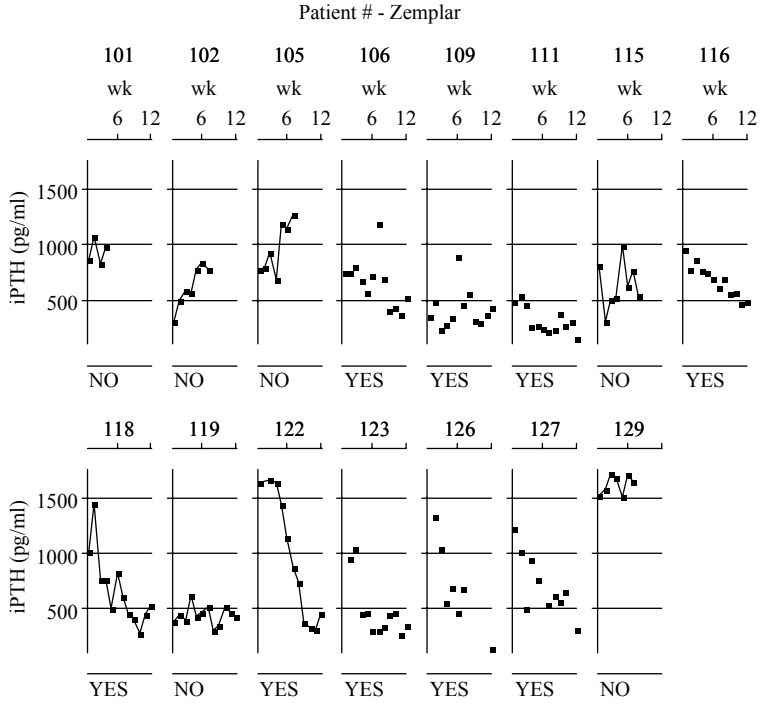


Figure 2 iPTH value from week 1 (no baseline) for responder (YES) and non-responder (NO)



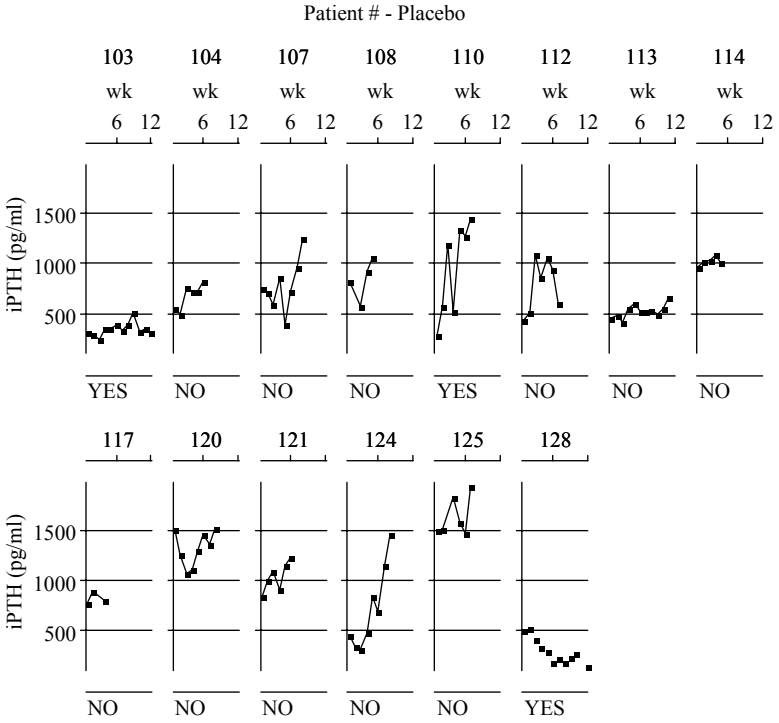

Patient # - Placebo
103
104
107
108
110
112
113
114
wk
6
12
iPTH (pg/ml)
1500
1000
500
YES
NO
NO
NO
YES
NO
NO
NO
117
120
121
124
125
128
iPTH (pg/ml)
1500
1000
500
NO
NO
NO
NO
NO
YES

Figure 3 iPTH change from baseline to endpoint by treatment group, age and response of 2 consecutive ≥30% reduction - ITT

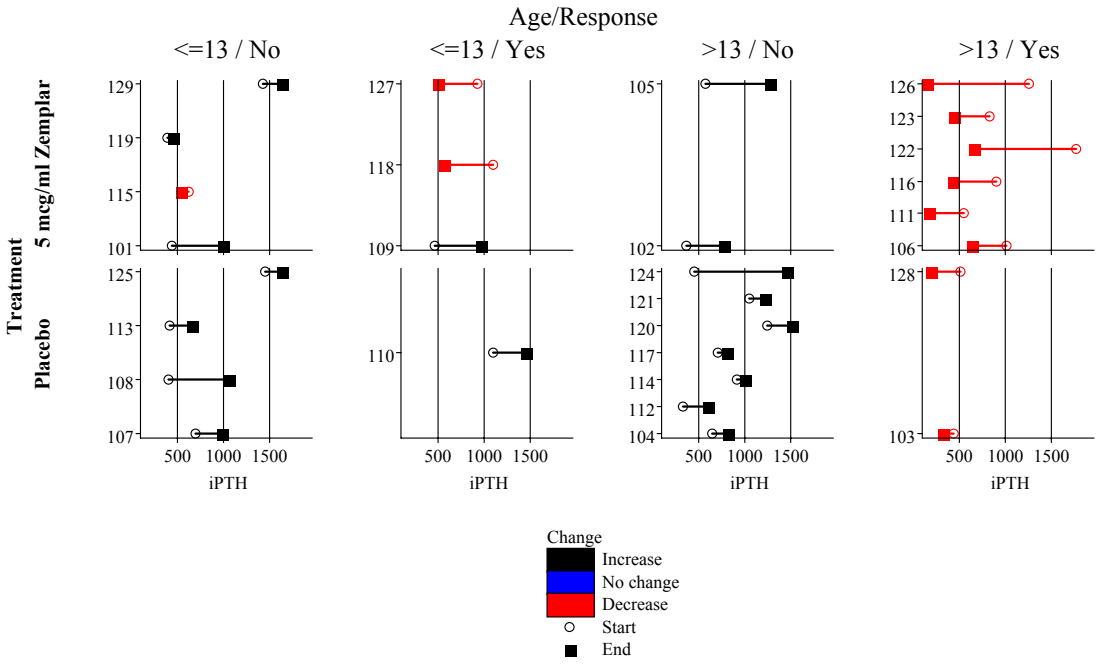


Figure 4 iPTH change from baseline to endpoint by treatment group, race and response of 2 consecutive ≥30% reduction - ITT

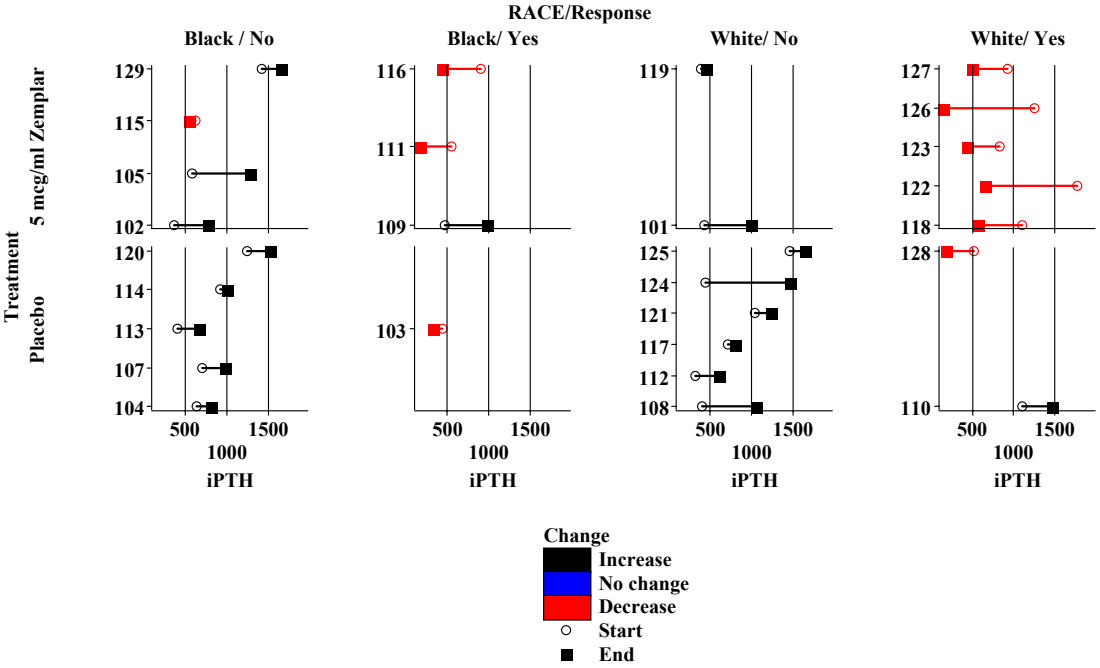


Figure 5 iPTH change from baseline to endpoint by treatment group, gender and response – ITT (LOCF)

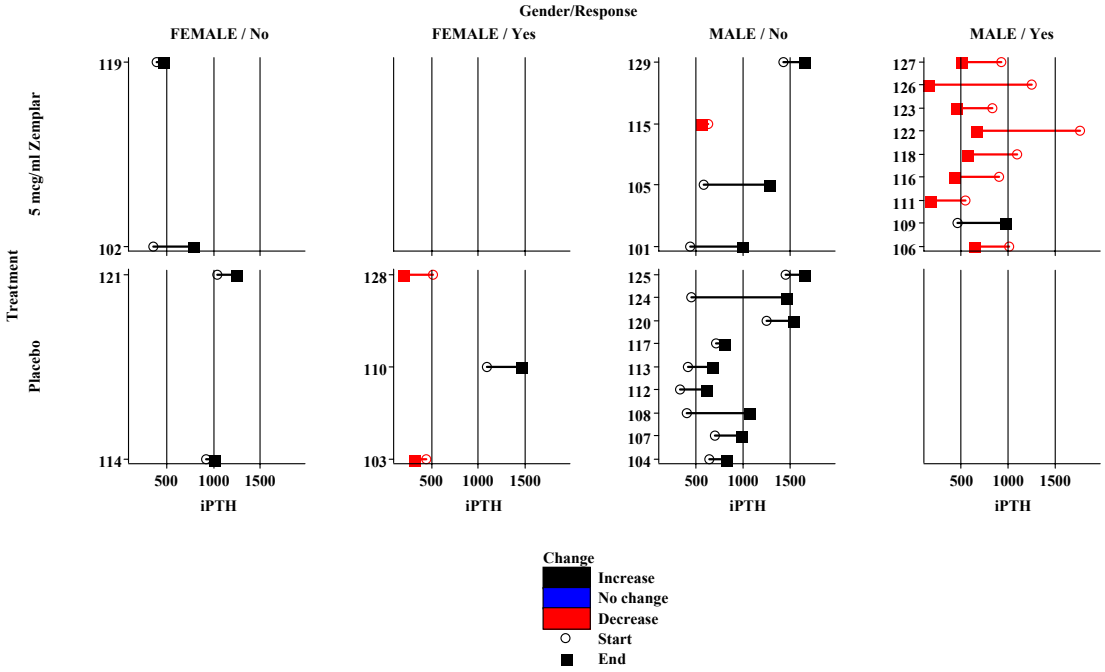


Figure 6 iPTH change from baseline to endpoint by endpoint level ≤ 300 or > 300 – ITT (LOCF)

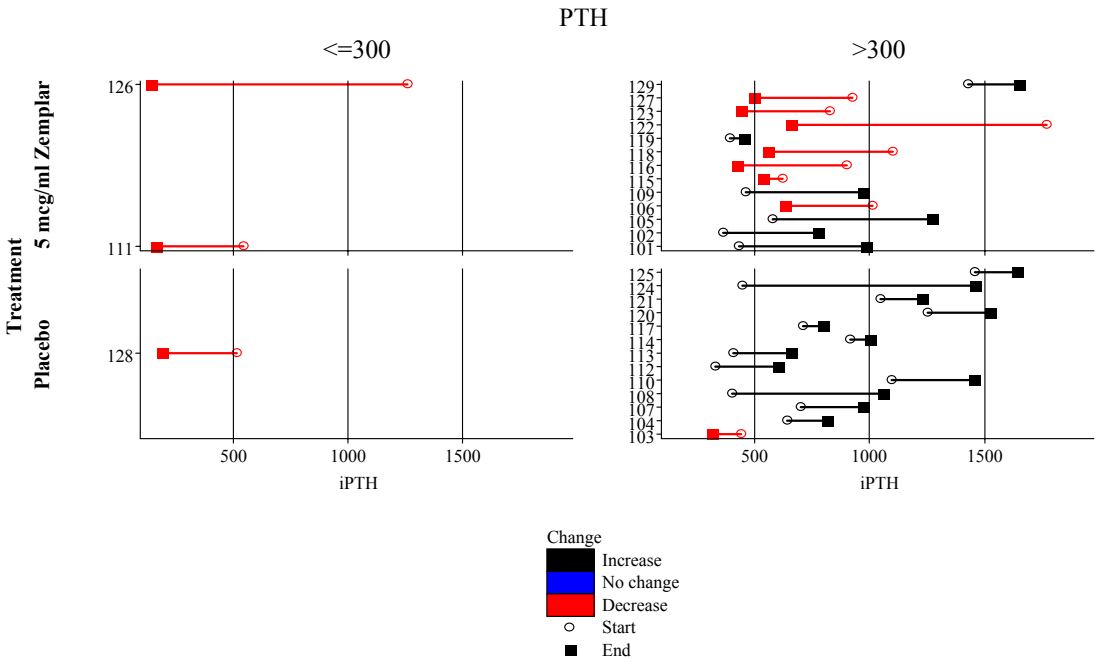


Figure 7 Mean Ca value by iPTH response – ITT (LOCF)

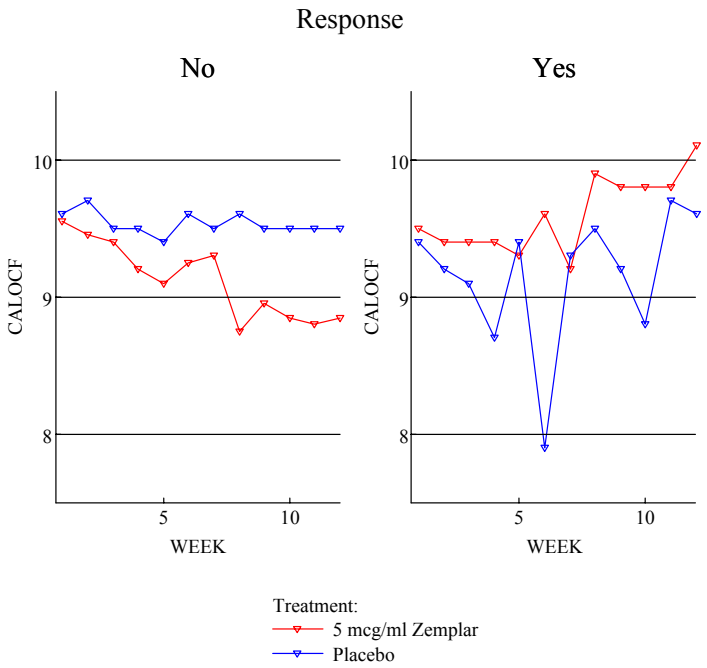


Figure 8 Individual patient Ca change from baseline (circle) to endpoint (square) by treatment and response (Yes, or No) of 2 consecutive 30% reduction from baseline in iPTH – ITT (LOCF)

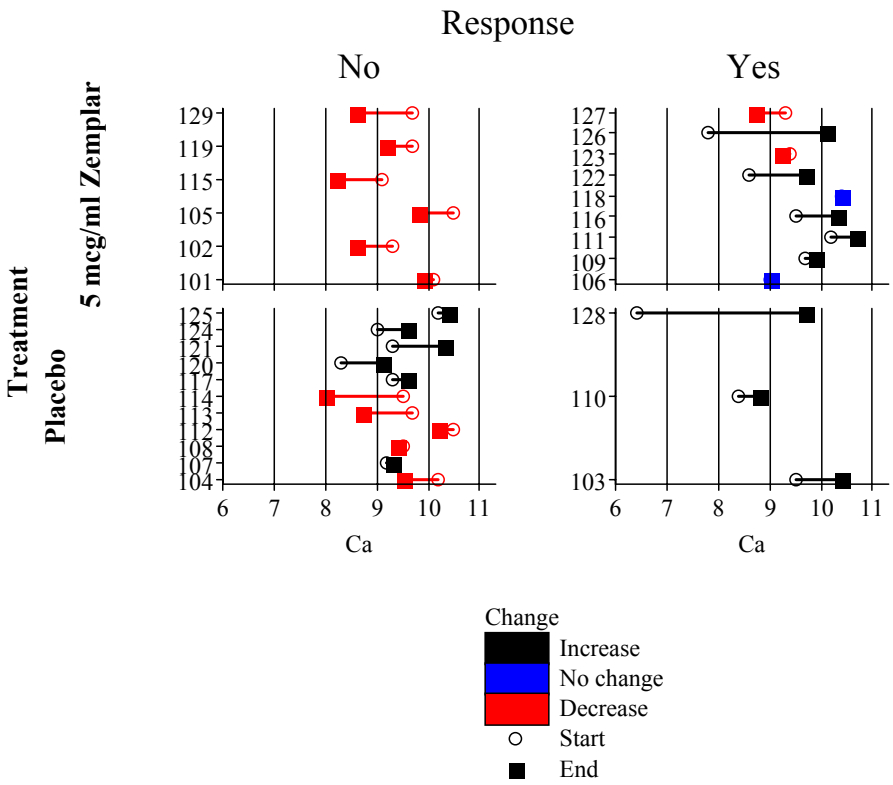
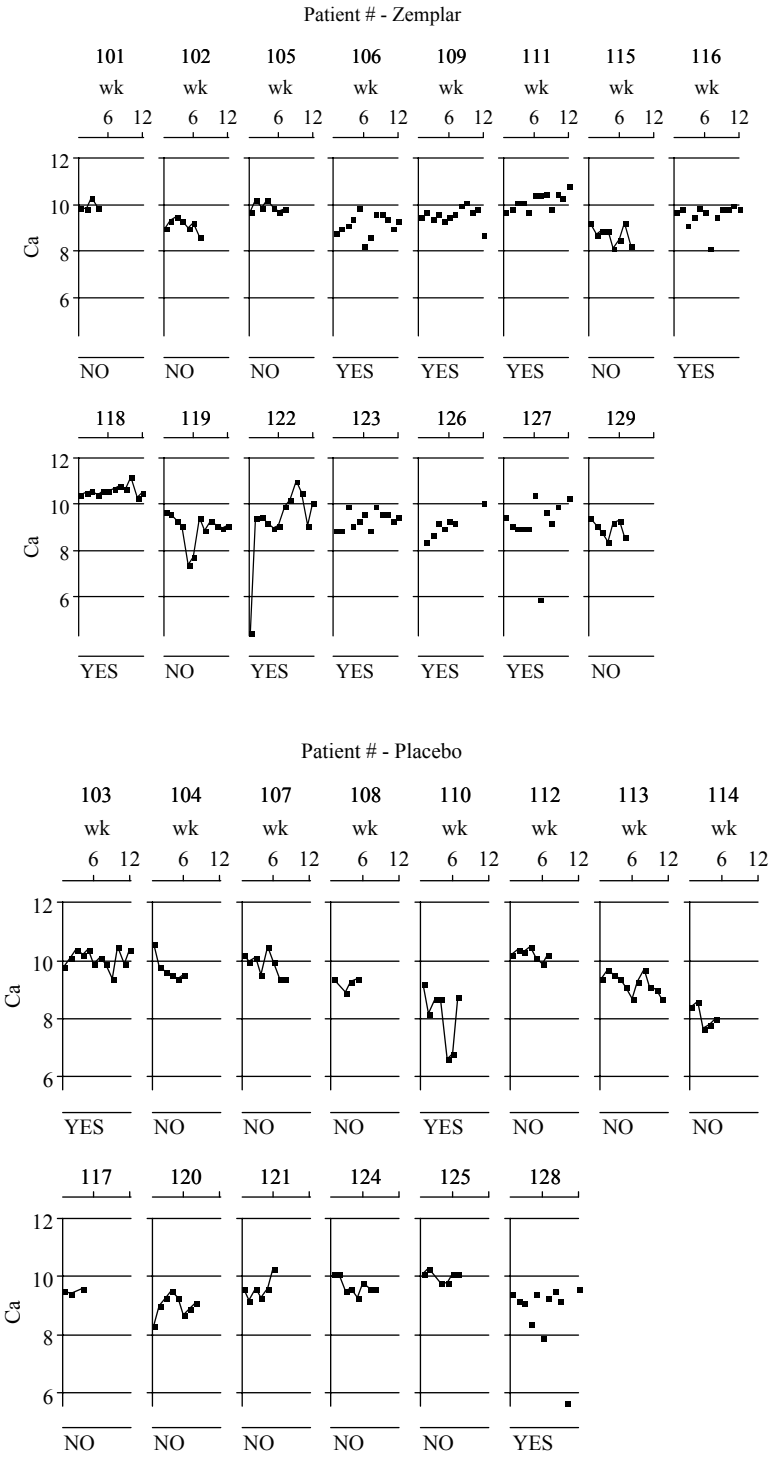


Figure 9 Patient Ca value over time with iPTH response (Yes, or No)



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