CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021068 and 18044/S025

STATISTICAL REVIEW(S)

Weber

Statistical Review and Evaluation

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NDA#: 18-044 S025/Class 3S

Applicant: Hoffmann-La Roche Inc.

Name of Drug: Rocaltrol Capsules/Oral Solution (Calcitriol)

Indication: Secondary Hyperparathyroidism in Patients with Moderate to Severe Chronic Renal Failure

Document Reviewed: Vols. 1, 23-34
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Medical Reviewer: Eric Colman M.D. (HFD-510)

Background:

Calcitriol is a hormone metabolically activated in the liver and the kidney from vitamin D3. It increases the absorption of calcium from the intestinal tract. Rocaltrol was approved in 1978 and is indicated in the management of hypocalcemia and the resultant metabolic bone disease in patients undergoing chronic renal dialysis. The off-label use is for treatment of secondary hyperparathyroidism in patients with moderate to severe chronic renal failure (creatine clearance of _____ mL/min), especially in children.

In this supplemental NDA, there are one Hoffmann-La Roche-sponsored, double-blind, placebo-controlled trial and five controlled trials from the literature which used calcitriol or alfacalcidol to support the indication of Rocaltrol in predialysis patients. Also, a literature-based review of 28 additional clinical studies in adults and 16 clinical studies in pediatric patients were included.

This review focuses on the Hoffmann-La Roche sponsored clinical trial, N2086.

Controlled Clinical Study N2086

This was a double-blind, parallel-group, placebo-controlled study at 3 U.S. centers. This 12-month study was conducted from December 1979 to January 1985.

The objective of the study was to assess the value of Rocaltrol for prevention and/or correction of renal osteodystrophy in predialysis renal insufficiency patients. Males and females 18 to 70 years old with a moderate renal failure were enrolled in the study. Moderate renal failure was defined as having creatinine clearances between _____ ml/min. Amendment 1 of the protocol decreased the lower limit from _____ (1/15/81).

After enrollment completion, the upper limit was increased from _____ because some patients were slightly above the 50 ml/min upper limit. The assignment to the treatment or control group was by matching patients (by a third party) with respect to the degree of renal insufficiency as determined by creatinine clearance. This assignment procedure was later changed to "Patients will be assigned sequentially to assure randomization with respect to administration of drug or placebo" (Amendment #2, 4/1/82).

The protocol planned to randomize 100 patients with predialysis renal insufficiency (creatinine clearance of _____ ml/min) for a year. Efficacy measurements included 1. anterior iliac crest biopsy after tetracycline labeling before treatment and after at least 1 year of treatment 2. serum iPTH, alkaline phosphatase and $1,25(OH)_2D_3$ 3. ^{47}Ca absorption (optional) and 4. Neutron activation and total body counting (optional).

The dose started at 2.5 µg/day. After two months, monthly increments of 2.5 µg/day to a maximum of four times of 2.5 µg/day (1.0 µg/day) was allowed. All patients received one multivitamin tablet per day containing 400 IU of vitamin D.

Statistical Analyses

The sponsor analyzed the trial data initially in 1988 using analysis of variance. The sponsor indicated that the results were statistically significant in favor of Rocaltrol. In this submission, the sponsor decided to reanalyze the data "because the original methodology lacked statistical rigor and did not thoroughly explicate the study results." Specifically, the present analysis was based on the analysis of covariance with baseline measurement as the covariate. In addition, to address the multiplicity issue, the present analysis used a statistical method (O'Brien, P.C., Biometrics 40, 1079-1087, 1984) to provide an overall assessment of treatment differences.

For analysis of data, the protocol stated that "Data will be subjected to standard statistical analyses to detect differences between the control and experimental groups."

Study Results:

A total of 51 patients were randomized, 25 to the Rocaltrol treatment group and 26 to the placebo treatment group. Five patients in each treatment group were withdrawn from the study prematurely. Seven of the 10 patients were lost to follow-up. One Rocaltrol patient refused treatment. Two placebo patients died during the study.

Patient Population

The intent-to-treat population includes all randomized patients who received at least one dose of treatment, had a baseline measurement, and at least one on-treatment measurement. For biochemical data, the last available observation was carried forward (LOCF). For the bone structural parameters, only patients with a baseline and one year histomorphometry data were evaluated in the analysis. The standard population (STD) included patients who met all inclusion and exclusion criteria, and completed one year of double-blind treatment. Table 1 displays the patient population.

Table 1 Patient Population by Center

	USC		NCMC		DCGH		Total	
	Rocaltrol	Placebo	Rocaltrol	Placebo	Rocaltrol	Placebo	Rocaltrol	Placebo
Randomized	16	16	7	7	2	3	25	26
ITT	16	16	7	6	2	3	25	25
STD	14	13	4	6	2	2	20	21
ITT (bone biopsy)	12	9	3	5	1	1	16	15

Patient demographic and baseline characteristics are displayed in Table 2.

Table 2 Patient Demographic and Baseline Characteristics

		Rocaltrol n=25	Placebo n=25	p
Sex	Male	16 (64%)	13 (52%)	0.6
	Female	9 (36%)	12 (48%)	
Age	Mean (SD)	50.3 (14.5)	50.4 (11.1)	1.0
	Median	49.0	49.0	
	Range			
Race	Caucasian	8 (32%)	12 (48%)	0.26
	Black	16 (64%)	13 (52%)	
	Oriental	1 (4%)	0	
Creatinine Clearance (ml/min)	Mean (SD)	30.3 (12.0)	31.9 (14.3)	0.7
	Median	29.2	28.3	
	Range			
Duration of Treatment (days)	Mean (SD)	360.3 (116.1)	386.5 (121.0)	0.4
	Median	388.0	396.0	
	Range			

Efficacy Results

A total of 31 patients (15 placebo, 16 Rocaltrol) were in the bone biopsy ITT population for histomorphometric assessment. The STD population is identical to the histomorphometry ITT population.

Primary bone histomorphometric outcomes were classified as bone resorption, bone formation, and bone mineralization indices. A total of 7 outcomes were in the three classes as follows:

- Bone Resorption
  1. Osteoclast Index (OCI) (count/mm^2)
  2. Surface density of bone-osteoclast interface (S-VOCL) (mm^2/cm^3)
  3. Percent fibrosis (FIB) (%) = percentage of bone surface touching areas of marrow fibrosis.

- Bone Formation
  1. Osteoblast index (OBI) (count/mm^2)=fraction of endosteal surface covered with osteoblasts
  2. Surface density of osteoid seams (S-VOS) (mm^2/cm^3)
  3. Volume density of osteoid (V-VOS) (mm^2/cm^3)

- Bone Mineralization
  1. Mineralization lag time (MLT) (days) = time between formation of osteoid and subsequent mineralization of this osteoid.

For each of the primary bone histological outcomes, a decrease means improvement.

The baseline bone histomorphometric characteristics are displayed in Table 3.

Table 3 Baseline Bone Histomorphometric Characteristics

	Rocaltrol				Placebo				p
Baseline	Mean	SD	Min	Max	Mean	SD	Min	Max	
Osteoblast Index	**4.93**	4.43			**5.81**	5.75			**0.64**
Percent Fibrosis	**1.28**	1.82			**1.57**	1.64			**0.64**
Mineralization Lag Time	**25.19**	12.72			**18.01**	9.90			**0.11**
Osteoclast Index	**0.99**	0.99			**1.45**	1.02			**0.20**
Surface Density of Interface	**43.16**	42.28			**59.86**	42.39			**0.28**
Volume Density of Osteoid	**14.10**	11.79			**12.61**	12.39			**0.73**
Surface Density of Osteoid Seams	**1673.98**	856.99			**1520.73**	745.79			**0.60**

Sponsor's Analysis

The sponsor performed covariance analysis for the primary outcome variables. The model included treatment, baseline (covariate) but center was not in the model. The sponsor's results are displayed in Table 4.

Table 4 Sponsor's Covariance Analysis – LSM Change from Baseline of Bone Histomorphometric Outcomes

	Rocaltrol n=16		Placebo n=15		Treatment Effect Rocaltrol – Placebo				p
Baseline	LSM	SE	LSM	SE	Diff	SE	LCL	UCL	ancova
Osteoblast Index	**-4.16**	1.67	**0.73**	1.73	**-4.88**	2.41	-9.82	0.06	**0.053**
Percent Fibrosis	**-1.04**	0.94	**1.03**	0.97	**-2.07**	1.35	-4.84	0.70	**0.137**
Mineralization Lag Time*	**-8.79**	1.76	**-3.76**	1.76	**-5.02**	2.53	-10.28	0.24	**0.060**
Osteoclast Index	**-0.81**	0.15	**-0.11**	0.15	**-0.70**	0.21	-1.14	-0.26	**0.003**
Surface Density of Interface	**-24.16**	8.17	**7.59**	8.44	**-31.76**	11.87	-56.06	-7.45	**0.012**
Volume Density of Osteoid	**-9.00**	2.15	**-24.16**	8.17	**-11.17**	3.09	-17.51	-4.83	**0.001**
Surface Density of Osteoid Seams	**-653.95**	229.58	**345.21**	237.14	**-999.17**	330.85	-1676.89	-321.44	**0.005**

* n=12 each group

The p-value from the O'Brien overall assessment was 0.011 between the treatment groups.

Sponsor's Analyses on Primary Biochemical Measurements

The primary biochemical indices of secondary hyperparathyroidism in this study were serum iPTH concentration and serum alkaline phosphatase (SAP) activity. The mean change from baseline was not statistically significant for either measurements (iPTH, p=0.338; SAP, p=0.083). Nonparametric analysis of the composite primary biochemical data based on the O'Brien test was also not statistically significant between treatment groups (p=0.190).

Table 5 Sponsor's Analyses on Primary Biochemical Parameters

Parameter	Rocaltrol		Placebo		p
	Mean	SD	Mean	SD	
Serum Parathyroid Hormone (iPTH), uLeq/mL)					
Baseline	**34.43**	21.66	**35.94**	25.04	
1 Year	**25.85**	19.38	**32.65**	25.11	
Change (Mean)	**-8.58**	26.68	**-3.29**	28.22	
Change (LS Mean)	**-9.07**	4.39	**-2.66**	4.92	0.338
Serum Alkaline Phosphatase (IU/L)					
Baseline	**125.73**	72.06	**148.24**	142.94	
1 Year	**92.18**	64.43	**142.56**	165.14	
Change	**-33.56**	51.08	**-5.68**	59.81	
Change (LS Mean)	**-33.64**	11.27	**-5.59**	11.27	0.083
Overall p-value based on O'Brien test					0.190

Reviewer's Comment

The O'Brien methodology is based on ranking each outcome variable and then sum the ranks of all the outcome variables for each subject to a total rank score. Wilcoxon rank sum test was carried out on the total rank score to compare treatment groups. In the article, the author stated that "We emphasize that the proposed procedures are suggested as a supplement (not an alternative) to univariate methods.'

Reviewer's Analysis

This reviewer performed analysis of variance as a sensitivity analysis on the bone histomorphometric outcomes. In addition, p-values from the nonparametric Wilcoxon rank sum test are displayed in Table 5.

Table 5 Reviewer's Analyses with Mean Change from Baseline of Bone Histomorphometric Outcomes

	Rocaltrol n=16		Placebo n=15		Treatment Effect Rocaltrol – Placebo				p	
Baseline	Mean	SE	Mean	SE	Diff	SE	LCL	UCL	t-test	Wilcoxon
Osteoblast Index	**-3.83**	1.92	**0.37**	1.98	**-4.20**	2.76	-9.84	1.44	0.139	0.109
Percent Fibrosis	**-1.04**	0.92	**1.03**	0.95	**-2.07**	1.33	-4.78	0.64	0.128	0.205
Mineralization Lag Time*	**-11.63**	3.50	**-1.04**	0.92	**-10.72**	4.96	-21.00	-0.44	0.042	0.035
Osteoclast Index	**-0.62**	0.26	**-0.32**	0.27	**-0.29**	0.37	-1.06	0.47	0.437	0.678
Surface Density of Interface	**-18.90**	10.52	**1.98**	10.87	**-20.88**	15.12	-51.81	10.06	0.178	0.138
Volume Density of Osteoid	**-9.40**	2.69	**2.59**	2.78	**-11.99**	3.87	-19.90	-4.08	0.004	0.004
Surface Density of Osteoid Seams	**-678.29**	234.56	**371.17**	242.25	**-1049.46**	337.19	-1739.10	-359.82	0.004	0.009

* n=12 each group

Conclusion

The sponsor planned to study 100 patients with predialysis renal insufficiency; however, the primary analysis on bone histomorphometry evaluated only 31 patients (24 patients on mineralization lag time). From the sponsor's analysis of covariance, 4 of the 7 variables were statistically significant and 3 showed trends favoring Rocaltrol. The overall assessment test of O'Brien was statistically significant. However, the O'Brien test is considered post hoc since the protocol referred to the use of "standard statistical analyses" which the O'Brien test is not. Three of the 7 variables were statistically significant favoring Rocaltrol using the 2-sample t-test.

/S/

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HFD-510
HFD-510/SSobel
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HFD-510/EColman
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