DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-690/N-000
Drug Name:	ORTHO TRI-CYCLEN® (norgestimate and ethinyl estradiol) Tablets
Indication(s):	Treatment of osteoporosis associated with anorexia nervosa
Applicant:	Ortho-McNeil Pharmaceutical, Inc.
Date(s):	Received 11/18/04; user fee (6 months) 05/19/05
Review Priority:	Priority (pediatric exclusivity)
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Treatment with ORTHO TRI-CYCLEN® after 6 months based on the whole intention-to-treat (ITT) population and after 1 year based on the completers showed statistically significant increases in mean change or mean % change from baseline in lumbar spine bone mineral density (BMD) compared with placebo. However, the strength of evidence was only marginal. In addition, the observed treatment differences between the 2 study groups in mean lumbar spine BMD at Cycles 6 and 13 were smaller than the expected 6-month (0.05 g/cm^2) and 1-year (0.076 g/cm^2) differences, respectively. Therefore, concluding a clinically meaningful difference in this case might be in question. Also, treatment with ORTHO TRI-CYCLEN® after 6 months and 1 year did not show any statistically significant positive findings when compared with placebo for total hip BMD and body weight. Nevertheless, numerically larger mean or mean % changes from baseline in lumbar spine BMD, total hip BMD, and body weight were generally observed in the ORTHO TRI-CYCLEN® group than in the placebo group.

The sponsor proposed to claim the statistical significance of ORTHO TRI-CYCLEN® following 6 months and 1 year of treatment compared with placebo in improving lumbar spine BMD. This reviewer suggests using only descriptive statistics, not statistical significance, in the label since the data did not provide strong and consistent evidence.

1.2 Brief Overview of Clinical Studies

ORTHO TRI-CYCLEN® is a progestin and estrogen combined oral contraceptive, approved for the prevention of pregnancy in women and for the treatment of moderate acne vulgaris in females ≥15 years of age. This submission to NDA 21-690 evaluates the effect of ORTHO TRI-CYCLEN® on BMD of lumbar spine (L1-L4) and total hip (non-dominant) in post-menarcheal female subjects (<18 years old) with confirmed anorexia nervosa.

The submission contains one Phase II, randomized, double-blind, placebo-controlled trial, conducted in 43 USA centers. A total of 123 subjects were treated with either ORTHO TRI-CYCLEN® or placebo (1:1 ratio) for 13 consecutive 28-day cycles. The primary efficacy variable was absolute change from baseline in lumbar spine BMD at Cycle 6.

From the statistical point of view, this pediatric study was conducted in accordance with the FDA's original Written Request (11/12/02) and the 2 amendments (01/15/03 and 08/15/03). In order to obtain marketing exclusivity extension, with the agency's agreement, the sponsor had submitted the 6-month (6-cycle) interim data on 09/24/03. The current submission for

the Final Clinical Study Report for Protocol CAPSS-169 is a response to the FDA's approvable letter dated 03/23/04.

1.3 Statistical Issues and Findings

There were no serious statistical issues noted in this submission. In general, this reviewer's findings agree with the sponsor's conclusions. The following table summarizes the results based on the 6-month and 1-year data using the sponsor's random center effect model. Similar results were also seen when center was treated as a fixed effect.

ITT Population with last observation carried forward	ORTHO TRI-CYCLEN (N = 53)	Placebo (N = 59)	Treatment Difference	95% (LCL, UCL)
Primary Efficacy Endpoint at Cycle 6				
Change in lumbar spine BMD	0.0201 ± 0.0041	0.0072 ± 0.0040	0.0129 *	(0.0020, 0.0237)
Secondary Efficacy Endpoint at Cycle 6				
% Change in lumbar spine BMD	2.5159 ± 0.4803	0.8866 ± 0.4651	1.6293 *	(0.3545, 2.9040)
Change in total hip BMD	0.0104 ± 0.0043	0.0026 ± 0.0043	0.0078	(-0.0028, 0.0184)
% Change in total hip BMD	1.3894 ± 0.5024	0.4566 ± 0.4969	0.9328	(-0.3055, 2.1711)
Change in body weight	4.1805 ± 0.7485	2.9822 ± 0.7396	1.1983	(-0.6564, 3.0530)
% Change in body weight	9.1822 ± 1.5633	6.6141 ± 1.5357	2.5681	(-1.4130, 6.5493)
Secondary Efficacy Endpoint at Cycle 13				
Change in lumbar spine BMD	0.0265 ± 0.0059	0.0177 ± 0.0058	0.0088	(-0.0061, 0.0236)
% Change in lumbar spine BMD	3.1984 ± 0.6996	2.2251 ± 0.6901	0.9734	(-0.7668, 2.7135)
Change in total hip BMD	0.0113 ± 0.0055	0.0132 ± 0.0054	-0.0019	(-0.0157, 0.0119)
% Change in total hip BMD	1.5075 ± 0.6298	1.7857 ± 0.6220	-0.2783	(-1.8435, 1.2870)
Change in body weight	6.7302 ± 1.0653	4.7710 ± 1.0277	1.9592	(-0.8911, 4.8094)
% Change in body weight	14.954 ± 2.2780	10.803 ± 2.1588	4.1514	(-2.1141, 10.417)

* = Significant at $0.01 < p \leq 0.05$; LCL = Lower confidence limit; UCL = Upper confidence limit

The mean increase or mean % increase from baseline in lumbar spine BMD at Cycle 6 was nominally significantly larger in the ORTHO TRI-CYCLEN® group than in the placebo group. However, no such significant finding was observed for lumbar spine BMD at Cycle 13 or for total hip BMD and body weight at either cycle.

Although the overall withdrawal rate by Cycle 13 was high (28%), this reviewer does not feel this was the reason for the lack of significant findings at Cycle 13 because the study was over powered for the 1-year endpoint of lumbar spine BMD. Rather, the insignificance observed at Cycle 13 for change in lumbar spine BMD was due to the differential effect of dropouts in

the two treatment groups, that is, the ORTHO TRI-CYCLEN® treated patients who withdrew early showed a mean decrease from baseline, while the placebo dropouts showed a mean increase. There was a nominally significant treatment effect of ORTHO TRI-CYCLEN® compared to placebo when completers (subjects who took 13 cycles of drug and completed all visits) were analyzed alone. This reviewer performed some sensitivity analyses for Cycle 13 data by taking the effects of dropouts into consideration and also found no significant evidence favoring ORTHO TRI-CYCLEN® in increasing lumbar spine BMD.

Since the medical officer has concerns about the eligibility of enrollment for some patients, several subgroups based on different definitions of anorexia nervosa considered by Dr. Gierhart were investigated. They are:

1. Baseline/Visit 2 body mass index (BMI) $\geq 10^{th}$ percentile for age on the CDC Growth Chart versus $< 10^{th}$ percentile
2. Subjects with identified factors such as high % of ideal body weight at screening, high baseline BMI, positive baseline lumbar spine Z-score, etc. versus subjects without these factors
3. Screening/Visit 1 body weight $\geq$ 90% of ideal body weight versus < 90%
4. Weight gain from screening to last visit > 20 lbs. versus $\leq$ 20 lbs.
5. Subjects with identified factors specified in No. 2 above plus weight gain > 20 lbs. versus subjects without these factors

All the analyses showed consistent treatment effects across the subgroups on mean change from baseline in lumbar spine BMD at Cycle 13 and non-significant treatment differences between the 2 study groups within each subgroup.

Overall, lumbar spine BMD, total hip BMD, and body weight of the study subjects in both groups were improved over the 13-cycle treatment period. Numerically larger mean or mean % changes from baseline in the 3 efficacy variables evaluated were generally observed in the ORTHO TRI-CYCLEN® group than in the placebo group.

2. INTRODUCTION

2.1 Overview

ORTHO TRI-CYCLEN® is a progestin and estrogen combined oral contraceptive, approved for preventing pregnancy in women and for treating moderate acne vulgaris in females ≥15 years old (see NDAs 19-653, 19-697, and 20-681). According to the sponsor, currently, there are no definitive placebo-controlled studies evaluating the effectiveness of oral contraceptive treatment on bone mineral density (BMD) in pediatric females with anorexia nervosa. In response to the FDA's Written Request, the sponsor has conducted a 1-year placebo-controlled trial and submitted its 6-month interim data to NDA 21-690 on 09/24/03, to evaluate the effect of ORTHO TRI-CYCLEN® on lumbar spine (L1-L4) and total hip (non-dominant) BMD in post-menarcheal female subjects (<18 years old) with a diagnosis of anorexia nervosa. In response to the FDA's approvable letter dated 03/23/04, the sponsor is now submitting the Final Clinical Study Report for Protocol CAPSS-169.

This submission contains the data and results for the whole 1-year randomized, double-blind, placebo-controlled, multicenter trial (see the table below). The subjects were treated with either ORTHO TRI-CYCLEN® or placebo for 13 consecutive 28-day cycles. Note that Cycle 6 was the primary time point for efficacy assessment and the related data had been reviewed statistically and summarized on 02/25/04 (DFS check-in date). This review report evaluates the 1-year data in its totality.

Protocol No. Investigators	Study Design Start Date – Completion Date	Dose (N)	Age/Gender/ Race	Primary Endpoint
CAPSS-169 43 investigators 43 centers in 22 states (USA)	Phase II, 1-year, randomized, double-blind, placebo-controlled, multicenter study to evaluate bone mineral density in pediatric subjects with anorexia nervosa 09/18/02 – 04/02/04	ORTHO TRI-CYCLEN in 28-day blistercard (61) Placebo (62)	10 – 17 years (Mean = 15.12) F: 123 (100%) White: 110 (89.4%) Others: 13 (10.6%)	Change from baseline in bone mineral density of lumbar spine at Cycle 6

N = Number of subjects randomized and received medication
Others include African-American, Asian, Hispanic, and Native American

2.2 Data Sources

The study report this reviewer reviewed is located in \\Cdsesub1\n21690\N_000\2004-11-18\clinstat\capss-169.pdf. The electronic data files this reviewer used are located in \\Cdsesub1\n21690\N_000\2004-11-18\crt\Datasets\CAPSS-169\FDA. In general, those files (primeff.xpt, secneff.xpt, and bodywgt.xpt) were easy to work with. However, the last-observation-carried-forward (LOCF) indicator was only linked with Cycle 13/Final Visit, not with Cycle 6 time point, which made the re-analyses of the first 6-month data somewhat difficult. Also, this reviewer found that the first 6 cycles of data for some subjects in this

submission are slightly different from the ones in the previous submission. The sponsor explained in the e-mail on 04/15/05 that the changes were due to having additional longitudinal instrument quality control data available at the end of the study which were not available for the interim analysis or were acquired after that time point.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Protocol CAPSS-169 was a Phase II, 1-year, randomized, double-blind, placebo-controlled, multicenter (in USA) trial, conducted in females from age 12 to, but not including, age 18 with confirmed anorexia nervosa according to the modified Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) guideline. The subjects were randomized in a 1:1 ratio to receive either ORTHO TRI-CYCLEN® or matching placebo for 13 consecutive 28-day cycles.

The objective of this study was to determine the effect of ORTHO TRI-CYCLEN® on lumbar spine and total hip BMD in pediatric subjects with anorexia nervosa. The primary efficacy variable was absolute change from baseline in lumbar spine BMD at Cycle 6. The secondary efficacy variables listed in the protocol were absolute change from baseline in lumbar spine BMD at Cycle 13 and absolute change from baseline in total hip BMD at Cycles 6 and 13. In addition, the Written Request also calls for percentage change from baseline in lumbar spine and total hip BMD at Cycles 6 and 13 and change and percentage change from baseline in body weight at Cycles 6 and 13 as the secondary variables.

Sixty subjects per group was expected to provide 80% power to detect a 0.050 gm/cm^2 difference in total lumbar spine BMD between the two treatment groups at Cycle 6 with a common SD = 0.096 g/cm^2. This was based on the assumption that a 2/3 of end of 1-year treatment difference, 0.076 g/cm^2, can be achieved by 6 months.

Note that Screening visit was Visit 1 (up to Day –7) which was different from Baseline visit/Visit 2 (Day 1). Dual Energy X-ray Absorptiometry (DXA) scans on lumbar spine and total hip were performed at Screening/Visit 1, Cycle 6/Visit 6, and Cycle 13/Final Visit. Body weights were taken at all visits, except Cycle 3/Visit 4. Therefore, the last measurement prior to the first dose of the double-blind treatment period was defined as baseline for change and percentage change in body weight. Throughout the report, whenever change and percentage change from ‘baseline’ in lumbar spine or total hip BMD appear, they refer to change and percentage change from ‘Screening’.

3.1.2 Statistical Methods

Absolute change from baseline in total lumbar spine BMD (primary efficacy endpoint) was analyzed by analysis of covariance (ANCOVA) techniques with treatment and center as the main factors and baseline lumbar spine BMD as the covariate. Since there were a large number of centers with a small number of subjects or with subjects in only 1 treatment group, the sponsor treated center as a random factor. To check the robustness of the results, this reviewer also analyzed the data by using center as a fixed effect. To avoid sparseness problem and reduce subjectivity during the combining process after the fact, study centers were pooled by this reviewer in 2 different approaches. First, they were combined according to Census Regions defined by the US Bureau of the Census (West, Midwest, Northeast, and South). Second, they were grouped into 5 categories based on their center numbers in the ascending order.

The same analysis technique was also used for all the aforementioned secondary efficacy variables. Intention-to-treat (ITT) population, defined as all randomized subjects who received at least 1 dose of double-blind study medication, had an baseline value, and had at least 1 on-treatment BMD measurement, was the primary efficacy data set. Last observation carried forward (LOCF) approach was used for subjects who withdrew early.

Since the submission of Cycle 6 data was to obtain marketing exclusivity, not to render an ultimate decision on the acceptability of the study, multiplicity adjustment between Cycle 6 and Cycle 13 analyses was not made.

3.1.3 Subject Disposition

A total of 146 subjects were randomized, but only 123 (from 43 centers in 22 states) received study medication. Among those 123 subjects, 61 of them received ORTHO TRI-CYCLEN® and 62 of them received matching placebo, which met the sample size requirement by the Written Request (60 per group).

The overall withdrawal rates prior to Cycle 6 and Cycle 13 were 14.6% (= 18/123) and 27.6% (= 34/123), respectively, where the ORTHO TRI-CYCLEN® group consistently showed a higher dropout rate by Cycles 6 and 13 than the placebo group (Table 1). However, the reasons for discontinuation were not statistically different between the two treatment groups (Fisher-Freeman-Halton exact test p = 0.4533). Subjects' choice was apparently the most common recorded reason for withdrawal in this trial.

In the current submission, there were 11 subjects with no on-treatment DXA scans compared to 13 subjects in the previous submission. According to the sponsor, this discrepancy was due to Center No. 16 that had failed to schedule the Cycle 6 DXA scans for 2 subjects prior

to the 6-month interim data cut-off date. They are now included in this submission and the ITT population consisted of 112 subjects (53 and 59 for ORTHO TRI-CYCLEN® and placebo, respectively).

Table 1 – Subject Disposition (Sponsor's End-of-Text Table 1)

	ORTHO TRI-CYCLEN	Placebo	Total
Randomized	73	73	146
Randomized and received medication	**61**	**62**	**123**
Completed through Cycle 6	48 (78.7%)	57 (91.9%)	105 (85.4%)
Discontinued prior to Cycle 6	13 (21.3%)	5 (8.1%)	18 (14.6%)
Completed through Cycle 13	40 (65.6%)	49 (79.0%)	89 (72.4%)
Discontinued prior to Cycle 13	21 (34.4%)	13 (21.0%)	34 (27.6%)
Reason: Subject choice	11 (18.0%)	6 (9.7%)	17 (13.8%)
Protocol violation	1 (1.6%)	0	1 (0.8%)
Limiting adverse event	3 (4.9%)	1 (1.6%)	4 (3.3%)
Lost to follow-up	4 (6.6%)	3 (4.8%)	7 (5.7%)
Other	2 (3.3%)	3 (4.8%)	5 (4.1%)

Tables 2 and 3 below show subject distributions after combining the study centers for the ITT population. The numbers of subjects between the 2 treatment groups were roughly similar across the 4 regions defined by the US Census Regions or the 5 categories defined by this reviewer (Fisher-Freeman-Halton exact test p = 0.3282 and 0.9945, respectively).

Table 2 – Number of ITT Subjects in Each US Census Region

US Census Region	Midwest	Northeast	South	West	Total
ORTHO TRY-CYCLEN	12	7	23	11	53
Placebo	15	12	16	16	59
Total Subjects	27	19	39	27	112
Total Centers Pooled	6	10	14	10	40

Midwest includes MN, MO, WI, IL, OH; Northeast includes CT, MA, RI, NJ, NY, PA; South includes OK, KY, FL, NC, WA, VA, MD; West includes WA, CA, UT, AZ.

Table 3 – Number of ITT Subjects in Each Category Based on Center Number

Category	1	2	3	4	5	Total
ORTHO TRI-CYCLEN	8	13	16	7	9	53
Placebo	10	14	19	8	8	59
Total Subjects	18	27	35	15	17	112
Total Centers Pooled	9	8	9	6	8	40

Category 1 contains Centers 001 to 015; Category 2 contains Centers 016 to 043; Category 3 contains Centers 050 to 070; Category 4 contains Centers 078 to 098; Category 5 contains Centers 100 to 114.

3.1.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics of the 123 randomized subjects, such as age, weight, height, body mass index (BMI), age at menarche, duration of secondary amenorrhea, lumbar spine BMD, total hip BMD, and Z-score of lumbar spine BMD, were similar between the 2 treatment groups (Table 4). Subject distributions in race, center, region, primary amenorrhea (yes/no), and previous estrogen use (yes/no) were also similar between the 2 study groups. Note that although the Written Request calls for recruiting pediatric patients from age 12 to 17 years, there were 1 patient enrolled at 10 and 1 patient at 11 years old. All patients were female in this study and almost 90% of them were Caucasian. The mean age was 15.1 years and approximately 90% of the subjects did not have any primary amenorrhea. In addition, almost 79% of the subjects were enrolled with a negative lumbar spine BMD Z-score. Similar findings were also observed for the 112 ITT subjects based on the sponsor's analyses.

Table 4 – Demographic and Baseline Characteristics of Randomized Subjects Receiving Medication

Characteristic		ORTHO TRI-CYCLEN	Placebo	Total
Age (year):	Mean ± SD	15.16 ± 1.37 (61)	15.08 ± 1.43 (62)	15.12 ± 1.39 (123)
	Range	10 – 17	11 – 17	10 – 17
	<12	1 (1.64)	1 (1.61)	2 (1.63)
	≥12	60 (98.36)	61 (98.39)	121 (98.37)
Race:	Caucasian (%)	55 (90.16)	55 (88.71)	110 (89.43)
	African-American (%)	1 (1.64)	2 (3.23)	3 (2.44)
	Asian (%)	0	2 (3.23)	2 (1.63)
	Other (%)	5 (8.20)	3 (4.84)	8 (6.50)
Weight (kg):	Mean ± SD	47.44 ± 7.17 (61)	46.98 ± 7.51 (62)	47.21 ± 7.32 (123)
	Range	35.83 – 84.13	28.57 – 70.07	28.57 – 84.13
Height (cm):	Mean ± SD	162.77 ± 7.69 (61)	162.94 ± 7.00 (62)	162.86 ± 7.32 (123)
	Range	139.70 – 179.07	147.32 – 180.34	139.70 – 180.34
BMI (kg/m^2):				
	Mean ± SD	17.89 ± 2.25 (61)	17.65 ± 2.27 (62)	17.77 ± 2.25 (123)
	Range	14.47 – 27.39	12.71 – 23.49	12.71 – 27.39
	≥10^{th} percentile for age	39 (63.93)	37 (59.68)	76 (61.79)
	<10^{th} percentile for age	22 (36.07)	25 (40.32)	47 (38.21)
Age at menarche (year):				
	Mean ± SD	12.31 ± 1.18 (52)	12.58 ± 1.34 (59)	12.45 ± 1.27 (111)
	Range	10 – 15	10 – 16	10 – 16
	≤13 (median)	55 (90.16)	49 (79.03)	104 (84.55)
	>13 (median)	6 (9.84)	13 (20.97)	19 (15.45)

Table 4 – Demographic and Baseline Characteristics of Randomized Subjects Receiving Medication (Contd.)

Characteristic	ORTHO TRI-CYCLEN	Placebo	Total
Duration of secondary amenorrhea (month):			
Mean ± SD	9.05 ± 8.23 (52)	8.89 ± 8.30 (59)	8.96 ± 8.23 (111)
Range	0.3 – 36.1	0.4 – 32.7	0.3 – 36.1
≤7.3 (median)	34 (55.74)	34 (54.84)	68 (55.28)
>7.3 (median)	27 (44.26)	28 (45.16)	55 (44.72)
Primary amenorrhea:			
No (%)	52 (85.25)	59 (95.16)	111 (90.24)
Yes (%)	9 (14.75)	3 (4.84)	12 (9.76)
Prior hormone therapy used:			
No (%)	58 (95.08)	56 (90.32)	104 (84.55)
Yes (%)	3 (4.92)	6 (9.68)	9 (15.45)
Lumbar spine BMD:			
Mean ± SD	0.9110 ± 0.1229 (61)	0.8928 ± 0.1212 (62)	0.9018 ± 0.1219 (123)
Range	0.597 – 1.216	0.635 – 1.254	0.597 – 1.254
Total Hip BMD:			
Mean ± SD	0.8825 ± 0.1047 (61)	0.8755 ± 0.1360 (62)	0.8790 ± 0.1211 (123)
Range	0.654 – 1.120	0.611 – 1.300	0.611 – 1.300
Z-score of lumbar spine BMD:			
Mean ± SD	-0.6839 ± 0.982 (61)	-0.8101 ± 0.979 (62)	-0.7475 ± 0.978 (123)
Range	-3.207 – 1.933	-3.189 – 1.300	-3.207 – 1.933
Negative (%)	47 (77.05)	50 (80.65)	97 (78.86)
Non-negative (%)	14 (22.95)	12 (19.35)	26 (21.14)

3.1.5 Efficacy Results and Discussion

Following are the sponsor's efficacy findings based on the 12-month data of ITT population.

- Treatment with ORTHO TRI-CYCLEN® for 6 cycles significantly increased the mean lumbar spine (L1-L4) BMD compared with placebo.
- Treatment with ORTHO TRI-CYCLEN® for 13 cycles did not significantly increase the mean lumbar spine (L1-L4) BMD compared with placebo. However, in a subgroup who completed >12 cycles (i.e., >336 days), the ORTHO TRI-CYCLEN® group had a significantly greater mean increase in lumbar spine BMD compared with placebo at both Cycles 6 and 13.
- Treatment with ORTHO TRI-CYCLEN® for 6 cycles and 13 cycles did not significantly increase the mean total hip BMD compared with placebo.
- Treatment with ORTHO TRI-CYCLEN® for 6 cycles and 13 cycles did not significantly increase the mean body weight compared with placebo.

In general, this reviewer's results agree with the sponsor's conclusions. The following are the discussions based on this reviewer's analyses.

BMD of Lumbar Spine (L1-L4). Both ORTHO TRI-CYCLEN® and placebo groups showed increased means in lumbar spine BMD from baseline to Cycle 6 and then to Cycle 13 in the ITT population with LOCF techniques (Table 5, Figure 1). The mean change from baseline at Cycle 6 (primary efficacy variable) was significantly larger in the ORTHO TRI-CYCLEN® group than in the placebo group using either random ($p = 0.0214$) or fixed center effect models. However, no such significant finding was observed for the mean change from baseline at Cycle 13 ($p = 0.2437$, Figure 2). Likewise, a significant mean % change from baseline was seen in the active treatment group compared to the placebo group at Cycle 6 ($p = 0.0130$), but not at Cycle 13 ($p = 0.2684$).

Since there were a few subjects in the ORTHO TRI-CYCLEN® group having extreme observations (see Appendix I for box-plots), this reviewer also performed a Wilcoxon-Mann-Whitney test (a non-parametric test) which used data from all the ITT subjects without excluding any outliers, and found similar results to the parametric test (i.e., exact $p = 0.0197$ and 0.3532 for mean change from baseline at Cycles 6 and 13, respectively). In addition, non-significant finding at Cycle 13 was also observed when prognostic factors such as duration of secondary amenorrhea at entry, age at menarche, baseline BMI, and baseline body weight, or confounding factor such as body weight change from screening to last visit (>20 lbs or ≤20 lbs) were included in the statistical model. Since the results between Cycles 6 and 13 were not consistent, this reviewer performed a repeated measures analysis of covariance, where cycle is the repeated factor, to examine the overall treatment effect. Both study groups showed a significantly mean increase from baseline in lumbar spine BMD; however, the overall treatment difference (= 0.01086 g/cm^2) between the 2 study groups after taking time factor into consideration were not statistically significant ($p = 0.0774$).

Note that the observed treatment difference in mean lumbar spine BMD at Cycle 6, 0.0329 g/cm^2 (= 0.9282 – 0.8953), was smaller than the expected difference, 0.05 g/cm^2, used for the power and sample size calculation in the study. Similar phenomenon was also observed for the mean % change from baseline at Cycle 6, where the treatment difference was only about 1.4%, much smaller than 6%, a clinically meaningful difference translated from 0.05 g/cm^2 by Dr. Shu-Chen Wu from Ortho-McNeil Pharmaceutical, Inc. in the telephone conference on 05/31/02.

Table 5 – Results for Lumbar Spine BMD Using ITT Population with LOCF Approach

	ORTHO TRI-CYCLEN	Placebo	Treatment Difference	p-value	95% (LCL, UCL)
Raw mean lumbar spine BMD ± standard deviation (sample size)					
Baseline	0.9085 ± 0.1176 (53)	0.8869 ± 0.1199 (59)	0.0216		
Cycle 6	0.9282 ± 0.1074 (53)	0.8953 ± 0.1168 (59)	0.0329		
Cycle 13	0.9349 ± 0.1164 (53)	0.9059 ± 0.1107 (59)	0.0290		
Change at Cycle 6	0.0197 ± 0.0361 (53)	0.0084 ± 0.0242 (59)	0.0113		
Change at Cycle 13	0.0264 ± 0.0458 (53)	0.0190 ± 0.0375 (59)	0.0074		
%Change at Cycle 6	2.4445 ± 4.4552 (53)	1.0379 ± 2.7230 (59)	1.4066		
%Change at Cycle 13	3.1358 ± 5.6311 (53)	2.4134 ± 4.4550 (59)	0.7224		
Least-squares mean change from baseline ± standard error (sample size) – using random effect model					
Cycle 6	0.0201 ± 0.0041 (53)	0.0072 ± 0.0040 (59)	0.0129	0.0214	(0.0020, 0.0237)
Cycle 13	0.0265 ± 0.0059 (53)	0.0177 ± 0.0058 (59)	0.0088	0.2437	(-0.0061, 0.0236)
Least-squares mean % change from baseline ± standard error (sample size) – using random effect model					
Cycle 6	2.5159 ± 0.4803 (53)	0.8866 ± 0.4651 (59)	1.6293	0.0130	(0.3545, 2.9040)
Cycle 13	3.1984 ± 0.6996 (53)	2.2251 ± 0.6901 (59)	0.9734	0.2684	(-0.7668, 2.7135)

Figure 1

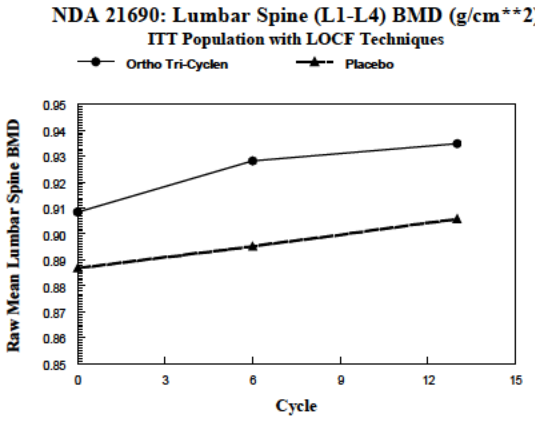
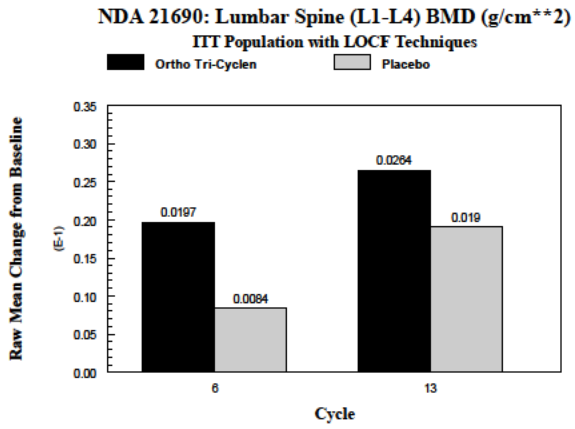


Figure 2



Since the overall withdrawal rate by Cycle 13 was high (28%) in this study, this reviewer analyzed the percentage change from baseline for the 89 completers (subjects who took 13 cycles of drug and completed all visits) and 23 dropouts (excluding the 11 subjects without any on-treatment scans) separately. As shown in Table 6, a significantly greater mean % increase in lumbar spine BMD from baseline at Cycle 13 was observed in the ORTHO TRI-CYCLEN® group than in the placebo group for the completers ($p = 0.0256$), but not for the dropouts ($p = 0.3544$). In fact, the dropout patients showed a mean % decrease from baseline

in the active treatment group, while the placebo group showed an increase (Figure 3). This finding explains why the treatment difference between the 2 study groups at Cycle 13 based on the whole ITT population using LOCF techniques was not significant (p = 0.2684). In other words, when those dropouts' last available observations were used as their Cycle 13 values, it produced a negative impact on the treatment effect of ORTHO TRI-CYCLEN®.

Table 6 – Additional Analyses for Lumbar Spine BMD Using ITT Population

	ORTHO TRI-CYCLEN	Placebo	Treatment Difference	p-value
Least-squares mean % change from baseline at Cycle 13 ± standard error (sample size)				
Completers	4.5548 ± 0.7083 (40)	2.3933 ± 0.6459 (49)	2.1615	0.0256
Dropouts	-0.4434 ± 1.2357 (13)	1.4696 ± 1.4092 (10)	-1.9131	0.3544
All w/ LOCF	3.1984 ± 0.6996 (53)	2.2251 ± 0.6901 (59)	0.9734	0.2684
All – 1 w/ LOCF	3.6392 ± 0.6307 (52)	2.2124 ± 0.6092 (59)	1.4268	0.0860
All w/ Imputation	3.7649 ± 0.5878 (53)	2.2360 ± 0.5669 (59)	1.5290	0.0566

All w/ LOCF: Last-observation-carried-forward technique used for the dropouts

All –1 w/ LOCF: Same as All w/ LOCF, but excluding an Ortho Tri-Cyclen treated subject (No. 010003)

All w/ Imputation: Replace % change from baseline of Ortho dropouts with mean value of placebo dropouts

Figure 3

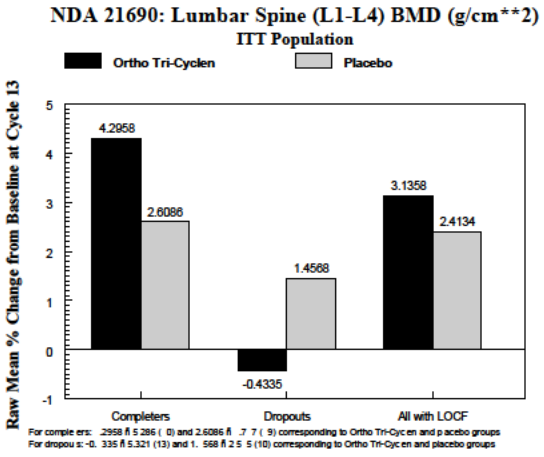
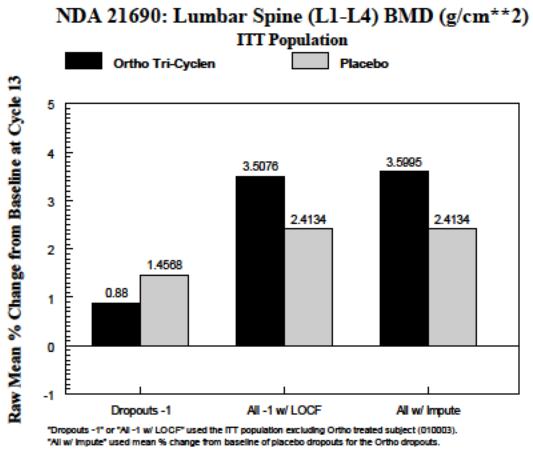


Figure 4



Figures 5 and 6 present the profiles of dropouts in the active treatment and placebo groups, respectively. Although the baselines of this sub-population were similar between the 2 study groups (0.8978 ± 0.093 and 0.8897 ± 0.092), one can see that there was more post-baseline variability among the ORTHO TRI-CYCLEN® treated patients than that of the placebo treated ones. Note that Subject 010003 in the active treatment group had more than 11% lumbar spine BMD loss from baseline at Cycle 6 and 16% at Cycle 9. This reviewer re-analyzed the whole ITT population without this particular subject and the non-significant

result at Cycle 13 remained (p = 0.0860, Table 6, Figure 4). Also, assuming the response pattern of the ORTHO TRI-CYCLEN® dropouts was similar to that of the placebo ones and replacing their % change values with the mean of the placebo dropouts, the testing result still did not give convincing evidence (p = 0.0566, Table 6, Figure 4) to strongly favor ORTHO TRI-CYCLEN® over placebo in increasing lumbar spine BMD.

Figure 5

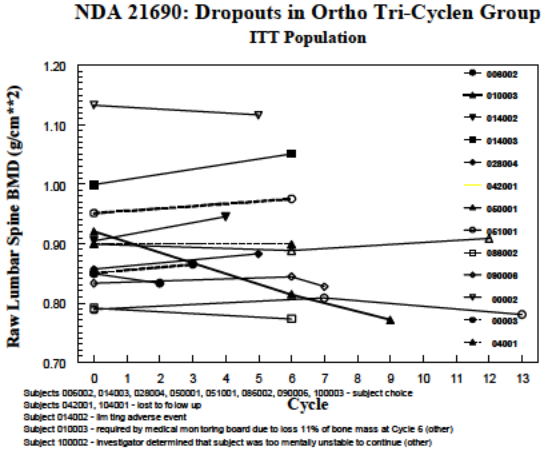
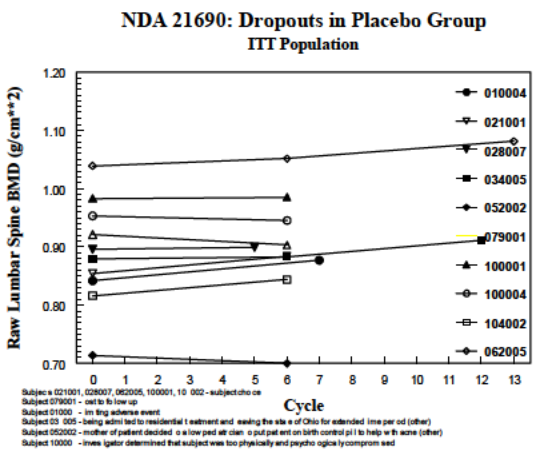


Figure 6



BMD of Total Hip (Non-dominant). Both ORTHO TRI-CYCLEN® and placebo groups showed increased means in total hip BMD from baseline to Cycle 6 and then to Cycle 13 in the ITT population with LOCF techniques (Table 7). The treatment differences in mean change and mean % change from baseline at both cycles were not statistically significant between the 2 study groups based on either random or fixed center effect models. In fact, a numerically greater increase from baseline was seen in the placebo group than in the active treatment group at Cycle 13.

Table 7 – Results for Total Hip BMD Using ITT Population with LOCF Approach

	ORTHO TRI-CYCLEN	Placebo	Treatment Difference	p-value	95% (LCL, UCL)
Raw mean total hip BMD ± standard deviation (sample size)					
Baseline	0.8828 ± 0.1081 (53)	0.8696 ± 0.1368 (59)			
Cycle 6	0.8928 ± 0.0964 (53)	0.8715 ± 0.1290 (59)			
Cycle 13	0.8939 ± 0.0970 (53)	0.8829 ± 0.1272 (59)			
Change at Cycle 6	0.0100 ± 0.0346 (53)	0.0019 ± 0.0287 (59)			
Change at Cycle 13	0.0111 ± 0.0408 (53)	0.0133 ± 0.0400 (59)			
%Change at Cycle 6	1.3806 ± 4.0403 (53)	0.4195 ± 3.4312 (59)			
%Change at Cycle 13	1.5308 ± 4.6748 (53)	1.8243 ± 4.7023 (59)			

	ORTHO TRI-CYCLEN	Placebo	Treatment Difference	p-value	95% (LCL, UCL)
Least-squares mean change from baseline ± standard error (sample size) – using random effect model					
Cycle 6	0.0104 ± 0.0043 (53)	0.0026 ± 0.0043 (59)	0.0078	0.1462	(-0.0028, 0.0184)
Cycle 13	0.0113 ± 0.0055 (53)	0.0132 ± 0.0054 (59)	-0.0019	0.7839	(-0.0157, 0.0119)
Least-squares mean % change from baseline ± standard error (sample size) – using random effect model					
Cycle 6	1.3894 ± 0.5024 (53)	0.4566 ± 0.4969 (59)	0.9328	0.1375	(-0.3055, 2.1711)
Cycle 13	1.5075 ± 0.6298 (53)	1.7857 ± 0.6220 (59)	-0.2783	0.7240	(-1.8435, 1.2870)

Body Weight. Both ORTHO TRI-CYCLEN® and placebo groups showed increased means in body weight from baseline to Cycle 6 and then to Cycle 13 in the ITT population with LOCF techniques (Table 8). However, the treatment differences in mean change and mean % change from baseline at both cycles were not statistically significant between the 2 study groups based on either random or fixed center effect models. The sponsor also reported no significant treatment difference observed between the 2 study groups in mean change or mean % change from baseline in BMI at either cycle (page 79 of the clinical study report).

Table 8 – Results for Body Weight Using ITT Population with LOCF Approach

	ORTHO TRI-CYCLEN	Placebo	Treatment Difference	p-value	95% (LCL, UCL)
Raw mean body weight ± standard deviation (sample size)					
Baseline	47.683 ± 7.6215 (53)	46.744 ± 7.5297 (59)			
Cycle 6	51.882 ± 9.6678 (53)	49.814 ± 8.3122 (59)			
Cycle 13	54.410 ± 10.092 (53)	51.591 ± 10.341 (59)			
Change at Cycle 6	4.1991 ± 5.1307 (53)	3.0697 ± 4.9656 (59)			
Change at Cycle 13	6.7271 ± 6.6629 (53)	4.8469 ± 8.2743 (59)			
%Change at Cycle 6	9.0993 ± 11.057 (53)	7.0510 ± 10.909 (59)			
%Change at Cycle 13	14.694 ± 14.841 (53)	11.037 ± 18.667 (59)			
Least-squares mean change from baseline ± standard error (sample size) – using random effect model					
Cycle 6	4.1805 ± 0.7485 (53)	2.9822 ± 0.7396 (59)	1.1983	0.2018	(-0.6564, 3.0530)
Cycle 13	6.7302 ± 1.0653 (53)	4.7710 ± 1.0277 (59)	1.9592	0.1748	(-0.8911, 4.8094)
Least-squares mean % change from baseline ± standard error (sample size) – using random effect model					
Cycle 6	9.1822 ± 1.5633 (53)	6.6141 ± 1.5357 (59)	2.5681	0.2025	(-1.4130, 6.5493)
Cycle 13	14.954 ± 2.2780 (53)	10.803 ± 2.1588 (59)	4.1514	0.1906	(-2.1141, 10.417)

Note: P-values here are slightly different from the sponsor's because of exclusion of center effect in the sponsor's model.

3.2 Evaluation of Safety

Safety is not the focus of this review. See Dr. Gierhart's review for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Treatment effects on change from baseline in lumbar spine BMD at Cycle 13 were consistent across the subgroups of race, as no significant treatment-by-race interaction was observed ($p > 0.10$). Since all the study subjects were pediatric females and 98% of them were ≥12 years old (the minimum age of participants specified in the Written Request), this reviewer did not perform any subgroup analyses for gender and age.

4.2 Other Special/Subgroup Populations

The reviewing medical officer raised a concern that 76 out of 123 (= 61.8%) treated subjects had a baseline BMI ≥10th percentile for age on the CDC Growth Chart and should not have been enrolled into the study based on the "modified" DSM-IV guideline described in the protocol. Therefore, this reviewer conducted a subgroup analysis for baseline BMI on the primary efficacy variable. Results indicated a non-significant treatment-by-baseline BMI interaction ($p > 0.10$) with consistent treatment effects between the subjects with baseline BMI ≥10th percentile and the subjects with that <10th percentile. In addition, within each subgroup, the treatment difference in change from baseline in lumbar spine BMD at Cycle 13 was not statistically significant between the ORTHO TRI-CYCLEN® and placebo groups (Table 9).

One of the diagnostic criteria for 307.1 Anorexia Nervosa described in the DSM-IV guideline is refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected). Therefore, the medical officer calculated the Ideal Body Weight (IBW) for each subject using the information from Height and Weight of Youths 12-17 Years United States in Vital and Health Statistics: Data from the National Health Survey, Series 11, Number 124, published by the U.S. Department of Health, Education, and Welfare (available at: http://www.cdc.gov/nchs/data/series/sr_11/sr11_124.pdf). By taking multiple factors into consideration (such as high % of IBW at Screening/Visit 1, high baseline BMI, positive baseline lumbar spine BMD Z-score, and/or large weight gain), she suggested that 29 out of 123 (= 23.6%) treated subjects be excluded from the efficacy analysis. This reviewer performed a subgroup analysis for the selected 29 subjects versus the rest on the primary efficacy variable and the testing result of treatment-by-subgroup interaction ($p > 0.10$) showed consistent treatment effects between the subjects with identified factors by Dr. Gierhart and the subjects without. In addition, within each subgroup, the treatment difference in change from baseline in lumbar spine BMD at Cycle 13 was not statistically

significant between the ORTHO TRI-CYCLEN® and placebo groups (Table 9). Similar consistent and non-significant findings were also observed when the subjects with Screening/Visit 1 body weight ≥ 90% of IBW were distinguished from the others (Table 9).

Table 9 – Change from Baseline in Lumbar Spine BMD at Cycle 13 for Special Defined Subgroups

ITT Population	Raw Mean ± SD (N)		Treatment Difference[2]	p-value[2]
	ORTHO TRI-CYCLEN	Placebo		
BMI ≥ 10th percentile	0.0289 ± 0.0454 (35)	0.0201 ± 0.0329 (35)	0.0083	0.3887
BMI < 10th percentile	0.0214 ± 0.0476 (18)	0.0173 ± 0.0440 (24)	0.0108	0.3934
Subjects selected by MO for exclusion[1]	0.0299 ± 0.0236 (14)	0.0202 ± 0.0393 (12)	0.0108	0.4947
Subjects not selected by MO for exclusion	0.0251 ± 0.0518 (39)	0.0187 ± 0.0374 (47)	0.0087	0.3157
Weight ≥ 90% of IBW	0.0369 ± 0.0195 (14)	0.0262 ± 0.0367 (13)	0.0123	0.4226
Weight < 90% of IBW	0.0226 ± 0.0519 (39)	0.0170 ± 0.0379 (46)	0.0082	0.3450
Weight Change > 20 lbs	0.0262 ± 0.0329 (13)	0.0193 ± 0.0449 (10)	0.0038	0.8210
Weight Change ≤ 20 lbs	0.0265 ± 0.0497 (40)	0.0189 ± 0.0363 (49)	0.0105	0.2221
With identified reasons[1] plus BW gain > 20 lbs	0.0300 ± 0.0283 (21)	0.0191 ± 0.0406 (20)	0.0100	0.4229
Without all the reasons	0.0240 ± 0.0547 (32)	0.0189 ± 0.0363 (39)	0.0090	0.3482
Negative Z-score	0.0286 ± 0.0492 (42)	0.0225 ± 0.0360 (49)	0.0078	0.3564
Non-negative Z-score	0.0180 ± 0.0303 (11)	0.0016 ± 0.0418 (10)	0.0182	0.3024

[1] Subjects with high % of Visit 1 IBW, high baseline BMI, positive baseline lumbar spine BMD Z-score, and/or large weight gain were selected by the reviewing medical officer (MO) for exclusion.
[2] Treatment difference and p-value were obtained using model with baseline lumbar spine BMD, treatment, subgroup, and treatment-by-subgroup.

There were several subjects showing huge body weight gains from Screening/Visit 1 to last visit (e.g., Subject 056004 had a 100-lb change). The medical officer found it confounding because a large amount of food intake over time may also have some impact on improving lumbar spine BMD. She arbitrarily used 20-lb as a cut off point and found 23 out of 123 (= 18.7%) treated subjects with weight gain more than 20 lbs. This reviewer conducted a subgroup analysis for body weight change on the primary efficacy variable and the testing result of treatment-by-body weight change interaction ($p > 0.10$) showed consistent treatment

effects between the subjects with weight gain >20 lbs and the subjects with that ≤20 lbs. In addition, within each subgroup, the treatment difference in change from baseline in lumbar spine BMD at Cycle 13 was not statistically significant between the 2 study groups (Table 9). Similar consistent and non-significant findings were also observed when the subjects with identified factors mentioned in the preceding paragraph plus weight gain of over 20 lbs were distinguished from the others (Table 9).

Since the Written Request calls for targeting subjects with a lumbar spine BMD Z-score, matched for ethnicity, of less than zero at baseline in the study design, a subgroup analysis for baseline Z-score was performed for the primary efficacy variable. The testing result of treatment-by-baseline Z-score interaction ($p > 0.10$) showed consistent treatment effects between the subjects with negative score and the subjects with non-negative one. In addition, within each subgroup, the treatment difference in change from baseline in lumbar spine BMD at Cycle 13 was not statistically significant between the 2 study groups (Table 9).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Although the dropout rates by Cycle 13 were high (34% and 21% for the active treatment and placebo groups, respectively), the number of subjects in each group completing the study was more than the needed sample size (26) based on the expected 1-year treatment difference (0.076 g/cm^2). Therefore, this reviewer does not feel that the high percentage of dropouts in this study under powered the trial in the determination of treatment efficacy.

Table 10 summarizes the efficacy findings for Cycles 6 and 13 for the ITT population with LOCF approach. The only significant finding among the 3 efficacy variables evaluated was the change in lumbar spine BMD from baseline to Cycle 6 ($p = 0.0214$). The insignificance at Cycle 13 for this variable was due to the ORTHO TRI-CYCLEN® treated patients who withdrew early and showed a mean decrease from baseline, while the placebo dropouts showed a mean increase. A nominally significant treatment effect of ORTHO TRI-CYCLEN® compared to placebo was seen among the completers ($p = 0.0208$). This reviewer performed some sensitivity analyses for Cycle 13 data by taking the effects of dropouts into consideration and also found no significant evidence favoring ORTHO TRI-CYCLEN® in increasing lumbar spine BMD. Similar phenomenon was also observed for the % change from baseline variables. According to the sponsor's analyses, the change in BMI (or in body weight) and the change in lumbar spine BMD from baseline to Cycle 13 were not strongly correlated (page 73-74 of clinical study report).

Table 10 – Summary of Efficacy Using ITT Population with LOCF Approach

	ORTHO TRI-CYCLEN	Placebo	Treatment Difference	p-value	95% (LCL, UCL)
Least-squares mean change from baseline at Cycle 6 ± standard error (sample size)					
Lumbar Spine	0.0201 ± 0.0041 (53)	0.0072 ± 0.0040 (59)	0.0129	0.0214	(0.0020, 0.0237)
Total Hip	0.0104 ± 0.0043 (53)	0.0026 ± 0.0043 (59)	0.0078	0.1462	(-0.0028, 0.0184)
Body Weight	4.1805 ± 0.7485 (53)	2.9822 ± 0.7396 (59)	1.1983	0.2018	(-0.6564, 3.0530)
Least-squares mean change from baseline at Cycle 13 ± standard error (sample size)					
Lumbar Spine	0.0265 ± 0.0059 (53)	0.0177 ± 0.0058 (59)	0.0088	0.2437	(-0.0061, 0.0236)
Total Hip	0.0113 ± 0.0055 (53)	0.0132 ± 0.0054 (59)	-0.0019	0.7839	(-0.0157, 0.0119)
Body Weight	6.7302 ± 1.0653 (53)	4.7710 ± 1.0277 (59)	1.9592	0.1748	(-0.8911, 4.8094)

Since the medical officer has concerns about the eligibility of enrollment for some patients, several subgroups based on different definitions of anorexia nervosa considered by Dr. Gierhart were investigated. All the analyses showed consistent treatment effects across the subgroups on mean change from baseline in lumbar spine BMD at Cycle 13 and non-significant treatment difference between the 2 study groups within each subgroup.

Despite a lack of statistical significance, a numerically larger mean change from baseline in lumbar spine BMD at Cycle 13 was observed in the ORTHO TRI-CYCLEN® group than in the placebo group in each of the subgroups as well as combined.

5.2 Conclusions and Recommendations

Treatment with ORTHO TRI-CYCLEN® after 6 months based on the whole ITT population and after 1 year based on the completers showed statistically significant increases in mean change or mean % change from baseline in lumbar spine BMD compared with placebo. However, the strength of evidence was only marginal. In addition, the observed treatment differences between the 2 study groups in mean lumbar spine BMD at Cycles 6 and 13 were smaller than the expected 6-month (0.05 g/cm^2) and 1-year (0.076 g/cm^2) differences, respectively. Therefore, concluding a clinically meaningful difference in this case might be in question. Also, treatment with ORTHO TRI-CYCLEN® after 6 months and 1 year did not show any statistically significant positive findings when compared with placebo for total hip BMD and body weight. Nevertheless, numerically larger mean or mean % changes from baseline in lumbar spine BMD, total hip BMD, and body weight were generally observed in the ORTHO TRI-CYCLEN® group than in the placebo group.

The sponsor proposed to claim the statistical significance of ORTHO TRI-CYCLEN® following 6 months and 1 year of treatment compared with placebo in improving lumbar spine BMD. This reviewer suggests using only descriptive statistics, not statistical significance, in the label since the data did not provide strong and consistent evidence.

Primary Statistical Reviewer: Cynthia Liu, MA

Concurring Reviewer: Todd Sahlroot, Ph.D., Statistical Team Leader
Ed Nevius, Ph.D., Director of Division of Biometrics II

CC: HFD-510/PMadara, EColman, BGierhart
HFD-715/ENevius, SWilson, TSahlroot, CLiu
HFD-700/CAnello

6. Appendix I

Ortho Group

Change from Baseline at Cycle 6

```
Stem Leaf                     #      Boxplot
  11 5                        1         0
  10
   9 9                        1         0
   8
   7 3                        1         |
   6 05                       2         |
   5 255                      3         |
   4 12257                    5         |
   3 1346688                  7      +-----+
   2 0234567799              10      *--+--*
   1 1569                     4      |     |
   0 01467                    5      |     |
  -0 6321                     4      +-----+
  -1 876331                   6         |
  -2 7                        1         |
  -3                                    |
  -4 3                        1         |
  -5 0                        1         |
  -6
  -7
  -8
  -9
 -10 6                        1         0
     ----+----+----+----+
 Multiply Stem.Leaf by 10**-2
```

Placebo Group

Change from Baseline at Cycle 6

```
Stem Leaf                     #      Boxplot
   7 2                        1         |
   6 1                        1         |
   5 2                        1         |
   4 2                        1         |
   3 023458                   6         |
   2 0115555688              10      +-----+
   1 0245599                  7      |     |
   0 223344455699            12      *--+--*
  -0 8877411                  7      +-----+
  -1 8754421                  7         |
  -2 7630                     4         |
  -3                                    |
  -4 5                        1         |
  -5
  -6 2                        1         0
     ----+----+----+----+
  Multiply Stem.Leaf by 10**-2
```

Ortho Group

Change from Baseline at Cycle 13

```
Stem Leaf                     #      Boxplot
  12 5                        1         |
  10 2503                     4         |
   8                                    |
   6 580                      3         |
   4 1228990224889           13      +-----+
   2 244678978                9      *--+--*
   0 3912556                  7      |     |
  -0 98762986651             11      +-----+
  -2 7600                     4         |
  -4
  -6
  -8
 -10
 -12
 -14 9                        1         0
     ----+----+----+----+
 Multiply Stem.Leaf by 10**-2
```

Placebo Group

Change from Baseline at Cycle 13

```
Stem Leaf                     #      Boxplot
   9 4                        1         |
   8 09                       2         |
   7 027                      3         |
   6 48                       2         |
   5 1144                     4         |
   4 1256799                  7      +-----+
   3 02345566                 8      |     |
   2 0288                     4      *-----*
   1 069                      3      |  +  |
   0 223599                   6      |     |
  -0 87                       2      |     |
  -1 886544320                9      +-----+
  -2 982                      3         |
  -3 6                        1         |
  -4 42                       2         |
  -5 1                        1         |
  -6                                    |
  -7 0                        1         |
     ----+----+----+----+
  Multiply Stem.Leaf by 10**-2
```

Note: In stem-and-leaf plot, (Stem.Leaf)*0.01 shows the response value of each ITT subjects. In box plot, the horizontal line inside the box shows the median and + sign shows the mean. Any value more than 1.5 interquartile range (= 75^{th} – 25^{th} percentiles) is marked with a 0.

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