

CLINICAL REVIEW

Application Type	NDA 21-690
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Submission Code	AM (Major Amendment-Clinical Information)/PM (Complete Pediatric Study Report)
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Reviewer Name	Brenda Gierhart, MD
Review Completion Date	May 6, 2005
Established Name	Norgestimate/Ethinyl Estradiol
Trade Name	Ortho Tri-Cyclen®
Therapeutic Class	3020425: Osteoporosis-HRT
Applicant	Ortho-McNeil Pharmaceutical, Inc
Priority Designation	S
Formulation	Oral
Dosing Regimen	One tablet daily
Indication	Treatment to increase lumbar spine bone mineral density in adolescent females with anorexia nervosa
Intended Population	Adolescent females with anorexia nervosa

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Recommend approving NDA 21-690 and incorporating the following sentence (revised wording is underlined) into the Ortho Tri-Cyclen Prescribing Information, **PRECAUTIONS** section, **Pediatric Use** subsection,

Safety and efficacy of ORTHO TRI-CYCLEN Tablets and ORTHO CYCLEN Tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents. There was no significant difference between ORTHO TRI-CYCLEN Tablets and placebo in mean change in total lumbar spine (L1-L4) and total hip bone mineral density between baseline and Cycle 13 in 123 adolescent females with anorexia nervosa in a double-blind, placebo-controlled, multicenter, one-year treatment duration clinical trial for the Intent To Treat (ITT) population. Use of this product before menarche is not indicated.

It should be noted that in the Complete Class 2 Response to Approvable Action Letter, letter date November 18, 2004, the sponsor had requested approval of the new indication “ORTHO TRI-CYCLEN is indicated for treatment to increase lumbar spine bone mineral density in adolescent females with anorexia nervosa.” This new indication was not granted due to lack of efficacy in the CAPSS-169 ITT population at Cycle 13 and due to insufficient safety data to support approval. On May 3, 2005, the sponsor accepted the above Division proposed labeling and agreed to incorporate the single new sentence into the Ortho Tri-Cyclen Prescribing Information, **PRECAUTIONS** section, **Pediatric Use** subsection.

1.2 Recommendation on Postmarketing Actions

This reviewer has no recommendations for any postmarketing actions.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The sponsor conducted one clinical study.

CAPSS-169 was a Phase 2, double-blind, placebo-controlled, multicenter, one-year treatment duration clinical study that evaluated the effect of Ortho Tri-Cyclen compared to placebo on bone mineral density in 123 adolescent females with anorexia nervosa.

1.3.2 Efficacy

At screening, the majority of the 123 subjects treated in CAPSS-169 did not meet either the DSM-IV diagnostic criteria for anorexia nervosa or the DSM-IV diagnostic criteria modified by the sponsor for anorexia nervosa.

In the ITT population, treatment with Ortho Tri-Cyclen was not associated with a significant change in mean total lumbar (L1-L4) bone mineral density from baseline to Cycle 13 when compared to placebo. In the ITT population, treatment with Ortho Tri-Cyclen was not associated with a significant change in mean total hip bone mineral density from baseline to Cycle 13 when compared to placebo. In the ITT population in subjects with negative Z-scores at baseline, treatment with Ortho Tri-Cyclen was not associated with a significant change in mean total lumbar spine (L1-L4) BMD from baseline to Cycle 13 when compared to placebo. In the ITT population, treatment with Ortho Tri-Cyclen from baseline to Cycle 6 had shown a statistically significant increase in mean change or mean % change from baseline in lumbar spine bone mineral density when compared with placebo. However, the observed treatment difference [i.e. 0.011 gm/cm²] between the two study groups was marginal and smaller than the expected difference from baseline to Cycle 6 (0.05 gm/cm² or 6%). Therefore, a clinically meaningful difference did not occur from baseline to Cycle 6 and neither a statistically or a clinically meaningful difference occurred from baseline to Cycle 13.

Multiple post-hoc analyses were performed by the sponsor and by the CDER statistician to evaluate subjects felt to have reasonably satisfied the criteria for anorexia nervosa at baseline and/or have not gained excessive weight during the trial. Per the sponsor, when subjects with a baseline BMI >18.5 kg/m² and/or IBW at Visit 1 >85% were excluded from the analysis, treatment with Ortho Tri-Cyclen was not associated with a significant change in mean total lumbar spine (L1-L4) BMD from baseline to Cycle 6 or to Cycle 13 when compared to placebo. Per the sponsor, when subjects with a weight gain of over 20 pounds from Visit 1 to last visit were excluded from the analysis, treatment with Ortho Tri-Cyclen was not associated with a significant change in mean total lumbar spine (L1-L4) BMD from baseline to Cycle 6 or to Cycle 13 when compared to placebo. Table 1 provides additional subgroup analyses performed by the NDA 21-690 CDER Statistical reviewer.

Table 1: CAPSS-169: Change from Baseline in Lumbar Spine BMD at Cycle 13 for Special Defined Subgroups Performed by NDA 21-690 CDER Statistical Reviewer

ITT Population	Raw Mean ± SD (N)		Treatment Difference	p-value
	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
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.

This reviewer believes that most, if not all, subjects, subject families, and investigators were unblinded due to the well-known changes in menses and adverse events associated with oral contraceptives. In addition, unblinded 6-month CAPSS-169 efficacy and safety data was submitted in the Original NDA 21-690 on September 25, 2003.

1.3.3 Safety

There were no deaths, no pregnancies, and no reports of venous thromboembolic events during the conduct of CAPSS-169. Significantly more treated subjects on Ortho Tri-Cyclen prematurely discontinued from the study (n=21, 34.4%) than placebo subjects (n=13, 21.0%). It is concerning that one subject was started on oral contraceptives and her imperforate hymen was not diagnosed until after 11 months on treatment. A visual examination of the vulva and vaginal introitus should have diagnosed the imperforate hymen at screening.

2 INTRODUCTION AND BACKGROUND

The current submission to NDA 21-690 consists of the final study report for **CAPSS-169**, which was conducted to obtain Pediatric Exclusivity by fulfilling the Agency's Written Request for Ortho Tri-Cyclen. The clinical study CAPSS-169 evaluated the effect on bone mineral density (BMD) of administering Ortho Tri-Cyclen for one year to adolescent female subjects with anorexia nervosa. The 146 randomized and 123 treated subjects were all female and aged 10 to 17 years at screening. It was appropriate to study female subjects in CAPSS-169 since more than 90% of cases of anorexia nervosa occur in females.¹ It was appropriate to study BMD in adolescents since the data suggests that vertebral and femoral bone mass attains maximal development during the first 2 decades of life.² In addition, there is a higher incidence of anorexia nervosa among adolescent females than among adult females. For the time period 1980-1989, the incidence (i.e. number of new cases in the population over a specified period of time) of anorexia nervosa among (b) (4) residents varied by age as follows³ (Note: all (b) (4) residents with anorexia nervosa were white, reflecting the racial composition in the community):

Females <10 years	0
Females 10-14 years	43.1/100,000 person-years
Females 15-19 years	135.7/100,000 person-years
Females 20-24 years	32.4/100,000 person-years
Females 25-29 years	17.3/100,000 person-years
Females 30-39 years	9.1/100,000 person-years
Females 40-49 years	11.4/100,000 person-years
Female ≥50 years	0

¹ American Psychiatric Association. DSM-IV™, Diagnostic and Statistical Manual of Mental Disorders. 4th Ed., Washington, DC, 1994, pg. 543.

² Theintz G et al. Longitudinal Monitoring of Bone Mass Accumulation in Healthy Adolescents: Evidence for a Marked Reduction after 16 years of Age at the Levels of Lumbar Spine and Femoral Neck in Female Subjects. *J Clin Endocrinol Metab*. 1992; 75: 1060-1065.

³ Lucas AR et al. The Ups and Downs of Anorexia Nervosa. *Int J Eat Disord* 26: 397-405, 1999.

Anorexia nervosa has a prevalence (i.e. the total number of cases in the population) of 0.2-0.5% in women and usually begins in adolescence or young adulthood.⁴ Although it is a low prevalence condition as is schizophrenia, anorexia nervosa is a serious disorder and may be chronic. The semistarvation of anorexia nervosa can result in significant associated general medical conditions, including **osteoporosis** (resulting from low calcium intake and absorption, reduced estrogen secretion, and increased cortisol secretion), anemia, impaired renal function (associated with chronic dehydration and hypokalemia), cardiovascular problems (severe hypotension, arrhythmias), and dental problems.⁵

According to the **ICD-10**, the diagnostic guidelines for anorexia nervosa are:

F50.0 Anorexia Nervosa

“Diagnostic Guidelines

For a definite diagnosis, all the following are required:

- A. Body weight is maintained at least 15% below that expected (either lost or never achieved), or Quetelet’s body-mass index is 17.5 or less. Prepubertal patients may show failure to make the expected weight gain during the period of growth.
- B. The weight loss is self-induced by avoidance of “fattening foods” and one or more of the following: self-induced vomiting; self-induced purging; excessive exercise; use of appetite suppressants and/or diuretics.
- C. There is body-image distortion in the form of a specific psychopathology whereby a dread of fatness persists as an intrusive, overvalued idea and the patient imposes a low weight threshold on himself or herself.
- D. A widespread endocrine disorder involving the hypothalamic-pituitary-gonadal axis is manifest in women as amenorrhea and in men as a loss of sexual interest and potency. (An apparent exception is the persistence of vaginal bleeds in anorexic women who are receiving hormonal therapy, most commonly taken as a contraceptive pill.) There may also be elevated levels of growth hormone, raised levels of cortisol, changes in the peripheral metabolism of the thyroid hormone, and abnormalities in insulin secretion.
- E. If onset is prepubertal, the sequence of pubertal events is delayed or even arrested (growth ceases; in girls the breasts do not develop and there is primary amenorrhea; in boys the genitals remain juvenile). With recovery, puberty is often completed normally, but the menarche is late.”⁶

According to the **DSM-IV**, the diagnostic criteria for anorexia nervosa are as follows:

“Diagnostic criteria for **307.1 Anorexia Nervosa**

- A. 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; or failure to make expected weight gain during the period of growth, leading to body weight less than 85% of that expected).
- B. Intense fear of gaining weight or becoming fat, even though underweight.
- C. Disturbance in the way in which one’s body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.

⁴ Beumont, P et al. Australian and New Zealand clinical practice guidelines for the treatment of anorexia nervosa. *Australian and New Zealand J of Psychiatry*. 2004; 38: 660.

⁵ American Psychiatric Association. DSM-IV™, Diagnostic and Statistical Manual of Mental Disorders. 4th Ed., Washington, DC, 1994, pg. 542.

⁶ World Health Organisation. ICD-10: classification of mental and behavioural disorders. World Health Organisation. Geneva; 1992.

D. In postmenarcheal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles. (A women in considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen, administration.)”⁷

It should be noted that large numbers of teenagers who have disordered eating do not meet the strict DSM-IV criteria for either anorexia nervosa or bulimia nervosa and are classified as “Eating Disorder-NOS (ED-NOS)”⁸. In addition, subjects who have recovered from anorexia nervosa, through treatment or spontaneous remission, differ from subjects with active anorexia nervosa.⁹ Subjects are generally judged to be in remission from anorexia nervosa on the basis of weight rehabilitation and/or spontaneous resumption of menses.¹⁰ The Written Request for Ortho Tri-Cyclen stated that all patients in the randomized, double-blind, placebo-controlled, efficacy and safety study of Ortho Tri-Cyclen (i.e. CAPSS-169) should have anorexia nervosa as defined by DSM-IV criteria. It is pertinent that a modified form of the above DSM-IV diagnostic criteria for anorexia nervosa was used as the inclusion criteria for **CAPSS-169**. The modification converted “body weight less than 85% of that expected” to “body mass index below the 10th percentile for age using the Center for Disease Control (CDC) Growth Chart” as the enrollment criteria at baseline. This reviewer agrees with the sponsor in **not** using the ICD-10 diagnostic criteria “BMI of 17.5 kg/m² or less” as an inclusion criterion for the adolescent population in CAPSS-169 since BMI in children and in adolescents is both gender and age specific. BMI should be plotted on gender specific growth charts in children and adolescents. Thus, it is not possible to set a single BMI diagnostic cutoff as an inclusion criterion for children or adolescents with anorexia nervosa. For example, on the latest October 16, 2000 Centers for Disease Control and Prevention (CDC) Growth Chart entitled “2 to 20 years Girls Body mass index-for-age percentiles”, the 50% BMI changes from 16.8 kg/m² for a 10 year old female to 20.8 kg/m² for a 17 year old female¹¹. The CDC classifies “underweight” as BMI for age \leq 5th percentile for children and adolescents.¹² The 5th percentile (i.e. “underweight”) for BMI changes from 14.0 kg/m² for a 10 year old female to 17.2 kg/m² for a 17 year old female. In contrast, the World Health Organization categorizes BMI for adults regardless of sex or age as: below 18.5 kg/m² =underweight; 18.5-24.9 kg/m² =normal; 25-29.9 kg/m² =overweight; 30.0 kg/m² and above=obese. Thus, the ICD-10 diagnostic cutoff for anorexia nervosa in adults (regardless of sex or age), i.e. BMI of 17.5 kg/m², is **not** even “underweight” per the CDC for females aged 10-17 years. However, if a specific BMI was used as a diagnostic cutoff, **30.9% (38/123)** of treated CAPSS-169 subjects had a baseline **BMI of 18.5 or greater** and **50.4% (62/123)** of treated CAPSS-169 subjects had a screening **BMI of 17.5 or greater**, which are both higher BMIs than the cut-off value for being underweight for 10 to 17 year old females on the CDC Body mass index-for age percentiles Growth Chart.¹³

Reviewer’s comment:

⁷ American Psychiatric Association. DSM-IV™, Diagnostic and Statistical Manual of Mental Disorders. 4th Ed., Washington, DC, 1994, pg. 544-545.

⁸ Fisher M et al. Eating Disorders in Adolescents: A Background Paper. *J Adol Health*. 1995; 16: 420-437.

⁹ Karlsson MK et al. Bone Size and Volumetric Density in Women with Anorexia Nervosa Receiving Estrogen Replacement Therapy and in Women Recovered from Anorexia Nervosa. *J Clin Endocrinol Metab*. 2000; 85: 3177-3182.

¹⁰ Bachrach LK et al. Recovery from Osteopenia in Adolescent Girls with Anorexia Nervosa. *J Clin Endocrinol Metab*. 1991; 72: 602-606.

¹¹ CDC Growth Chart entitled “2 to 20 years: Girls Body mass index-for-age percentiles” at: <http://www.cdc.gov/nchs/data/nhanes/growthcharts/set1clinical/cj411024.pdf> ; accessed on April 6, 2005.

¹² <http://www.cdc.gov/nccdphp/dnpa/bmi/bmi-for-age.htm>; accessed on January 11, 2005.

¹³ Reviewer analysis of CAPSS-169 Final Study Report, Appendix 3.12: Vital Signs and Body Weight pg. 2285-2330.

- 1) *It would have been reasonable to use a single BMI to exclude adolescents from enrolling in CAPSS-169, i.e. exclude subjects if they had a baseline BMI of more than 17.5 kg/m²; however, this was not done.*

Regarding the modification used by the sponsor as inclusion criteria for CAPSS-169, it is difficult to convert the DSM-IV criteria “body weight less than 85% of that expected” into any specific “% BMI for age” cutoff. Regardless of whether “5% BMI for age” or “10% BMI for age” was utilized as a diagnostic cutoff, a significant percentage of subjects treated in CAPSS-169 did not meet that diagnostic cutoff. When the baseline BMI for each CAPSS-169 patient was charted on the CDC Growth Chart by their age by this reviewer, **61.8% (76/123)** of the treated **CAPSS-169 subjects** had a baseline BMI at or above the **10th percentile** and **75.6% (93/123)** of the **treated CAPSS-169 subjects** had a baseline BMI at or above the **5th percentile**. By using 10% instead of 5% BMI for age using the CDC Growth Chart as a diagnostic criteria of anorexia nervosa in CAPSS-169, **13.8 % (17/123)** of the treated **CAPSS-169** subjects were at or above the 5th percentile and less than the 10th percentile and met the CAPSS-169 inclusion criteria; however, they were **not** even considered to be underweight by the CDC gender specific growth charts.

Reviewer’s comment:

- 1) *It would have been more reasonable to have used the DSM-IV diagnostic criteria of “less than 85% expected IBW” rather than “BMI below the 10th percentile for age” as an inclusion criterion for CAPSS-169 since height is squared when calculating BMI. Squaring the height when calculating BMI, places more emphasis on an individual’s height than weight and creates inequities for subjects at the extremes of height (i.e. short or tall). For girls with the same age, it is more difficult for a short girl than a tall girl to have a low BMI.*

Indeed, the inclusion criterion “less than 85% expected IBW” was used in the prospective observational study of 50 adolescents with anorexia nervosa that evaluated the effect of oral contraceptives on bone mineral density published by Neville Golden et al in 2002.¹⁴ In Dr. Golden’s study, subjects at baseline were malnourished (79.5% ± 7.6% IBW), hypoestrogenemic (estradiol 24.7 ± 10.7 pg/mL), and had reduced bone mass (lumbar spine BMD -20.1 ± 0.69 SD below the young adult reference mean). Only 57.7% (71/123) of treated subjects in CAPSS-169 had a Visit 1 weight ≤ 85% IBW for height and age, 38.2% (47/123) had a baseline Z-Score ≤ 1.00 (i.e. osteopenia), and 21.9% (27/123) had a Visit 1 weight ≤ 85% IBW for height and age AND a baseline Z-Score ≤ 1.00.¹⁵

The number of subjects in CAPSS-169 who were hypoestrogenemic at baseline is unknown since a screening estradiol level was not obtained. Screening estradiol levels were not obtained despite this being specifically recommended in the outside expert review of CAPSS-169 requested by the sponsor and performed by Dr. (b)(6).¹⁶ Since persistently low estradiol levels are associated with amenorrhea, a reasonable surrogate marker for a subject’s baseline estradiol level is the subject’s baseline menstrual history. At Visit 1, only 74.8% (92/123) of the CAPSS-169 treated subjects provided a last menstrual period (LMP) that was at least 3 months prior to the Visit 1 date and thus, had amenorrhea.

Lastly, only 62.6% (77/123) of the CAPSS-169 treated subjects had the word “anorexia” listed anywhere in their Medical History obtained at screening.¹⁷ The remaining subjects frequently had “restricts food”,

¹⁴ Golden NH et al. The Effect of Estrogen-Progestin Treatment on Bone Mineral Density in Anorexia Nervosa. *J Pediatr Adolesc Gynecol.* 2002; 15: 135-143.

¹⁵ Per this reviewer’s data analysis.

¹⁶ The expert review by Dr. (b)(6) was submitted to IND 61,239 in N-005.

¹⁷ Per this reviewer’s data analysis of CAPSS-169 Final Study Report Appendix 3.5 entitled “Medical History” on pg. 1697-1724 of 2369 and the JMP dataset “MHIST”

“picky eater”, “poor caloric intake”, “low caloric intake”, “eating disorder”, or “diminished food intake” listed in their Medical History.

Reviewer’s comment:

- 1) *Subjects who gave no history of anorexia nervosa in the screening Medical History, who did not have amenorrhea based on their LMP obtained at Visit 1, who had a normal BMI, and/or who weighed at least 85% of expected IBW at Visit 1 were included in CAPSS-169. This may have occurred due to investigators including subjects in CAPSS-169 who were classified as “eating disorder NOS” or who had a past history of anorexia nervosa and had recovered. Subjects should not have been included in CAPSS-169 unless they met the diagnostic criteria for anorexia nervosa at screening.*

Regarding the effect of oral contraceptives (OC) on bone mineral density (BMD), “prior research on BMD and OC is contradictory and confusing”.¹⁸ Some studies have demonstrated an increase in BMD associated with the administration of OC, while other studies have shown no effect of OCs on BMD or even a loss in BMD. Changes in BMD may be related to the specific progestin and/or the dose of estrogen in the OC. A study by Berenson et al reported the following mean adjusted change in BMD from baseline to 24 months in women aged 18 to 33 years: -1.53% (loss in BMD) associated with a norethindrone OC (Ortho-Novum 1/35, n=25), -2.57% (loss in BMD) associated with a desogestrel OC (Mircette, n=42), and +1.80% (gain in BMD) in the control group (users of nonhormonal contraception, n=44).¹⁹ In this same study, it was interesting to note that the norethindrone OC subjects demonstrated a mean adjusted +2.12% gain in BMD from baseline to 12 months (n=28) that changed to a mean adjusted -1.53% loss in BMD when subjects were followed from baseline to 24 months (n=25). Thus, interim bone mineral density results can not predict final study results. Polatti et al concluded that long-term treatment with a desogestrel OC may even prevent healthy young women from achieving their physiologic peak of bone mass.²⁰ In the study by Polatti, a total of 200 women aged 19-22 years were treated with a desogestrel OC (Mercilon, n=100) or no treatment (n=100) with the following results: from baseline to the end of Year 5, the BMD in the OC group (n=76 at Year 5) did not show any significant change (i.e. BMD decreased from 1.16 g/cm² at baseline to 1.15 g/cm² at Year 5), while the BMD in the no treatment group (n=71 at Year 5) significantly increased (p<0.01) +7.8% (i.e. BMD increase from 1.15 g/cm² at baseline to 1.24 g/cm² at Year 5). It should be noted that the Polatti study was not randomized.

Reviewer’s comment:

- 1) *To determine the effect of oral contraceptives on bone mineral density, it would be optimal to conduct prospective, randomized, placebo controlled, long-term (i.e., minimum of 5 years duration) clinical trials in a large number of subjects (i.e., minimum of 1000 subjects) evaluating several oral contraceptives with different progestins and different doses of ethinyl estradiol in women of different age groups. However, this reviewer does not believe that such studies will be conducted due to a combination of factors including: lack of funding, the difficult of keeping women for long time periods on oral contraceptives, ethical concerns regarding randomizing a group to less reliable nonhormonal contraceptives, and relatively low OC acceptance rate in very young teenagers. Thus, clinical decisions must be made on the data currently available. Moreover, the question of greatest clinical relevance is whether treating adolescents with anorexia nervosa with an oral contraceptive (for whatever duration) increases peak bone mass*

¹⁸ Petitti DB et al. Steroid Hormone Contraception and Bone Mineral Density: A Cross-Sectional Study in an International Population. *Obstet Gynecol.* 2000; 95: 736-44.

¹⁹ Berenson AB et al. Effects of Hormonal Contraception on Bone Mineral Density After 24 Months of Use. *Obstet Gynecol.* 2004; 103: 899-906.

²⁰ Polatti F et al. Bone Mass and Long-Term Monophasic Oral Contraceptive Treatment in Young Women. *Contraception* 1995; 51: 221-224.

and significantly reduces the risk for fracture later in life. It would take a monumental effort to conduct such a study

2.1 Product Information

Ortho Tri-Cyclen 21 Tablets and 28 Tablets (Code Name RWJ 10131) is a combination drug product supplied in a DIALPAK Tablet Dispenser containing 21 tablets of alternating strengths of the progestational compound, norgestimate, combined with a constant strength of the estrogenic compound, ethinyl estradiol, as follows: 7 white tablets of norgestimate 0.18 mg and ethinyl estradiol 0.035 mg (Day 1-7), followed by 7 light blue tablets of norgestimate 0.215 mg and ethinyl estradiol 0.035 mg (Day 8-14), followed by 7 blue tablets of norgestimate 0.25 mg and ethinyl estradiol 0.035 mg (Day 15-21). Ortho Tri-Cyclen 28 Tablets also contains 7 green tablets containing inert ingredients (Day 22-28). Ortho Tri-Cyclen was approved under NDA 19-697 on July 3, 1992 as a triphasic oral contraceptive for the prevention of pregnancy. Ortho Tri-Cyclen is currently approved for the following two indications:

- prevention of pregnancy in women who elect to use oral contraception as a method of contraception
- treatment of moderate acne vulgaris in females ≥ 15 years of age, who have no known contraindications to oral contraceptive therapy, desire contraception, have achieved menarche and are unresponsive to topical anti-acne medications

The sponsor for Ortho Tri-Cyclen NDA 19-697 is Ortho-McNeil Pharmaceutical, Inc. and the authorized US Agent is Johnson & Johnson Pharmaceutical Research & Development, LLC. Per the Orange Book, the original patent expiration dates for all Ortho Tri-Cyclen patents were September 26, 2003; thus, fulfilling the requirements listed in the Written Request and obtaining pediatric exclusivity would have extended these patents and granted exclusivity until March 26, 2004. However, Barr Laboratories reached a settlement of pending litigation regarding Ortho-McNeil Pharmaceutical Inc's patents protecting Ortho Tri-Cyclen oral contraceptive. Under the terms of this settlement, Barr had the right to launch its generic version of Ortho Tri-Cyclen no later than December 29, 2003, if Ortho-McNeil was granted pediatric exclusivity by the FDA. Ortho Tri-Cyclen was granted pediatric exclusivity on December 18, 2003. On December 29, 2003, a generic for Ortho Tri-Cyclen (Tri-Sprintec) sponsored by Barr Laboratories was approved under ANDA #75-808. On January 9, 2004, a tentative approval letter of a generic for Ortho Tri-Cyclen (Tri-Previfem) under ANDA #76-335 was sent to Andrx Pharms; however, due to pediatric exclusivity it was not approved until March 26, 2004. There are currently no unexpired patents or exclusivity for Ortho Tri-Cyclen.

Applications related to Ortho Tri-Cyclen and filed with the Agency by Ortho-McNeil Pharmaceutical, Inc. or Johnson & Johnson Pharmaceutical Research & Development, LLC are as follows:

- IND 11,391: norgestimate and ethinyl estradiol tablets oral contraceptive for prevention of pregnancy-opened on March 19, 1975
- IND 34,653: norgestimate and ethinyl estradiol tablets buccal oral contraceptive for prevention of pregnancy-opened on April 4, 1990 and withdrawn on August 3, 1994
- IND 43,394: Ortho Tri-Cyclen (norgestimate 0.18, 0.215, 0.25 mg/ethinyl estradiol 0.035 mg) for acne vulgaris indication-opened on September 9, 1993 and inactivated on October 27, 2004
- IND 44,227: Prefest (norgestimate/estradiol) Tablets for menopausal symptom therapy indications-opened on December 23, 1993; current sponsor is Duramed
- IND 50,488: Ortho-Evra (17-deacetylnorgestimate, also known as norelgestromin/ethinyl estradiol) transdermal patch; non-oral contraceptive for prevention of pregnancy indication-opened on May 1, 1996

- IND 61,239: Ortho Tri-Cyclen (norgestimate 0.18, 0.215, 0.25 mg/ethinyl estradiol 0.035 mg) for treatment of low bone mineral density in adolescents with anorexia nervosa-opened on November 26, 2001
- IND 63,087: Ortho Tri-Cyclen Lo (norgestimate 0.18, 0.215, 0.25 mg/ethinyl estradiol 0.025 mg) for acne vulgaris-opened on August 20, 2001 and withdrawn on October 23, 2001
- NDA 18-177: Ortel Tablets (norgestimate 0.125 mg/ethinyl estradiol 0.035 mg) non-oral contraceptive for prevention of pregnancy-submitted on September 28, 1978 and not approvable on March 27, 1979
- NDA 19-653: Ortho-Cyclen Tablets (norgestimate 0.25 mg/ethinyl estradiol 0.035 mg) monophasic oral contraceptive for prevention of pregnancy-approved on December 29, 1989
- NDA 19-697: Ortho Tri-Cyclen (norgestimate 0.18, 0.215, 0.25 mg/ethinyl estradiol 0.035 mg) triphasic oral contraceptive for prevention of pregnancy-approved on July 3, 1992
- NDA 20-681: Ortho Tri-Cyclen (norgestimate 0.18, 0.215, 0.25 mg/ethinyl estradiol 0.035 mg) for treatment of moderate acne vulgaris in females, >15 years of age, who have no known contraindications to OC therapy, desire contraception, have achieved menarche, and are unresponsive to topical anti-acne medications-approved on December 31, 1996
- NDA 21-040: Prefest (norgestimate/estradiol) Tablets; treatment of moderate to severe vasomotor symptoms associated with the menopause, vulvar and vaginal atrophy, prevention of osteoporosis-approved on October 22, 1999; current sponsor is Duramed
- NDA 21-180: Ortho-Evra (norelgestromin/ethinyl estradiol) transdermal patch non-oral contraceptive for prevention of pregnancy-approved on November 20, 2001
- NDA 21-241: Ortho Tri-Cyclen Lo (norgestimate 0.18, 0.215, 0.25 mg/ethinyl estradiol 0.025 mg) triphasic oral contraceptive for prevention of pregnancy-approved on August 22, 2002
- NDA 21-690: Ortho Tri-Cyclen (norgestimate 0.18, 0.215, 0.25 mg/ethinyl estradiol 0.035 mg) for treatment of low bone mineral density in adolescents with anorexia nervosa-current submission

2.2 Currently Available Treatment for Indication

The sponsor is seeking the following indication: “Ortho Tri-Cyclen is indicated for treatment to increase lumbar spine bone mineral density in adolescent females with anorexia nervosa.” This indication has never been granted by the Agency in the past. Although no treatment is currently approved for this indication, oral contraceptives are readily available for off-label use for this indication.

For the prevention of pregnancy indication, dozens of oral contraceptives are currently marketed in the United States in addition to the applications listed above in Section 2.1 of this review. Approved oral contraceptives utilize various progestins (i.e. norethindrone, norethindrone acetate, norgestrel, norgestimate, drospirenone, desogestrel, levonorgestrel, ethynodiol diacetate) most commonly combined with the estrogen, ethinyl estradiol. The exceptions are a few oral contraceptives that use mestranol as the estrogen component (i.e. Norethin 1/50, Norinyl 1 + 50, Ortho-Novum 1/50) and the progestin-only oral contraceptives [i.e. Micronor (norethindrone), Ovrette (norgestrel), and Nor-QD (norethindrone)].

Two oral contraceptives are currently approved in the USA for the secondary indication “treatment of acne”: Ortho Tri-Cyclen (NDA 20-681 was approved on December 31, 1996) and Estrostep (NDA 21-276 was approved on July 1, 2001; current sponsor is Galen). The oral contraceptive Alesse (NDA 21-325; Wyeth Ayerst) received a non-approval for the treatment of acne indication on August 30, 2001.

2.3 Availability of Proposed Active Ingredient in the United States

See Section 2.1 Product Information.

2.4 Important Issues With Pharmacologically Related Products

Estrogens are among the most commonly prescribed drugs in the United States.²¹ The two major uses of estrogen are as a component of combination oral contraceptives and for menopausal hormone therapy. Since the adverse reactions of estrogens are dose-dependent, the incidence and severity of adverse reactions reported for oral contraceptives are significantly greater than those for menopausal hormone therapy when prescribed to similarly aged women. However, oral contraceptives are generally prescribed for significantly younger women and menopausal hormone therapy is generally prescribed to significantly older women. In addition, the incidence and severity of adverse events reported for older oral contraceptives containing higher doses of estrogens (i.e. 50 to 150 mcg of mestranol or ethinyl estradiol) are significantly greater than those reported for the newer oral contraceptives (i.e. 20 to 35 mcg of ethinyl estradiol). Adverse reactions listed in class labeling for oral contraceptives include death, thromboembolic disorders such as myocardial infarction, thrombophlebitis, arterial thromboembolism, pulmonary embolism, thrombotic stroke, mesenteric thrombosis, and retinal thrombosis, hemorrhagic stroke, breast cancer, benign hepatic adenomas, gallbladder disease, glucose intolerance, hypertension, headache, bleeding irregularities, nausea, vomiting, fullness and tenderness of the breast, edema, migraines, reactivation or exacerbation of endometriosis resulting in pain, and anaphylactic/anaphylactoid reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms.

As noted in Section 2 “INTRODUCTION AND BACKGROUND” of this review, prior research on the effect of oral contraceptives on bone mineral density is contradictory.

2.5 Presubmission Regulatory Activity

Significant Presubmission Regulatory Activity:

- *December 22, 2000:* Ortho Tri-Cyclen PPSR was submitted to NDA 19-697 [Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580] by R.W. Johnson Pharmaceutical Research Institute and Ortho-McNeil Pharmaceutical Inc. to evaluate Ortho Tri-Cyclen in two studies: one in adolescents with primary dysmenorrhea and one in adolescents with von Willebrand’s disease; primary Medical Officer Review by current reviewer was finalized in DFS on 3/27/01.
- *April 13, 2001-DRUDP regulatory letter to sponsor:* Inadequate PPSR letter sent to NDA 19-697 denying Written Request due to these conditions not being unique to the pediatric population. The proposed trials could be conducted in the adult population and the results extrapolated to the postmenarcheal pediatric population. Requested pediatric studies should provide scientific rationale justifying an anticipated difference in the safety and/or efficacy of the drug product for the proposed indications in the postmenarcheal pediatric female population as compared to the adult female population; otherwise, the current labeling is adequate.
- *June 11, 2001-Request for teleconference:* submitted by sponsor to DRUDP for NDA 19-697 regarding the April 13, 2001 Inadequate letter and the off-label prescribing of Ortho Tri-Cyclen in adolescent females with anorexia nervosa, with the goal of decreasing bone demineralization. The meeting request was consulted to the Division of Metabolic and Endocrine Drug Products (DMEDP),

²¹ Hardman LG et al, Editors. Goodman & Gilman’s The Pharmacological Basis of Therapeutics. 9th Edition. McGraw-Hill. New York. 1996. pg. 1421.

HFD-510; however, since the request did not include an outline of a proposed protocol in anorexia nervosa, it was the conclusion of DMEDP on August 22, 2001 that there was nothing for DMEDP to review at that time.

- *October 23, 2001-DRUDP regulatory letter to sponsor:* Inadequate PPSR letter sent to NDA 19-697 denying Written Request for prevention of osteoporosis in patients with anorexia nervosa (since this indication is reviewed by DMEDP) and denying request for teleconference.
- *November 27, 2001-Submission M000 to preIND 61,239:* Sponsor submitted new PPSR and protocol CAPSS-169 to DMEDP. CAPSS-169 was proposed by the sponsor to be a randomized, double blind, placebo controlled, multicenter, 12 week treatment duration clinical trial to evaluate the effects of Ortho Tri-Cyclen on biochemical markers of bone metabolism in pediatric subjects with anorexia nervosa. The cover letter stated that the sponsor intended to begin the pediatric study as soon as possible since patent protection for Ortho Tri-Cyclen would expire on September 26, 2003. The submission also included letters from two experts (Anne Klibanski, M.D. from Massachusetts General Hospital and Ann J. Davis, M.D. from Harvard Medical School) who advocated for the conduct of bone mineral density studies in adolescents with anorexia nervosa since “literature on the effects of estrogen replacement on bone metabolism in menopause cannot be extrapolated to the state of high bone turnover associated with attainment of peak bone mass in adolescence”.
- *February 15, 2002-DMEDP regulatory letter to sponsor:* Inadequate PPSR letter sent to preIND 61,239 denying Written Request for prevention of osteoporosis in patients with anorexia nervosa. The letter stated that any future proposal should be a double-blind, placebo-controlled, at least one year treatment duration study with change in lumbar spine bone mineral density as the primary efficacy endpoint, change in hip bone mineral density as the secondary efficacy endpoint, and body weight as the primary safety outcome. The letter also stated that a pharmacokinetic study protocol in pediatric patients should be submitted. A safety concern raised in the MO Review of CAPSS-169 was that women with anorexia nervosa are at increased risk of dehydration, which increases the risk of venous thromboembolism, and treatment with oral contraceptives can be expected to further increase this risk.
- *March 28, 2002:* Revised PPSR and request a Type A meeting submitted to preIND 61,239. The revised PPSR incorporated some of the revisions suggested in DMEDP’s February 15, 2002 regulatory letter. The sponsor proposed to change CAPSS-169 to be a six-month duration study in 60 postmenarcheal female pediatric subjects with anorexia nervosa and to conduct a separate three-month pediatric pharmacokinetic study, CAPSS-225, in 18 subjects. The sponsor proposed to submit the final study reports for both studies in order to obtain Pediatric Exclusivity.
- *April 11, 2002-DMEDP regulatory letter to sponsor:* Meeting request was denied since the Division’s recommended general design of a study of Ortho Tri-Cyclen in adolescent females with anorexia nervosa had not changed and sponsor was only proposing to conduct a six-month study.
- *April 26, 2002-Request for brief teleconference:* Sponsor proposed to have subjects in CAPSS-169 continue in a separate 6-month extension study to provide the Agency with one-year data on bone mineral density and biochemical markers of bone metabolism. The sponsor anticipated that 40 of the 60 enrolled subjects in CAPSS-169 would complete one-year of treatment
- *May 3, 2002-DMEDP regulatory letter to sponsor:* Inadequate PPSR letter denying Written Request (for March 28, 2002 PPSR) sent to preIND 61,239 for prevention of osteoporosis in patients with anorexia nervosa. Letter also stated that a detailed review of CAPSS-225 would be deferred until the requested one-year study protocol CAPSS-169 was submitted.
- *May 20, 2002-Teleconference with DMEDP:* The Division stated that they still felt strongly that one-year BMD data are necessary to assess both the efficacy and safety. The Division also stated that osteoporosis study durations have been up to 3 years with some products. The sponsor stated that in order to comply with the one-year requirement, they would only be able to complete 10 to 20 subjects by September 26, 2003-assuming an immediate initiation of the study. The Division agreed to consider

accepting a six-month study and would let the sponsor know at a later date the required sample size. The Division planned to recalculate the sample size using 1-year mean and standard deviation estimates provided by the sponsor, and modifying the 1-year treatment effect to reflect the fact that most of the change in BMD occurs during the first six months.

- *May 31, 2002-Teleconference with DMEDP:* Sponsor meeting minutes state that the Division would consider pediatric exclusivity on the basis of submitting 6-month data from a 1-year trial; however, a larger sample size of 120 subjects would be required. Sponsor submitted their meeting minutes to IND 61,239. No official Division meeting minutes were prepared since the teleconference was documented in the project manager's phone conversation logbook. Sponsor was reminded by Dr. Orloff that there was no guarantee that the Pediatric Committee (PdIT) would approve the PPSR. He reminded the sponsor that what was discussed during the teleconference was only the Division's recommendations and could not be taken as an agreement reached for the Written Request, and the final requirements may be different.
- *July 12, 2002-Submission N000 to IND 61,239:* Submission contained revised PPSR and Final Protocol CAPSS-169 dated June 11, 2002. Protocol CAPSS-169 was planned to be a multicenter, double-blind, placebo-controlled, 1:1 randomized clinical study in 120 postmenarcheal adolescent subjects (<17 years old) with anorexia nervosa.
- *August 7, 2002-Submission N001 to IND 61,239:* Submission contained a revised Protocol CAPSS-169 dated July 12, 2002 due to Amendment #1. The sponsor opted to begin the study prior to obtaining a Written Request.
- *September 16, 2002-DMEDP regulatory letter to sponsor:* Seven statistical comments re: Protocol CAPSS-169 sent to sponsor. Specifically, the letter stated that subgroup analyses with respect to center and other potential prognostic factors (e.g., duration of amenorrhea, age of menarche, prior estrogen use, and BMI), if any, should be explored by testing treatment-by-subgroup interactions at $p \leq 0.10$.
- *October 2, 2002-Presentation to PdIT:* PdIT questioned the ethics of doing this study in patients who were not old enough to give informed consent. The division could not say with certainty that bone density response would be different in the pediatric population than it is in the adult population. In the study proposed by the written request, PdIT recommended that one-half of the patients must have a body weight of 70% or less of the ideal body weight at baseline. PdIT was concerned that since oral contraceptives had not been proven efficacious in women over 70% of ideal body weight, there were concerns about including that population in the study. PdIT also recommended adding bradycardia in the exclusion criteria, considering stratifying the study to check for a nutrition effect, and sending several issues to the Ethics Working Group meeting to be held on October 9, 2002.
- *October 23, 2002-Submission N006 to IND 61,239:* Response to Information Request: sponsor stated that at 6 months the mean change in BMD between groups from baseline is estimated to be 0.05 gm/cm^2 (placebo=0.83 gm/cm^2 at 6 months with 0% change from baseline BMD of 0.83 gm/cm^2 ; Ortho Tri-Cyclen 0.88 gm/cm^2 at 6 months with 6% mean change from baseline 0.83 gm/cm^2).
- *November 12, 2002-ODE II Written Request to sponsor:* The Written Request included a 1-year (13 cycle) study of approximately 120 pediatric females aged 12 through 16 years with anorexia nervosa defined by DSM-IV criteria evaluating 6-month and 12-month DXA results. The subjects were to be no more than 70% of ideal body weight. The primary efficacy analyses were to be performed after cycle 6, the Agency would consider submission of the primary efficacy and standard safety data through Cycle 6 as satisfying the Written Request, and all patients were to be continued in the study for an additional 6 months of double-blind therapy. A separate pharmacokinetic study in 18 completed adolescents aged 12-16 years was also requested.
- *January 15, 2003-ODE II Written Request Amendment #1:* Amendment #1 deleted the requirement that all subjects should be no more than 70% of ideal body weight at baseline and added the

requirement that all subjects should have a baseline lumbar spine BMD Z-score, matched for ethnicity, of less than zero.

- *July 8, 2003-Pre-sNDA/NDA teleconference:* At the pre-sNDA/NDA teleconference between sponsor and DMEDP, agreement was obtained on the content and format of the submission and on the proposed process for submitting 6-month study data without compromising the blinding of the ongoing study.
- *August 15, 2003-ODE II Written Request Amendment #2:* Amendment #2 contained the following changes:
 - Inclusive age range was broadened to 12-17 years of age for both studies.
 - The one-year study should “target” subjects with a lumbar spine BMD Z-score less than 0.
 - The inclusion criteria for the one-year study were changed to delete the post-menarchal requirement and allow enrollment of patients with primary amenorrhea due to anorexia nervosa. Subjects with primary amenorrhea due to a condition other than anorexia nervosa continued to be excluded from the one-year study.
 - Deleted exclusion criterion #11 for the one-year study: resting heart rate below 60 beats per minute was deleted.
 - The option was given to perform a population pharmacokinetic (PK) study (per the February 1999, Guidance for Industry: Population Pharmacokinetics guidance) as a substudy of the clinical study or carry out a separate PK study.
- *September 25, 2003-Receipt of Original NDA 21-690:* The supplement to NDA 19-697 Ortho Tri-Cyclen to evaluate the effects of bone mineral density in adolescents with anorexia nervosa was administratively assigned to be NDA 21-690, since the review would be performed by a different division (DMEDP, HFD-510) than the division assigned to NDA 19-697 (DRUDP, HFD-580). Priority review was granted.
- *December 18, 2003- Pediatric Exclusivity Granted*
- *March 23, 2004-DMEDP regulatory letter to sponsor:* NDA 21-690 approvable letter stated that submission and review of the final results from the 12-month study, CAPSS-169 and satisfactory resolution to deficiencies noted during a recent inspection of the manufacturing facilities for this application are required before approval of the application. The letter also stated that a safety update must be included when the sponsor responded to the listed deficiencies.

Reviewer’s comment:

- 1) *Enrollment for CAPSS-169 ended on April 1, 2003; thus, the CAPSS-169 Inclusion/Exclusion criteria changes to the Written Request as listed in Written Request Amendment #2 (dated August 15, 2003) did not result in the sponsor enrolling a different study population. Instead, the Written Request Amendment #2 simply changed the study population to be studied to better “match” the study population that the sponsor had already enrolled into CAPSS-169.*

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

NDA 21-690 Chemistry review #1 by Yvonne Yang, Ph. D. was finalized in the first review cycle on March 12, 2004. The review contained the following recommendation:

- From the standpoint of chemistry, manufacturing and controls, NDA 21-690 is approvable pending resolution of all issues related to a **Withhold** recommendation from the Office of Compliance on March 11, 2004.

In a memorandum finalized on April 21, 2005, Yvonne Yang, Ph. D. stated that a complete response was submitted on November 18, 2004 regarding the **Withhold** recommendation from Office of Compliance for one of the manufacturing facilities. An overall **Acceptable** cGMP status was granted by the Office of Compliance on December, 21, 2004. From the standpoint of chemistry, manufacturing and controls, this NDA can be approved pending a satisfactory review of the revised labeling.

3.2 Animal Pharmacology/Toxicology

No Pharmacology review was conducted for NDA 21-690 due to Item 5: NonClinical Pharmacology and Toxicology of NDA 21-690 being cross-referenced in its entirety to the Ortho Cyclen IND 11, 391 and NDA 19-653, to the Ortho Tri-Cyclen IND 11,391 and NDA 19-697, and to the Ortho Tri-Cyclen Lo NDA 21-241, in accordance with 21 CFR 314.50(g)(1) and per the July 8, 2003 pre-NDA meeting agreement with DMEDP (HFD-510). The sponsor stated in the Original NDA 21-690 submission that the referenced NonClinical Pharmacology and Toxicology material is located in Volumes 12-38, pages 04-00001 through 04-13184 of NDA 19-653. The sponsor also stated in the Original NDA 21-690 submission that there had been no new information reported that was pertinent to this section since the original submission of NDA 19-653 on 24 March 1987, NDA 19-697 on 20 July 1987, and NDA 21-241 on 25 August 2000.

In the current NDA 21-690 Complete Response to Approvable Action Letter submission, Item 5: NonClinical Pharmacology and Toxicology contained no information.

3.3 Biometrics

NDA 21-690 Statistical review #1 by Cynthia Liu, MA was finalized in the first review cycle on February 25, 2004. The review contained the following conclusions and recommendations:

Treatment with Ortho Tri-Cyclen after 6 months showed a statistically significant increase in mean change or mean % change from baseline in lumbar spine bone mineral density when compared with placebo. However, the observed treatment difference [i.e. 0.011 gm/cm²] between the 2 study groups was marginal and smaller than the expected difference at 6 months (0.05 gm/cm² or 6%). Therefore, concluding a clinically meaningful difference in this case might be in question. Also, treatment with Ortho Tri-Cyclen after 6 months did not show any statistically significant positive finding when compared with placebo for total hip bone mineral density and body weight. Since the study is still ongoing, final conclusions should be made after Cycle 13/Final Visit data are reviewed.

NDA 21-690 Statistical review #2 by Cynthia Liu, MA was finalized in the second review cycle on May 2, 2005. The review contained the following conclusions and recommendations:

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/cm²). 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.

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)

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

NDA 21-690 clinical data consisted of one Phase 2, placebo-controlled study, CAPSS-169. See Section 10.1.1 (located in the Appendix of this review) for a detailed review of CAPSS-169.

4.4 Data Quality and Integrity

DSI inspections were not requested or conducted for CAPSS-169. See Section 10.1.1.3.3 (located in the Appendix of this review) for details regarding CAPSS-169 protocol violations and subject compliance.

4.6 Financial Disclosures

The financial disclosure information submitted by the sponsor for key personnel who participated in clinical study CAPSS-169 was reviewed. The sponsor stated in the attached Form FDA 3454 that no key personnel who participated in clinical study CAPSS-169 held financial interests or participated in financial arrangements that are required to be disclosed. However, financial disclosure information was not obtained (after Ortho-McNeil Pharmaceuticals made two written requests) from 3 investigators and from 15 sub-investigators. The sponsor does not appear to have performed due diligence in attempting to obtain this information by sending certified letters or faxes, performing Internet searches, or making telephone calls. The three principal investigators who failed to submit financial disclosure are as follows:

- (b) (4)-site enrolled a total of (b) (6), on Ortho Tri-Cyclen
- (b) (6)-site enrolled a total of (b) (6), placebo
- (b) (6)-site enrolled a total of (b) (6) each on Ortho Tri-Cyclen and placebo

This reviewer noted that in addition to Dr (b) (6) failing to submit financial disclosure, all four subinvestigators at his site failed to submit financial disclosure.

It is this reviewer's conclusions that while the sponsor could have used other means to obtain documentation from non-compliant investigators, the rate of return is acceptable. Adequate documentation was submitted to comply with 21 CFR 54. There was no disclosure of financial interests that could bias the outcome of CAPSS-169.

5 CLINICAL PHARMACOLOGY

The CAPSS-169 population pharmacokinetic data were reviewed by Steven B. Johnson, Pharm.D. in DPE-2 (HFD-870) in the first review cycle for NDA 21-690. The review was finalized on March 8, 2004 and it stated:

- The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the Clinical Pharmacology section of NDA 21-690 and finds the results to be unacceptable due to the scarcity of the data.
- Results of this study were confounding.
- The sampling technique ultimately used by the sponsor was a hybrid method somewhere between a single-trough and full population PK sampling design, but failed to hit either mark.
- Since the sponsor was unable to conduct this study in a manner consistent with recognized protocol, the value of the calculated apparent clearance is clearly suspect. This finding is apparently consistent with the sponsor's as they are not requesting a labeling change to include apparent clearance for this pediatric population at his time.

See Section 10.1.1.4.5 (located in the Appendix of this review) for a summary of the CAPSS-169 pharmacokinetic data.

6 INTEGRATED REVIEW OF EFFICACY

Note: all efficacy results are for CAPSS-169. CAPSS-169 efficacy data is also presented in Section 10.1.1.4 (located in the Appendix of this review).

Primary Efficacy Results-for efficacy variable and population prespecified in the protocol:

- For the 112 randomized subjects who took study medication and had an on-treatment DXA scan (defined as the ITT population), treatment with Ortho Tri-Cyclen for **6 cycles statistically significantly increased** the mean total lumbar spine (L1-L4) bone mineral density (BMD) compared with placebo (mean change Ortho Tri-Cyclen=0.0197 g/cm² and mean change placebo=0.0084 g/cm²; p=0.021).

Reviewer's comment:

- 1) *This reviewer concurs with the primary NDA 21-690 Statistical reviewer that for the CAPSS-169 primary efficacy endpoint, the 0.011 g/cm² observed treatment difference between the two study groups was marginal and significantly smaller than the expected difference at 6 months (0.05 gm/cm² or 6%); therefore, concluding a clinically meaningful difference in this case might be in question.*

Key Secondary Efficacy Results-for efficacy variables and population prespecified in the protocol:

- For the ITT population, there was **no significant difference** between Ortho Tri-Cyclen and placebo in mean change in total lumbar spine (L1-L4) BMD between baseline and **Cycle 13** (mean change Ortho Tri-Cyclen=0.0264 g/cm² and mean change placebo=0.0190 g/cm²; p=0.244).

- In the ITT population, there was **no significant difference** in mean change in total hip BMD between Ortho Tri-Cyclen and placebo at **Cycle 6** (mean change Ortho Tri-Cyclen=0.0100 g/cm² and mean change placebo=0.0019 g/cm²; p=0.146) and at **Cycle 13** (mean change Ortho Tri-Cyclen=0.0111 g/cm² and mean change placebo=0.0133 g/cm²; p=0.784).

Primary Efficacy Results-for post-hoc sponsor defined “treated” population:

- When a post-hoc analysis was performed by the sponsor for the 123 randomized subjects who took study medication (defined as the “treated” population), treatment with Ortho Tri-Cyclen for 6 cycles still **statistically significantly increased** the mean total lumbar spine (L1-L4) BMD compared with placebo (mean change Ortho Tri-Cyclen=0.0171 g/cm² and mean change placebo=0.0080 g/cm²; p=0.042); however, the p-value was lower than for the ITT population analysis and the observed treatment difference between the two study groups was only 0.009 gm/cm².

Additional Secondary Efficacy Results:

- In the ITT population, there was **no significant difference** in mean weight gain between Ortho Tri-Cyclen and placebo at **Cycle 6** (4.2 kg and 3.1 kg; p=0.235) and at **Cycle 13** (6.7 kg and 4.9 kg; p=0.174).
- In the subgroup of ITT subjects with negative Z-scores at baseline, there was a **significant difference** between Ortho Tri-Cyclen and placebo in mean change in total lumbar spine (L1-L4) BMD between baseline and **Cycle 6** (0.0238 g/cm² and 0.0092 g/cm²; p=0.012) and in the subgroup of ITT subjects with non-negative Z-scores at baseline, there was **no significant difference** between Ortho Tri-Cyclen and placebo in mean change in total lumbar spine (L1-L4) BMD between baseline and **Cycle 6** (0.0040 g/cm² and 0.0042 g/cm²; p=0.900).
- In the subgroup of ITT subjects with negative Z-scores at baseline, there was **no significant difference** between Ortho Tri-Cyclen and placebo in mean change in total lumbar spine (L1-L4) BMD between baseline and **Cycle 13** (0.0286 g/cm² and 0.0225 g/cm²; p=0.435); in the subgroup of ITT subjects with non-negative Z-scores at baseline, there was **no significant difference** between Ortho Tri-Cyclen and placebo in mean change in total lumbar spine (L1-L4) BMD between baseline and **Cycle 13** (0.0180 g/cm² and 0.0016 g/cm²; p=0.283).
- In the post-hoc sponsor defined Completers/Efficacy subgroup (i.e. all ITT subjects who completed >12 cycles (i.e., >336 days) AND provided a Cycle 13 Final BMD measurement), there was a **significant difference** between Ortho Tri-Cyclen and placebo in mean change in total lumbar spine (L1-L4) BMD between baseline and **Cycle 6** (0.0251 g/cm² and 0.0091 g/cm²; p=0.002) and at **Cycle 13** (0.0374 g/cm² and 0.0218 g/cm²; p=0.018).
- In the post-hoc sponsor defined Non-Completers/Efficacy subgroup (i.e. all ITT subjects who had not completed >12 cycles (i.e., >336 days) OR had not provided a Cycle 13 Final BMD measurement), there was **no significant difference** between Ortho Tri-Cyclen and placebo in mean change in total lumbar spine (L1-L4) BMD between baseline and **Cycle 13** (-0.0043 g/cm² and 0.0054 g/cm²; p=0.441).
- In the ITT population, 14/53 (26.4%) Ortho Tri-Cyclen subjects and 20/59 (33.9%) placebo subjects had a **Cycle 6** total lumbar spine bone density less (i.e. negative change) than their baseline total lumbar spine bone density.
- In the ITT population, 16/53 (30.2%) Ortho Tri-Cyclen subjects and 19/59 (32.2%) placebo subjects had a **Cycle 13** total lumbar spine bone density less (i.e. negative change) than their baseline total lumbar spine bone density.

- In the ITT population, 16/53 (30.2%) Ortho Tri-Cyclen subjects and 26/59 (44.1%) placebo subjects had a **Cycle 6** total hip bone density less (i.e. negative change) than their baseline total lumbar spine bone density.
- In the ITT population, 17/53 (32.1%) Ortho Tri-Cyclen subjects and 22/59 (37.3%) placebo subjects had a **Cycle 13** total hip bone density less (i.e. negative change) than their baseline total lumbar spine bone density.
- In the ITT population, an improvement in body weight (>5%, n=80) was associated with a change in total lumbar spine bone mineral density from baseline to **Cycle 13** of 0.0333 in the Ortho Tri-Cyclen subjects (n=40) and 0.0321 in the placebo subjects (n=40).

Reviewer's comment:

- 1) *It is the conclusion of this reviewer that any improvement in total lumbar spine BMD seen in adolescent subjects with anorexia nervosa in CAPSS-169 was primarily due to an improvement in body weight. Treatment with oral contraceptives in this population did not demonstrate a significant improvement in total lumbar spine or total hip BMD from baseline to Cycle 13 when compared to placebo. Indeed, treatment with oral contraceptives in subjects with anorexia nervosa may decrease their motivation to gain weight due to the resultant resumption of regular menses and the false belief that they are now "normal". The absence of menses is an important reminder to subjects with anorexia nervosa that they are ill.*

6.1 Indication

The sponsor is seeking the following indication: "Ortho Tri-Cyclen is indicated for treatment to increase lumbar spine bone mineral density in adolescent females with anorexia nervosa." This indication has never been granted by the Agency in the past. This reviewer could find no references to the sponsor specifically mentioning that they intended to submit the Phase 2 study CAPSS-169 to obtain this indication. The stated purpose of conducting CAPSS-169, in all the reviewed submissions to IND 61,239, official meeting minutes, and DMEDP regulatory letters, was to obtain pediatric exclusivity. No agreements had been made between the sponsor and DMEDP regarding the number and types of clinical trials necessary to support such an indication.

Reviewer's comment:

- 1) *It is unclear to this reviewer on what basis the sponsor requests receiving this indication since only one Phase 2 study was conducted and there was no significant difference in mean change in either total lumbar spine (L1-L4) or total hip bone mineral density between Ortho Tri-Cyclen and placebo at Cycle 13 for the prespecified Intent to Treat (ITT) population. This reviewer considers all results submitted by the sponsor for the post-hoc Completers/Efficacy subpopulation to be exploratory and insufficient to support efficacy.*

7 INTEGRATED REVIEW OF SAFETY

CAPSS-169 safety data is presented in greater detail in Section 10.1.1.5 (located in the Appendix of this review).

7.1 Methods and Findings

7.1.1 Deaths

No subjects died during the conduct of CAPSS-169.

7.1.2 Other Serious Adverse Events

A total of 22 CAPSS-169 subjects reported a total of 44 serious adverse events during treatment: 8 (13.1%) subjects on Ortho Tri-Cyclen and 14 (22.6%) subjects on placebo. The majority of SAEs were due to hospitalizations for worsening anorexia nervosa. Two subjects required receiving activated charcoal after a suicide gesture or drug overdose (Subject 050001 on Ortho Tri-Cyclen after a suicide gesture with 15 Naprosyn tablets; Subject 010001 after a drug overdose with 30 tablets of Paxil 10 mg during screening). One subject deliberately overdosed on Celexa (Subject 100002). None of the serious adverse events were considered by the investigators to be related to study medication.

7.1.3 Dropouts and Other Significant Adverse Events

Four CAPSS-169 subjects were withdrawn from the study due to adverse events: 3 (4.9%) in the Ortho Tri-Cyclen group (Subject 112003 due to nausea and vomiting, Subject 014002 due to weight gain, and Subject 016001 due to “menstrual disorder-irregular menses”; however, it was actually the onset of first menses in a premenarchal 10 year old) and 1 (1.6%) in the placebo group (Subject 010004 due to headache and nausea). In addition, the CRF for Subject 050001 (on Ortho Tri-Cyclen) stated that the subject discontinued prematurely due to a weight increase from 85 lbs on 11/1/02 to 108 lbs on 9/17/03; however, Subject 050001 was coded by the sponsor as discontinuing due to “subject choice”. Subject 100003 on Ortho Tri-Cyclen was listed in CFR as discontinuing due to “subject choice” with the comment “felt her mood had worsened since starting study medication”; however, the comment was later deleted per 7/7/2003 data clarification form since “comments were not supposed to be provided if subject discontinued due to subject choice”.

One subject on Ortho Tri-Cycle (Subject 086003-Dr. Gersten’s site) experienced the significant adverse event “imperforate hymen” (genital malformation) starting on Day 313. All Physical Examination results, including “Genitourinary”, for Subject 086003 were normal at both screening and final visits, except for the screening Physical Examination comments “thin” and “scaphoid abdomen”.

Reviewer’s comment:

- 1) *A visual examination of the vulva and vaginal introitus should have diagnosed Subject 086003’s imperforate hymen at screening and prior to the initiation of treatment with oral contraceptives. No LMP was listed for Subject 086003 at Visit 1. The menses induced by treatment with oral contraceptives would have been trapped in the vagina by the imperforate hymen and may have resulted in cyclic pelvic pain, back pain or difficulty with defecation or urination secondary to mass effect from the vaginal distension. Blood may also fill the uterus (hematometra) and exit through the fallopian tubes into the peritoneal cavity, resulting in endometriosis.*

7.1.5 Common Adverse Events

Table 2: Incidence of Adverse Events Reported in \geq 5% of CAPSS-169 Subjects (n=123)

	Ortho Tri-Cyclen	Placebo
	(N=61)	(N=62)
Number (%) of Subjects with Any Adverse Event	48 (78.7%)	49(79.0%)
Body as a Whole-General Disorders		
Back Pain	0	5 (8.1%)
Influenza-like Symptoms	7 (11.5%)	0
Injury	2 (3.3%)	6 (9.7%)
Central & Peripheral Nervous System Disorders		
Headache	10 (16.4%)	10(16.1%)
Gastro-intestinal System Disorders		
Abdominal Pain	7 (11.5%)	2 (3.2%)
Nausea	4 (6.6%)	6 (9.7%)
Metabolic and Nutritional Disorders		
Hypoglycemia	1 (1.6%)	6 (9.7%)
Psychiatric Disorders		
Anorexia Nervosa	2 (3.3%)	11(17.7%)
Anxiety	2 (3.3%)	4 (6.5%)
Depression	6 (9.8%)	8 (12.9%)
Emotional Lability	1 (1.6%)	4 (6.5%)
Reproductive Disorders, Female		
Dysmenorrhea	10 (16.4%)	3 (4.8%)
Resistance Mechanism Disorders		
Infection	5 (8.2%)	1 (1.6%)
Infection Viral	2 (3.3%)	4 (6.5%)
Respiratory System Disorders		
Sinusitis	7 (11.5%)	1 (1.6%)
Upper Respiratory Tract Infection	6 (9.8%)	14(22.6%)

Source: Table 11 in CAPSS-169 Final Study Report on pg. 154 of 2369

Note: Reported in >=5% of subjects in either treatment group.

Note: If a subject experienced more than one adverse event within a category, the subject is counted once under that category.

WHOART dictionary (Version 1992, 3rd Quarter) was used for coding

7.1.7 Laboratory Findings

All pregnancy tests performed were negative. Mean baseline and final visit hemoglobin (13.41-13.53) and hematocrit (39.4-39.8) were high normal, compatible with mild dehydration. No clinically significant changes in mean hematology or chemistry tests were noted. This reviewer detected no signal of any significantly increased abnormal laboratory values associated with Ortho Tri-Cyclen treatment when compared to placebo treatment.

7.1.8 Vital Signs

No significant change in mean blood pressure or pulse from baseline to final visit was noted. One placebo subject had a markedly low pulse, two subjects had a markedly low systolic blood pressure and one Ortho Tri-Cyclen subject had a markedly high systolic blood pressure. Mean weight gain from baseline to final

visit for the 61 Ortho Tri-Cyclen subjects in the “treated” population was 5.88 kg (range -7.3 to +24.9 kg). Mean weight gain from baseline to final visit for the 62 Placebo subjects in the “treated” population was 4.71 kg (range -18.8 to +42.6 kg).

When comparing weight at Visit 1 to weight at last visit, more subjects in the Ortho Tri-Cyclen group (n=13) than in the placebo group (n=9) gained 20 or more pounds. The 13 Ortho Tri-Cyclen subjects (who gained 20 or more pounds) gained a total of 480.6 pounds. The 9 subjects in the placebo group (who gained 20 or more pounds) gained a total of 365.7 pounds. This discrepancy in total weight gain between the two treatment groups may have confounded the change in BMD, so this reviewer requested that the sponsor perform a subgroup analysis by excluding subjects who gained 20 or more pounds. On April 19, 2005, the sponsor submitted the requested subgroup analysis (see Table 8). In this post-hoc efficacy subgroup analysis requested by the Division and performed by the sponsor, excluding subjects who gained 20 or more pounds (i.e. Population II) resulted in the Ortho Tri-Cyclen treated subjects being not statistically different from placebo treated subjects for the endpoint “change from baseline in total lumbar spine bone mineral density” at both time points, i.e. at Cycle 6 and at Cycle 13.

No effect of treatment on height was detected by this reviewer.

7.1.9 Electrocardiograms (ECGs)

No ECGs were obtained in CAPSS-169.

7.1.15 Assessment of Effect on Growth

See Section 7.1.8 “Vital Signs” in this review for a discussion of the effect of treatment on weight and height.

7.1.16 Overdose Experience

No overdose on treatment medication was reported during the conduct of CAPSS-169.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

See Section 10.1.1.5.2 (located in the Appendix of this review) for a discussion of the extent of exposure in CAPSS-169. The sponsor provided duration of therapy (i.e. “date of last dose minus date of first dose + 1”) for CAPSS-169 and did not provide number of treated days. Thus, extent of exposure in CAPSS-169 is unknown.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.2 Postmarketing experience

The sponsor provided a 55 page Periodic Safety Update Report (PSUR) of serious (labeled and unlabeled) and non-serious (unlabeled) adverse events for Johnson & Johnson's oral contraceptive product Cilest from the foreign marketing experience covering the time period October 31, 2001 to October 30, 2002. It included 161 reports of adverse events in 102 subjects that were either spontaneous reports or reports from regulatory bodies. There were no serious adverse events reported from study cases, literature cases, or other cases. The reports were reviewed. No changes to the current Ortho Tri-Cyclen labeling are recommended based upon this review.

7.2.3 Adequacy of Overall Clinical Experience

This reviewer considers the data in the Phase 2 study CAPSS-169 to be insufficient to address safety concerns regarding the use of Ortho Tri-Cyclen in subjects with anorexia nervosa. This is based on the reviewer assessment that a significant number of subjects treated in CAPSS-169 did not meet the DSM-IV diagnostic criteria for anorexia nervosa at the time of screening, the small number (n=123) of treated subjects, the small number (n=103) of subjects known to have had a duration of treatment of at least 169 days (6 Cycles), the small number (n=90) of subjects known to have had a duration of treatment of at least 337 days (12 Cycles), and the small number of subjects (n=8) known to have had a duration of treatment of at least 365 days (13 Cycles).

9 OVERALL ASSESSMENT

9.1 Conclusions

The majority of the 123 subjects treated in CAPSS-169 did not meet the DSM-IV diagnostic criteria for anorexia nervosa or the DSM-IV diagnostic criteria modified by the sponsor for anorexia nervosa at baseline.

In the ITT population, treatment with Ortho Tri-Cyclen was not associated with a significant change in mean total lumbar (L1-L4) bone mineral density from baseline to Cycle 13 when compared to placebo. In the ITT population, treatment with Ortho Tri-Cyclen was not associated with a significant change in mean total hip bone mineral density from baseline to Cycle 13 when compared to placebo. In the ITT population in subjects with negative Z-scores at baseline, treatment with Ortho Tri-Cyclen was not associated with a significant change in mean total lumbar spine (L1-L4) BMD from baseline to Cycle 13 when compared to placebo. This reviewer believes that most, if not all, subjects, subject families, and investigators were unblinded due to the well-known changes in menses and adverse events associated with oral contraceptives. In addition, unblinded 6-month CAPSS-169 efficacy and safety data was submitted in the Original NDA on September 25, 2003.

There were no deaths, no pregnancies, and no reports of venous thromboembolic events during the conduct of CAPSS-169. Significantly more treated subjects on Ortho Tri-Cyclen (n=21, 34.4%) prematurely discontinued from the study than placebo subjects (n=13, 21.0%). It is concerning that one subject was started on oral contraceptives and her imperforate hymen was not diagnosed until 11 months

on treatment. A visual examination of the vulva and vaginal introitus should have diagnosed the imperforate hymen at screening.

9.2 Recommendation on Regulatory Action

Recommend approving NDA 21-690 and incorporating the following sentence (underlined) into the Ortho Tri-Cyclen Prescribing Information, **PRECAUTIONS** section, **Pediatric Use** subsection.

Safety and efficacy of ORTHO TRI-CYCLEN Tablets and ORTHO CYCLEN Tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents. There was no significant difference between ORTHO TRI-CYCLEN Tablets and placebo in mean change in total lumbar spine (L1-L4) and total hip bone mineral density between baseline and Cycle 13 in 123 adolescent females with anorexia nervosa in a double-blind, placebo-controlled, multicenter, one-year treatment duration clinical trial for the Intent To Treat (ITT) population. Use of this product before menarche is not indicated.

It should be noted that in the Complete Class 2 Response to Approvable Action Letter, letter date November 18, 2004, the sponsor had requested approval of the new indication “ORTHO TRI-CYCLEN is indicated for treatment to increase lumbar spine bone mineral density in adolescent females with anorexia nervosa.” This new indication was not granted due to lack of efficacy in the CAPSS-169 ITT population at Cycle 13 and due to insufficient safety data to support approval. On May 3, 2005, the sponsor accepted the above Division proposed labeling and agreed to incorporate the single new sentence into the Ortho Tri-Cyclen Prescribing Information, **PRECAUTIONS** section, **Pediatric Use** subsection.

9.3 Recommendation on Postmarketing Actions

This reviewer has no recommendations for any postmarketing actions.

9.4 Labeling Review



2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this

page

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study Report for the Phase 2 study **CAPSS-169**

10.1.1.1 Summary

Title: “The Effect of Ortho Tri-Cyclen® on Bone Mineral Density in Pediatric Subjects with Anorexia Nervosa: A Double-Blind, Placebo-Controlled Study” dated June 11, 2002. The study was initiated on September 18, 2002, the first subject was allocated medication on September 27, 2002, the last Visit 1 occurred on April 1, 2003, and the date of the last subject visit was April 2, 2004. Thus, the study duration was 18.5 months. Enrollment lasted 6.5 months.

Amendment #1 dated July 10, 2002, added a new Inclusion Criteria #6 regarding a family history of Factor V Leiden; added determining at the Screening Visit whether subject has a Factor V Leiden family history; clarified Exclusion Criteria #10 by adding the example “e.g. a pattern of bingeing and purging incompatible with absorption of an oral medication”; added the supervision of a Data Safety Monitoring Board to Section 9.4: “Safety Evaluations” to monitor subject safety periodically during the study; and deleted updating the medical history review at the Baseline Visit (Visit 2).

Amendment #2 dated February 5, 2003, changed the study population from “females post-menarcheal up to but not including 17 years” to “up to but no including 18 years” at screening; changed the Exclusion Criteria #3 regarding subjects with primary amenorrhea to allow investigators to determine if a subject with primary amenorrhea was an appropriate candidate for hormonal therapy based on whether the subject had obtained an acceptable adult height; and added that if possible, blood samples for PK analysis should be drawn just prior to taking study medication on that day.

10.1.1.1.1 Objectives

The overall objective of Protocol **CAPSS-169** was to evaluate the effect of Ortho Tri-Cyclen on lumbar spine (L1-L4) and total hip bone mineral density (BMD) in pediatric subjects with anorexia nervosa.

10.1.1.1.2 Overall Design

This was a Phase 2, multicenter (43 US sites), 1:1 randomized, double-blind, placebo-controlled, efficacy and safety study to evaluate the effect of 13 consecutive 28-day cycles of Ortho Tri-Cyclen on bone mineral density (BMD) in 146 randomized (123 treated) pediatric subjects with anorexia nervosa. Per the protocol, 120 female subjects were to be enrolled. A total of 8 visits were planned: Visit 1 (Screening), Visit 2 (Baseline), and 6 visits while on treatment [Visit 3 (Cycle 1), Visit 4 (Cycle 3 on Days 4-7), Visit 5 (Cycle 3 on Days 18-21), Visit 6 (Cycle 6), Visit 7 (Cycle 9), and Visit 8 (Cycle 13)]. An interim report summarizing unblinded data collected through Cycle 6 (i.e. Visits 1-6) was submitted in the Original NDA 21-690 for review on September 15, 2003. The current final study report contains the data from the entire study [Cycles 1-13 (Visits 1-8)].

10.1.1.2 Study Procedures and Conduct

10.1.1.2.1 Schedule of Study Assessments

Table 3: CAPSS-169 Time and Events Schedule

	Visit 1 Screening Up to Day -7	Visit 2 Baseline Day 1	Visit 3 Cycle 1 Days 21-28	Visit 4 Cycle 3 Days 4-7	Visit 5 Cycle 3 Days 18-21	Visit 6 Cycle 6 Days 22-25	Visit 7 Cycle 9 Days 21-28	Visit 8 Early Termination or Cycle 13 Days 21-28
Informed Consent/Assent Signed	X							
Medical, Dietary & Gynecological History	X							
Physical Exam	X							X
Hematology	X					X		X
Serum Chemistry	X				X ¹	X ¹		X
Thyroid-stimulating Hormone	X							
Follicle-stimulating Hormone	X							
PK Blood Draw for Determination of Norelgestromin, Norgestrel and Ethinyl Estradiol				X ⁴	X ⁴			
Urine Pregnancy Test	X	X	X		X	X	X	X
Dual Energy X-ray Absorptiometry	X					X		X
Vital Signs ³	X	X	X		X	X	X	X
Randomization		X						
Dispense Study Medication		X			X	X	X	
Dispense Multivitamin and Calcium Supplement		X	X		X	X	X	
Adverse Event Review		X	X	X	X	X	X	X
Current/Concomitant Medications Review	X	X	X	X	X	X	X	X
Collect Unused Drug/Empty Blistercards			X		X	X	X	X

Source: CAPSS-169 Final Study Report pg. 49

¹ Electrolytes only (sodium; potassium; chloride; bicarbonate; blood urea nitrogen [BUN]; glucose).

² Dual Energy X-ray Absorptiometry (DXA) of the lumbar spine and total hip (non-dominant) was performed with a Hologic or Lunar DXA machine.

³ Blood pressure, pulse, and weight were taken at all visits, except Visit 4, and height at Visits 1, 6, and 8. Subjects were to be weighted using the same scale to the nearest pound or 0.5 kg, with shoes and clothes removed (i.e., in gown only).

⁴ If possible, blood samples were drawn just prior to taking study medication on that day.

10.1.1.2.2 Study Drugs

Dose Selection: No dose finding study was conducted to determine the optimal dose of estrogen and/or progestin in the oral contraceptives to be used in subjects with anorexia nervosa for preservation of bone mineral density. The sponsor selected using Ortho Tri-Cyclen or placebo for 13 consecutive 28-day cycles. A cycle of Ortho Tri-Cyclen consists of the following daily dosages of the progestin, norgestimate and the estrogen, ethinyl estradiol:

Days 1 - 7	0.180 mg norgestimate/0.035 mg ethinyl estradiol
Days 8 - 14	0.215 mg norgestimate/0.035 mg ethinyl estradiol
Days 15 - 21	0.250 mg norgestimate/0.035 mg ethinyl estradiol
Days 22 - 28	inactive tablets

Choice of Comparator: A placebo control was used that was color matched and identically packaged to Ortho Tri-Cyclen in a 28-day blistercard.

Assignment to Study Drug: An interactive voice response system (IVRS) was used to randomize all subjects to either Ortho Tri-Cyclen or placebo on a 1:1 allocation ratio.

10.1.1.3 Patient Population

10.1.1.3.1 Inclusion and Exclusion Criteria

Inclusion Criteria

The protocol stated that subjects must satisfy the following criteria before entering the study:

1. Female subjects must be post-menarcheal, up to but not including 18 years of age at the time of consent, with a health status consistent with anorexia nervosa as confirmed by:

- Medical history
- Gynecologic history
- Physical examination
- Negative urine pregnancy test at time of the Baseline visit.

2. Subjects who in the opinion of the investigator, meet the modified DSM-IV guideline (Attachment 1) for anorexia nervosa.

Reviewer's note:

1) Attachment 1 to Protocol CAPSS-169 is as follows:

Attachment 1: Modified DSM IV Classification of Anorexia Nervosa:

- 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 mass index below the 10th percentile for age; or failure to make expected weight gain during the period of growth, leading to body mass index below the 10th percentile for age using the CDC Growth Chart).
- Intense fear of gaining weight or becoming fat, even though underweight.
- Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.
- In postmenarcheal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles. (A women in considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen, administration.)²²

3. Subjects are to have discontinued the following prior to the Baseline visit:

- hormonal contraceptives for three months
- hormonal IUD for 1 month

²² American Psychiatric Association. DSM-IV™, Diagnostic and Statistical Manual of Mental Disorders. 4th Ed., Washington, DC, 1994, pg. 544-545.

- NORPLANT® for three months
 - DEPO-PROVERA® and other depot hormonal injections for six months
 - GnRH-analogues (Lupron®, Lupron Depot® 3.75 mg and 7.5 mg, Synarel®, Zoladex®, and Cetrotide™ for 3 months); (Lupron Depot® 11.25 mg, 15 mg, 22.5 mg and 30 mg for 6 months)
 - Hepatic enzyme inducing drugs/nutraceuticals such as rifampin, phenobarbital, griseofulvin and St. John's Wort for 2 weeks
4. Subject is a non-smoker or, if a smoker, smokes \leq 15 cigarettes per day
5. Subject agrees to use a reliable non-hormonal alternate method of birth control during the study (e.g., abstinence, condoms, diaphragm and spermicide, or any other medically approved non-hormonal barrier method of contraception or a non-hormonal IUD)
6. Subjects without a known family history of Factor V Leiden; or subjects who have a known family history of Factor V Leiden in a first degree relative (i.e. mother, father, brother, sister) who do not have Factor V Leiden demonstrated on a coagulation profile obtained at the Screening Visit.
7. A parent or guardian has provided written permission (Informed Consent) and child assent to participate (informed assent) has been documented in accordance with the requirements of the approving IRB, after the nature of the study has been fully explained.

Exclusion Criteria

The protocol stated that potential subjects who meet any of the following criteria would be excluded from participating in the study:

1. History or presence of disorders commonly accepted as contraindications to steroid hormonal therapy including, but not limited to the following:
 - active or history of deep vein thrombophlebitis or thromboembolic disorders or known hypercoagulation disorders
 - cerebral vascular or coronary artery disease, uncontrolled hypertension, or migraines with focal aura
 - benign or malignant liver tumor which developed during the use of oral contraceptives or estrogen containing products
 - known or suspected carcinoma of any body system, including the breast or genital tract
 - diabetes mellitus with vascular involvement
 - known or suspected estrogen-dependent neoplasia
 - cholestatic jaundice
 - undiagnosed abnormal vaginal bleeding
 - any neurovascular lesion of the eye
 - any impairment of liver function, liver disease or renal disease
2. A recent history (within 12 months prior to the screening visit) of alcohol or other substance abuse
3. Subjects with primary amenorrhea who, in the opinion of the investigator, are not appropriate candidates for hormonal therapy (e.g., females who have not achieved an acceptable adult height)
4. Subjects who are suicidal

5. Has received any experimental drug and/or used any experimental device within 30 days prior to the Baseline Visit
6. Subjects using any of the following medications: systemic or high potency topical cortisone preparations, any medication used to treat bone loss (e.g., calcitonin, bisphosphonate), thiazide diuretics, and anti-seizure medications (i.e. Dilantin)
7. Subjects who in the opinion of the investigator should not be enrolled in the study based on the product labeling including potential drug-drug interactions
8. Untreated hyperthyroidism or hypothyroidism; history of other medical conditions that account for low weight and/or amenorrhea
9. Subjects who have a known hypersensitivity to any component of the study drug
10. Any subject deemed by the investigator to have questionable reliability in her ability to comply with the protocol and provide accurate information (e.g., a pattern of bingeing and purging incompatible with absorption of an oral medication)
11. Subjects who have any medical condition, or planned surgical procedure, which, in the opinion of the investigator, may be exacerbated by treatment with study medication or a subject receiving any concurrent therapy that could be affected by treatment with study medication
12. TSH outside of the normal range, or FSH ≥ 40 mIU/ml
13. Subjects who are pregnant or lactating

10.1.1.3.2 Demographics and Baseline Disease Characteristics

A total of 146 subjects were randomized (i.e. gave parental consent and subject assent and received an IVRS number), 23 subjects were screen failures and were not treated (12 on Ortho Tri-Cyclen and 11 on placebo), 123 subjects (61 on Ortho Tri-Cyclen and 62 on placebo) were randomized and received at least one dose of study medication (i.e., the “treated” population-for safety analysis), and 112 subjects (53 on Ortho Tri-Cyclen and 59 on placebo) were randomized, received at least one dose of study medication, and had an available baseline and at least one on-treatment BMD measurement (i.e., the “ITT” population-for efficacy analysis). The treated subjects without at least one on-treatment BMD measurement were: Ortho Tri-Cyclen Subjects 016001, 051002, 051003, 051006, 062008, 089001, 112003, 112004 and Placebo Subjects 010001, 025001, 078001. A total of 89 subjects (40 on Ortho Tri-Cyclen and 49 on placebo) completed the Cycle 13 Visit. A total of 88 subjects (39 on Ortho Tri-Cyclen and 49 on placebo) were in the post-hoc “Completers/Efficacy” population (i.e. ITT subjects with therapy duration > 336 days and who had an available Cycle 13 BMD measurement).

It should be noted that for the CAPSS-169 interim Cycle 6 report dated September 15, 2003, the ITT population consisted of 110 treated subjects who had at least one on-treatment DXA scan result. One site (Site #16) had failed to schedule the Cycle 6 (Visit 6) DXA scans for 2 subjects prior to the 27 August 2003 cut-off for data submission. These subjects (Subjects #016002 and #016003) were not included in the ITT population for the interim Cycle 6 report dated September 15, 2003, but are now included (with added post-baseline BMD values) in the ITT population analyses within this final CAPSS-169 clinical study report. The sponsor stated that the addition of these 2 subjects (both in the Ortho Tri-Cyclen

treatment group) did not affect the overall results of the Cycle 6 (Visit 6) analyses, however, some of the numerical values have been changed reflecting new data. Thus, the ITT population for the final study report is 112 subjects.

Per the July 8, 2003 Sponsor preNDA meeting minutes, approximately 90 sites were recruited for CAPSS-169. Only 43 sites (all US sites) randomized at least one subject; thus, approximately 50% of sites treated no subjects. The sites enrolling the most subjects were Dr. Strokosch's site (10 subjects), Dr. Zweig's site (9 subjects), and Dr. Lubner's site (9 subjects).

In the ITT population, the majority of the subjects were Caucasian (90.2%). There were 11 non-Caucasian subjects in the ITT population (3 Black, 1 Asian, and 7 "Other"). The mean age was 15.1 years (range 11-17 years) and the mean body mass index was 17.77 kg/m². Mean total lumbar spine BMD was 0.8971 g/cm² and mean total hip bone BMD was 0.8749 g/cm². There were no significant differences in the demographic and baseline characteristics listed for the two treatment groups in the CAPSS-169 ITT population. Numerically, there were more subjects in the Ortho Tri-Cyclen group with primary amenorrhea (n=8) than in the placebo group (n=3). Numerically, the baseline Z-scores in the Ortho Tri-Cyclen group were higher (-0.7495) than in the placebo group (-0.8507). Seven subjects had a history of prior estrogen use (1 on Ortho Tri-Cyclen and 6 on Placebo).

10.1.1.3.3 Withdrawals, compliance, and protocol violations

Withdrawals

Of the 123 treated subjects, 89 subjects completed the Cycle 13 Visit: 40 (65.6%) in the Ortho Tri-Cyclen group and 49 (79%) in the placebo group. A total of 34 subjects discontinued prematurely from the trial (21 on Ortho Tri-Cyclen and 13 on placebo). The number of subjects who discontinued for each specific reason are as follows:

- n=17: "subject choice" (11 in the Ortho Tri-Cyclen group and 6 in the placebo group); Subject 100003 on Ortho Tri-Cyclen was listed in CFR as discontinuing due to "subject choice" with the comment "felt her mood had worsened since starting study medication"; however, the comment was later deleted per 7/7/2003 data clarification form since "comments were not supposed to be provided if subject discontinued due to subject choice".
- n=7: "lost to follow-up" and withdrawn from the study [4 in the Ortho Tri-Cyclen group (Subjects 042001, 051002, 051003, 104001) and 3 in the placebo group (Subjects 025001, 078001, 079001)]
- n=4: adverse events: [3 in the Ortho Tri-Cyclen group (Subject 112003 due to nausea and vomiting, Subject 014002 due to weight gain, and Subject 016001 due to "menstrual disorder-irregular menses"; however, it was actually the onset of first menses in a premenarchal 10 year old) and 1 (1.6%) in the placebo group (Subject 010004 due to headache and nausea)]. In addition, the CRF for Subject 050001 (on Ortho Tri-Cyclen) stated that the subject discontinued prematurely due to a weight increase from 85 lbs on 11/1/02 to 108 lbs on 9/17/03; however, Subject 050001 was coded by the sponsor as discontinuing due to "subject choice".
- n=2; Investigator considered subject physically and/or mentally unstable and unreliable to continue safely in the study (Subject 100002 on Ortho Tri-Cyclen was withdrawn on Day 116 after being hospitalized for a deliberate drug overdose with 4600 mg Celexa and 3 grand mal seizures; Subject 100004 on placebo was withdrawn on Day 148 when her weight fell to 70 lbs and she developed bradycardia-pulse 48, hypotension-B/P 78/57, leukopenia, hyponatremia, and hypochloridemia; Subject 100004 was hospitalized from Days 166-182)
- n=1; subject was discontinued based on recommendations from the DSMB due to loss of total lumbar spine BMD of 11% at Cycle 6/Visit 6 (Subject 010003 on Ortho Tri-Cyclen returned

unused Cycle 7 and 9 pill packs and was not discontinued from the study until after she had completed her Cycle 10 pill pack on July 23, 2003. It is unclear to this reviewer why Subject 010003 was permitted to stay in the study for an additional 4 months after her Cycle 6/Visit 6 BMD measurements demonstrated an 11% loss in BMD.)

- n=1; protocol violation-positive Factor V Leiden screen (Subject 089001 on Ortho Tri-Cyclen)
- n=1; subject relocated to another state for extended inpatient treatment (Subject 034005 on placebo)
- n=1; subject was prescribed oral contraceptives to control acne (Subject 052002 on placebo: “mother of patient decided to allow pediatrician to put patient on birth control pill to help with acne problem; mother did not think patient was on birth control pill, therefore wanted her withdrawn from study”)

Reviewer comment:

- 1) *It is concerning to this reviewer that at least one mother correctly surmised that her daughter was on placebo. This reviewer believes that due to the regular menses and the commonly known set of adverse events associated with oral contraceptives, most subjects, their families, and their physicians were unblinded to treatment.*
- 2) *This reviewer notes that the only subject discontinued from CAPSS-169 due to a significant loss in BMD during treatment was on Ortho Tri-Cyclen. This reviewer is concerned that the use of oral contraceptives may significantly worsen BMD in selected subjects.*
- 3) *Significantly more subjects in the Ortho Tri-Cyclen group discontinued (n=21, 34.4%) than subjects in the placebo group (n=13, 21.0%).*

The (b) (4) (Site #68) required that their 2 subjects (Subject 068002 on Ortho Tri-Cyclen and Subject 068001 on placebo) and 1 member of the study staff be unblinded. The sponsor stated that subjects were instructed not to share the study medication information with the investigator or blinded study staff.

Compliance

The investigator was to maintain a log of all study drugs dispensed and returned. Drug supplies for each subject were to be inventoried and accounted for throughout the trial. The subject was to be instructed on the importance of compliance and the procedures to be followed in the event any doses were missed or in the absence of menses. Subjects who had minor problems with compliance were to receive additional counseling. Subjects who had a major compliance problem were to be reassessed for continuation in the study by site personnel.

Appendix 3.7 entitled “Subject Medication Accountability” was reviewed (pg. 1793-1881 of 2369). Some subjects returned unused complete pill packs when they prematurely discontinued (ex. **Subject 006002** returned Cycle 2 and 3 pill packs when she discontinued on Study Day 25). Some subjects returned complete unused pills packs during in the middle of treatment (ex. **Subject 010003** returned Cycle 7 and Cycle 9 unused pill packs-thus she only took 8 of 10 pill packs prior to being required to withdraw due to loss of 11% of bone mass at 6 month visit; **Subject 051003** returned Cycle 4 unused pill pack). Some subjects were issued duplicate pill packs and returned the duplicate pill packs (ex. **Subject 011002** returned one Cycle 6, two Cycle 7, and on Cycle 8 unused pill packs-however, she had been issued two packs for Cycles 6 and 8, three packs for Cycle 7 and she took a total of 13 pill packs). Some subjects did not take part of a pill pack (ex. **Subject 016003** returned 7 white, 7 light blue, and 4 blue tablets of Cycle 10 pill pack and she had taken 3 blue tablets and 7 green tablets of the Cycle 10 pill pack; **Subject 070001** returned 4 light blue, 7 blue, and 6 green tablets of the Cycle 1 pack and she had taken 7 white, 3 light blue, and one green tables of the Cycle 1 pack).

Subject 051002 (on Ortho Tri-Cycle) was listed as having duration of therapy=139 days and taking her first dose on 1/15/03 and her last dose on June 2, 2003; however, the pill count demonstrated that she had taken all 28 Cycle 1 pills and then stopped treatment on Day 29. Subject 051002 returned complete unused Cycle 2 and Cycle 3 pill packs. It should be noted that duration of therapy was simply the “date of last dose minus date of first dose + 1” and was not the number of treated days (ex. duration of treatment for **Subject 010001** was listed as 47 days; however, her pill count documented that she took 6 white piles of Cycle 1 and 2 white pills in Cycle 3. Subject 010001 did not return her Cycle 2 pill pack for counting and it was noted that the subject stated that she had not taken all Cycle 2 pills. Thus, Subject 010001 was only known to have taken a total of 8 pills during her 47 days of treatment).

Some Ortho Tri-Cyclen subjects (i.e. for Visit 4: Subjects 16003, 35002, 51003, 70001, 86001, 86002, 90003; for Visit 5: Subjects 38005, 70001, 86001, 86002, 90003, 112004) had all three values (i.e. for NGMN, NG and EE) below the level of quantitation and contributed no pharmacokinetic data for that visit. The low hormone levels in these 9 subjects could not be explained by their pill counts (CAPSS-169 Final Study Report: Appendix 3.7).

Reviewer’s comment:

- 1) *The sponsor did not provide an analysis of treatment compliance. The sponsor stated without any supporting analysis that “most subjects were compliant with their study medication, based on counts of dispensed and returned study medication tablets”.*²³
- 2) *The sponsor did not provide any data regarding compliance with protocol procedures (i.e. protocol deviations). The reviewer considers it to be insufficient evidence to demonstrate compliance that no subjects were withdrawn from CAPSS-169 due to non-compliance.*
- 3) *This reviewer considers the nine Ortho Tri-Cyclen subjects who had all three hormone pharmacokinetic levels for at least one visit below the level of quantitation (i.e., Subjects 16003, 35002, 38005, 51003, 70001, 86001, 86002, 90003, 112004) to have been noncompliant with their treatment.*

Protocol violators/deviators

Appendix 3.14 entitled “Subjects Who Did Not Meet Entry Criteria” (CAPSS-169 Final Study Report pg. 2366-2369) lists **18 subjects** who **violated** inclusion/exclusion criteria. The subjects were listed by a 6 digit subject identification number: the first 3 numbers identified the site and the last 3 numbers identified the subject. Appendix 3.14 listed 10 subjects who were aged 17 years and were enrolled prior to CAPSS-169 Amendment #2, which was dated February 5, 2003 (i.e. Subjects 010002, 028006, 028008, 034003, 055003, 055004, 062001, 090002, 090004, and 090006), 4 subjects with primary amenorrhea who were enrolled prior to Amendment #2, which was dated February 5, 2003 (i.e. Subjects 011002, 028004, 035002, 035003), 2 subjects who had less than a 3 month washout for oral contraceptives (i.e. Subjects 051003 and 051006), 1 subject who did not meet the DSM-IV criteria for anorexia nervosa (Subject 028007, who had a screening BMI of 21.97 kg/m²), and 1 subject with Factor V Leiden (Subject 089001). The subject with Factor V Leiden was discontinued due to the protocol violation.

In addition to the above 18 subjects listed by the sponsor, this reviewer notes the following protocol violators:

- Subject **010001** did not meet Inclusion Criteria #2 (“meets modified DSMIV guidelines”) and her CRF stated that an exemption form had been signed and attached to the CRF regarding the inclusion #2 criteria.

²³ CAPSS-169 Final Study Report pg. 67 of 2369.

- Subject **014001** did not meet Inclusion Criteria #2 (“meets modified DSMIV guidelines”) due to having regular menses and she was granted an exemption from the sponsor on 11/1/02; however, the CRF states that the investigator later felt that the “patient was lying about having regular menses” and the CRF was changed so that the subject did meet Inclusion Criteria #2.
- Subject **001001** did not meet Exclusion Criteria #13 on 12/30/02 since she was using an anti-seizure medication, Topamax. However, on 8/30/03, a data clarification form for Subject 001001 stated that since Topamax was prescribed for the indication “mood disorders” and not for use as an anti-seizure medication, then the subject did not violate any inclusion/exclusion criteria.
- Subject **028-010** did not meet Exclusion Criteria #13 on 3/20/03 due to using an anti-seizure medication, Trileptal; however, per the CRF, Dr. Andrew Friedman (representing the sponsor) granted an exemption on April 26, 2004.

The sponsor stated that exceptions to the inclusion and exclusion criteria “were generally minor and judged to have no significant impact on the impact of the study”.²⁴ However, this reviewer noted that 76 of the 123 treated subjects in CAPSS-169 (i.e. 61.8% of treated subjects) had a baseline Body Mass Index (BMI) **at or above** the 10th percentile for age and should not have been enrolled into the study per the first bullet under Inclusion Criteria #2: “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 mass index below the 10th percentile for age; or failure to make expected weight gain during the period of growth, leading to body mass index **below** the 10th percentile for age using the CDC Growth Chart)”. The sponsor was sent the following Table 4 on January 12, 2005 with the request that they confirm that 61.8% of the treated subjects in CAPSS-169 were ineligible for enrollment based on the modified DSM-IV guideline utilized in CAPSS-169 due to their elevated baseline BMI.

Table 4: CAPSS-169 Subject Baseline Body Mass Index (BMI) and Inclusion Criteria #2: Body Mass Index (BMI) below the 10th percentile for age using the CDC Growth Chart (Treated Subjects, n=123)

Subject Initials	Subject #	Birthdate	Visit #	Visit Date	Age at Visit 1 (years) ¹	Baseline BMI ¹	Baseline BMI less than 10% for age on CDC Growth Chart (First bullet in Attachment 1)
(b) (6)	001001	(b) (6)	1	12/23/2002	16	16.79	Yes
	004001		1	09/30/2002	13	14.21	Yes
	006001		1	01/22/2003	16	20.72	No
	006002		1	02/17/2003	16.33	17.54	Yes
	008001		1	02/28/2003	16	14.11	Yes
	010001		1	10/28/2002	15	19.75	No
	010002		1	11/04/2002	17	17.58	Yes
	010003		1	11/14/2002	15.58	17.32	No
	010004		1	11/25/2002	16	20.52	No
	011001		1	11/08/2002	14	26.03	No
	011002		1	01/02/2003	15	15.69	Yes
	012001		1	01/17/2003	13	17.89	No
	012002		1	02/27/2003	15	17.57	No
	014001		1	10/31/2002	14.50	16.72	No
	014002		1	12/30/2002	14	22.31	No
	014003		1	01/17/2003	16	18.64	No
	014004		1	03/13/2003	15	18.01	No

²⁴ CAPSS-169 Final Study Report pg. 66 of 2369

Clinical Review
 Brenda Gierhart, M.D.
 NDA 21-690: Complete Class 2 Response to Approvable Action Letter
 Ortho Tri-Cyclen (norgestimate/ethinyl estradiol)

Subject Initials	Subject #	Birthdate	Visit #	Visit Date	Age at Visit 1 (years) ¹	Baseline BMI ¹	Baseline BMI less than 10% for age on CDC Growth Chart (First bullet in Attachment 1)
(b) (6)	014005	(b) (6)	1	03/28/2003	15	18.00	No
	015002		1	03/21/2003	15	15.47	Yes
	016001		1	03/10/2003	10	17.73	No
	016002		1	03/11/2003	14	17.38	No
	016003		1	03/11/2003	14	17.08	No
	021001		1	12/27/2002	13	16.64	No
	025001		1	11/11/2002	16	16.62	Yes
	028001		1	09/18/2002	13	15.36	Yes
	028002		1	09/25/2002	15	18.13	No
	028003		1	10/09/2002	15	15.05	Yes
	028004		1	10/17/2002	13	16.62	No
	028005		1	12/13/2002	16	19.30	No
	028006		1	01/08/2003	17	21.56	No
	028007		1	01/28/2003	12	21.97	No
	028008		1	03/10/2003	15	20.78	No
	028010		1	03/20/2003	14	15.58	Yes
	034001		1	12/09/2002	16	17.25	Yes
	034002		1	12/17/2002	16	19.47	No
	034003		1	02/10/2003	17.08	18.09	No
	034004		1	02/17/2003	14	17.33	No
	034005		1	03/03/2003	15	18.23	No
	034006		1	03/17/2003	16	14.58	Yes
	034007		1	03/17/2003	15	16.55	Yes
	034008		1	03/18/2003	14	16.20	Yes
	035001		1	11/05/2002	15	18.92	No
	035002		1	12/04/2002	15	18.16	No
	035003		1	02/17/2003	13.42	16.29	No
	038004		1	03/06/2003	14	16.14	Yes
	038005		1	03/06/2003	17	14.47	Yes
	042001		1	02/27/2003	14	16.31	Yes
	043001		1	02/21/2003	13	21.58	No
	050001		1	11/01/2002	15	16.15	Yes
	051001		1	09/26/2002	14	17.70	No
	051002		1	01/06/2003	16	18.02	No
	051003		1	01/17/2003	14.42	16.59	No
	051006		1	03/06/2003	16.83	17.74	Yes
	052001		1	10/11/2002	15	18.20	No
	052002		1	11/19/2002	13	15.55	Yes
	052004		1	02/12/2003	16.50	17.54	Yes
	055001		1	11/15/2002	16	18.10	No
	055002		1	11/19/2002	16	13.50	Yes
	055003		1	11/26/2002	17	20.24	No
	055004		1	12/06/2002	17.42	18.14	No
	055006		1	01/31/2003	16	18.37	No
	055007		1	02/03/2003	15	16.55	Yes
	055008		1	03/07/2003	13	17.20	No
	055009		1	03/14/2003	15	19.22	No
	055010		1	03/14/2003	11	13.16	Yes
	055011		1	03/19/2003	16	17.17	Yes

Clinical Review
 Brenda Gierhart, M.D.
 NDA 21-690: Complete Class 2 Response to Approvable Action Letter
 Ortho Tri-Cyclen (norgestimate/ethinyl estradiol)

Subject Initials	Subject #	Birthdate	Visit #	Visit Date	Age at Visit 1 (years) ¹	Baseline BMI ¹	Baseline BMI less than 10% for age on CDC Growth Chart (First bullet in Attachment 1)
(b) (6)	056001	(b) (6)	1	10/11/2002	14	13.90	Yes
	056002		1	11/12/2002	13	17.33	No
	056003		1	01/30/2003	17	16.64	Yes
	056004		1	02/11/2003	15.58	17.00	Yes
	056005		1	02/27/2003	17	19.53	No
	056006		1	03/11/2003	14	15.95	Yes
	056007		1	03/14/2003	15	17.85	No
	059001		1	01/16/2003	15	15.20	Yes
	059002		1	01/23/2003	14.42	16.82	No
	062001		1	01/10/2003	17	18.29	No
	062002		1	02/22/2003	13	13.94	Yes
	062003		1	02/28/2003	16	17.27	Yes
	062004		1	03/11/2003	17	16.36	Yes
	062005		1	03/11/2003	15	18.35	No
	062006		1	03/17/2003	15	17.71	No
	062007		1	03/17/2003	15	18.07	No
	062008		1	03/18/2003	13	15.35	Yes
	062009		1	04/01/2003	15	16.14	Yes
	068001		1	03/05/2003	17.92	18.14	No
	068002		1	03/17/2003	14	18.46	No
	070001		1	09/27/2002	15.67	17.10	Yes
	078001		1	01/08/2003	16	18.13	No
	079001		1	02/13/2003	17	16.91	Yes
	086001		1	01/09/2003	14	18.01	No
	086002		1	01/13/2003	16	19.30	No
	086003		1	02/14/2003	16	17.05	Yes
	089001		1	12/13/2002	16	16.75	Yes
	090001		1	11/11/2002	16	19.53	No
	090002		1	11/11/2002	17	19.12	No
	090003		1	11/21/2002	15	27.39	No
	090004		1	01/08/2003	17	18.71	No
	090006		1	01/14/2003	17	15.06	Yes
	090007		1	02/13/2003	15	15.84	Yes
	095001		1	03/14/2003	14	17.89	No
	097001		1	02/18/2003	14	15.41	Yes
	097002		1	02/27/2003	17	20.50	No
	097003		1	03/11/2003	15	17.43	No
	098002		1	02/26/2003	16	17.27	Yes
	100001		1	02/25/2003	15	23.49	No
	100002		1	03/03/2003	16	18.58	No
	100003		1	03/14/2003	16	21.12	No
	100004		1	03/14/2003	17	19.44	No
	104001		1	02/24/2003	16	18.04	No
	104002		1	02/12/2003	15	12.71	Yes
	105001		1	03/05/2003	13	16.47	No
	106001		1	01/28/2003	16	19.23	No
	106002		1	02/11/2003	17	19.33	No
	106003		1	03/06/2003	17	19.33	No
	109001		1	03/12/2003	16	19.39	No

Subject Initials	Subject #	Birthdate	Visit #	Visit Date	Age at Visit 1 (years) ¹	Baseline BMI ¹	Baseline BMI less than 10% for age on CDC Growth Chart (First bullet in Attachment 1)
(b) (6)	109002	(b) (6)	1	03/26/2003	16	19.06	No
	109003		1	03/26/2003	17	18.39	No
	112001		1	02/26/2003	17	18.65	No
	112003		1	02/28/2003	15	20.67	No
	112004		1	02/28/2003	17	17.64	Yes
	113001		1	03/04/2003	14	18.07	No
	113002		1	03/04/2003	14	20.75	No
	114002		1	03/14/2003	15	16.13	Yes

Source: From Final Study Report CAPSS-169 Appendix 3.2 Demographic and Baseline Characteristics on pg. 1619-1628 and Appendix 3.12: Vital Signs and Body Weight pg. 2285-2330

¹ BMI is expressed as kg/m². If BMI was close to 10% for age curve, age at Visit 1 was calculated to two decimal points.

Baseline BMI values were analyzed by the baseline subject age (see Table 5).

Table 5: CAPSS-169 Baseline Body Mass Index (BMI)¹ by Baseline Subject Age

Age (years)	# treated subjects (n=123)	Mean baseline BMI (range, if >1 subject)	# treated subjects with baseline BMI less than 10% for age (CDC Growth Chart)
10	1	17.7	0
11	1	13.2	1 (100%)
12	1	22.0	0
13	13	16.5 (13.9-21.6)	5 (38%)
14	20	17.4 (13.9-26.0)	7 (35%)
15	34	18.0 (12.7-27.4)	13 (38%)
16	29	17.7 (13.5-21.1)	13 (45%)
17	24	18.2 (14.5-21.6)	8 (33%)

¹BMI is expressed as kg/m².

In submission BM to NDA 21-690, letter date January 21, 2005 and stamp date January 25, 2005, the sponsor responded that the modified DSM IV guidelines, including BMI <10th percentile, were incorporated as an attachment to the protocol and were not specific diagnostic criteria. The sponsor felt that it was important to enroll all subjects with the diagnosis of anorexia nervosa, including those with a BMI >10th percentile, to be able to generalize results from this study to the adolescent female population with anorexia nervosa. In addition, the sponsor stated:

Anorexia nervosa is a psychiatric diagnosis made by a constellation of clinical signs and symptoms that include, but is not limited to, an individual's weight. Anorexia nervosa is a chronic disease that waxes and wanes and assessments at a single time point may be misleading with regard to diagnosis. The DSM IV manual provides four *guidelines*, not criteria, for clinicians to consider when making the diagnosis of anorexia nervosa in adults. There are no specific guidelines for growing adolescents.

Reviewer's comments:

- 1) Only 77 of the 123 treated subjects in CAPSS-169 had the word "anorexia" listed anywhere in their Medical History.²⁵ The remaining subjects frequently had "restricts food", "picky eater",

²⁵ CAPSS-169 Final Study Report Appendix 3.5 entitled "Medical History" on pg. 1697-1724 of 2369 and the JMP dataset "MHIST"

“poor caloric intake”, “low caloric intake”, “eating disorder”, or “diminished food intake” listed in their Medical History.

- 2) This reviewer rejects the sponsor’s opinion that the modified DSM IV guidelines were not specific diagnostic criteria since Inclusion Criteria #2 specifically stated that subjects were to be included in CAPSS-169 “who in the opinion of the investigator, **meet the modified DSM-IV guideline (Attachment 1)** for anorexia nervosa” (bolding added by the reviewer). It was appropriate for this reviewer to determine whether the CAPSS-169 investigators made errors by enrolling subjects who failed to meet the modified DSM-IV guideline in Attachment 1. Several of the subjects enrolled in CAPS-169 with high BMI may have been adolescents who had recovered from anorexia nervosa. Women recovered from anorexia nervosa have a higher BMI than women with anorexia nervosa (see Table 6).

Table 6: Age, weight, body mass index (BMI) and body composition of women with anorexia nervosa, women with anorexia nervosa treated with estrogen replacement therapy (ERT), women recovered from anorexia nervosa, and healthy age-matched controls

Variables	Women with anorexia nervosa		Women recovered from anorexia nervosa (n=26)	Healthy age-matched controls (n=205)
	Untreated (n=77)	ERT treated (n=58)		
Age (yr)	25.9 ± 0.8	28.4 ± 1.0	27.3 ± 1.3	27.3 ± 0.4
Height (cm)	164.6 ± 0.7	165.5 ± 0.9	163.7 ± 1.1	165.5 ± 0.4
Weight (kg)	42.2 ± 0.6	42.3 ± 0.8	54.4 ± 1.3	63.1 ± 0.8
BMI (kg/m ²)	15.6 ± 0.2	15.4 ± 0.2	20.3 ± 0.4	23.1 ± 0.3
Lowest BMI (kg/m ²)	13.0 ± 0.4	12.2 ± 0.3	14.4 ± 0.3	
Total body fat (kg)	6.2 ± 0.3	4.6 ± 0.4	15.4 ± 1.3	21.7 ± 0.7
Total lean body mass (kg)	33.8 ± 0.5	35.3 ± 0.7	38.5 ± 0.7	39.3 ± 0.3

Source: Abridged from Karlsson et al²⁶

Baseline BMI is a significant issue since it is well known that the incidence and severity of osteopenia occurring in nutritionally replete subjects is significantly higher than in nutritionally deplete amenorrheic women. The bone densities of anterior-posterior spine, total hip, and total body measured by dual energy x-ray absorptiometry have been shown to be reduced in both amenorrheic groups compared to those in control subjects, but are significantly lower in nutritionally deplete subjects with anorexia nervosa than in nutritionally replete subjects with hypothalamic amenorrhea.²⁷ In 130 women with anorexia nervosa, weight was the most consistent predictor of bone mass density (BMD) at all skeletal sites and patients with normal BMD, osteopenia, and osteoporosis at the total hip had a mean weight of 48.7 ± 0.8 kg, 45.9 ± 0.8 kg, and 39.0 ± 0.7 kg, respectively.²⁸ In a non-blinded trial of estrogen with progestin in amenorrheic women with anorexia nervosa, only those with low body weight benefited.²⁹ Thus, anorexia nervosa subjects with either a body mass index (BMI) or a body weight categorized as

²⁶ Karlsson MK, Weigall SJ, Duan Y, and E Seeman. Bone Size and Volumetric Density in Women with Anorexia Nervosa Receiving Estrogen Replacement Therapy and in Women Recovered from Anorexia Nervosa. *J Clin Endocrinol Metab.* 2000; 85: 3179.

²⁷ Grinspoon S et al. Severity of Osteopenia in Estrogen-Deficient Women with Anorexia Nervosa and Hypothalamic Amenorrhea. *J Clin Endocrinol Metab* 84: 2049-2055, 1999.

²⁸ Grinspoon S et al. Prevalence and Predictive Factors for Regional Osteopenia in Women with Anorexia Nervosa. *Ann Intern Med.* 2000; 133: 790-794.

²⁹ Klibanski A et al. The effects of estrogen administration on trabecular bone loss in young women with anorexia nervosa. *J Clin Endocrinol Metab.* 1995; 80: 898-904.

normal, overweight, or obese are not be expected to have significant bone loss, and enrolling a large number of such subjects would make it difficult to demonstrate the efficacy of any treatment intended to improve bone mass density.

In addition, the protocol did not permit the enrollment of subjects who had recovered from anorexia nervosa or who had a history of anorexia nervosa. Enrolled subjects were to meet the modified DSM-IV guidelines in the opinion of the investigators at the time of enrollment. This reviewer reviewed the scientific literature and noted that published anorexia nervosa bone density/bone turnover marker clinical trials enrolled subjects with the following ages and BMIs at baseline (see Table 7). This reviewer has concluded that the mean body mass index (BMI) for the treated CAPSS-169 subjects (i.e. 17.77 kg/m²) is significantly higher than the mean BMI for adolescents (and for most adults) in published anorexia nervosa bone density and bone turnover marker scientific articles.

Table 7: Summary of Baseline Demographics for Anorexia Nervosa (AN) Subjects in Bone Density and Bone Turnover Marker Scientific Publications (n=21 publications)

Author and Publication Date; # AN Subjects	Mean Age of Subjects with AN (years)	Mean Body Mass Index (kg/m ²)	Mean Duration of Illness (months)	Mean Age at Menarche (years)	Mean Time since Last Menstrual Period (months)
Bachrach ³⁰ (1990); n=18	16.6 ± 2.5 (12.78-20.2)	15.5 ± 1.8	26.4 ± 24	N/A	median=1 year (range 0.3-3.7 yrs); primary amenorrhea=8 subjects; secondary=10
Biller ³¹ (1989); n=26	7 adolescents: range 14.9-17 yrs; 19 adults: range 18-39 yrs	BMI not provided; adolescent % IBW= 73±10 (range 63-89); adult % IBW=71±8 (range 57-84)	N/A	N/A	adolescent =1.2 ± 0.6 years; adult =4.5 ± 4.3 years; all subjects had secondary amenorrhea except for 1 adolescent with primary amenorrhea
Castro ³² (2000); n=170	15.2 ± 1.5	15.7 (SD=1.4); average % weight loss=21.6% (SD 6.1)	14.4 (SD 13.2)	N/A	10.1 months; premenarchal or primary amenorrhea=21 subjects; secondary=149; all subjects had at least 3 months of amenorrhea; subjects with oligomenorrhea or

³⁰ Bachrach LK et al. Decreased Bone Density in Adolescent Girls with Anorexia Nervosa. *Pediatrics*. 1990; 86: 440-447.

³¹ Biller BMK et al. Mechanisms of Osteoporosis in Adult and Adolescent Women with Anorexia Nervosa. *J Clin Endocrinol Metab* 68: 548-554.

Author and Publication Date; # AN Subjects	Mean Age of Subjects with AN (years)	Mean Body Mass Index (kg/m ²)	Mean Duration of Illness (months)	Mean Age at Menarche (years)	Mean Time since Last Menstrual Period (months)
					irregular menses were excluded
Golden ³³ (2002) n=50	16.8 ± 2.3 (range=13-21)	16.9 ± 1.5; % IBW=79.5% ± 7.6%; mean Weight=43.9 kg ± 4.7 kg	21.9 ± 20.6	N/A	16.0 ± 8.8 months; all had primary amenorrhea or secondary amenorrhea of greater than 6 months duration
Gordon ³⁴ (1999) n=15	17.3 ± 2.7 years (range 15-22)	17.3 ± 1.5 (range 14.0-20.2); % IBW 77.3 ± 6.1 (range 67-84); Weight 46.4 ± 6.0 kg (range 37-57 kg)	29.1 ± 17.6 (range 3-99)	N/A	20.9 ± 14.1 months (range 4-48 months)
Grinspoon ²⁷ (1999); n=30*	24 ± 1	16.7 ± 0.3	N/A	13.7 ± 0.2	22 ± 5 months; all subjects had amenorrhea for 3 months before the study
Grinspoon ²⁸ (2000); n=130*	24.4 ± 0.5	17.1 ± 0.2	65.9 ± 6.1	13.5 ± 0.1	22.5 ± 2.9 months; primary amenorrhea=7; secondary amenorrhea=123
Grinspoon ³⁵ (2001); n=27* at baseline	26.6 ± 1.2	16.1 + 0.3 (% IBW=74.4 ± 1.4 %)	N/A	N/A	N/A (AN was diagnosed on the basis of DSM-IV criteria)
Grinspoon ³⁶ (2002) n=60	25.2 ± 0.7 (range 18-38)	17.8 + 0.3 (all weighed less than 85% IBW)	N/A	N/A	28.9 ± 7.6 months for IGF-I group and 26.8 ± 6.1 months for the placebo group; all were amenorrheic for at least 3 months before the study;

³² Castro J et al. Predictors of Bone Mineral Density Reduction in Adolescents with Anorexia Nervosa. *J Am Acad Child Adolesc Psychiatry*. 2000; 39 (11); 1365-1370.

³³ Golden NH et al. The Effect of Estrogen-Progestin Treatment on Bone Mineral Density in Anorexia Nervosa. *J Pediatr Adolesc Gynecol*. 2002; 15: 135-143.

³⁴ Gordon CM et al. Changes in Bone Turnover Markers and Menstrual Function After Short-term Oral DHEA in Young Women with Anorexia Nervosa. *J Bone Miner Res*. 1999; 14: 136-145.

³⁵ Grinspoon S et al. Changes in regional fat redistribution and the effects of estrogen during spontaneous weight gain in women with anorexia nervosa. *Am J Clin Nutr* 2001; 73: 865-9.

Author and Publication Date; # AN Subjects	Mean Age of Subjects with AN (years)	Mean Body Mass Index (kg/m ²)	Mean Duration of Illness (months)	Mean Age at Menarche (years)	Mean Time since Last Menstrual Period (months)
Jagielska ³⁷ (2001); n=42	14.7 ± 2.4	14.7 ± 2.4	14.1 ± 17.4	N/A	10.4 ± 6.5 months; 27=secondary amenorrhea; 15=premenarchal
Klibanski ²⁹ (1995); n=48	23.7 (range 16.3-42)	BMI not provided; % IBW estrogen group=72 ± 9 (range 53-85); % IBW untreated AN group=72 ± 8 (range 48-84)	N/A	Estrogen group=13.2 ± 1.2 (range 11.2-16); untreated AN group=12.5 ± 1.5 (range 10.5-16.0)	estrogen group=3.3 ± 3.1 years and untreated=4.6 ± 5.1 years; secondary amenorrhea of at least 6 months duration=46 subjects; primary amenorrhea=1 (age 24.4 years)
Miller ³⁸ (2005); n=38	Untreated group=22 ± 1 (range 18-37); testosterone group=25 ± 1	Untreated=16.1 ± 0.7; testosterone=16.9 ± 0.3; BMI range 12.4-19.9; all subjects % IBW less than 86.2% at time of screening	N/A	N/A	14 ± 6 months in untreated group and 20 ± 5 months in testosterone group; all subjects had amenorrhea for at least 3 months when screening for study
Miller ³⁹ (2004); n=10	28.6 ± 2.6	All subject weights less than 85% IBW; weight 44 ± 1.4 kg	N/A	N/A	33 ± 9 months; all subjects had amenorrhea for at least 3 months
Misra ⁴⁰ (2004); n=60	15.8 ± 1.6 (range 12.0-18.8)	16.6 ± 1.4; % IBW <85% for all subjects; weight 46.4 ± 5.9 kg	10.5 ± 10.4	12.4 ± 1.4	10.8 ± 9.8 months (range 3-36 months); premenarchal=17 subjects; secondary amenorrhea=43 subjects
Munoz ⁴¹ (2002); n=38	17.3	BMI based on normative data	N/A	Interval between	2 ± 1 years

³⁶ Grinspoon S et al. Effects of Recombinant Human IGF-I and Oral Contraceptive Administration on Bone Density in Anorexia Nervosa. *J Clin Endocrinol Metab.* 2002; 87: 2883-2891.

³⁷ Jagielska G et al. Bone mineral content and bone mineral density in adolescent girls with anorexia nervosa-a longitudinal study. *Acta Psychiatr Scand.* 2001; 104: 131-137.

³⁸ Miller KK et al. Testosterone administration in women with anorexia nervosa. *J Clin Endocrinol Metab.* 2005; 90 (3): 1428-33.

³⁹ Miller KK et al. Effects of Risedronate on Bone Density in Anorexia Nervosa. *J Clin Endocrinol Metab.* 2004; 89 (8): 3903-3906.

⁴⁰ Misra M et al. Effects of Anorexia Nervosa on Clinical, Hematologic, Biochemical, and Bone Density Parameters in Community-Dwelling Adolescent Girls. *Pediatrics.* 2004; 114 (6): 1574-1583.

Author and Publication Date; # AN Subjects	Mean Age of Subjects with AN (years)	Mean Body Mass Index (kg/m ²)	Mean Duration of Illness (months)	Mean Age at Menarche (years)	Mean Time since Last Menstrual Period (months)
		from Spanish women -1.4 + 0.5 kg/m ²		menarche and onset of amenorrhea was 2.6 ± 0.8 years	
Rigotti ⁴² (1984); n=18	25 ± 5 (range 19-36)	BMI not provided; % IBW=71 (range 37-86%)	5.6 (median=4 years and range 2-16 years)	N/A	Median=4 years (range 1.3-13 years); primary amenorrhea=1; secondary amenorrhea=17
Rigotti ⁴³ (1991); n=27	26 ± 5 (range 19-37)	BMI not provided; % IBW=69 ± 9 (range 50-81%)	6.7 ± 4.7 (range 1-17)	N/A	5.8 ± 4.4 (range 1-17)
Seeman ⁴⁴ (1992); n=65	Primary amenorrhea=20.1 ± 1.2; untreated secondary amenorrhea=24.4 ± 1.4; secondary amenorrhea on OC=27.6 ± 1.9 months	Primary amenorrhea=15.0 ± 0.6; untreated secondary amenorrhea=16.6 ± 0.4; secondary amenorrhea on OC=17.2 ± 0.8	Primary amenorrhea=73.0 ± 10.3; untreated secondary amenorrhea=34.1 ± 4.8; secondary amenorrhea on OC=66.5 ± 15.5	N/A	N/A; primary amenorrhea=12 subjects; secondary amenorrhea=53
Soyka ⁴⁵ (1999); n=19*	16.0 ± 0.4 (range=12.8-18.5)	16.5 ± 0.4	19 ± 5 (range 2-72)	N/A	24 ± 4 months (range 6-48 months); premenarchal=5 subjects; primary amenorrhea=2; secondary amenorrhea=12
Weinbrenner ⁴⁶ (2003); n=51	24.2 ± 1.0 (range 15.6-54.9)	15.2 ± 0.2; all BMI were <17.5	91.1 ± 13.2 (range 7-502)	N/A	N/A; secondary amenorrhea=30 subjects; 21 subjects were on oral contraceptives
Wong ⁴⁷	14 (range 8-16)	All met DSM-IV	7.6 (range 2.5-11)	N/A	N/A; Premenarchal

⁴¹ Munoz MT et al. The effects of estrogen administration on bone mineral density in adolescents with anorexia nervosa. *European Journal of Endocrinology*. 2002; 146: 45-50.

⁴² Rigotti NA et al. Osteoporosis in Women with Anorexia Nervosa. *NEJM*. 1984; 311 (25): 1601-6.

⁴³ Rigotti NA et al. The Clinical Course of Osteoporosis in Anorexia Nervosa. A Longitudinal Study of Cortical Bone Mass. *JAMA*. 1991; 265: 1133-1138.

⁴⁴ Seeman E et al. Osteoporosis in Anorexia Nervosa: The Influence of Peak Bone Density, Bone Loss, Oral Contraceptive Use, and Exercise. *J Bone Miner Res*. 1992; 7 (12): 1467-1474.

⁴⁵ Soyka L et al. The Effects of Anorexia Nervosa on Bone Metabolism in Female Adolescents. *J Clin Endocrinol Metab*. 1999; 84: 4489-4496.

⁴⁶ Weinbrenner T et al. Body mass index and disease duration are predictors of disturbed bone turnover in anorexia nervosa. A case-control study. *European Journal of Clinical Nutrition*. 2003; 57: 1262-1267.

Author and Publication Date; # AN Subjects	Mean Age of Subjects with AN (years)	Mean Body Mass Index (kg/m ²)	Mean Duration of Illness (months)	Mean Age at Menarche (years)	Mean Time since Last Menstrual Period (months)
(2001); n=24		criteria			=50%

*Results are the mean ± SE

**Results are the mean ± SEM

N/A =not available in the publication; IBW=ideal body weight; OC=oral contraceptives

*Lastly, the sponsor is incorrect in stating that the DSM-IV manual provides four guidelines, not criteria, for clinicians to consider when making the diagnosis of anorexia nervosa in adults. The DSM-IV clearly titles and discusses that they provide “**Diagnostic criteria** for 307.1 Anorexia Nervosa”.⁴⁸ This reviewer does concur with the sponsor that it is unreasonable to specify a single standard for minimally normal weight that applies to all adolescents. However, if the criteria in the DSM-IV are not followed, and if the alternative and somewhat stricter guideline (used in ICD-10 Diagnostic Criteria for Research) of requiring the individual to have a body mass index equal to or below 17.5 kg/m² is not followed, then a investigator should have provided a clear rationale as to why subjects not meeting these diagnostic criteria would qualify for enrollment into CAPSS-169. In addition, this reviewer disagrees with the sponsor’s statement that the DSM-IV criteria established for the diagnosis of anorexia nervosa do not apply to adolescents. The DSM-IV on pg. 540 discusses that in prepubertal females with anorexia nervosa that menarche may be delayed by the illness and discusses that family members often bring the individual with anorexia nervosa to professional attention, which would more commonly occur in adolescents. The DSM-IV on pg. 543 discusses that there are suggestions that the severity of mental disturbances associated with anorexia nervosa may be greater among prepubertal individuals who develop the illness and that if anorexia nervosa begins during early adolescence (between 13 and 18 years), it may be associated with a better prognosis. Thus the sponsor may state that DSM-IV should not apply to adolescents; however, it was intended to apply to adolescents.*

Based upon this analysis of the literature and consultation with experts in the field, this reviewer requested that the efficacy analysis be recalculated after excluding the 76 subjects who did not meet the modified DSM-IV weight criteria in Attachment 1. In addition, this reviewer requested that the efficacy analysis be recalculated after excluding the 29 subjects with a Visit 1 % IBW >85%. On April 19, 2005, the sponsor responded to these requests by providing two tables (C1 and C2) containing efficacy analyses for 3 post-hoc populations as follows:

Population I: All randomized subjects who received study medication except for subjects as identified by the FDA reviewer with Baseline BMI > 18.5 kg/m² and/or IBW at Visit 1 > 85%.

Population II: All randomized subjects who received study medication except for subjects as identified by the FDA reviewer with weight gain of over 20 pounds from Visit 1 to last visit.

Population III: All randomized subjects who received study medication except for subjects as identified by the FDA reviewer with Baseline BMI > 18.5 kg/m² and/or IBW at Visit 1 > 85% and/or weight gain of over 20 pounds from Visit 1 to last visit.

⁴⁷ Wong JCH et al. Bone Mineral Density in Adolescent Females with Recently Diagnosed Anorexia Nervosa. *Int J Eat Disord.* 2001; 29: 11-16.

⁴⁸ American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). 1994 pg.545.

In these post-hoc efficacy analyses performed by the sponsor, none of the findings were statistically significant for the above 3 populations when comparing Ortho Tri-Cyclen treated subjects to placebo treated subjects at either time point, i.e. at Cycle 6 and at Cycle 13, for the endpoint “change from baseline in total lumbar spine bone mineral density”.

Table 8: Sponsor Analysis of Total Lumbar Spine Bone Mineral Density* in 3 Post-Hoc Populations at Baseline, at Cycle 6, Change from Baseline to Cycle 6, at Cycle 13, and Change from Baseline to Cycle 13

	Population I**		Population II**		Population III**	
	Ortho Tri-Cyclen (N=45)	Placebo (N=49)	Ortho Tri-Cyclen (N=48)	Placebo (N=52)	Ortho Tri-Cyclen (N=38)	Placebo (N=41)
Baseline (g/cm²)						
n	45	49	48	52	38	41
Mean	0.8989	0.8754	0.8980	0.8751	0.8919	0.8564
S.D.	0.11554	0.11717	0.11883	0.11724	0.11571	0.10994
Median	0.8990	0.8790	0.9060	0.8795	0.8960	0.8740
Min, Max	0.597, 1.179	0.635, 1.140	0.597, 1.179	0.635, 1.254	0.597, 1.179	0.635, 1.113
Cycle 6*** (g/cm²)						
n	45	49	48	52	38	41
Mean	0.9151	0.8832	0.9164	0.8846	0.9092	0.8657
S.D.	0.10526	0.11500	0.11299	0.11655	0.10511	0.11099
Median	0.9130	0.8830	0.9195	0.8875	0.9110	0.8720
Min, Max	0.712, 1.179	0.660, 1.134	0.630, 1.179	0.660, 1.259	0.712, 1.179	0.660, 1.134
Change from Baseline to Cycle 6 (g/cm²)						
n	45	49	48	52	38	41
Mean	0.0162	0.0078	0.0185	0.0095	0.0173	0.0092
S.D.	0.03727	0.02519	0.03579	0.02384	0.03929	0.02534
Median	0.0110	0.0090	0.0170	0.0055	0.0085	0.0090
Min, Max	-0.106, 0.115	-0.062, 0.072	-0.106, 0.115	-0.062, 0.072	-0.106, 0.115	-0.062, 0.072
p-value	0.094		0.088		0.135	
Percent Change from Baseline to Cycle 6 (%)						
n	45	49	48	52	38	41
Mean	2.10	0.98	2.29	1.15	2.26	1.13
S.D.	4.719	2.826	4.527	2.728	5.021	2.893
Median	1.32	0.93	1.96	0.66	0.99	0.93
Min, Max	-11.5, 19.3	-6.5, 7.6	-11.5, 19.3	-6.5, 7.6	-11.5, 19.3	-6.5, 7.6
p-value	0.054		0.062		0.074	
Cycle 13*** or Final Visit (g/cm²)						
n	45	49	48	52	38	41
Mean	0.9207	0.8933	0.9200	0.8929	0.9121	0.8745
S.D.	0.11237	0.10733	0.11772	0.10802	0.11077	0.10115
Median	0.9150	0.8890	0.9190	0.8935	0.9140	0.8780
Min, Max	0.732, 1.179	0.682, 1.118	0.630, 1.179	0.682, 1.264	0.732, 1.179	0.682, 1.118

	Population I**		Population II**		Population III**	
	Ortho Tri-Cyclen (N=45)	Placebo (N=49)	Ortho Tri-Cyclen (N=48)	Placebo (N=52)	Ortho Tri-Cyclen (N=38)	Placebo (N=41)
Change from Baseline to Cycle 13 or Final Visit (g/cm²)						
n	45	49	48	52	38	41
Mean	0.0218	0.0179	0.0221	0.0178	0.0202	0.0180
S.D.	0.04886	0.03684	0.04633	0.03553	0.05084	0.03567
Median	0.0090	0.0220	0.0155	0.0175	0.0015	0.0200
Min, Max	-0.149, 0.135	-0.070, 0.089	-0.149, 0.135	-0.051, 0.094	-0.149, 0.135	-0.051, 0.089
p-value	0.398		0.471		0.562	
Percent Change from Baseline to Cycle 13 (%)						
n	45	49	48	52	38	41
Mean	2.70	2.33	2.69	2.31	2.59	2.37
S.D.	6.073	4.416	5.773	4.402	6.396	4.453
Median	1.00	2.50	1.78	1.86	0.15	2.37
Min, Max	-16.2, 22.6	-6.1, 13.1	-16.2, 22.6	-5.3, 13.1	-16.2, 22.6	-5.3, 13.1
p-value	0.361		0.480		0.469	

*All Lunar values were converted to Hologic equivalent values. P-value based on ANCOVA model including Treatment as fixed main effect, Center as random main effect and Total Lumbar Spine BMD at Baseline as a covariate.

** Population I: All randomized subjects who received study medication except for subjects as identified by the FDA reviewer with Baseline BMI > 18.5 kg/m² and/or IBW at Visit 1 > 85%. Population II: All randomized subjects who received study medication except for subjects as identified by the FDA reviewer with weight gain of over 20 pounds from Visit 1 to last visit. Population III: All randomized subjects who received study medication except for subjects as identified by the FDA reviewer with Baseline BMI > 18.5 kg/m² and/or IBW at Visit 1 > 85% and/or weight gain of over 20 pounds from Visit 1 to last visit.

***Summary statistics calculated using last observation carried forward.

In addition to the post-hoc efficacy analyses performed by the sponsor, the CDER statistical reviewer performed multiple subgroup analysis of the Cycle 13 lumbar spine BMD data and within each subgroup, the treatment difference for change in lumbar spine BMD from baseline to Cycle 13 was not statistically significant between the Ortho Tri-Cyclen and placebo groups.

Table 9: CAPSS-169: Change from Baseline in Lumbar Spine BMD at Cycle 13 for Special Defined Subgroups Performed by NDA 21-690 CDER Statistical Reviewer

ITT Population	Raw Mean ± SD (N)		Treatment Difference	p-value
	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

ITT Population	Raw Mean ± SD (N)		Treatment Difference	p-value
	Ortho Tri-Cyclen	Placebo		
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
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.

If the sponsor continues to argue that all treated subjects did indeed have anorexia nervosa during the screening, this reviewer recommends that they submit for review a justification for each omitted subject in the above subgroup analyses. Such justifications could be based on individual body build, weight history, skinfold-thickness data, or DXA measurements used to determine the percentage body fat, total fat mass, and total fat-free mass. In any future BMD clinical trial in subjects with anorexia nervosa, DXA measurements of percentage body fat (TBF%), total fat mass, and total fat-free mass could be used as the “gold standard” to determine trial eligibility. Although DXA TBF% has been considered not technically ideal, due to the absence of normal population values, this method is felt to offer a rational way to deal with the growth and development issues occurring with increasing age in children.⁴⁹

10.1.1.4 Efficacy

10.1.1.4.1 Key Efficacy Assessments

Dual Energy X-Ray Absorptiometry (DXA) of the lumbar spine (L1-L4) and total hip (non-dominant) was to be measured at Screening (Visit 1), Cycle 6/Visit 6 and Cycle 13/Final Visit. Each site was encouraged to use the same DXA instrument and mode of scanning and, to the greatest extent possible, the same DXA technician throughout the course of the study. DXA scans were only to be performed with a Hologic or Lunar DXA machine. Efficacy variables included the change in total lumbar spine (L1-L4) and total hip (non-dominant) bone mineral density (BMD) from Screening (Visit 1) to Cycle 6/Visit 6 and Cycle 13/Final Visit.

10.1.1.4.2 Pharmacokinetic Assessments

No pre-treatment blood was drawn for pharmacokinetic assessments. Blood was drawn for post-treatment serum levels of norelgestromin (NGMN), norgestrel (NG) and ethinyl estradiol (EE) during Cycle 3 (one sample drawn between Days 4-7) and Cycle 3 (one sample drawn between Days 18-21). If possible, blood samples for PK analysis were to be drawn just prior to taking study medication on that day (i.e. trough samples). Due to the range in sample collection times, C_{trough} was defined post-hoc as between 16 to 26.5 and 16 to 27.5 hours for Visits 4 and 5, respectively. Population pharmacokinetic parameters of NGMN, NG, and EE were to estimate using non-linear mixed effect modeling techniques based upon the

⁴⁹ Lazarus R et al. Body mass index in screening for adiposity in children and adolescents: systematic evaluation using receiver operating characteristics curves. *Am J Clin Nutr* 1996; 63: 500-6.

collected samples. It was planned to compare population pharmacokinetic parameters of NGMN and NG as a function of NGM dose (180 and 250 mcg) using techniques appropriate for the comparison of population data. It was planned to compare estimates in the pediatric population to historical pharmacokinetic data in the adult population in previous studies by nonstatistical means.

10.1.1.4.3 Primary Efficacy Endpoint Analysis

Dual Energy X-ray Absorptiometry (DEXA) scans on lumbar spine (L1-L4) and total hip (non-dominant) were performed at Screening (Visit 1), Cycle 6 (Visit 6), and at the Cycle 13 (Final Visit). The efficacy analysis data set prespecified in the protocol was a modified intent-to-treat population (designed in the final study report as “ITT”) based on all randomized subjects who received at least one dose of study medication AND for whom a baseline AND at least one on-treatment bone mineral density (BMD) measurement (i.e. post-randomization efficacy data) was available. The sponsor also performed efficacy analyses on the following 2 populations, which were not prespecified in the protocol:

- All randomized subjects who received at least one dose of double-blind study medication AND had an available baseline BMD measurement; the LOCF approach was used if a subject withdrew early and the baseline observation carried forward (BOCF) approach was used if a subject did not provide any on-treatment BMD measurement
- “Completers/Efficacy” population: all ITT subjects with a duration of therapy >336 days (12 cycles [28-days of treatment] plus at least 1 dose of Cycle 13) AND who had an available Cycle 13 BMD measurement

The primary efficacy analysis prespecified in the protocol was a comparison of mean change in total lumbar spine (L1-L4) BMD from Screening to Cycle 6/Visit 6 between the two treatment groups based on an analysis of covariance with treatment and center as qualitative factors and total lumbar spine (L1-L4) BMD at Screening (Visit 1) as the covariate. Since there were a large number of centers in the study, including many with a small number of subjects and many with subjects in only 1 treatment, a random center effect was incorporated into the ANCOVA model. Statistical analyses without center effect in the ANCOVA model were also to be performed on the primary efficacy variable. In the case that a subject withdrew early, the last observation carried forward (LOCF) approach was applied. Although the 6-cycle efficacy data was analyzed and reported, it was stated in the protocol that it would not be considered an interim analysis and no multiplicity adjustment was to be made. All statistical tests were two-tailed at the 0.05 level of significance.

It should be noted that 81.3% of subjects had a negative Z-score for total lumbar spine bone mineral density (BMD). Only 38.2% (47/123) of the CAPSS-169 treated subjects had a baseline BMD Z-score <1.0 (43 subjects) or <2.5 (4 subjects). The distribution of the subjects with baseline BMD Z-score <2.5 or <1.00 was unequal between the two treatment groups: 100% (4/4) of the subjects with baseline BMD Z-score <2.5 and 57.4% (27/47) of the subjects with baseline BMD Z-score <1.0 were randomized to placebo compared to 42.6% (20/47) of the subjects with osteopenia were randomized to Ortho Tri-Cyclen. Thus, it was harder for the Ortho Tri-Cyclen treatment group to demonstrate a treatment effect since none had a baseline BMD Z-score <2.5 and fewer subjects in the Ortho Tri-Cyclen group had a baseline BMD Z-score <1.0 when compared to the placebo treatment group (see Table 10).

Table 10: CAPSS-169 Subjects with Baseline Z-score <1.00

Subject #	Z-Score	Treatment
001001	-1.107	PLACEBO
004001	-1.792	PLACEBO
006002	-1.272	ORTHO

Subject #	Z-Score	Treatment
008001	-3.189	PLACEBO
010004	-1.325	PLACEBO
011002	-3.207	ORTHO
014005	-1.013	PLACEBO
016001	-1.239	ORTHO
028001	-1.869	PLACEBO
028002	-1.248	PLACEBO
028005	-1.986	PLACEBO
034002	-1.138	ORTHO
034005	-1.115	PLACEBO
035001	-1.507	ORTHO
051001	-1.672	ORTHO
051006	-1.518	ORTHO
052002	-1.61	PLACEBO
055002	-1.233	PLACEBO
055003	-1.164	PLACEBO
055004	-2.223	ORTHO
055006	-1.22	PLACEBO
055007	-1.978	PLACEBO
055011	-2.777	PLACEBO
056004	-1.651	PLACEBO
056006	-2.213	ORTHO
056007	-1.523	PLACEBO
059001	-1.387	PLACEBO
062001	-2.334	ORTHO
062004	-1.533	PLACEBO
062006	-2.421	ORTHO
062007	-1.566	PLACEBO
086001	-1.33	ORTHO
086002	-1.748	ORTHO
090001	-1.409	ORTHO
090002	-1.337	PLACEBO
090004	-1.066	PLACEBO
090006	-1.634	ORTHO
090007	-1.973	ORTHO
100003	-1.33	ORTHO
104002	-1.606	PLACEBO
106001	-2.434	PLACEBO
106002	-1.604	ORTHO
106003	-2.434	PLACEBO
109001	-1.456	ORTHO
113001	-1.212	ORTHO
113002	-1.397	PLACEBO
114002	-2.773	PLACEBO

Primary Efficacy Results:

For the 112 subjects who had an on-treatment DXA scan and were included in the ITT population, treatment with Ortho Tri-Cyclen for 6 cycles significantly increased the mean total lumbar spine (L1-L4) BMD compared with placebo (0.0197 g/cm² and 0.0084 g/cm²; p=0.021). It should be noted that all BMD values from Lunar DEXA machines were converted to Hologic equivalent values. When the post-hoc analysis was performed for the 123 “treated” subjects, treatment with Ortho Tri-Cyclen for 6 cycles significantly increased the mean total lumbar spine (L1-L4) BMD compared with placebo (0.0171 g/cm² and 0.0080 g/cm²; p=0.042); however the p-value was lower.

10.1.1.4.4 Secondary Efficacy Endpoint Analysis

Secondary efficacy variables prespecified in the protocol (pg. 30) were:

changes in total lumbar spine (L1-L4) BMD from Screening to Cycle 13/Final Visit and changes in total hip (nondominant) BMD from Screening (Visit 1) to Cycle 6/Visit 6 and to Cycle 13/Final Visit. Treatment differences in the changes of these efficacy variables were to be evaluated using analysis of covariance. Other analyses to be performed included changes in BMD over time, responder analyses, and an analysis assessing the relationship of weight change and BMD change in each treatment group.

In the final study report, the sponsor stated that the following were the secondary efficacy variables:

- 1) percent change in total lumbar spine (L1-L4) BMD from baseline to Cycle 6
- 2) change and percent change in total lumbar spine (L1-L4) BMD from baseline to Cycle 13/Final Visit
- 3) change and percent change in total hip (nondominant) BMD from baseline to Cycle 6/Visit 6
- 4) change and percent change in total hip (nondominant) BMD from baseline to Cycle 13/Final Visit
- 5) change and percent change in body weight from baseline to Cycle 6
- 6) change and percent change in body weight from baseline to Cycle 13
- 7) change in total lumbar spine (L1-L4) BMD versus change in body mass index (BMI) and change in body weight from baseline to Cycle 13.

In the final study report, the sponsor stated that the following subgroup analyses of the change and percent change in total lumbar spine (L1-L4) BMD from baseline to Cycle 6 and Cycle 13 had been performed:

- subjects ≥ 12 years of age
- subjects with negative Z-scores at baseline
- subjects with non-negative Z-scores at baseline

In the final study report, the sponsor stated that post-hoc analyses were proposed and performed after the treatment groups were unblinded for the Completers/Efficacy (i.e. all ITT subjects with a duration of therapy >336 days (12 cycles [28-days of treatment] plus at least 1 dose of Cycle 13) and who had an available Cycle 13 BMD measurement) and Non-Completers/Efficacy subpopulations using the following variables:

- change and percent change in total lumbar spine (L1-L4) BMD from baseline to Cycle 6 and Cycle 13
- change and percent change in body weight from baseline to Cycle 6 and Cycle 13
- change and percent change in BMI from baseline to Cycle 6 and Cycle 13.

In addition, the final study report stated that post-hoc analyses on BMI were also performed using the ITT population.

Secondary Efficacy Results:

- For the ITT population, there was **no significant difference** between Ortho Tri-Cyclen and placebo in mean change in total lumbar spine (L1-L4) BMD between baseline and **Cycle 13** (0.0264 g/cm² and 0.0190 g/cm²; p=0.244);
- In the ITT population, there was **no significant difference** in mean change in total hip BMD between Ortho Tri-Cyclen and placebo at **Cycle 6** (0.0100 g/cm² and 0.0019 g/cm²; p=0.146) and at **Cycle 13** (0.0111 g/cm² and 0.0133 g/cm²; p=0.784).
- In the ITT population, there was **no significant difference** in mean weight gain between Ortho Tri-Cyclen and placebo at **Cycle 6** (4.2 kg and 3.1 kg; p=0.235) and at **Cycle 13** (6.7 kg and 4.9 kg; p=0.174).
- In the subgroup of ITT subjects with negative Z-scores at baseline, there was a **significant difference** between Ortho Tri-Cyclen and placebo in mean change in total lumbar spine (L1-L4) BMD between baseline and **Cycle 6** (0.0238 g/cm² and 0.0092 g/cm²; p=0.012) and in the subgroup of ITT subjects with non-negative Z-scores at baseline, there was **no significant difference** between Ortho Tri-Cyclen and placebo in mean change in total lumbar spine (L1-L4) BMD between baseline and **Cycle 6** (0.0040 g/cm² and 0.0042 g/cm²; p=0.900).
- In the subgroup of ITT subjects with negative Z-scores at baseline, there was **no significant difference** between Ortho Tri-Cyclen and placebo in mean change in total lumbar spine (L1-L4) BMD between baseline and **Cycle 13** (0.0286 g/cm² and 0.0225 g/cm²; p=0.435); in the subgroup of ITT subjects with non-negative Z-scores at baseline, there was **no significant difference** between Ortho Tri-Cyclen and placebo in mean change in total lumbar spine (L1-L4) BMD between baseline and **Cycle 13** (0.0180 g/cm² and 0.0016 g/cm²; p=0.283).
- In the post-hoc Completers/Efficacy subgroup (i.e. all ITT subjects who completed >12 cycles (i.e., >336 days) AND provided a Cycle 13 Final BMD measurement), there was a **significant difference** between Ortho Tri-Cyclen and placebo in mean change in total lumbar spine (L1-L4) BMD between baseline and **Cycle 6** (0.0251 g/cm² and 0.0091 g/cm²; p=0.002) and at **Cycle 13** (0.0374 g/cm² and 0.0218 g/cm²; p=0.018).
- In the post-hoc Non-Completers/Efficacy subgroup (i.e. all ITT subjects who had not completed >12 cycles (i.e., >336 days) OR had not provided a Cycle 13 Final BMD measurement), there was **no significant difference** between Ortho Tri-Cyclen and placebo in mean change in total lumbar spine (L1-L4) BMD between baseline and **Cycle 13** (-0.0043 g/cm² and 0.0054 g/cm²; p=0.441).
- In the ITT population, 14/53 (26.4%) Ortho Tri-Cyclen subjects and 20/59 (33.9%) placebo subjects had a **Cycle 6** total lumbar spine bone density less (i.e. negative change) than their baseline total lumbar spine bone density.
- In the ITT population, 16/53 (30.2%) Ortho Tri-Cyclen subjects and 19/59 (32.2%) placebo subjects had a **Cycle 13** total lumbar spine bone density less (i.e. negative change) than their baseline total lumbar spine bone density.
- In the ITT population, 16/53 (30.2%) Ortho Tri-Cyclen subjects and 26/59 (44.1%) placebo subjects had a **Cycle 6** total hip bone density less (i.e. negative change) than their baseline total lumbar spine bone density.
- In the ITT population, 17/53 (32.1%) Ortho Tri-Cyclen subjects and 22/59 (37.3%) placebo subjects had a **Cycle 13** total hip bone density less (i.e. negative change) than their baseline total lumbar spine bone density.
- In the ITT population, an improvement in body weight (>5%, n=80) was associated with a change in total lumbar spine bone mineral density from baseline to **Cycle 13** of 0.0333 in the Ortho Tri-Cyclen subjects (n=40) and 0.0321 in the placebo subjects (n=40).

All the secondary analyses except for body weight were to be based on a mixed effect ANCOVA model with treatment as a fixed factor and center as a random factor, and the respective baseline values as the covariate. A random center effect was to be incorporated into the ANCOVA model. Similar analyses were also to be performed for change and percent change from baseline in total lumbar spine (L1-L4) BMD at Cycle 13 based on the ITT population using an ANCOVA model without center effect. Total lumbar spine (L1-L4) BMD analyses were also to be stratified by duration of secondary amenorrhea, age of menarche, baseline body mass index (BMI [in kg/m²]) and prior estrogen use (yes or no). Change from baseline to Cycle 13 in total lumbar spine (L1-L4) BMD was to be summarized separately by change in BMI and change in body weight at Cycle 13. The change from baseline in BMI was to be categorized as worsening (<-0.5 kg/m²), no change (≥-0.5 to ≤0.5 kg/m²), or improvement (>0.5 kg/m²). The percent change from baseline in body weight was to be categorized as worsening (<-5%), no change (≥-5% to ≤5%), or improvement (>5%).

This reviewer requested on March 23, 2004 that the sponsor conduct several post-hoc analyses. The sponsor was first asked to exclude subjects who were less than 85% IBW from the efficacy analysis and to recalculate the efficacy data, i.e. exclude subjects 006001, 010001, 010004, 011001, 012001, 014002, 016001, 028006, 028007, 028008, 034002, 035001, 043001, 055009, 056005, 062003, 068002, 090001, 090002, 090003, 100001, 100003, 100004, 106002, 109002, 109003, 112001, 112003, and 113002. In addition, since weight gain of over 20 pounds from Visit 1 to the last Visit was considered to be a significant confounding factor, the sponsor was asked to recalculate the efficacy data after excluding such subjects from the "all treated" (n=123) population and from the above subgroup which excluded subjects with Visit 1 IBW >85% (n=94). The 23 CAPSS-169 subjects with a weight gain of over 20 pounds were: subjects 012001, 012002, 014002, 028003, 028010, 034006, 034008, 035001, 050001, 051001, 055002, 055008, 056004, 062003, 062005, 079001, 090001, 090003, 097001, 097003, 105001, 109002, and 112001. On April 19, 2005, the sponsor responded to these requests by providing two tables (C1 and C2) containing efficacy analyses for 3 post-hoc populations as follows:

Population I: All randomized subjects who received study medication except for subjects as identified by the FDA reviewer with Baseline BMI > 18.5 kg/m² and/or IBW at Visit 1 > 85%.

Population II: All randomized subjects who received study medication except for subjects as identified by the FDA reviewer with weight gain of over 20 pounds from Visit 1 to last visit.

Population III: All randomized subjects who received study medication except for subjects as identified by the FDA reviewer with Baseline BMI > 18.5 kg/m² and/or IBW at Visit 1 > 85% and/or weight gain of over 20 pounds from Visit 1 to last visit.

In these post-hoc efficacy analyses performed by the sponsor, none of the findings were statistically significant for the above 3 Populations when comparing Ortho Tri-Cyclen treated subjects to placebo treated subjects at either time point, i.e. at Cycle 6 and at Cycle 13, for the endpoint "change from baseline in total lumbar spine bone mineral density" (see Table 8).

10.1.1.4.5 Pharmacokinetic Data Summary (PK Subgroup)

Descriptive statistics (mean, standard deviation, minimum and maximum) for the trough ethinyl estradiol (EE), norelgestromin (NGMN), and norgestimate (NG) concentration were to be calculated. The analysis was to be carried out in order to evaluate the effect of (1) race, age, and body weight and (2) race, age, and BMI on the trough EE concentration provided a reasonable numbers of subjects were enrolled from each race group. Otherwise models were to be fitted without race effect. Similar analyses were to be

carried out on the trough concentrations for NGMN and NG. The trough concentrations were dose-normalized to 0.250 mg of NGM prior to analysis.

The pharmacokinetics methods and results from this report were reported in Appendix 2.4 of the clinical study report (pg. 1498-1605). Samples were collected from a total of 51 subjects treated with Ortho Tri-Cyclen and 61 subjects treated with placebo. Samples were supposed to be contributed as a single trough sample between Days 4-7 of Cycle 3 or 4 and between Days 18-21 of Cycle 3 or 4; however samples were actually collected between 1 and 40 hours postdose. The sponsor noted that the trough concentration analysis was based on data from only 26 subjects (43% of the planned 60 subjects) and these samples were obtained between 16 to 26.5 hour postdose for Visit 4 and from 16 to 27.5 hours postdose for Visit 5. It should be noted that due to a number of samples being below the limit of quantitation, only 14-19 subjects had detectable trough concentrations of NGMN, NG, or EE in samples obtained between 16 to 26.5 hour postdose for Visit 4 and from 16 to 27.5 hours postdose for Visit 5. Some subjects (i.e. for Visit 4: Subjects 16003, 35002, 51003, 70001, 86001, 86002, 90003; for Visit 5: Subjects 38005, 70001, 86001, 86002, 90003, 112004) had all three values (i.e. for NGMN, NG and EE) below the level of quantitation and contributed no pharmacokinetic data for that visit. The low hormone levels in these subjects could not be explained by their pill counts (CAPSS-169 Final Study Report: Appendix 3.7). Using all concentrations for each analyte up to 24 hours for Visit 4 and up to 27.5 hours for Visit 5, a serum concentration-time curve was plotted. A composite AUC₂₄ was then estimated for both study visits using linear trapezoidal summation (see Table 12). Race was not included in the regression model because of unbalanced number of subjects for each race group (88% Caucasians and 12% all other races). Regarding the CAPSS-160 pharmacokinetic data, the sponsor concluded:

- Pharmacokinetic results in post-menarcheal pediatric subjects with anorexia nervosa appeared to be generally similar to those observed previously in healthy adult females-see Table 11, Table 12, and Table 13
- Age and body weight (BWT)/BMI had no statistically significant effect on the trough concentration ethinyl estradiol (EE), norelgestromin (NGMN), and norgestimate (NG)-see Table 14 and Table 15.

Table 11: CAPSS-169 Pharmacokinetic Data: Trough Concentrations

Parameter	Visit Number	N	Mean	SD	Minimum	Maximum
NGMN (ng/mL)*	4	14	0.32	0.09	0.16	0.44
	5	15	0.37	0.20	0.11	0.81
NG (ng/mL)*	4	19	1.17	0.60	0.33	2.72
	5	15	2.10	0.83	0.70	3.83
EE (pg/mL)	4	18	23.07	9.84	6.8	41.1
	5	15	33.19	15.94	11.9	67.1

Source: Table 3 in CAPSS-169 Final Study Report pg. 1505 of 2369

*Dose-normalized to 0.250 mg

Note: The number of samples varied due to some results being below limit of quantitation (i.e. NGMN, NG= (b) (4) EE= (b) (4))

Table 12: CAPSS-169 Composite AUC₂₄ Values for Norelgestromin, Norgestrel, and Ethinyl Estradiol during Visits 4 and 5 of Cycle 3; Ortho Tri-Cyclen Treatment Group

Analyte	Visit 4	Visit 5*
NGMN	10.0 ng h/mL	13.2 ng h/mL

NG	32.0 ng h/mL	51.3 ng h/mL
EE	1452 pg h/mL	1219 pg h/mL

Source: Table 2 in CAPSS-169 Final Study Report pg. 1556 of 2369
 *AUC₀₋(average of 21 and 27.5)

Table 13: Comparison of Mean (SD) Pharmacokinetic Parameters from Studies NRGTRI-OC-115 and CAPSS-169

Analyte	Parameter	0.180 mg NGM/0.035mg EE		0.250 mg NGM/0.035mg EE	
		OC-115	CAPSS-169	OC-115	CAPSS-169
NGMN	C _{min} (ng/mL)	0.30 (0.09) ^a	0.23 (0.07) ^c	0.45 (0.13) ^a	0.36 (0.19) ^d
		0.35 (0.13) ^b		0.59 (0.11) ^b	
	C _{max} (ng/mL)	1.8 (0.46)	1.36	2.66 (0.47)	2.34
	AUC ₂₄ (ng·h/mL)	15.0 (3.88)	10.0	21.4 (3.46)	13.2 ^e
	CL/F (L/h)	12.6 (3.49)	18.0	12.0 (1.79)	18.9
NG	C _{min} (ng/mL)	0.99 (0.47) ^a	0.84 (0.44) ^c	2.33 (0.67) ^a	2.15 (0.83) ^d
		1.33 (0.62) ^b		2.41 (0.96) ^b	
	C _{max} (ng/mL)	1.94 (0.82)	2.55	3.66 (1.15)	4.80
	AUC ₂₄ (ng·h/mL)	34.8 (16.5)	32.0	69.3 (23.8)	51.3 ^d
	CL/F (L/h)	6.54 (3.46)	5.63	4.10 (1.64)	4.87
EE	C _{min} (pg/mL)	22.8 (11.4) ^a	23.1 (9.84) ^c	21.3 (9.85) ^a	33.1 (15.4) ^d
		23.9 (10.2) ^b		31.2 (17.6) ^b	
	C _{max} (pg/mL)	124 (39.5)	186	126 (34.7)	149
	AUC ₂₄ (pg·h/mL)	1130 (420)	1452	1090 (359)	1219 ^e
	CL/F (L/h)	35.0 (12.9)	24.1	36.0 (13.5)	28.7

Source: Table 3 in CAPSS-169 Final Study Report pg. 1561 of 2369

^a Mean C_{min} values Days 6-8

^b Mean C_{min} values Days 20-22

^c Mean (SD) C_{trough} over 16-26.5 hours

^d Mean (SD) C_{trough} over 16-27.5 hours

^e AUC₀₋(average of 21 and 27.5)

Table 14: CAPSS-169 Effect of Age and Body Weight on Pharmacokinetic Data

Parameter	Effects in Model	P-value		
		Age	BWT	Age*BWT
<i>Full model</i>				
NGMN (ng/mL) ^b	Age, BWT, Age*BWT	0.786	0.737	0.765
NG (ng/mL) ^b	Age, BWT, Age*BWT	0.591	0.723	0.670
EE (pg/mL)	Age, BWT, Age*BWT	0.301	0.368	0.350
<i>Reduced model</i>				
NGMN (ng/mL) ^b	Age, BWT	0.871	0.631	-
NG (ng/mL) ^b	Age, BWT	0.279	0.330	-
EE (pg/mL)	Age, BWT	0.454	0.686	-

Source: Table 5 in CAPSS-169 Final Study Report pg. 1506 of 2369

^a Age*BWT = Age by BWT Interaction
^b Dose-normalized to 0.250 mg

Table 15: CAPSS-169 Effect of Age and Body Mass Index (BMI) on Pharmacokinetic Data

Parameter	Effects in Model ^a	P-value		
		Age	BMI	Age*BMI
Full model				
NGMN (ng/mL) ^b	Age, BMI, Age*BMI	0.797	0.789	0.806
NG (ng/mL) ^b	Age, BMI, Age*BMI	0.954	0.941	0.982
EE (pg/mL)	Age, BMI, Age*BMI	0.488	0.587	0.543
Reduced Model				
NGMN (ng/mL) ^b	Age, BMI	0.918	0.777	-
NG (ng/mL) ^b	Age, BMI	0.430	0.530	-
EE (pg/mL)	Age, BMI	0.482	0.439	-

Source: Table 6 in CAPSS-169 Final Study Report pg. 1506 of 2369

^a Age*BWT = Age by BMI Interaction
^b Dose-normalized to 0.250 mg

Reviewer's comment:

- 1) *The CAPSS-169 population pharmacokinetic data were reviewed by Steven B. Johnson, Pharm.D. in DPE-2 (HFD-870) in the first review cycle for NDA 21-690. The review was finalized on March 8, 2004 and it stated:*
 - *The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the Clinical Pharmacology section of NDA 21-690 and finds the results to be unacceptable due to the scarcity of the data.*
 - *Results of this study were confounding.*
 - *The sampling technique ultimately used by the sponsor was a hybrid method somewhere between a single-trough and full population PK sampling design, but failed to hit either mark.*
 - *Since the sponsor was unable to conduct this study in a manner consistent with recognized protocol, the value of the calculated apparent clearance is clearly suspect. This finding is apparently consistent with the sponsor's as they are not requesting a labeling change to include apparent clearance for this pediatric population at his time.*

10.1.1.4.6 Sample Size Determination

The sample size was estimated based upon the assumption that for 80% power, there would be a 0.050 gm/cm² difference in the mean value of posterior total lumbar spine (L1-L4) BMD at Cycle 6/Visit 6 between the two treatment groups and assuming that the common standard deviation was 0.096 gm/cm². Using a two-sided test, conducted at a 5% significance level with 80% power, 60 subjects were estimated to be required in each treatment group or a total of 120 subjects.

Reviewer's comment:

- 1) *The 0.050 gm/cm² assumed difference at Cycle 6 was not confirmed by CAPSS-169 data. The actual treatment difference demonstrated in CAPSS-169 at Cycle 6 was 0.011 gm/cm². Due to the significantly smaller treatment difference demonstrated at Cycle 6, CAPSS-169 may have been significantly underpowered.*

10.1.1.5 Safety

The majority of the subjects in the safety (“treated”) study population were aged 15 or 16 years at randomization (33 Ortho Tri-Cyclen subjects and 32 placebo subjects). Only three subjects in the safety (“treated”) study population were aged <13 years at randomization (1 Ortho Tri-Cyclen subject=10 years, 1 placebo subject=11 years, and 1 placebo subject=12 years). A total of 21 subjects in the safety (“treated”) study population were aged 17 years at randomization (10 Ortho Tri-Cyclen subjects and 11 placebo subjects).

10.1.1.5.1 Safety Measurements

CAPSS-169 safety endpoints:

- Body weight, blood pressure, pulse, and adverse events, recorded at every visit
- Height was measured at Screening/Visit 1, Cycle 6/Visit 6, and Cycle 13/Final Visit
- Physical examinations, performed at Screening/Visit 1 and Cycle 13/Final Visit
- Pregnancy testing was conducted at every visit except Visit 4. Any subject who became pregnant during participation in a clinical study for which pregnancy was a standard exclusion criterion was to be promptly withdrawn from the study. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant was required.
- Routine serum chemistry (sodium; potassium; chloride; bicarbonate; albumin; total protein; total bilirubin; calcium; alkaline phosphatase; glucose; uric acid; inorganic phosphorus; blood urea nitrogen; and creatinine; SGOT; SGPT), performed at Screening/Visit 1 and at Cycle 13/Final Visit
- Serum chemistry (electrolytes only) was measured at Cycle 3/Visit 5 and Cycle 6/Visit 6
- Hematology (hemoglobin; hematocrit; RBC, WBC, platelet count), performed at Screening/Visit 1, Cycle 6/Visit 6 and at Cycle 13/Final Visit
- FSH and TSH, performed at Screening/Visit 1
- Factor V Leiden screen was only performed at Screening/Visit 1 if a first degree relative has a Factor V Leiden.
- Additional laboratory tests could have been performed at anytime during the study, if clinically indicated.

Safety analyses were to be performed on the Subjects Evaluable for Safety population, defined in the protocol as all subjects who took at least 1 dose of double-blind study medication and had at least 1 post-randomization safety measurement. Adverse events were reported between the first study-related procedure and the last study-related procedure. Adverse event data were collected by means of interviewing subjects in a non-directed manner at each visit. All adverse events were coded to preferred terms using a standardized coding dictionary (World Health Organization Adverse Reaction Terms [WHOART], Version 1992, 3rd Quarter).

A Data Safety Monitoring Board (DSMB) was established to monitor individual and treatment group safety and BMD data from the trial as well as aspects of trial conduct and criteria for altering its course. Specifically, the DSMB had the responsibility to review serious adverse events on an ongoing basis and to evaluate safety data at pre-determined intervals. The DSMB evaluated any subject who exhibited greater than a 10% reduction in BMD at the lumbar spine (L1-L4) or the hip and made a recommendation whether or not the subject should be discontinued from the study.

10.1.1.5.2 Extent of exposure

The mean duration of therapy was significantly shorter in the Ortho Tri-Cyclen group (mean=279.5 days) than in the placebo group (mean=329.1 days). It should be noted that in Table 16, the sponsor included 7

subjects with missing data: for 2 subjects the day of the last dose was missing and for 5 subjects both the day and month of the last dose was missing. If the day of last dose was missing, day 15 was used by the sponsor and the date of last dose was estimated as the earlier of the date of last dose and the date of withdrawal. If both day and month of last dose were missing, then the date of withdrawal was used by the sponsor.

It should be noted that duration of therapy was simply the “date of last dose minus date of first dose + 1” and was not the number of treated days, as noted in the following examples:

- Duration of treatment for **Subject 010001** was listed as 47 days with date of first dose 11/6/02 and date of last dose 12/22/02; however, her pill count (Appendix 3.7) documented that she took 6 white pills in Cycle 1 and 2 white pills in Cycle 3. Subject 010001 did not return her Cycle 2 pill pack for counting and it was noted that the subject stated that she had not taken all Cycle 2 pills. Thus, the pill count for Subject 010001 documented her taking only 8 pills during her 47 days of treatment.
- Duration of treatment for **Subject 010004** was listed as 219 days with date of first dose 12/4/02 and date of last dose as 7/10/03; however, her pill count (Appendix 3.7) documented her returning complete, unused Cycle 7, 8, and 9 pill packs. The last day she took a pill by her pill count was on May 27, 2003. Thus, the pill count for Subject 01004 documented her taking only 168 pills during her 219 days of treatment.

Table 16: CAPSS-169 Duration of Therapy (Treated Subjects, n=123)

	Ortho Tri-Cyclen	Placebo
Duration (Days) on Study Medication	(n=61)	(n=62)
Days 1-28	3 (4.9%)	0
Days 29-56	1 (1.6%)	1 (1.6%)
Days 57-84	2 (3.3%)	0
Days 85-112	2 (3.3%)	0
Days 113-140	4 (6.6%)	2 (3.2%)
Days 141-168	2 (3.3%)	3 (4.8%)
Days 169-196	3 (4.9%)	0
Days 197-224	2 (3.3%)	1 (1.6%)
Days 225-252	0	2 (3.2%)
Days 253-280	1 (1.6%)	0
Days 281-308	1 (1.6%)	0
Days 309-336	1 (1.6%)	2 (3.2%)
Days 337-364	37 (60.7%)	45(72.6%)
Days 365-392	2 (3.3%)	6 (9.7%)
n	61	62
Mean	279.5	329.1
S.D.	119.08	73.47
Median	356.0	357.0
Min, Max	4, 374	47, 383

Source: CAPSS-169 Final Study Report, Table 9 (pg 152 of 2369)

10.1.1.5.3 Serious adverse events

No subjects died during CAPSS-169. A total of 22 subjects reported a total of 44 serious adverse events during treatment: 8 (13.1%) subjects on Ortho Tri-Cyclen and 14 (22.6%) subjects on placebo (see Table 17). All submitted subject narratives and Case Report Forms (n=29) were reviewed. The outcome of all SAEs was listed by the sponsor as “resolve”, except for Subject 078001: “unknown”. The majority of SAEs were due to hospitalizations for worsening anorexia nervosa. One subject (Subject 100002 on Ortho Tri-Cyclen) had five separate hospitalizations for worsening anorexia nervosa during treatment. Two subjects required receiving activated charcoal after a suicide gesture or drug overdose (Subject 050001 on Ortho Tri-Cyclen after a suicide gesture with 15 Naprosyn tablets; Subject 010001 after a drug overdose with 30 tablets of Paxil 10 mg during screening). One subject deliberately overdosed on Celexa (Subject 100002). None of the serious adverse events were considered by the investigators to be related to study medication. Four CAPSS-169 subjects were withdrawn from the study due to adverse events: 3 (4.9%) in the Ortho Tri-Cyclen group (Subject 112003 due to nausea and vomiting, Subject 014002 due to weight gain, and Subject 016001 due to “menstrual disorder-irregular menses”-however, it was actually the onset of first menses in a premenarchal 10 year old) and 1 (1.6%) in the placebo group (Subject 010004 due to headache and nausea). Subject 050001 on Ortho Tri-Cyclen was coded by the sponsor as discontinuing due to “subject choice”; however, her CRF stated that the subject discontinued prematurely due to a weight increase from 85 lbs on 11/1/02 to 108 lbs on 9/17/03. Subject 100003 on Ortho Tri-Cyclen was listed in CFR as discontinuing due to “subject choice” with the comment “felt her mood had worsened since starting study medication”; however, the comment was later deleted per 7/7/2003 data clarification form since “comments were not supposed to be provided if subject discontinued due to subject choice”.

Two randomized subjects each had a single serious adverse event prior to randomization (Subject 010001 on placebo-alleged drug overdose on Day -3; Subject 010003 on Ortho Tri-Cyclen-worsening anorexia, depression, self-mutilation on Day -20). One subject who was a screen failure had a single serious adverse event (Subject 038001-malnutrition secondary to anorexia nervosa).

Table 17: CAPSS-169 Serious Adverse Events (SAE), excluding SAEs during Screening

Subject Number; Treatment	SAE-Preferred Term	SAE-Investigator Term/Details from Narrative	AE Start Date (Study Day)	AE Stop Date (Study Day)
001001; placebo	Anorexia nervosa	Hospitalized for exacerbation of anorexia nervosa	1/4/03 (5)	(b) (6)
	Anorexia nervosa; Depression (2 events)	Hospitalized for exacerbation of anorexia nervosa; Major depressive disorder (2 events)	4/29/03 (120)	
	Anorexia nervosa; Depression (2 events)	Hospitalized for exacerbation of anorexia nervosa; Major depressive disorder (2 events)	9/16/03 (260)	
006001; placebo	Emotional lability	Transferred from inpatient eating disorder unit to hospital for disruptive, non-compliant behavior	2/26/03 (31)	
	Suicidal ideation	Transferred from inpatient eating disorder unit to hospital suicidal ideation	5/28/03 (122)	
	Anorexia nervosa	Hospitalized for Eating disorder NOS ; Worsening eating disorder	9/25/03 (242)	

Subject Number; Treatment	SAE-Preferred Term	SAE-Investigator Term/Details from Narrative	AE Start Date (Study Day)	AE Stop Date (Study Day)
		(purging/rapid weight loss)		(b) (6)
	Anorexia nervosa	Hospitalized for Eating disorder NOS ; Worsening eating disorder	1/12/04 (351)	
010003; Ortho Tri-Cyclen	Depression	Hospitalized for worsening anorexia, depression, self-mutilation	12/15/02 (4)	
014001; placebo	Anorexia nervosa	Hospitalized for worsening of anorexia nervosa; study med stopped temporarily for 2 weeks	12/7/02 (31)	
014004; placebo	Anorexia nervosa	Hospitalized for worsening of anorexia nervosa	5/21/03 (65)	
014005; placebo	Anorexia nervosa	Hospitalized for worsening of anorexia nervosa	10/17/03 (197)	
	Anorexia nervosa	Hospitalized for worsening of anorexia nervosa	1/2/04 (274)	
	Anorexia nervosa	Hospitalized for worsening of anorexia nervosa; Subject completed study on Day 357	3/15/04 (347)	
028010; placebo	Anorexia nervosa	Hospitalized for anorexia nervosa, increased weight loss	5/12/03 (43)	
034005; placebo	Suicide attempt	Hospitalized after suicide attempt by aspirin overdose (40 aspirin tablets-325 mg)	9/29/03 (203)	
034006; Ortho Tri-Cyclen	Bradycardia; Hypothermia (2 events)	Hospitalized for bradycardia; Hypothermia (2 events)	4/1/03 (12)	
034008; placebo	Cachexia	Hospitalized after failing to gain weight in outpatient program; Protein calorie malnutrition	5/14/03 (55)	
035002; Ortho Tri-Cyclen	Suicidal ideation	Hospitalized for suicide watch secondary to worsened depression	3/6/03 (86)	
050001; Ortho Tri-Cyclen	Suicidal ideation	Hospitalized after suicide gesture with 15 Aleve tablets; discontinued on day of suicide gesture (Day 305) due to subject choice; prematurely discontinued on (b) (6) due to being unhappy with increased-23 lb- weight gain	9/7/03 (305)	
055010; placebo	Anorexia nervosa	Hospitalized for worsening anorexia	3/20/03 (1)	
078001; placebo	Depression aggravated	Hospitalized out of state for worsening depression (suspected); subject was discontinued due to lost to	Unknown, 2003	

Subject Number; Treatment	SAE-Preferred Term	SAE-Investigator Term/Details from Narrative	AE Start Date (Study Day)	AE Stop Date (Study Day)
		follow-up on Day 167 (b) (6)		(b) (6)
097001; placebo	Anorexia nervosa	Hospitalized for worsening of anorexia nervosa	4/14/03 (46)	
	Suicidal ideation	Hospitalized for suicidal ideation	1/22/04 (329)	
097002; placebo	Anorexia nervosa	Hospitalized for worsening of anorexia nervosa	4/10/03 (36)	
	Urticaria	Hospitalized for hives	8/7/03 (155)	
100002; Ortho Tri- Cyclen	Anorexia nervosa	Hospitalized for exacerbation of anorexia nervosa, malnutrition	4/7/03 (29)	
	Anorexia nervosa	Hospitalized for exacerbation of anorexia nervosa	5/2/03 (54)	
	Anorexia nervosa	Hospitalized for exacerbation of anorexia nervosa, malnutrition	5/25/03 (77)	
	Anorexia nervosa	Hospitalized for exacerbation of anorexia nervosa	6/14/03 (97)	
	Convulsions grand mal; Drug abuse (2 events)	Hospitalized, 3 grand mal seizures; Deliberate overdose of 4600 mg Celexa (2 events)	6/19/03 (102)	
	Anorexia nervosa	Hospitalized for exacerbation of anorexia nervosa, malnutrition; Investigator discontinued subject on Day 115 due to being too mentally unstable to safely continue in study	6/25/03 (108)	
100003; Ortho Tri- Cyclen	Suicide attempt	Hospitalized for eating disorder NOS , suicide attempt, hospitalized; discontinued Day 66 due to subject choice	5/14/03 (55)	
100004; placebo	Anorexia nervosa	Hospitalized for anorexia, severe exacerbation (weight 70 lbs, pulse 48, B/P 78/57, leukopenia); Subject prematurely withdrawn on Day 148 when Investigator determined subject too physically and psychologically compromised to safely continue in study	8/12/03 (145)	
	Anorexia nervosa	Hospitalized for severe exacerbation anorexia, chest pain, bradycardia, malnutrition	9/2/03 (166=Post treatment)	
106001; placebo	Weight decrease	Hospitalized for weight loss, anorexia nervosa (weight 97 lbs); had medical history of eating disorder -decreased food intake and purging	7/7/03 (154)	
109001;	Abdominal pain;	Hospitalized for abdominal pain	6/6/03 (79)	

Subject Number; Treatment	SAE-Preferred Term	SAE-Investigator Term/Details from Narrative	AE Start Date (Study Day)	AE Stop Date (Study Day)
Ortho Tri-Cyclen	Dehydration (2 events)	S/P cystoscopic removal of renal stones; Dehydration (2 events)		
112004; Ortho Tri-Cyclen	Anorexia nervosa	Hospitalized for worsening anorexia nervosa	7/3/03 (120)	(b) (6)

Source: Table 12, CPASS-169 Final Study Report pg. 155 -174 of 2369

Reviewer's comment:

- 1) This reviewer notes that the admitting diagnosis for two CAPSS-169 subjects (Subjects 006001 and 100003) during treatment was "eating disorder" and not anorexia nervosa. If subjects had anorexia nervosa at screening, it seems unusual that they would have improved during treatment to only having an eating disorder, yet still required hospitalization. In addition, the SAE for Subject 106001 stated that she had a medical history of "eating disorder". This reviewer believes that these subjects who were hospitalized during treatment had the diagnosis of "eating disorder" when enrolled into CAPSS-169, as supported by the above medical history and the following baseline BMI and % IBW: Subject 006001 had a baseline BMI of 20.72 kg/m² and a % IBW of 96%, Subject 100003 had a baseline BMI of 21.12 kg/m² and a % IBW of 101%, and Subject 106001 had a baseline BMI of 19.23 kg/m² and a % IBW of 91%.

10.1.1.5.4 Frequent adverse events

A total of 97 of the 123 treated subjects reported any adverse event: 48 (78.7%) on Ortho Tri-Cyclen and 49 (79.0%) on placebo. The sponsor concluded that the incidence of adverse events was similar between the treatment groups except for the adverse event "anorexia nervosa" (Ortho Tri-Cycle 2 subjects; placebo: 11 subjects), which they interpreted as meaning "worsening anorexia nervosa". One subject on Ortho Tri-Cycle (Subject 086003-Dr. (b) (6) site) reported imperforate hymen (genital malformation) as an adverse event starting on Day 313. All Physical Examination results, including "Genitourinary", for Subject 086003 were normal at both screening and final visits, except for the screening comments "thin" and "scaphoid abdomen". No LMP was listed for Subject 086003 at Visit 1.

Reviewer's comment:

- 1) The rationale for the sponsor's interpretation for the adverse event "anorexia nervosa" as meaning "worsening anorexia nervosa" is unclear to this reviewer. In addition, this reviewer rejects any sponsor conclusion that fewer subjects on Ortho Tri-Cyclen experienced worsening anorexia nervosa than subjects on placebo due to unblinding issues. This reviewer believes that most, if not all, subjects, subject families, and investigators were unblinded due to the well-known regular menses and adverse events associated with oral contraceptives. In addition, unblinded 6-month CAPSS-169 efficacy and safety data was submitted in the Original NDA on September 25, 2003.

Table 18: Incidence of Adverse Events Reported in >=5% of CAPSS-169 Subjects (n=123)

	Ortho Tri-Cyclen (N=61)	Placebo (N=62)
Number (%) of Subjects with Any Adverse Event	48 (78.7%)	49(79.0%)
Body as a Whole-General Disorders		
Back Pain	0	5 (8.1%)

	Ortho Tri-Cyclen	Placebo
	(N=61)	(N=62)
Influenza-like Symptoms	7 (11.5%)	0
Injury	2 (3.3%)	6 (9.7%)
Central & Peripheral Nervous System Disorders		
Headache	10 (16.4%)	10(16.1%)
Gastro-intestinal System Disorders		
Abdominal Pain	7 (11.5%)	2 (3.2%)
Nausea	4 (6.6%)	6 (9.7%)
Metabolic and Nutritional Disorders		
Hypoglycemia	1 (1.6%)	6 (9.7%)
Psychiatric Disorders		
Anorexia Nervosa	2 (3.3%)	11(17.7%)
Anxiety	2 (3.3%)	4 (6.5%)
Depression	6 (9.8%)	8 (12.9%)
Emotional Lability	1 (1.6%)	4 (6.5%)
Reproductive Disorders, Female		
Dysmenorrhea	10 (16.4%)	3 (4.8%)
Resistance Mechanism Disorders		
Infection	5 (8.2%)	1 (1.6%)
Infection Viral	2 (3.3%)	4 (6.5%)
Respiratory System Disorders		
Sinusitis	7 (11.5%)	1 (1.6%)
Upper Respiratory Tract Infection	6 (9.8%)	14(22.6%)

Source: Table 11 in CAPSS-169 Final Study Report on pg. 154 of 2369

Note: Reported in >=5% of subjects in either treatment group.

Note: If a subject experienced more than one adverse event within a category, the subject is counted once under that category.

WHOART dictionary (Version 1992, 3rd Quarter) was used for coding

10.1.1.5.5 Laboratory Values

Mean baseline and final visit hemoglobin (13.41-13.53) and hematocrit (39.4-39.8) were high normal, compatible with mild dehydration. No clinically significant changes in mean hematology or chemistry tests were noted. Ten subjects had a total of 13 markedly abnormal laboratory values:

- WBC markedly low: Subject 034006 Ortho Tri-Cyclen Screening (WBC=2.81)
- WBC markedly low: Subject 100004 Placebo Cycle 6 (WBC=2.51)
- WBC markedly high: Subject 100001 Placebo Screening (WBC=16.30)
- Bicarbonate markedly low: Subject 062003 Ortho Tri-Cyclen Screening (bicarbonate=14.7)
- Bicarbonate markedly low: Subject 028002 Placebo Cycle 3 (bicarbonate=16.7)
- Bicarbonate markedly high: Subject 112004 Ortho Tri-Cyclen Cycle 6 (bicarbonate=36.5)
- BUN markedly high: Subject 008001 Placebo Cycle 3 (BUN=46)
- Chloride markedly low: Subject 100004 Cycle 6 (chloride=89)
- Glucose markedly low: Subject 106003 Ortho Tri-Cyclen Cycle 6 (glucose=39)
- Glucose markedly low: Subject 034004 Placebo Cycle 3 (glucose=35)
- Glucose markedly low: Subject 034004 Placebo Cycle 6 (glucose=28)
- Potassium markedly low: Subject 112004 Ortho Tri-Cyclen Cycle 6 (potassium =2.6)
- Potassium markedly low: Subject 106003 Placebo Cycle 13 (potassium =2.5)

Reviewer's comment:

1) *This reviewer detected no signal of any significantly increased abnormal laboratory values associated with Ortho Tri-Cyclen treatment when compared to placebo treatment.*

All pregnancy tests performed were negative (CAPSS-169 Final Study Report: Appendix 3.4 pg. 1658-1696)

10.1.1.5.6 Concomitant Medications

The concomitant use of a multivitamin and calcium supplement was required by the protocol. No other concomitant medications were to be used during the study. Specifically prohibited therapies were hormonal contraceptives, GnRH-analogues, and hepatic enzyme inducing drugs/nutraceuticals such as rifampin, phenobarbital, Griseofulvin, and St. John's Wort.

The 1019 line listings for recent/concomitant medications in CAPSS-169 Final Study Report Appendix 3.6 (pg. 1725-1792) were reviewed. The mean number of line listings per subject was 8.28 with each subject required by the protocol to concomitantly take 2 medications: a multivitamin (usually Flintstone multiple vitamins) and a calcium supplement (usually Tums). At least 74 of the 123 treated subjects reported the use of 1 to 3 different antidepressants such as Celexa (citalopram), Effexor (venlafaxine), Lexapro (escitalopram), Paxil (paroxetine), Prozac (fluoxetine), Strattera (atomoxetine), Desyrel (trazodone), Wellbutrin (bupropion hydrochloride), or Zoloft (sertraline).⁵⁰ At least 9 subjects reported taking a medication primarily for anxiety, such as Ativan, Buspar, Klonopin, lorazepam, Neurontin, Vistaril, or Xanax.⁵⁰ One of these 9 subject received Ativan for anxiety due to episodic cutting self abuse (Subject 105001 on Ortho Tri-Cyclen). Two subjects required receiving activated charcoal after a suicide gesture or drug overdose (Subject 050001 on Ortho Tri-Cyclen after a suicide gesture with 15 naprosyn tablets; Subject 010001 after a drug overdose).

Reviewer's comment:

- 1) *This reviewer considers it significant that 68 pages of medications were listed as having been administered to the 123 treated adolescent subjects in CAPSS-169 during screening ("recent") or as concomitant medications during active treatment.*
- 2) *No concomitant use of estrogen or progestin drug products or specifically prohibited concomitant medications was identified.*
- 3) *The concomitant medications dataset was difficult to analyze since medications used during the screening period were not separated from the medications used during the treatment period. The medications were only listed by the "verbatim" name, which could be a generic or one of several trade names. In addition, only the "verbatim" reason for therapy was provided. Thus, it was difficult to sort the concomitant medication dataset by drug treatment group or by indication.*

10.1.1.5.7 Vital Signs

No significant change in mean blood pressure or pulse from baseline to final visit was noted. One placebo subject had a markedly low pulse Subject 034001=44). Two subjects had a markedly low systolic blood pressure (placebo Subject 034001=70 and Ortho Tri-Cyclen Subject 012002=70). One Ortho Tri-Cyclen subject had a markedly high systolic blood pressure (Subject 016001=160). Mean weight gain from baseline to final visit for the 61 Ortho Tri-Cyclen subjects in the "treated" population was 5.88 kg (range -7.3 to +24.9 kg). Mean weight gain from baseline to final visit for the 62 Placebo subjects in the "treated" population was 4.71 kg (range -18.8 to +42.6 kg).

⁵⁰ Medical Reviewer analysis of JMP data set entitled "CURM".

When comparing weight at Visit 1 to weight at last visit, more subjects in the Ortho Tri-Cyclen group (n=13) than in the placebo group (n=9) gained 20 or more pounds. The 13 Ortho Tri-Cyclen subjects (who gained 20 or more pounds) gained a total of 480.6 pounds. The 9 subjects in the placebo group (who gained 20 or more pounds) gained a total of 365.7 pounds. This discrepancy in total weight gain between the two treatment groups may have confounded the change in BMD, so this reviewer requested a subgroup analysis excluding subjects who gained 20 or more pounds. On April 19, 2005, the sponsor submitted the requested subgroup analysis (see Table 8). In this post-hoc efficacy subgroup analysis performed by the sponsor, excluding subjects who gained 20 or more pounds (i.e. Population II) resulted in the Ortho Tri-Cyclen treated subject being not statistically different from placebo treated subjects for the endpoint “change from baseline in total lumbar spine bone mineral density” at both time points, i.e. at Cycle 6 and at Cycle 13.

Height was obtained during the conduct of CAPSS-169 at Visit 1 (Screening), Visit 6 (Cycle 6), and at Visit 8 (Cycle 13 or early Termination). The sponsor did not submit any analyses regarding change in height in CAPSS-169; however, height was included in the data line listing Appendix 3.12 in the CAPSS-169 Final Study Report on pg. 2285-2330. Of the 117 CAPSS-169 subjects who received at least one dose of study medication and had both a screening and at least one during treatment height measurement (58 subjects on Ortho Tri-Cyclen and 59 subjects on placebo), the change in height from Visit 1 to end of study as listed in Appendix 3.12 was determined by this reviewer and is summarized as follows:

- 18 subjects experienced a **decrease** in height:
 - 9 subjects on Ortho Tri-Cyclen: Subjects 010003 (0.5 cm), 016001 (1.3 cm), 042001 (1.1 cm), 051006 (0.1 cm), 068002 (0.4 cm), 086001 (2.6 cm), 104001 (1.3 cm), 109001 (0.1 cm), 112004 (2.5 cm)
 - 9 subjects on placebo: Subjects 010004 (0.5 cm), 021001 (1.1 cm), 028002 (1.3 cm), 028006 (1.3 cm), 028007 (1.3 cm), 034001 (0.5 cm), 104002 (2.6 cm), 106001 (1.3 cm), 106003 (1.3 cm)
- 48 subjects experienced **no change** in height:
 - 23 subjects on Ortho Tri-Cyclen: Subjects 006002, 011001, 011002, 012002, 014002, 014003, 038005, 050001, 052004, 055004, 056003, 056005, 062006, 070001, 086002, 089001, 090001, 090003, 090006, 100003, 109003, 112001, 113001
 - 25 subjects on placebo: Subjects 001001, 012001, 014001, 014004, 014005, 043001, 052002, 055002, 055003, 056001, 056002, 056004, 059002, 062002, 062005, 062007, 062009, 068001, 090002, 090004, 095001, 097001, 100004, 113002, 114002
- 51 subjects experienced an **increase** in height:
 - 26 subjects on Ortho Tri-Cyclen: Subjects 015002 (1.3 cm), 016002 (3.1 cm), 016003 (3.8 cm), 028003 (0.7 cm), 034002 (1.3 cm), 034006 (0.8 cm), 034007 (0.2 cm), 035001 (1.5 cm), 035002 (1.1 cm), 035003 (5.8 cm), 038004 (1.3 cm), 051001 (3.8 cm), 051003 (3.1 cm), 052001 (0.6 cm), 055001 (0.1 cm), 055008 (0.1 cm), 055009 (1.4 cm), 056006 (2.5 cm), 062001 (5.1 cm), 062003 (2.6 cm), 086003 (0.6 cm), 090007 (3.8 cm), 100002 (0.6 cm), 105001 (0.5 cm), 106002 (1.2 cm), 112003 (0.6 cm)
 - 25 subjects on placebo: Subjects 004001 (1.9 cm), 006001 (1.3 cm), 008001 (1.7 cm), 010002 (1.0 cm), 028001 (3.5 cm), 028005 (2.6 cm), 028008 (1.3 cm), 028010 (1.3 cm), 034003 (1.5 cm), 034004 (3.8 cm), 034005 (0.1 cm), 034008 (0.9 cm), 055006 (0.3 cm), 055007 (0.6 cm), 055010 (3.3 cm), 055011 (1.2 cm), 056007 (2.5 cm), 059001 (3.2 cm), 062004 (0.5 cm), 079001 (0.7 cm), 097002 (1.3 cm), 097003 (1.3 cm), 098002 (0.5 cm), 100001 (1.3 cm), 109002 (1.2 cm)

No effect of treatment on height was detected by this reviewer.

10.1.1.5.8 Physical examination

Minimal information was provided in the Physical Examination line listing and Physical Examination-Comments line listings. The line listings were reviewed. No clinically significant changes were documented as having occurred during the study.

10.1.1.5.9 ECG

No ECGs were obtained.

10.1.1.6 Reviewer's assessment of **CAPSS-169** efficacy and safety

The majority of the 123 subjects treated in CAPSS-169 did not meet the DSM-IV diagnostic criteria for anorexia nervosa or the DSM-IV diagnostic criteria modified by the sponsor for anorexia nervosa at baseline.

In the ITT population, treatment with Ortho Tri-Cyclen was not associated with a significant change in mean total lumbar (L1-L4) bone mineral density from baseline to Cycle 13 when compared to placebo. In the ITT population, treatment with Ortho Tri-Cyclen was not associated with a significant change in mean total hip bone mineral density from baseline to Cycle 13 when compared to placebo. In the ITT population in subjects with negative Z-scores at baseline, treatment with Ortho Tri-Cyclen was not associated with a significant change in mean total lumbar spine (L1-L4) BMD from baseline to Cycle 13 when compared to placebo. This reviewer believes that most, if not all, subjects, subject families, and investigators were unblinded due to the well-known changes in menses and adverse events associated with oral contraceptives. In addition, unblinded 6-month CAPSS-169 efficacy and safety data was submitted in the Original NDA on September 25, 2003.

There were no deaths, no pregnancies, and no reports of venous thromboembolic events during the conduct of CAPSS-169. Significantly more treated subjects on Ortho Tri-Cyclen (n=21, 34.4%) prematurely discontinued from the study than placebo subjects (n=13, 21.0%). It is concerning that one subject was started on oral contraceptives and her imperforate hymen was not diagnosed until 11 months on treatment. A visual examination of the vulva and vaginal introitus should have diagnosed the imperforate hymen at screening.

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