CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-011/S-021

MEDICAL REVIEW(S)

NDA 20-011/s021
NDA 20-708/s011

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review of Efficacy Supplements

NDAs	NDA 20-011/s021 and NDA 20-708/s011
Applicant	TAP Pharmaceutical Products 675 North Field Drive Lake Forrest, IL 60045
Submission Type	Efficacy Supplement
Drug	
Established name	Leuprolide acetate for depot suspension
Trade name	Lupron Depot 3.75 mg (NDA 20-011) Lupron Depot 3 Month 11.25 mg (NDA 20-708)
Chemical class	Synthetic peptide
Chemical name	5-oxo-L-propyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-proamide acetate salt
Drug Class	Gonadotropin releasing hormone (GnRH) agonist
Indication	Management of endometriosis
Route of Administration	Intramuscular injection
Dosage Form	Sterile depot suspension for injection
Dose	3.75 mg or 11.25 mg per dosing
Dosing Regimen	Once a month (3.75 mg formulation) or Once every 3 months (11.25 mg formulation)
Dates	
Submitted	November 21, 2000
CDER stamp date	November 22, 2000
PDUFA date	November 22, 2001
Related NDAs	NDAs 19-010, 19-732, and 20-517 (prostate cancer); NDA 19-943 (uterine leiomyomata); NDA 20-263 (precocious puberty)
Related IND	[redacted]
Medical Reviewer	Scott Monroe MD
Date Review Completed	September 7, 2001

FINAL

21 September 2001

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

EXECUTIVE SUMMARY

1 RECOMMENDATIONS

1.1 Recommendations Regarding Approval

1.1.1 Approvability

The following recommendations apply to both NDA 20-011/s021 and NDA 20-708/s011:

1. Information about the benefits and potential risks of co-treatment with Lupron plus 5 mg norethindrone acetate (NETA) can be added to labeling for both Lupron Depot 3.75 mg and Lupron Depot 3 Month 11.75 mg. Information should be added to labeling regarding which patients are most likely to benefit from co-treatment with NETA and which patients should not receive co-treatment with NETA.
2. A single course of retreatment with Lupron plus NETA, not to exceed 6 months, can be permitted based on the information provided in this application. The present restriction concerning retreatment should be modified accordingly in the label. Lupron alone should not be used for retreatment.
3. The maximum duration of a single course of treatment with Lupron (or Lupron plus NETA) should continue to be 6 months. The Sponsor's request to extend a single course of treatment for up to 12 months should not be approved. The Sponsor has not demonstrated that there would be significant and additional long-lasting clinical benefit if a single course of treatment were to be extended beyond 6 months.

1.1.2 Basis for Recommendation Regarding Approvability

Addition of information regarding co-treatment with NETA to label. The sponsor has adequately demonstrated in 2 clinical trials that co-treatment with monthly Lupron Depot 3.75 mg plus 5 mg daily NETA attenuates the decrease in bone mineral density (BMD) that is associated with Lupron treatment alone without reducing the efficacy of Lupron. Women with endometriosis treated with Lupron Depot plus NETA for up to 1 year had mean changes in BMD from baseline at Week 24 and Week 52 of treatment of –0.2% and –1.0%, respectively. Women treated with Lupron alone had mean changes in BMD at Week 24 and Week 52 of –3.2% and –6.3%, respectively. Co-treatment with Lupron plus NETA also reduced the frequency and severity of hot flashes compared to treatment with Lupron alone. This information should be added to labeling since (1) loss of BMD is the most clinically significant and potentially serious adverse consequence of therapy with Lupron and (2) hot flashes, often severe in intensity, are the most commonly reported adverse event. Treatment with 5 mg of NETA, however, has an adverse effect on serum lipid profiles that is manifested predominantly by a decrease in serum concentrations of HDL-cholesterol. Labeling should include information regarding (1) the benefits and adverse effects of co-therapy with Lupron plus NETA and (2) the types of patients that are most likely to benefit from co-treatment to assist physicians in safely maximizing the therapeutic potential of Lupron for the management of endometriosis.

Retreatment of women with endometriosis. Symptomatic benefit is usually noted after 1 or 2 months of treatment with Lupron and may continue for many months or even years after completion of 6 months of treatment. However, there are patients for whom retreatment is warranted because of recurrence of symptoms. Present labeling for Lupron does not recommend retreatment because of concerns about excessive loss of BMD. In the present applications, the Sponsor has shown that co-treatment with Lupron plus NETA can effectively attenuate the decrease in BMD associated with Lupron therapy alone. Among the patients treated with Lupron plus NETA in the 2 clinical trials submitted in support of these applications were 40 women with endometriosis who had previously

been treated with Lupron or Synarel, another gonadotropin releasing hormone (GnRH) analog. Posttreatment BMD data from 32 patients (Week 24 assessment) and 25 patients (Week 52 assessment) previously treated with Lupron or Synarel were available. Separate analyses of the BMD and primary efficacy data did not reveal any clinically significant differences in the responses of these women to therapy with Lupron plus NETA compared to the responses in women not previously treated with a GnRH analog. These data are sufficient to support the safety and efficacy of a single 6-month course of retreatment with Lupron plus NETA. The data are not adequate, however, to support the safety of repeated courses of retreatment. Prior to retreatment, the patient's BMD should be measured to ensure that it is within acceptable limits. Lupron alone should not be used for retreatment as this may result in excessive loss in BMD.

Applicability of submitted clinical data to 11.25-mg formulation of Lupron. All data submitted in support of the present applications were obtained with the 3.75-mg formulation of Lupron that is administered once a month. An 11.75-mg formulation of Lupron that is administered once every 3 months also is approved for the management of endometriosis. An earlier study conducted by the Sponsor as part of a Phase IV commitment for the approval of this latter formulation did not reveal any clinically significant differences between the 3.75-mg and the 11.75-mg formulations in terms of either efficacy (reduction in painful symptoms of endometriosis) or magnitude of the decrease in BMD. Based on the findings from this earlier comparative study, it is reasonable to conclude that co-treatment with NETA will have the same protective effect on BMD (i.e., attenuation of BMD decreases) in women treated with the 11.25 mg formulation of Lupron. Labeling changes for the 11.25-mg formulation are warranted regarding (1) the potential benefits and risks of co-therapy with NETA and (2) retreatment.

Extension of recommended treatment period to up-to-1-year. Present labeling recommends against treatment with Lupron beyond 6 months because of concerns about excessive decrease in BMD. In the present application, the Sponsor has shown that the mean change in BMD in women treated with Lupron for up to 1 year was approximately –1%. However, 10 of 157 women had a decrease of more than 5.0% in one or more post baseline BMD measurements. All but one of these decreases was observed after the Week 24 visit. In the present application, the sponsor has not presented any data indicating that treatment for up to 1 year, as opposed to 6 months, results in better suppression of the painful symptoms of endometriosis or prolongation of the period of therapeutic benefit after completion of a course of therapy. In the absence of data supporting the clinical benefits of a single course of treatment of greater than 6 months and the continuing, albeit limited, decrease in BMD, approval for extending the duration of treatment beyond 6 months is not warranted. A more rational and safer approach would be to retreat with Lupron plus NETA for up to 6 months if symptoms warrant further therapy.

1.2 Specific Recommendations to the Sponsor

1. Specific recommendations concerning revisions to the proposed labels were communicated to the Sponsor on September 14, 2001.
2. If the Sponsor wishes to obtain a labeling change supporting 1 year of continuous co-treatment with Lupron plus NETA, the Sponsor will need to submit new clinical data showing that there is additional and sustained long-lasting clinical benefit resulting from the longer treatment period.
3. If the Sponsor wishes to obtain a labeling change permitting more than one 6-month course of retreatment, the Sponsor will need to submit new clinical data supporting the safety and efficacy of repeated courses of retreatment.

2 SUMMARY OF CLINICAL FINDINGS

2.1 Overview of Clinical Program

2.1.1 Drug

Lupron (leuprolide acetate for depot suspension) is a synthetic analog of naturally occurring GnRH in which D-leucine has replaced glycine in position 6 of the natural peptide. Two depot formulations are presently approved for the management of endometriosis: a 3.75-mg formulation that is administered by IM injection once a month and an 11.75-mg formulation that is administered once every 3 months. Aygestin (norethindrone acetate) is a progestin in the class of 19-nortestosterone derivatives. It is approved for the treatment of endometriosis and abnormal menstrual bleeding in the absence of organic pathology. The approved daily dose ranges from 5 to 15 mg.

2.1.2 Clinical Program and Study Design

The sponsor conducted 2 clinical trials in the United States in which women with endometriosis were treated with Lupron plus "hormone add-back therapy" for up to 1 year. The first clinical trial (Study M92-878) was a randomized, blinded, 4-arm, multicenter study in which a total of 201 women were enrolled and treated with Lupron alone (Group 1), Lupron plus 5 mg norethindrone acetate (NETA, Aygestin®) per day (Group 2), or Lupron plus 5 mg NETA plus either 0.625 mg or 1.25 mg of conjugated equine estrogen (Groups 3 and 4). Women were randomly assigned to one of the treatment groups in a 1:1:1:1 ratio. The second trial (Study M97-777) was an open-label, single-arm, multicenter study in which 136 women with endometriosis were enrolled. All patients were treated with once monthly Lupron and 5 mg NETA per day. In both studies, Lupron Depot 3.75 mg was administered by IM injection once every 4 weeks (a total of 13 injections) during the Treatment Period and oral hormonal add-back therapy (e.g., 5 mg NETA daily) or placebo was administered daily. Calcium supplementation consisting of 1000 mg elemental calcium (OsCal® tablets) was supplied throughout the Treatment and Follow-up Periods.

The studies were conducted to support a change in the labeling for Lupron Depot 3.75 mg and Lupron Depot 11.25 mg, reflecting the benefit of co-treating with Lupron plus hormone add-back therapy (i.e., NETA) to (a) extend the approved Lupron treatment period for endometriosis to up to one year and (b) permit retreatment. Safety was the primary objective of the 2 clinical trials, and samples sizes were determined based on estimates of the anticipated changes in BMD. Efficacy was a secondary objective. Although the 2 clinical studies submitted in support of this application differed significantly in terms of overall designs, the efficacy and safety assessments and endpoints of the 2 studies were very similar. Since the Sponsor is seeking a labeling change that concerns only the co-administration of Lupron plus NETA, this review does not discuss the findings in the NETA plus estrogen treatment arms in Study M92-878.

2.2 Efficacy

2.2.1 Primary Efficacy Assessment and Efficacy Endpoints

The primary efficacy variables in each study were based on the Investigator's and/or patient's assessment of the severity of each of 5 symptoms or signs of endometriosis. The disease variables that were assessed were dysmenorrhea, pelvic pain, deep dyspareunia, pelvic tenderness, and pelvic induration. Each symptom or sign was rated at each visit during the Treatment Period and at each visit during the first year of follow-up. Each symptom or sign was assigned a numeric score, based on its severity, of either 1 (not present); 2 (mild); 3 (moderate); or 4 (severe) for the purpose of analyses. These numeric scores were referred to as the "symptom severity scores." The 5 primary

efficacy endpoints were based on the changes from baseline values for both the numeric symptom severity scores and the proportion of patients with the respective symptom.

2.2.2 Efficacy Results (Primary Endpoints)

In Study M92-878, 51 and 55 patients were enrolled into the Lupron alone (LD) and Lupron plus NETA (LD/N) treatment groups. In Study M97-777, 136 patients were enrolled and treated with Lupron plus NETA. Table 1 below summarizes for each treatment group and each of the symptoms or signs of endometriosis the changes from baseline in (1) the proportion of patients with the respective symptom or sign and (2) the mean change in the clinical pain severity score. At the final treatment visit in each treatment group, there was a statistically significant decrease in each of the efficacy variables for both (1) the proportion of patients with the respective symptom or sign and (2) the mean clinical pain severity score. In Study M92-878, there were no significant differences in the clinical responses in the LD and LD/N treatment groups. Co-treatment with LD/N therefore does not appear to decrease the efficacy of Lupron treatment in women with endometriosis.

Table 1 Percentages of Patients with Symptoms of Endometriosis and Mean Clinical Severity Scores

			Percent of Patients with Symptom			Clinical Pain Severity Score		
			Baseline		Final	Baseline		Final
Variable	Study	Group	N [1]	(%) [2]	(%)	N [1]	Value	Change
Dysmenorrhea	M92	LD	51	(100)	(4)	50	3.2	-2.0
		LD/N	55	(100)	(4)	54	3.1	-2.0
	M97	LD/N	136	(99)	(9)	134	3.3	-2.1
Pelvic Pain	M92	LD	51	(100)	(66)	50	2.9	-1.1
		LD/N	55	(96)	(56)	54	3.1	-1.1
	M97	LD/N	136	(99)	(63)	134	3.2	-1.2
Deep Dyspareunia	M92	LD	42	(83)	(37)	25	2.4	-1.0
		LD/N	43	(84)	(45)	30	2.7	-0.8
	M97	LD/N	102	(91)	(53)	94	2.7	-1.0
Pelvic Tenderness	M92	LD	51	(94)	(34)	50	2.5	-1.0
		LD/N	54	(91)	(34)	52	2.6	-0.9
	M97	LD/N	136	(99)	(39)	134	2.9	-1.4
Pelvic Induration	M92	LD	51	(51)	(12)	50	1.9*	-0.4
		LD/N	54	(46)	(17)	52	1.6	-0.4
	M97	LD/N	136	(75)	(21)	134	2.2	-0.9

[1] Number of patients that were included in the assessment.
[2] Percentage of patients with the symptom/sign.
Source: Statistical Tables 1.11 (ISE), 2.11 (ISE), 1.15 (ISE), and 2.15 (ISE).

Among the patients treated with Lupron plus NETA in Studies M92-878 and M97-777 were 40 women who had previously been treated with either Lupron or Synarel. A subset analysis of the efficacy data for these patients did not reveal any clinically significant differences in the responses of these women to therapy with Lupron plus NETA compared to the responses in women not previously treated with a GnRH analog.

2.2.3 Other Efficacy Assessments

During the treatment period, total serum estradiol levels were determined at each protocol-scheduled visit. Statistically significant within-group mean decreases from baseline were noted in all treatment groups at each visit during the Treatment Period. Mean total serum estradiol levels during the

treatment period were lower in the 2 LD/N treatment groups (8.6 pg/mL and 8.4 pg/mL) compared to the LD treatment group (14.5 pg/mL).

2.2.4 Proposed Label Claim

The Sponsor's request to include in labeling a statement that co-treatment with Lupron plus NETA did not reduce the efficacy of Lupron therapy is supported by the submitted data.

2.3 Safety

2.3.1 Exposure to Study Drug

In Study M92-878, 32 of 51 patients (63%) randomized into the LD-treatment group and 31 of 55 patients (56%) randomized into the LD/N treatment group received all 13 injections of Lupron. In Study M97-777, 83 of 136 (61%) patients received all 13 injections. The extent of exposure to Lupron was comparable in each treatment group. Both Lupron Depot and Aygestin (NETA) are approved therapies for endometriosis with well-known safety profiles. The number of patients treated with Lupron plus NETA and the duration of treatment in Studies M92-878 and M97-777 were sufficient to assess the safety of the combination therapy in the intended population.

2.3.2 General Safety Findings

The proportions of patients experiencing any adverse event, treatment-related adverse events, and treatment-related serious adverse events as well as premature withdrawals due to adverse events were similar across the LD treatment group and the two LD/N treatment groups. A lower proportion of patients treated with LD/N reported adverse events that were rated as severe in intensity. This difference was most likely a consequence of the reduction in the severity and frequency of severe hot flashes in the LD/N-treated patients. Adjunct treatment with NETA did not raise any new safety concerns, with one exception, regarding the use of Lupron for the management of endometriosis. The exception concerned the androgenic adverse effects of NETA, particularly on serum lipids as described below in Section 2.3.4.

2.3.3 Patient Deaths

There were no reported patient deaths in either clinical trial.

2.3.4 Safety Issues of Special Interest

Changes in bone mineral density. The effects of treatment with Lupron alone or with Lupron plus 5 mg NETA on BMD are summarized below in Table 2. The decreases in BMD from baseline at both Week 24 and Week 52 were smaller in the patients treated with Lupron plus NETA.

Table 2 Summary of BMD Changes from Baseline during Treatment with LD or LD/N

Time of Assessment	Study M92-878						Study M97-777		
	LD (n=51)			LD/N (n=55)			LD/N (n=136)		
	N	Percent Change	95% CI [3]	N	Percent Change	95% CI	N	Percent Change	95% CI
Week 24 [1]	41	-3.2	(-3.8, -2.6)	42	-0.3	(-0.8, 0.3)	115	-0.2	(-0.6, 0.2)
Week 52 [2]	29	-6.3	(-7.1, -5.4)	32	-1.0	(-1.9, -0.1)	84	-1.1	(-1.6, -0.5)

[1] Includes on-treatment measurements that fell within 2-252 days after the first day of treatment.
[2] Includes on-treatment measurements > 252 after the first day of treatment.
[3] Two-sided 95% confidence interval about the mean difference from baseline.
Source: Statistical Tables 3.1.1 (Submission of August 10, 2001) and 2.7 (ISS).

Post baseline BMD data were available from 32 patients who had previously been treated with Lupron or Synarel. Although the sample size was small (only 32 and 25 patients with prior GnRH treatment had BMD measurements at Weeks 24 and 52, respectively), there was no suggestion, based on changes in mean BMD values, that NETA was less effective in preventing a decrease in BMD in the retreated patients.

Changes in serum lipids and other potential adverse effects of NETA co-therapy. The major impact of treatment with Lupron plus NETA on serum lipid profiles, compared to treatment with Lupron alone, was to significantly (1) decrease mean serum HDL-cholesterol concentrations and (2) increase mean LDL/HDL ratios as shown in Table 3. These changes were largely or entirely reversed during the 1-year posttreatment follow-up period.

Table 3 Serum Lipid Concentrations: Percent Changes from Baseline

	Week 24				Week 52			
	LD Gp (n=39)		LD/N Gp (n=158)[1]		LD Gp (n=23)		LD/N Gp (n=113)[1]	
Measurement	Baseline mg/dL	Tx Visit % Change[2]	Baseline mg/dL	Tx Visit % Change	Baseline mg/dL	Tx Visit % Change	Baseline mg/dL	Tx Visit % Change
Total Cholesterol	170.5	8.6%	180.7	1.6%	168.0	9.6%	179.4	3.6%
HDL-Cholesterol	52.4	6.9%	51.2	-17.4%	49.1	1.8%	51.0	-18.1%
LDL-Cholesterol	96.6	9.0%	107.1	10.6%	95.5	12.8%	105.0	12.8%
LDL/HDL RATIO	2.0*	5.6%	2.2*	33.9%	2.1*	14.1%	2.2*	38.8%
Triglycerides	107.8	10.4%	111.8	3.8%	117.1	12.9%	109.0	15.8%

[1] Integrated results from Studies M92-878 and M97-777.
[2] Percent changes of the mean value from baseline and not the mean of the individual percent changes from baseline.
* No unit as value is a ratio.
Source: Statistical Tables 1.1.1 and 1.1.2.2 (Submission of August 10, 2001).

Severe depression (a known adverse effect of high doses of progestins) was reported for 5 of 191 (3%) LD/N-treated patients and for no LD-treated patients. Hypertension also was reported as an adverse event for 8 of 191 (4.3%) LD/N-treated patients and for no LD-treated patients.

2.4 Dosing

The 3.75-mg monthly dose of Lupron Depot that was used in these Studies is the approved dose for the treatment of endometriosis. A daily dose of 5-15 mg of norethindrone acetate is approved for the treatment of endometriosis. No dose-ranging studies with NETA were conducted to determine if a lower dose would have provided adequate bone–protecting effects.

2.5 Special Populations

Women and children. Endometriosis is a disease that affects primarily reproductive–aged women. It does not affect prepubertal girls. The youngest patient treated with LD/N was 17 years of age.

Renal and hepatic impairment. Studies in women with renal or hepatic impairment have not been conducted with Lupron. Present labeling does not address this issue. Norethindrone acetate is contraindicated (present label) in women with "markedly impaired liver function or liver disease."

Racial differences in efficacy and safety. The total number (percentage) of black women in the 2 studies submitted in support of this application was small, 25 of 243 patients (10%). It was felt that a subset analysis based on race would be of limited value, and consequently it was not performed.

CLINICAL REVIEW

3 INTRODUCTION AND BACKGROUND

3.1 Drug

• **Established Name**	Leuprolide acetate for depot suspension
• **Trade Name**	Lupron Depot 3.75 mg (NDA 20-011) Lupron Depot 3 Month 11.25 mg (NDA 20-708)
• **Drug Class**	Gonadotropin releasing hormone (GnRH) agonist
• **Chemical Class**	Synthetic decapeptide
• **Chemical name**	5-oxo-L-propyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-proamide acetate salt
• **Indication**	Management of endometriosis
• **Dosage Form**	Sterile depot suspension for injection
• **Dose**	3.75 mg or 11.25 mg per dosing
• **Dosing Regimen**	Once a month (3.75-mg formulation) or Once every 3 months (11.25-mg formulation)

3.2 Overview of Disease and Treatment Options

3.2.1 Endometriosis

Endometriosis may be defined as the presence of functioning endometrial tissue outside of the uterus. It is usually confined to the pelvis in the region of the ovaries, uterosacral ligaments, cul-de-sac, and uterovesical peritoneum. It is a common gynecologic disorder that is present in up to 10% of reproductive-aged women. The most common symptom of endometriosis is pain that may include dysmenorrhea, chronic pelvic pain that is not associated with menses, and/or dyspareunia. Endometriosis is also frequently associated with infertility. The clinical presentation and severity of the symptoms of endometriosis are related to some degree to the anatomic location and the extent of the disease. However, some women with anatomically advanced disease may have few pain symptoms while other women with minimal anatomic disease may have severe and disabling symptoms. Although the etiology of endometriosis remains controversial, the disease is dependent on estrogen in most instances and is rarely seen after the menopause. Current therapies for endometriosis include analgesics, sex steroid hormones, agonistic analogs of gonadotropin releasing hormone (GnRH), and surgery. Hormonal therapies such as combination hormonal contraceptives, progestins (medroxyprogesterone acetate or norethindrone) or danazol may act both directly on the ectopic endometrial tissue and indirectly via a reduction in circulating levels of ovarian estrogens. In contrast, agonistic analogs of GnRH such as Lupron act only indirectly on the ectopic endometrium by inducing a hypoestrogenic state and reducing serum estradiol concentrations to postmenopausal levels in most women.

3.2.2 GnRH Analogs for the Management of Endometriosis

Chronic administration of agonistic analogs of GnRH to women either by twice daily nasal spray (Synarel®), monthly or less frequent depot injection (Lupron Depot®), or implant (Zoladex®) initially stimulates and then suppresses the secretion of pituitary luteinizing hormone (LH), and to a

lesser degree, follicle stimulating hormone (FSH). These changes in LH and FSH secretion, in turn, initially stimulate the secretion of ovarian steroids. However, within 2 to 4 weeks of the onset of GnRH therapy, ovarian function is markedly reduced because of the absence of gonadotropin stimulation. In most women treated with approved doses of GnRH analogs, serum concentrations of estradiol are reliably suppressed to postmenopausal levels (i.e., ≤ 20 pg/mL).

The first GnRH analog to receive regulatory approval by the FDA for the management of endometriosis was nafarelin (Synarel®) in February 1990. This was followed by approvals for leuprolide (Lupron Depot® 3.75 mg under NDA 20-011) and goserelin (Zoladex®). Because of the side effects attributable to the hypoestrogenic environment induced by GnRH analogs, principally loss of bone mineral density [BMD]), the approved duration of treatment with GnRH agonists for the management of endometriosis is presently restricted to 6 months and retreatment is generally not recommended.

Symptomatic relief is usually noted during the first month of treatment with GnRH analogs and may continue for many months or even years after completion of 6 months of treatment. However, there are patients for whom retreatment is warranted because of recurrence of symptoms. Approaches to increasing the permissible duration of GnRH agonist treatment or to eliminating the recommendation against retreatment have investigated ways to limit the hypoestrogenic side effects, most importantly the loss of BMD. Co-treatment with a GnRH analog and sex-steroid hormones, referred to as "add-back" therapy, has been evaluated for its potential ability to minimize bone loss and to ameliorate vasomotor symptoms while preserving efficacy. Treatment protocols have included the addition of progestins alone and progestins plus estrogen. Other approaches have include co-administration of a GnRH analog and an anti-resorptive agent (e.g., a bisphosphonate).

3.3 Regulatory History of Lupron and Lupron plus Norethindrone Acetate

3.3.1 Background

In an effort to change the labeling for Lupron to permit primary treatment for up to 1 year as well as retreatment, TAP Pharmaceuticals initially conducted a randomized, blinded, 4-arm clinical trial (Study M92-878) in which women with endometriosis were treated with either Lupron Depot alone (LD, 3.75 mg every 28 days) or LD plus one of 3 daily add-back therapies for up to 1 year. The 3 add-back therapies were (1) 5 mg norethindrone acetate (NETA, Aygestin®) per day, (2) 5 mg NETA plus 0.625 mg conjugated equine estrogen (CEE), and (3) 5 mg NETA plus 1.25 mg CEE. All of the treatments were evaluated for their ability to ameliorate hypoestrogenic side effects while maintaining the efficacy of Lupron (i. e., reduction in the severity of endometriosis associated pain). The findings of Study M92-878 suggested that co-treatment with norethindrone acetate 5 mg per day, either alone or in combination with CEE, and Lupron reduced the incidence and severity of hot flashes and reduced the degree of bone loss as assessed by BMD measurements of the lumber spine. There were no clinically significant added benefits, however, from the inclusion of CEE above that provided by NETA alone. A numerically higher percentage of patients treated with LD plus NETA plus 1.25 mg CEE also terminated prematurely from the study. Based on the findings from this study, TAP submitted an efficacy supplement to NDA 20-011 in 1996 in order to change the labeling for Lupron to allow for treatment of women with endometriosis for up to 1 year as well as retreatment if NETA was co-administered with Lupron. The Division of Reproductive and Urologic Drug Products (DRUDP) refused to file the application because (1) it was based on a single study (M92-878) and (2) adequate dose ranging data were not provided for the add-back or hormone replacement therapies

for either a progestin alone or a progestin plus estrogen. However, TAP was allowed to add the following information to then current Lupron labeling:

> **"Changes in Bone Density:**
>
> A controlled study in endometriosis patients showed that vertebral bone density as measured by dual energy x-ray absorptiometry (DEXA) decreased by an average of 3.2% at six months compared with the pretreatment value. In this same study, LUPRON DEPOT 3.75 mg alone and LUPRON DEPOT 3.75 mg plus three different hormonal add-back regimens were compared for one year. All add-back groups demonstrated mean changes in bone mineral density of ≤ 1% from baseline and showed statistically significantly (P-value <0.001) less loss of bone density than the group treated with LUPRON DEPOT 3.75 mg alone, at all time points. Clinical studies suggest that the addition of hormonal replacement therapy (estrogen and/or progestin) to LUPRON is effective in reducing loss of bone mineral density which occurs with LUPRON, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis. The optimal drug/dose is not established."

DRUDP also requested that the Sponsor conduct a second study to confirm that add-back therapy reduced the degree of BMD loss resulting from 1 year of treatment with Lupron.

3.3.2 Subsequent Regulatory Interactions and Decisions

- TAP submitted a new clinical protocol (Study M97-777) to DRUDP in December 1997 to study the effects of 1 year of treatment with Lupron plus NETA (5 mg/day) on BMD and the signs and symptoms of endometriosis. The protocol was reviewed by DRUDP and a few suggestions, primarily statistical, were conveyed to the Sponsor. The Sponsor also was informed that a successful outcome, in terms of reducing or preventing bone loss, would be a change in BMD from baseline at 1 year of treatment of no greater than –2.2% (i.e., the lower bound of a 2-sided 95% CI of the difference from baseline could be no lower than -2.2%).
- The medical reviewer of the protocol did not comment upon the Sponsor's selection of 5 mg of NETA, without further supportive dose ranging data, as the only dose to be investigated.
- In July 2000, a teleconference was held with TAP to discuss the content of the revised efficacy supplement for NDA 20-011. Based on the information provided by TAP at that time, the Sponsor was told that they could proceed with submission of the efficacy supplement.
- In November 2000, TAP submitted efficacy supplements to NDA 20-011 (Lupron Depot 3.75 mg) and NDA 20-208 (Lupron Depot 3 Month 11.25 mg). The submission included the data from Study M92-878, the treatment phase of Study M97-777, proposed labeling, and literature references. Data from the 1-year posttreatment follow-up phase for Study M97-777 were not included. The objectives of the efficacy supplements were to make the following changes in the label for Lupron Depot 3.75 mg and Lupron Depot 3 Month 11.25 mg:

  1. To add information describing the beneficial effects of co-administration of 5 mg NETA with Lupron on reducing the hypoestrogenic adverse effects associated with Lupron treatment alone.
  2. To extend the allowable treatment period from 6 months to a maximum of 12 months if Lupron were co-administered with 5 mg NETA.
  3. To allow for retreatment if Lupron were co-administered with 5 mg NETA.

3.3.3 Regulatory and Clinical Background of Lupron Depot 3 Month 11.25 Mg

Both clinical studies submitted in support of the labeling changes requested in these applications were conducted with Lupron Depot 3.75 mg (LD) which is administered once monthly. No clinical data regarding co-treatment with Lupron Depot 11.25 mg (LD-3), which is administered once every 3 months, were submitted. The Sponsor stated that clinical findings obtained with Lupron Depot 3.75 mg also would be applicable to patients treated with Lupron Depot 11.25 mg plus NETA since the approval of the latter formulation in 1997 for the treatment of endometriosis was based on demonstrating pharmacodynamic "equivalence" to the monthly formulation. Pharmacodynamic equivalence of the 2 formulations was investigated in Study M94-139 in which 20 normal women received a single IM dose of Lupron 11.25 mg. Based on the serum concentrations of estradiol in these women, Lupron 11.25 mg was considered to be pharmacodynamically equivalent to the 1-month formulation and was approved for the treatment of endometriosis. At the time of approval, the Sponsor also was conducting a comparative clinical trial of Lupron 3.75 mg and Lupron 11.25 mg (Study M96-506) in women with endometriosis. Completion and timely submission of the data from Study M96-506 under a Phase IV commitment was a condition of approval for Lupron 11.25 mg under NDA 20-708.

Study M96-506 was a, 2 arm, open label study in which 41 women with endometriosis were randomly assigned to 6 months of treatment with either Lupron 3.75 mg (6 monthly injections) or Lupron 11.25 mg (two 3-month injections). The study included assessments of clinical efficacy (reduction in the painful symptoms of endometriosis), general safety, changes in bone mineral density (BMD), and pharmacokinetic/pharmacodynamic assessments (serum concentrations of leuprolide and estradiol). Based on his review of this study, the Medical Officer in DRUDP did not believe that there were any clinically significant differences between the 2 formulations in terms of efficacy or general safety. He also stated in his review that "there were no statistically significant differences in changes from baseline in estradiol levels between the Lupron 3.75 mg and Lupron 11.25 mg groups at any visit."

Bone mineral density of the lumbar spine (L1-L4) was to be measured at baseline, at the end of 6 months of treatment, and at 6-months posttreatment. The Medical Officer stated in his review that "there was a statistically significant mean percent change in BMD from baseline to the end of treatment noted for both the Lupron 3.75 mg and the Lupron 11.25 mg groups ... but there was not a statistically significant difference between the two treatment groups in the mean percent change in BMD from baseline values." The mean changes from baseline at the end of treatment (regardless of duration of treatment) according to the Medical Officer were –3.0% (LD group) and –2.8% (LD-3 group). In his review, the Medical Officer expressed some concern about the observed decreases in BMD in the Lupron 11.25 mg group because (1) BMD values had not returned to baseline values in many of the patients by the 6-month posttreatment assessment and (2) BMD values in 6 patients at the 6-month posttreatment assessment were numerically lower than those at the end of treatment. Five of these 6 patients had been treated with Lupron 11.25 mg.

Medical Officer's Comment

- *The magnitude of the BMD decreases from the end-of-treatment to 6-months posttreatment, however, did not exceed –1% in any of the patients, a change well within the error of the BMD measurements.*

The Sponsor's Interim and Final Reports for Study M96-506 included the BMD summary data listed in Table 4 below. In the Lupron 11.25 mg group, the mean percent decrease in BMD from baseline values was numerically less at the end-of-treatment and at 6-months posttreatment, but numerically greater at the final posttreatment assessment than in the Lupron 3.75 mg group.

Table 4 Mean Percent Changes in Bone Mineral Density from Baseline (Study M96-506)

Assessment Time	Lupron Depot (3.75 mg)			Lupron Depot (11.25 mg)	
	N	Mean % change		N	Mean % change
End of Treatment	18 [1]	-3.0%		19	-2.8%
6-Months Posttreatment	9	-1.8%		14	-1.5%
Any Time Posttreatment [2]	14	-1.6%		18	-2.5%

[1] Includes 2 patients treated for less than 3 months.

[2] Includes posttreatment BMD values obtained less than 6 months after completion of treatment.

Source: Final Study Reports for M96-506 (Treatment Phase and Posttreatment Phase Reports).

Medical Officer's Comments

- *Based on the data represented in Table 4, there is no suggestion that the decrease in BMD in patients treated with 2 doses of Lupron 11.25 mg (6 months of treatment) will be clinically significantly greater at the end of Treatment Month 6 or at 6-months posttreatment than that in patients receiving 6 monthly doses of Lupron 3.75 mg (the formulation used in the 2 clinical studies submitted in support of the efficacy supplements for NDA 20-011 and NDA 20-708).*
- *The numerically greater decrease in mean BMD in the Lupron 11.25 mg group at the "any time posttreatment" assessment is due to the inclusion of BMD values from 4 patients with end-of-treatment BMD decreases ranging from –2.3% to –7.3% whose posttreatment follow-up BMD assessments were obtained within 90 days of the end of treatment. Bone mineral density changes from baseline at the posttreatment follow-up visit in these 4 patients ranged from –2.2% to -9.5%. The period of time that had elapsed between the end-of-treatment and the posttreatment follow-up assessments in these patients was insufficient to permit maximal recovery of BMD.*
- *It has been shown in other studies with GnRH agonists that maximal BMD changes are often observed several months after the completion of treatment as the period of hypoestrogenemia may persist for several months after completion of the treatment period.*
- *Bone mineral density data submitted in the present application also indicate that recovery of BMD can continue through at least 1 year after completion of treatment with a GnRH agonist.*
- *In summary, the data submitted in support of the use of NETA to reduce Lupron-induced decreases in BMD (data obtained with the once monthly formulation) also should be applicable to patients treated with Lupron 11.25 administered once every 3 months for a period not to exceed 6 months (i.e. 2 doses) either as initial treatment or retreatment. This reviewer's recommendations concerning labeling changes therefore apply to both efficacy supplements submitted by the Sponsor.*

3.4 Other Relevant Information

3.4.1 Regulatory Status of Norethindrone Acetate (Aygestin®)

Norethindrone acetate (NETA) was approved by the FDA for marketing in 1982. It is available in 5 mg scored tablets. Present labeling states that Aygestin is indicated for the treatment of "secondary amenorrhea, endometriosis, and abnormal uterine bleeding due to hormonal imbalance in the absence

of organic pathology." For the treatment of endometriosis the following dosage regimen is recommended per labeling:

> "Initial daily dosage of 5 mg Aygestin for two weeks. Dosage should be increased by 2.5 mg per day every two weeks until 15 mg of Aygestin is reached. Therapy may be held at this level for six to nine months or until annoying breakthrough bleeding demands temporary termination."

Contraindications to the use of Aygestin include the following:

1. Use in the first four months of pregnancy (this appears as a boxed warning).
2. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a history of these conditions.
3. Markedly impaired liver function or liver disease.
4. Known or suspected carcinoma of the breast.
5. Undiagnosed vaginal bleeding.
6. Missed abortion.
7. As a diagnostic test for pregnancy.

The following warnings and precautions are included in present labeling:

1. Discontinue medication pending examination if there is a sudden partial or complete loss of vision or if there is sudden onset of proptosis, diplopia, or migraine.
2. Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Medical Officer's Comments

- *Migraine headaches were reported in 7.3 and 19.1 percent of patients treated with Lupron plus NETA in Studies M92-878 and M97-777, respectively. Depression was reported in 14.5 and 25 percent of patients treated with Lupron plus NETA in Studies M92-878 and M97-777, respectively.*

3.4.2 Foreign Marketing Status of Lupron

Lupron Depot 3.75 mg as monotherapy is presently approved in most major markets for 6 months of treatment for the management of endometriosis. The Sponsor was asked to provide a list of markets and the relevant labeling where (1) treatment with Lupron is approved for a duration of greater than 6 months and (2) retreatment is approved. The Sponsor replied as follows:

> "One year of treatment for endometriosis was not approved in any countries without add-back. Add-back was approved in the Philippines (March 29, 2001) and Ireland (September 2000)."

In response to the question about retreatment, the Sponsor referred to labeling from Japan and Italy that was included in the Submission of August 10, 2001.

Medical Officer's Comments

- *Review of the approved drug labels for Japan and Italy, however, did not identify any specific references to retreatment.*

4 CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS

4.1 Toxicology Review

No preclinical toxicology data were submitted with these efficacy supplements.

4.2 Clinical Pharmacology and Biopharmaceutics Review

No significant new clinical pharmacology data, other than that related to suppression of serum estradiol concentrations, were submitted. These data were reviewed both by Dr. J. Lau in his Biopharmaceutics Review and briefly in the Efficacy Section of this review (see Section 8.5.3).

4.3 Chemistry Review

No significant new chemistry data were submitted with these efficacy supplements.

5 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

5.1 Pharmacokinetics

No pharmacokinetic data were submitted with these applications.

5.2 Pharmacodynamics

The effect of treatment with Lupron alone (LD) and Lupron plus norethindrone acetate (LD/N) on serum estradiol concentrations was assessed in the clinical studies submitted in support of these applications. These data are summarized briefly in the Efficacy Section of this review (see Section 8.5.3) and more thoroughly in the Biopharmaceutical Review.

6 DESCRIPTION OF CLINICAL DATA AND SOURCES

6.1 Clinical Data Submitted in Support of Efficacy Supplements

6.1.1 Clinical Trials

The clinical program supporting these efficacy supplements consisted of 2 multicenter studies (Study M92-878 and Study M97-777) in which women with painful symptoms of endometriosis were treated with Lupron Depot 3.75 mg either alone or in combination with hormonal add-back therapy. Both studies were conducted in the United States. Across the two studies, a total of 337 female patients with a diagnosis of endometriosis, confirmed by laparoscopy or laparotomy, were enrolled. Of these patients, 242 were treated with either Lupron alone or Lupron plus norethindrone acetate (NETA), the treatment regimens under review in this application. The remaining 95 patients were treated with Lupron plus NETA plus conjugated estrogens.

6.1.2 Secondary Sources of Clinical Data

A peer-reviewed, published communication summarizing the results of Study M92-878 was provided in the application (Hornstein M and et.: Leuprolide Acetate Depot and Hormonal Add-Back Therapy in Endometriosis: a 12-month Study, in Obstetrics and Gynecology 1998; 9116-24). The Sponsor also submitted several additional published communications (both original research and review articles) concerning co-treatment of women with endometriosis using a GnRH analog and a progestin and/or an estrogen.

6.2 Overview of Clinical Studies Included in the NDA

6.2.1 Study Objectives

Two clinical studies were submitted in support of this application (see Table 5 for an overview of the studies). The objectives of these studies were to evaluate the efficacy and safety of Lupron Depot 3.75 mg in combination with hormone add-back therapy (either 5 mg NETA alone or NETA plus estrogen) administered for one year for the management of endometriosis. The studies were designed and conducted to support a change in the labeling for Lupron Depot 3.75 mg and Lupron Depot 11.25 mg, reflecting the benefit of co-treating with Lupron plus NETA to extend the approved treatment period for endometriosis for up to one year and to permit retreatment.

The primary safety objective was to determine the degree of preservation of bone mineral density. Additional safety parameters included evaluation of adverse events and clinical laboratory measurements, particularly changes in serum lipid levels. Efficacy outcome measurements were secondary endpoints, and focused on improvement in the patient's painful symptoms and signs of endometriosis.

6.2.2 Clinical Studies

Study M92-878. This was a double blind, randomized, parallel group, multicenter study. Twenty-six (26) investigative sites participated in the conduct of the study. The study was conducted from November 1993 until December 1997. The objective was to determine the safety and efficacy of 1 year of treatment of women with endometriosis with (1) Lupron 3.75 mg alone or (2) Lupron in combination with (a) 5 mg norethindrone acetate (NETA) or (b) norethindrone acetate plus 1 of 2 doses of estrogen. Two hundred one (201) patients were enrolled and randomly assigned to 1 of the 4 treatment arms. Patients were followed for up to 24 months after completion of the 1 year Treatment Period.

Study M97-777. This was an open-label, single-arm, multicenter study. Twenty-four (24) investigative sites participated in the conduct of the study. The Treatment Period of the study was from February 1998 until March 2000. The objectives were (1) to evaluate the safety and efficacy of Lupron Depot 3.75 mg in combination with 5 mg norethindrone acetate administered for one year for the management of endometriosis and (2) to increase the number of women who were studied with this treatment regimen. One hundred thirty six (136) women were enrolled. Patients were followed for up to 12 months after completion of the Treatment Period.

Table 5 Studies Supporting the Safety and Efficacy of Lupron 3.75 mg plus NETA

Study No. Study Title	Study Design	No. Sites Country	Number Of Patients and Treatment [2]			
			LD	LD+N	LD+N+ 0.625 CE	LD+N+ 1.25 CE
M92-878 Combination Lupron Depot – Hormonal Add-Back in the Management of Endometriosis	Double-blind, randomized, 4-arm, parallel-group, multicenter study with a 52-week Treatment Period and a 24-month Follow-up Period.	26 US	51	55	47	48
M97-777 Combination Lupron Depot and Aygestin® Add-Back in the Management of Endometriosis [1]	Open-label, single arm, multicenter study with a 52-week Treatment Period and a 12-month Follow-up Period.	24 US		136		

[1] Aygestin = norethindrone acetate.
[2] LD = Lupron Depot 3.75 mg; LD+N = LD plus 5 mg norethindrone acetate; (3) LD+N+0.625 CE = LD + 5 mg N plus 0.625 mg conjugated equine estrogens (CEE); LD+N+1.25 CE = LD + 5 mg N + 1.25 mg CEE.
Source: Tables 10.1b of Final Report for Study M92-878 and 3.1b of the ISS.

7 CLINICAL REVIEW METHODS

7.1 Materials Submitted by the Sponsor

Submissions to NDA 20-011(ES)

- Original efficacy supplement submitted on November 21, 2000. The supplement consisted of 26 paper volumes (narratives and primary statistical tables only) and data listings and case report forms (CRFs) in electronic format.
- First Safety and Efficacy Update submitted on March 21, 2001 (primarily an electronic submission).
- Second Safety and Efficacy Update submitted on June 20, 2001 (paper and electronic submission). This submission included all efficacy and safety data from the 1 year post treatment Follow-up phase of Study M97-777.
- Submission of August 10, 2001. This submission was a response by the Sponsor to questions from the Medical Officer submitted on July 26 and July 27, 2001.
- Submission of August 24, 2001. This submission was a response by the Sponsor to questions from the Medical Officer submitted on August 17, 2001.
- Submission of August 31, 2001. This submission was a response by the Sponsor to questions from the Medical Officer submitted on August 23, 2001.
- Submission of September 4, 2001. This submission was a response by the Sponsor to questions from the Medical Officer submitted on August 17, 2001 and August 30, 2001.
- Submission of September 12, 2001 containing requested serum prolactin levels in women with reported galactorrhea.

Submissions to NDA 20-708 (ES)

- No original data or information specific to NDA 20-708, other than background information and revised labeling, was submitted. The application otherwise consisted entirely of cross-references to the materials submitted in support in NDA 20-011/s021.

7.2 Materials Reviewed and Overview of Review Procedures

7.2.1 Materials Reviewed

- All paper volumes included in the submission of November 21, 2000 (other than Volume No. 4 [CMC information]) as well as electronic data listing for adverse events, bone mineral density, laboratory safety data, and reasons for premature terminations were reviewed.
- Selected electronic CRFs were reviewed for clarification of safety or efficacy issues.
- All narratives and primary Statistical Tables in the Submission of June 20, 2001 (Final Safety Update) as well as associated data listings for adverse events, bone mineral density, laboratory safety data, and reasons for premature terminations were reviewed.
- A limited review of the information submitted on March 21, 2001 was conducted since all materials in this submission were included in the submission of June 20, 2001.
- All information in the Sponsor's responses to requests for additional information submitted August 10, 2001, August 24, 2001, August 31, 2001, September 4, 2001, and September 12, 2001 was reviewed.
- Interim and Final Reports for Study M96-506 and Medical Officer's Review of these reports.
- Medical Officer's Review of Original NDA 20-708 (Lupron Depot 11.25 mg).
- Medical Officer's Reviews of NDA 20-011/s012 (request to change labeling for Lupron Depot to allow treatment for up to 1 year that was not accepted for filing) and NDA 20-011/s014 (request to add information about hormone add-back therapy to label).
- Minutes of regulatory meetings and telephone conferences with Sponsor that were contained in Division Files regarding hormone "add-back therapy" in women receiving Lupron for the treatment of endometriosis.
- Publications submitted by the Sponsor that were included in the Submission of November 21, 2000.
- Publications known to the reviewer based on ongoing review of the medical literature in the area of medical treatment of endometriosis and the effects of GnRH treatment for endometriosis on bone mineral density.

7.2.2 Safety Updates

The sponsor submitted interim and final Safety Updates on March 21, 2001 and June 20, 2001. The final update contained all safety data obtained during the 1 year posttreatment Follow-up Period for Study M97-777. Information contained in the final Safety Update is included in the body of this review in Sections 9.4.6 (serious adverse events), 9.6.4 (posttreatment recovery of BMD), and 9.9.3.3 (serum lipids in the posttreatment period). These data were considered in the Medical Officer's final recommendations regarding the safety and efficacy of the Sponsor's applications.

7.2.3 Overview of Review Procedures

All narrative material provided by the Sponsor and primary statistical tables were reviewed by the Medical Officer. In addition, the Medical Officer prepared listings for safety laboratory data, bone mineral density measurements, and adverse events based on electronic files provided by the Sponsor.

When additional information or clarification was required, electronic CRFs were reviewed. If additional information was still required, queries were submitted to the Sponsor.

The accuracy of the Sponsor's primary efficacy analyses (reduction in painful symptoms of endometriosis) and primary safety analyses (changes in bone mineral density) were reviewed and confirmed by Kate Meaker MS, FDA statistician. Ms. Meaker's review did not identify any issues that would invalidate the Sponsor's analyses.

7.3 Overview of Methods Used to Evaluate and Ensure Data Quality

DSI audits. The primary objective and endpoint of the studies, namely, change in bone mineral density, was monitored and reviewed by an independent organization ——— Consequently, it was decided that DSI audits of specific investigative sites would not be necessary for this efficacy supplement.

Financial disclosure statements. Information concerning financial conflicts of interest was reviewed by Ms. Jeanine Best, Regulatory Project Manager, DRUDP. Her conclusion was as follows: "Adequate documentation was submitted to comply with 21 CFR 54. While the Sponsor could have used other means to obtain documentation from non-compliant investigators, the rate of return is acceptable. There was no disclosure of financial interests that could bias the outcome of the trials." The Medical Officer concurs with Ms. Best's assessment that there were no financial disclosures that would suggest the overall outcomes of either Study M92-878 or M97-777 was biased.

Site monitoring. According to the Sponsor the investigative sites were visited by a TAP Pharmaceutical Products Inc. study monitor at the start of the study. All sites were initiated and monitored regularly by a CRO ———— [Study M97-777]). Selected sites also underwent external quality assurance audits.

Laboratory Assessments. Serum chemistry and hematology measurements were performed centrally at ———— for Study M92-878 and at ———— for Study M97-777. Serum estradiol levels for Study M97-777 were measured at ————

BMD measurements. According to the Sponsor, bone mineral density measurements were performed by ——— trained technicians utilizing DEXA technology and Quantitative Digital Radiography machines (QDR). All DEXA scans were reviewed by ——— (currently known as ————) prior to electronic transmission of data to the Sponsor.

Data entry. According to the Sponsor, data entry into the computer database utilized in the analyses for the Study Reports included in this submission was performed using a procedure of double-entry of case report form and hormone data. The bone mineral density data file received from ———— and the clinical laboratory data file received from ———— were electronically loaded into the database.

Medical Officer's Comments

- *The ———— utilized by the Sponsor are well known laboratories that are often used by pharmaceutical companies for laboratory safety or endocrine measurements.*
- *DEXA is the current standard methodology for measuring BMD. ——— is the manufacturer of the QDR imaging machines that were used to measure BMD. ——— QDR machines are widely used both in clinical practice and in clinical trials.*

8 INTEGRATED REVIEW OF EFFICACY (PRINCIPAL CLINICAL STUDIES)

8.1 Efficacy Assessments

Although the 2 clinical studies submitted in support of this application differed significantly in terms of overall designs, the efficacy and safety assessments and endpoints of the 2 studies were very similar. Consequently, the studies are presented and evaluated in an integrated review. Since the Sponsor is seeking a labeling change concerning only the co-administration of Lupron plus NETA, this review will not discuss the findings in the NETA plus estrogen treatment arms in Study M92-878.

8.1.1 Primary Efficacy Assessments and Endpoints

Clinical Assessment of Pain. The primary efficacy variables in each study were based on the Investigator's and/or patient's assessment of the severity of each of 5 symptoms or signs of endometriosis. The disease variables that were assessed were dysmenorrhea, pelvic pain, deep dyspareunia, pelvic tenderness, and pelvic induration. Dysmenorrhea, pelvic pain, and deep dyspareunia were rated by the study coordinator after questioning the patient. Pelvic tenderness and pelvic induration were assessed by the investigator by performing a pelvic examination. Each symptom or sign was rated at each visit during the Treatment Period and at each visit during the first year of follow-up based on the grading scales listed in Table 6. Each symptom or sign was assigned a numeric score, based on its severity, of either 1 (not present); 2 (mild); 3 (moderate); or 4 (severe) for the purpose of analyses. This numeric scores were referred to as the "clinical symptom severity scores."

Table 6 Grading of Symptoms and Signs of Endometriosis [1]

Symptom	Grade	Descriptor
Dysmenorrhea	Mild Moderate Severe	Some loss of work efficiency In bed part of day, occasional loss of work In bed 1 or more days – Incapacitation
Pelvic Pain	Mild Moderate Severe	Occasional pelvic discomfort Noticeable discomfort for most of cycle Requires strong analgesics [2] Persistent during cycle other than during menstruation
Deep Dyspareunia	Mild Moderate Severe	Tolerated discomfort Intercourse painful to the point of causing interdiction Avoids intercourse because of pain.
Pelvic Tenderness	Mild Moderate Severe	Minimal tenderness on palpation Extensive tenderness on palpation Unable to palpate because of tenderness
Pelvic Induration	Mild Moderate Severe	Uterus freely mobile, induration in the cul-de-sac Thickened and indurated adnexa and cul-de-sac, restricted uterine mobility Nodular adnexa and cul-de-sac, uterus frequently frozen

[1] Clinical grading scale of Biberoglu and Behrman. From Biberoglu KO and Behrman SJ, Dosage aspects of danazol therapy in endometriosis: Short-term and long-term effectiveness. Am J Obstet Gynecol, 139:645, 1981.
[2] Any narcotic analgesic.

The primary efficacy endpoints were the improvement from baseline for each of the 5 symptoms or signs of endometriosis. Clinical improvement (i.e., reduction in pain or induration) was expressed in terms of (1) the mean change in the symptom severity scores from baseline to the time of the assessment and (2) the proportion of patients who had complete resolution of the symptom or sign at the time of the assessment. (See Section 8.1.4 for an overview of the statistical analyses.)

8.1.2 Rationale for Efficacy Endpoints

The Biberoglu and Behrman grading scale is widely used to assess the severity of pain associated with endometriosis in clinical trials. This scale (or a modification) was used in the original NDAs for Lupron and the other GnRH analogs presently approved for the management of endometriosis.

Medical Officer's Comment

- *The primary efficacy assessments were referred to as the "clinical assessment of pain" by the Sponsor. This terminology (although not entirely accurate because the assessment of pelvic induration is not pain-based) will also be used in this review. A secondary efficacy assessment, based on the patient's completing a 10 point analogue pain scale, was referred to as the "patient assessment of pain" by the Sponsor (see Section 8.1.3 below).*

8.1.3 Secondary Efficacy Assessments and Endpoints

Secondary efficacy assessments and endpoints in both studies were:

- **Serum estradiol concentrations.** Serum estradiol concentrations were measured at 28 day intervals to determine if treatment with Study Drugs had suppressed estradiol to values similar to those observed in post menopausal women (i.e., ≤ 20 pg/mL).
- **Menstrual bleeding pattern.** Patients recorded in a daily diary whether they had menstrual bleeding. Based on these data, the proportion of women who had cessation of menstrual bleeding during treatment (i.e., developed amenorrhea) was determined for each treatment group.
- **Patient assessment of pain.** Patients assessed the severity of their symptoms of dysmenorrhea, pelvic pain, and deep dyspareunia on a 10 point analogue scales (0 = not present, 10 = intolerable). Based on these data, changes in the "patient's assessment of pain" during and following treatment with Study Drug was assessed.

8.1.4 Overview of Statistical Analyses for Primary Efficacy Endpoints

For each of the 5 clinical pain variables, the effects of treatment were analyzed and presented in several ways. These included the following:

1. The numerical change from the baseline value for the severity score at each on-treatment clinical visit.
2. The average numerical change from the baseline value, based on the severity scores at each clinical visit, during the treatment period.
3. The percentage of patients with the painful symptom or sign at baseline and at each clinical visit during treatment.

Further details concerning the primary and secondary efficacy analyses are presented in the separate statistical review prepared by the FDA statistician (Ms. K. Meaker).

Medical Officer's Comments

- *Based on the severity grading scale used by the Sponsor, the mean score for each of the 5 pain categories could range from 1 (all patients reported that the painful symptom was not present) to 4 (all patients reported severe or incapacitating pain for that symptom).*
- *According to the Sponsor, the planned sample size of 50 patients per treatment group would ensure 80% power to detect (at the 0.05 significance level, using two-sided tests and assuming a standard deviation of 0.9 severity levels) a difference in the reduction of pelvic pain between the Lupron-alone group and any add-back plus Lupron of 0.51 severity levels.*

8.2 Principal Clinical Trials to Support Efficacy Claim

8.2.1 Overall Study Design

Study M92-878. This was a double-blind, randomized, parallel group, multicenter study. Twenty-six (26) investigative sites participated in the conduct of the study. The study was conducted from November 1993 until December 1997. Two hundred one (201) patients with symptomatic endometriosis were enrolled and randomly assigned in a 1:1:1:1 ratio to treatment with 1 of 4 Study Drugs for up to 1 year. The 4 treatment arms were (1) Lupron 3.75 mg alone or (2) Lupron 3.75 mg in combination with either (a) 5 mg norethindrone acetate or (b) 5 mg norethindrone acetate plus 1 of 2 doses of estrogen. Patients were followed for up to 24 months after completion of the Treatment Period. The primary objective of this study was to investigate the efficacy and safety (e.g., preservation of BMD) of each of the 3 add-back regimens compared to treatment with Lupron alone.

Study M97-777. This was an open-label, single-arm, multicenter study. Twenty-four (24) investigative sites participated in the conduct of the study. The Treatment Period of the study was from February 1998 until March 2000. One hundred thirty six (136) women with symptomatic endometriosis were enrolled and treated for up to 1 year with Lupron 3.75 mg in combination with 5 mg norethindrone acetate. Patients were followed for up to 12 months after completion of the Treatment Period. The primary objective of this study was to increase the number of women who were treated with Lupron plus NETA to assess further the safety and efficacy of this treatment regimen.

8.2.2 Patients

Both Study M92-878 and Study M97-777 enrolled women with painful symptoms of endometriosis. The studies were designed to have similar patient selection criteria. Patients were considered for inclusion in the Studies if they met the following criteria.

8.2.2.1 Inclusion Criteria

1. Patients were females between 18 and 40 years of age, inclusive.
2. Patients had a history of regular menstrual periods (three or more consecutive days of bleeding requiring protection) with cycle lengths of 21–35 days for at least three months prior to study enrollment.
3. Patients had a diagnosis of endometriosis established and staged (American Fertility Society [AFS] classification) at the time of laparoscopy or laparotomy, which was performed within 12 months prior to study entry.

4. Patients had pain in at least one of the following categories:
   - moderate or severe pelvic pain (not related to menstruation), or
   - moderate or severe deep dyspareunia accompanied by non-menstrual pelvic pain, or
   - moderate or severe dysmenorrhea accompanied by non-menstrual pelvic pain.
5. If patients had surgical reduction of endometriosis performed and/or received medical therapy for endometriosis, patients must have experienced persistence or recurrence of the same symptoms (as were present prior to either treatment) 3 or more months after completion of the treatment, and prior to study enrollment.
6. Patients must have had a negative result for a pregnancy test performed within one week prior to study entry. Unless patients had been surgically sterilized, they were required to agree to begin use of at least one form of barrier contraception during the pre-study period and to continue use throughout the entire Treatment Period and until onset of the first post-treatment normal menstrual period.

Differences in inclusion criteria were minimal, with Study M97-777 specifying that pre-study laboratory values had to be within 15% above or below the normal range unless considered by the Investigator to be within the limits of clinical acceptability and approved by the Sponsor.

Patients were excluded from participation if they met any of the following criteria.

8.2.2.2 Exclusion Criteria

1. Patients with a hysterectomy and/or bilateral oophorectomy.
2. Patients whose surgical findings (i.e., evidence of endometriosis) were limited to adhesions or endometriomas.
3. Patients with prior therapy for endometriosis who had not met the minimum required washout period (6 months for GnRH analogs and 3 months for all other treatments). A minimum of 3 normal menses after cessation of prior therapy was required prior to the first dose of study drug.
4. Patients who were pregnant or had been pregnant within 3 months prior to the first dose of study drug.
5. Mothers who were still nursing.
6. Patients with undiagnosed abnormal genital/vaginal bleeding.
7. Patients with a history of thrombophlebitis or thromboembolic disorders.
8. Patients with cerebrovascular or coronary artery disease.
9. Patients with a calcium metabolism disorder, including urinary tract stone disease.
10. Patients with osteoporosis or other metabolic bone disease, or a bone mineral density of less than 80% of the age-matched control value.
11. Patients with a history of emotional disorder which precluded treatment with GnRH analogs.
12. Patients concurrently participating in another investigational study or who had received an investigational drug within one month prior to the first dose of study drug.
13. Patients with a history of hypersensitivity to previous hormonal therapy to which they might be exposed in the study.

Differences in exclusion criteria between the studies were limited to criteria about concurrent cancer. Study M92-878 excluded patients with known or suspected estrogen-dependent carcinomas (e.g., breast and endometrium). Study M97-777 had broader criteria, excluding patients with known or suspected cancer (other than basal or squamous cell cancer of the skin) that had not been in remission for five or more years prior to the first dose of study drug or who had received any systemic cancer chemotherapy within five years prior to the first dose of study drug.

Patients who had participated in Study M92-878 were precluded from participation in Study M97-777.

8.3 Study Drugs

8.3.1 Primary Study Drugs

Study M92-878. This was a 4 arm study in which patients were randomly assigned to 1 of 4 treatment groups.

- Group 1. Lupron Depot 3.75 mg (LD) alone
- Group 2. LD plus 5 mg norethindrone acetate (NETA, Aygestin®)
- Group 3. LD plus 5 mg NETA plus 0.625 mg conjugated equine estrogens (CEE, Premarin®)
- Group 4. LD plus 5 mg NETA plus 1.25 mg CEE.

Patients were randomly assigned in a 1:1:1:1 ratio to 1 of the 4 treatment groups.

Study M97-777. This was a single arm study in which all patients were treated with Lupron Depot 3.75 mg plus 5 mg NETA.

In both studies, patients were treated for up to 1 year (52 weeks).

8.3.2 Supplemental Study Drugs

In both studies, patients received supplemental calcium. In Study M92-878, calcium was provided as OsCal (500 mg elemental calcium [1250 mg calcium carbonate] per tablet). In Study M97-777, calcium was provided as OsCal 500 + vitamin D (500 mg elemental calcium and 125 mg vitamin D) per tablet. Patients were instructed to take 2 tablets daily.

8.3.3 Dosing Schedule

The initial Lupron Depot injection was to be administered between days 1-4 of the first menstrual cycle following the pre-study visit. Patients were to receive an IM dose of Lupron Depot 3.75 mg every 28 days. Patients who completed the treatment phase of the study received a total of thirteen injections of LD (52 weeks). Add-back therapy, or its corresponding placebo, was self-administered by the patients as one capsule daily. All patients were instructed to self-administer one calcium tablet twice each day. Patients were to continue taking calcium supplementation throughout the Treatment and Follow-up Periods.

8.3.4 Rationale for Dose Selection

In both studies the dose of Lupron Depot administered was the marketed and approved dose for the treatment of endometriosis.

Study M92-878. Norethindrone acetate 5 mg was selected based on previous research publications by academic investigators. These publications were based on limited exploratory studies that indicated that doses of norethindrone or norethindrone acetate in the range of 1.2 mg to 10 mg per day

could attenuated the decrease in bone mineral density that was associated with GnRH treatment of endometriosis. Conjugated equine estrogens 0.625 mg and CEE 1.25 mg were standard dosages used in estrogen replacement therapy at the time of study initiation for treatment of vasomotor symptoms and prevention of osteoporosis.

Study M97-777. Norethindrone acetate 5 mg was selected to confirm the results obtained in the NETA 5 mg treatment arm in Study M92-878.

Medical Officer's Comments

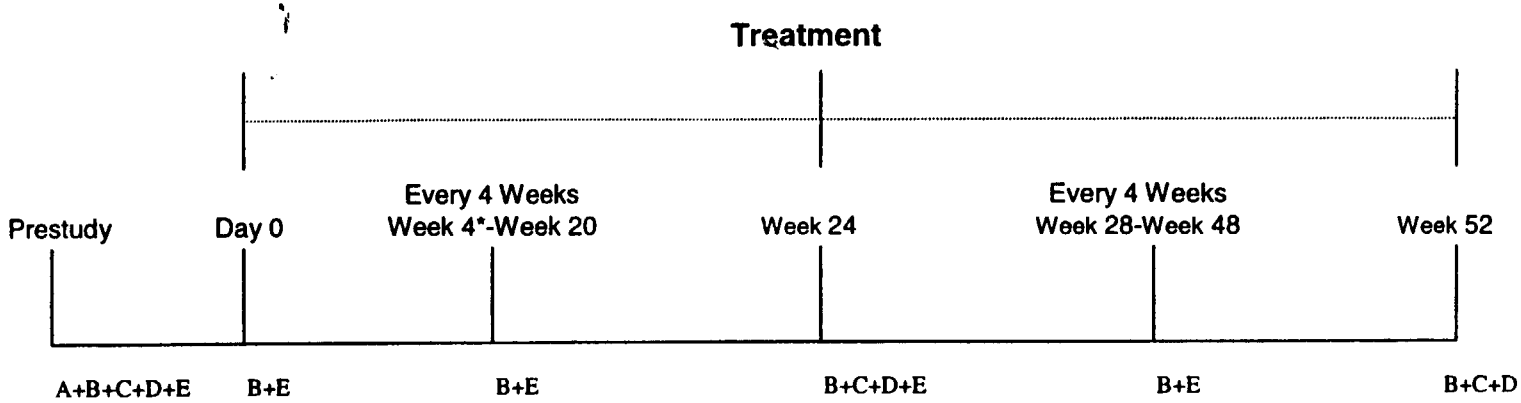
- *Studies cited by the Sponsor did not exclude the possibility that a daily dose of 2.5 mg of NETA would provide substantial protection against loss of BMD during treatment with Lupron with less adverse effects on lipid profiles (see Section 9.9.3).*
- *The Sponsor stated that the 2.5 mg dose was not investigated because a 2.5 mg dosage form of NETA is not presently marketed in the US. However, the 5 mg tablet that was investigated in the 2 clinical trials is scored, and thus a 2.5 mg dose could have been investigated.*

8.4 Study Conduct and Assessments

8.4.1 Schedule of Screening and Assessments

During the screening period, the patient's eligibility for the study was determined according to the inclusion and exclusion criteria described in Section 8.2.2). Laboratory procedures performed during screening included measurements of lumbar bone mineral density (BMD), serum chemistries, and hematology parameters. After the first injection of Study Drug on Day 0 (also referred to Day 1 in some data listings), patients were to return to the Study Center every 28 days for clinical and laboratory assessments and dosing with Lupron according to the schedule presented in Figure 1. After completion of the 1 year Treatment Period, subjects entered into a 12 month (Study M97-777) or 24 month (Study 92-878) posttreatment monitoring period in accordance with the schedule presented in Figure 2.

Figure 1 Overview of Study Procedures (Treatment Period)



Start Barrier Contraception, Prestudy

A. Surgical Diagnosis Of Endometriosis
Pregnancy Test
Endometriosis History
Fertility History
Medical History
Menstrual History
Informed Consent

B. Clinical Evaluation
-Symptoms
-Pelvic Examination
Patient Pain Evaluation
Blood Draw for E2
Menstrual Record/Daily Log
Adverse Events
Concomitant Medications
Vasomotor Symptoms **

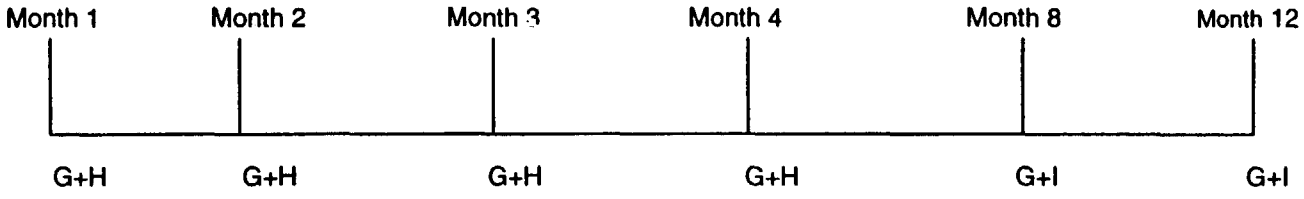
C. Bone Mineral Density

D. Physical Examination
Clinical Laboratory

E. Injection of Lupron

* At Week 4 only. Urine pregnancy test should be collected prior to dosing to confirm patient is not pregnant.
** Study M92-878 only.

Figure 2 Overview of Study Procedures (Post-Treatment Period)



G. Clinical Evaluation *
-Symptoms
-Pelvic Examination
Patient Pain Evaluation
Blood Draw For Lipid Profile **
Menstrual Record/Daily Log
Adverse Events
Concomitant Medications

H. Blood Draw For E2
(After First Cycle Only)

I. Bone Mineral Density *

* A small number of patients in M92-878 were also monitored at Months 16, 20, and 24 for serum lipids, adverse events, and bone mineral density.

** In Study M92-878, posttreatment lipids were not collected prior to posttreatment Month 8.

8.4.2 Efficacy Assessments

The times at which the primary efficacy assessment (clinical evaluation of pain) and the secondary efficacy assessments (serum estradiol levels, menstrual suppression, and patient evaluations of pain) were to be performed are listed in Table 7 below.

Table 7 Summary of Efficacy Evaluation Schedule

Efficacy Evaluation	Treatment Period	Follow-up Period
Clinical Evaluation of Pain	Day 0 and every 4 weeks through Week 52	Every month through Month 4, then at Months 8 and 12
Serum Estradiol Levels	Day 0 and every 4 weeks through Week 52	Follow-up data considered safety data and not included in efficacy
Menstrual Suppression	Day 0, daily recording in patient diaries and summarized at each 4-week visit	Follow-up data considered safety data and not included in efficacy
Patient Evaluation of Pain	Day 0 and every 4 weeks through Week 52	Every month through Month 4, then at Months 8 and 12

8.4.3 Pharmacokinetic Assessments

No pharmacokinetic data were collected in these clinical trials

8.5 Results

Since the Sponsor is not pursing a claim for treatment with Lupron plus NETA and estrogen, the remainder of this review will focus on the clinical findings from Lupron alone and the Lupron plus NETA treatment groups in Study M92-878 and the single treatment arm (Lupron plus NETA) in Study M97-777.

8.5.1 Study Population and Disposition of Subjects

8.5.1.1 Demographics and Baseline Disease Characteristics

A total of 201 and 136 patients were enrolled into Studies M92-878 and M97-777, respectively. Of these 337 patients, 242 patients were randomized to treatment with either Lupron alone (51 patients in study M92-878) or Lupron plus NETA (55 patients in Study M92-878 and 136 patients in Study M97-777) and 95 patients were randomized to treatment with Lupron + NETA plus conjugated estrogens. The baseline demographic characteristics of the 242 patients randomized to treatment with Lupron or Lupron plus NETA are summarized in Table 8. There were no statistically significant differences between the 3 treatment groups with respect to age, height, or weight. The ages of the patients across the 3 treatment groups ranged from 17 to 43 years. The mean ages of the patients in each treatment group were very similar, ranging from 28.4 to 28.8 years. Although the weight of individual patients ranged widely, from 88 to 286 pounds, the mean weights of the 3 treatment groups were similar and ranged from 145.4 to 150.9 pounds. The majority of patients in the 2 clinical trials were Caucasian (211 of 242 [87%]). There was, however, a greater percentage of Black patients in the LD group (18%) than in either of the Lupron + NETA groups (5% and 10% in Studies M92-878 and M97-777, respectively). The difference between the distribution of races in the LD group in Study M92-878 and the LD/N group in Study M97-777 was statistically significant.

Table 8 Baseline Demographic Characteristics

Parameter		Study M92-878 LD N=51		Study M92-878 LD/N N=55		Study M97-777 LD/N N=136	
Age (yrs)	Mean	28.4		28.7		28.8	
	Range						
Height (in)	Mean	65.0		64.7		64.6	
	Range						
Weight (lbs)	Mean	145.4		147.3		150.9	
	Range						
Race [•]		N	(%)	N	(%)	N	(%)
Caucasian		39	(76)	50	(91)	122	(90)
Black		9	(18)	3	(5)	13	(10)
Hispanic		3	(6)	2	(4)	0	(0)
Oriental		0	(0)	0	(0)	1	(1)

[•] Statistically significant difference between groups (LD/N [Study M97-777] vs. LD [Study M92-878]; $p < 0.05$).
Source: Text Table 3.2a, pg. 53 (ISS).

Time to diagnosis of endometriosis, prior pregnancies, prior treatment for endometriosis, prior GnRH analog usage, and mean baseline American Fertility Society (AFS) scores for the 242 patients who were randomized to the LD or LD/N treatment groups in both studies are presented in Table 9. There were no statistically significant differences between the treatment groups with respect to time since the diagnosis of endometriosis or the percentage of patients with a prior pregnancy. The mean endometrial implant scores for the LD and LD/N groups (6.4 and 6.0) were similar in Study M92-878 and numerically lower than that in Study M97-777. The mean total AFS score (the sum of the endometrial implant and adhesion scores) was lower in the LD/N group (9.8) in Study M92-878 than in either of the other 2 treatment groups (15.7 and 18.4, respectively). The differences, however, were not statistically significant. A higher percentage of patients in the LD treatment group (39%) had a history of prior GnRH use than in either of the LD/N treatment groups (18% and 21 %, respectively).

Medical Officer's Comment

- *AFS scores are based on the extent of endometriosis as assessed at the time of laparoscopy or laparotomy. There is not a strong correlation between the AFS score and the severity of the patient's painful symptoms of endometriosis (the endometriosis clinical pain scores) that were used to assess the efficacy of treatment with either LD or LD/N. Mean baseline endometriosis clinical pain scores (see Table 13 and Table 14) were similar in all treatment groups.*

Table 9 Disease and Fertility History

	Study M92-878				Study M97-777	
	LD-Only N=51		LD/N N=55		LD/N N=136	
Parameter	N	(%)	N	(%)	N	(%)
Time since diagnosis						
<1 yr	26	(51)	29	(53)	64	(47)
1 yr to <3 yrs	10	(20)	11	(20)	22	(16)
3 yrs to <5 yrs	7	(14)	5	(9)	21	(15)
≥5 yrs	8	(16)	10	(18)	29	(21)
Mean (yrs)	2.2		2.6		3.1	
Prior pregnancy	28	(55)	24	(44)	85	(63)
Prior treatment for endometriosis	42	(82)	49	(89)	114	(84)
Prior GnRH analog usage	20	(39)	10	(18) [1]	29	(21) [1]
Mean AFS scores [2]						
Endometriosis Implants	6.4		6.0		9.4	
Total Score [3]	15.7		9.8		18.4	

[1] Statistically significantly different from LD-Only group ($p < 0.05$).
[2] AFS = American Fertility Society.
[3] Total score based on the sum of the endometriosis implant and adhesion scores.
Source: Text Table 3.2b, pg. 47 (ISE).

8.5.1.2 Disposition of Subjects

In Study M92-878, 51 and 55 patients were randomized to the LD and LD/N treatment groups, respectively. Of these patients, 42 of 51 LD patients (82%) and 42 of 55 LD/N patients (76%) completed 6 months (24 weeks) of treatment (Table 10). Thirty-two (32) of the 51 LD patients (63%) and 31 of the 55 LD/N patients (56%) completed the full 1-year (52-week) treatment period. In Study M97-777, 136 patients were enrolled into the LD/N treatment group. Of these, 103 patients (76%) and 82 patients (60%) completed 6 months and 1 year of treatment. Thirty nine (39) of 51 LD patients (76%) and 39 of 55 LD/N patients (71%) in Study M92-878 entered the first year of the 2 year follow-up period. Fourteen (14) of the 39 LD patients (36%) and 10 of the 39 LD/N patients (26%) completed 1 year of follow-up. In Study M77-777, 119 of 136 patients (88%) entered the 1-year follow-up period. Sixty-four (64) of the 119 patients (54%) completed follow-up.

Table 10 Disposition of Patients

Outcome	Study M92-878				Study M97-777	
	LD-Only		LD/N		LD/N	
	N	(%)	N	(%)	N	(%)
Randomized	51		55		136	
Completed 24 Weeks Treatment	42	(82)[+]	42	(76)[+]	103	(76)[+]
Completed Full Treatment (52 Weeks)	32	(63)[+]	31	(56)[+]	82	(60)[+]
Entered Follow up Year 1[●]	39	(76)[+]	39	(71)[+]	119	(88)[+]
Completed Follow-up Year 1	14	(36)[$]	10	(26)[$]	64	(54)[$]
Entered Follow-up Year 2	18	(35)[+]	13	(24)[+]	NA	NA[4]
Completed Follow-up Year 2	4	(22)[$]	6	(46)[$]	NA	NA

[●] Patients did not have to complete the Treatment Period in order to enter the Follow-up Period
[+] Based on the percentage of patients randomized.
[$] Based on the percentage of patients who entered the follow up period.
[4] NA – Year 2 of the Follow-up Period is not applicable to Study M97-777.
Source: Text Table 3.1a, pg. 48 (ISS) and Statistical Report of FDA Statistician.

Medical Officer's Comment

- *The percentages of patients who completed treatment in each of the 3 treatment groups were very similar, suggesting that the addition of NETA neither increased nor decreased the overall acceptability of Lupron therapy.*

8.5.1.3 Number of Days in Treatment and Follow-up Periods

Thirty-two (32) of 51 patients (63%) enrolled into the LD treatment group and 31 of 55 patients (56%) enrolled into the LD/N treatment group received all 13 injections of Lupron in Study M92-878. In Study M97-777, 83 of 136 LD/N patients (61%) received all 13 injections. Table 11 summarizes the median and range for the number of days in the Treatment and Follow-up Periods. The median number of days of Lupron treatment for each group was as follows: LD-group in Study M92-878, 366 days; LD/N group in Study M92-878, 365 days, and LD/N group in Study M97-777, 364 days.

Table 11 Number of Days in Treatment and Follow-up Periods

Study Period		Study M92-878		Study M97-777
		LD-Only	LD/N	LD/N
Treatment Period	No. Patients	N=51	N=55	N=136
	Median (days)	366	365	364
	Range (days)	29–456	29–420	29–410
Follow-up Period	No. Patients	N=39	N=39	N=119
	Median	329	245	362
	Range	7–736	5–786	7-473

Source: Text Table 3.1a, pg. 49 (ISS).

Medical Officer's Comment

- *Based on the upper values for the ranges of the treatment periods, it appears that one or more patients in each treatment group may have received more than 13 doses of Lupron.*

8.5.2 Primary Efficacy Assessments and Endpoints

8.5.2.1 Treatment Period

The proportion (%) of patients with symptoms of endometriosis at baseline, Treatment Weeks 24 and 48, and the final treatment visit in each of the 3 treatment groups are listed in Table 12. The proportion (%) of patients with painful symptoms was numerically lower at each of these on-treatment assessment times compared to baseline.

Table 12 Proportion of Patients with Symptoms of Endometriosis at Baseline, Treatment Weeks 24 and 48, and Final Treatment Visit (Studies M92-878 and M97-777)

			Baseline		Week 24		Week 48		Final Visit	
Variable	Study	Group	N [1]	(%) [2]	N	(%)	N	(%)	N	(%)
Dysmenorrhea	M92-878	LD	51	(100)	37	(3)	31	(0)	50	(4)
		LD/N	55	(100)	38	(3)	30	(0)	54	(4)
	M97-777	LD/N	136	(99)	104	(5)	80	(0)	134	(9)
Pelvic Pain	M92-878	LD	51	(100)	37	(76)	31	(48)	50	(66)
		LD/N	55	(96)	38	(66)	30	(50)	54	(56)
	M97-777	LD/N	136	(99)	105	(69)	80	(55)	134	(63)
Deep Dyspareunia	M92-878	LD	42	(83)	29	(38)	24	(33)	46	(37)
		LD/N	43	(84)	27	(41)	19	(26)	42	(45)
	M97-777	LD/N	102	(91)	74	(61)	54	(54)	111	(53)
Pelvic Tenderness	M92-878	LD	51	(94)	35	(49)	30	(33)	50	(34)
		LD/N	54	(91)	37	(24)	30	(23)	53	(34)
	M97-777	LD/N	136	(99)	105	(39)	79	(32)	134	(39)
Pelvic Induration	M92-878	LD	51	(51)	35	(11)	30	(13)	50	(12)
		LD/N	54	(46)	37	(19)	30	(17)	53	(17)
	M97-777	LD/N	136	(75)	105	(29)	79	(22)	134	(21)

[1] Number of patients evaluated for the symptom/sign.
[2] Percent of patients evaluated who reported the symptom/sign.
Source: Statistical Tables 1.11 and 2.11 of ISE.

Medical Officer's Comments

- *There were no consistent numerical differences in the reduction in the proportion of patients with painful symptoms/signs of endometriosis between the LD and the LD/N treatment groups in Study M92-878.*
- *The percentages of patients with dyspareunia and pelvic induration were numerically larger in Study M97-777. These differences tended to persistent in the treatment period.*
- *In Table 12 and other efficacy tables in which represented data were obtained at monthly visits, the data presented or summarized in a specific column generally includes only data obtained within ±2 weeks of the column label. For bone mineral density and general laboratory safety data the intervals were generally much broader (see Section 9.9.1 and the footer to Table 37).*
- *In most efficacy tables, Week 48 data, instead of Week 52, data are shown. The decision to present Week 48 data was made because the number of patients evaluated at Week 52 for some assessments appeared to be considerably smaller than at Week 48.*

Mean clinical pain scores at baseline and the changes from baseline at Study Weeks 24 and 48 and the Final Treatment Visit for both treatment groups in Study M92-878 are listed in Table 13. Also

listed in Table 13 are the average changes in clinical pain scores throughout the treatment period. There were no statistically significant differences between the LD and LD/N treatment groups in mean pain scores at baseline with the exception of pelvic induration ($p = 0.050$), where the mean score for the LD group was greater than that of the LD/N group. Statistically significant decreases from baseline values (clinical improvement) for all parameters at each of the assessment times listed in Table 13 were observed in both the LD and LD/N treatment groups. The improvements were generally statistically significant by Week 4 and were maintained throughout the Treatment Period.

Table 13 Clinical Pain Scores: Changes from Baseline Values during Treatment with LD or LD/N (Study M92-878)

Variable	Group	N	Baseline Mean	Average Change*	Final Change*	Week 24		Week 48	
						N	Change*	N	Change*
Dysmenorrhea	LD	50	3.2	-1.9	-2.0	36	-2.0	28	-2.1
	LD/N	54	3.1	-1.9	-2.0	33	-2.1	26	-2.1
Pelvic Pain	LD	50	2.9	-0.9	-1.1	36	-1.1	28	-1.5
	LD/N	54	3.1	-0.8	-1.1	33	-1.1	26	-1.5
Deep Dyspareunia	LD	25	2.4	-0.6	-1.0	10	-1.0	8	-1.0
	LD/N	30	2.7	-0.8	-0.8	12	-0.8	7	-1.1
Pelvic Tenderness	LD	50	2.5	-0.8	-1.0	33	-0.9	27	-1.0
	LD/N	52	2.6	-0.8	-0.9	32	-1.2	26	-1.3
Pelvic Induration	LD	50	1.9+	-0.4	-0.4	33	-0.5	27	-0.5
	LD/N	52	1.6	-0.4	-0.4	32	-0.3	26	-0.4

* Statistically significantly different from LD/N group.
* Statistically significant within-group decreases from baseline for all symptoms/signs.
Source: Statistical Table 1.15 of ISE.

Medical Officer's Comment

- *In general, there were no significant differences between the two treatment groups in mean changes from baseline at any of the treatment visits for any of the pain scores. There also were no statistically significant differences between the two treatment groups in the changes from baseline averaged over the Treatment Period for any of the pain scores.*

Mean clinical pain scores at baseline and the changes from baseline at Study Weeks 24 and 48 and the Final Treatment Visit for patients in Study M97-777 are listed in Table 14. Statistically significant decreases from baseline (i.e., improvements) in all clinical pain scores generally occurred by Week 4 and were maintained throughout the Treatment Period. The mean changes from baseline averaged over the Treatment Period also were statistically significant for all of the clinical pain parameters.

APPEARS THIS WAY
ON ORIGINAL

Table 14 Clinical Pain Scores: Changes from Baseline Values during Treatment with LD/N (Study M97-777)

Variable	Group	N	Baseline Mean	Average Change*	Final Change*	Week 24		Week 48	
						N	Change*	N	Change*
Dysmenorrhea	LD/N	134	3.3	-2.0	-2.1	104	-2.2	80	-2.2
Pelvic Pain	LD/N	134	3.2	-1.1	-1.2	105	-1.2	80	-1.5
Deep Dyspareunia	LD/N	94	2.7	-0.9	-1.0	68	-0.9	48	-1.0
Pelvic Tenderness	LD/N	134	2.9	-1.2	-1.4	105	-1.5	79	-1.5
Pelvic Induration	LD/N	134	2.2	-0.8	-0.9	105	-0.8	79	-0.9

* Statistically significant within-group decreases from baseline for all symptoms/signs.
Source: Statistical Table 2.15 of ISE.

Medical Officer's Comments

- *Comparison of the findings in Study M97-777 to those in M92-878 must be interpreted with caution, particularly since M97-777 was an open label study and efficacy assessments in both were subjective. Based on the data represented in Table 13 and Table 14, however, there are no findings that suggest that treatment with LD/N in Study M97-777 was less effective than treatment with LD alone in Study M92-878.*
- *At the request of the Medical Officer, the FDA statistician summarized the efficacy results for Study M92-878 in terms of the percent of subjects who had clinical improvement at their final Treatment Visit (Table 15). The between-group differences and the 2-sided 95% confidence intervals (CIs) for the differences are also listed. The differences between the LD and LD/N treatment groups (i.e., LD-LD/N) were relatively small and ranged from –4% to +9%. However, the 95% CIs were wide due to the relatively small sample size.*
- *The outcome of the analysis summarized in Table 15 is consistent with the Sponsor's efficacy analyses in that it did not show a difference in the efficacy of LD/N compared to that of LD alone.*

Table 15 Percent of Patients with Symptom at Baseline Who Improved at their Final Treatment Visit Based on Clinical Pain Scores (Study M92-878)

	LD Group			LD/N Group			Between Group Comparison**	
Primary Efficacy Variables	N [1]	# improved/ # with symptom at baseline	% Improved	N [1]	# improved/ # with symptoms at baseline	% Improved	Difference (LD – LD/N)	95% 2-sided CI on Difference
Dysmenorrhea	50	48/50	96%	54	54/54	100%	-4%	(-9%, 1%)
Pelvic Pain	50	33/50	66%	54	38/52	73%	-7%	(-25%, 11%)
Dyspareunia	40	24/34	71%	42	25/35	71%	0%	(-22%, 21%)
Tenderness	50	35/47	75%	52	40/48	83%	-8%	(-25%, 8%)
Pelvic Induration	50	22/25	88%	52	19/24	79%	+9%	(-12%, 30%)

[1] Number of patients assessed for the efficacy variable at baseline.
Source: Table 6 of FDA Statistical Review.

8.5.2.2 Post Treatment Period

Efficacy assessments and endpoints in the posttreatment Follow-up Period included the time (i.e., number of months) until the patient's painful symptoms/signs of endometriosis had returned to baseline severity. Separate analyses were performed based on (1) all patients who were treated with each Study Drug (ITT population) and (2) only those patients considered to have successfully completed the Treatment Period (i.e., those who received all 13 injections of Lupron). Changes from baseline clinical pain scores at follow-up visits, another assessment of the persistence of therapeutic benefit, also were calculated and summarized by the Sponsor. These latter analyses included only data from patients who had successfully completed the Treatment Period.

Table 16 lists the mean and median post treatment times until each of the symptoms/signs of endometriosis had returned to baseline severity (duration of therapeutic improvement measured in months). Among all patients in Study M92-878, mean posttreatment improvement times ranged from 5.4 months (pelvic tenderness, LD group) to 9.2 months (pelvic induration, LD group). Among successful completers in Study M92-878, mean posttreatment improvement times ranged from 6.8 months (dysmenorrhea, LD/N group) to 13.0 months (pelvic induration, LD group). The durations of therapeutic improvement in the LD/N patients in Study M97-777 were similar to those in Study M92-878.

Table 16 Time (Months) to Return to Baseline Pain Severity - Clinical Pain Evaluations

Variable	Study	Treatment Group	All Patients			Successful Completers		
			N	Mean	Median	N	Mean	Median
Dysmenorrhea	M92-878	LD	50	7.1	4.0	31	8.6	8.0
		LD/N	54	6.4	4.0	31	6.8	4.0
	M97-777[1]	LD/N	133	7.5	4.0	88	8.9	8.0
Pelvic Pain	M92-878	LD	50	6.1	3.0	23	9.5	8.0
		LD/N	52	7.0	8.0	27	10.0	12.0
	M97-777	LD/N	133	7.3	4.0	77	9.8	12.0
Deep Dyspareunia	M92-878	LD	34	6.4	1.0	15	10.5	12.0
		LD/N	36	6.0	2.0	16	9.9	12.0
	M97-777	LD/N	87	8.4	12.0	47	12.6	16.0[1]
Pelvic Tenderness	M92-878	LD	47	5.4	2.0	23	8.7	8.0
		LD/N	48	7.7	8.0	27	9.3	12.0
	M97-777	LD/N	133	8.8	8.0	85	10.9	16.0[1]
Pelvic Induration	M92-878	LD	27	9.2	12.0	15	13.0	16.0
		LD/N	26	6.9	8.0	13	10.0	8.0
	M97-777	LD/N	101	9.8	16.0[1]	60	12.6	16.0[1]

[1] Patients censored at 12 months (follow-up period was 12 months in Study M97-777) were assigned a value of 16 months for calculation of mean and median values.

Source: Statistical Tables 1.17 and 1.18 and Appendices A.1 and A.2 for Study M92-878.
Source: Statistical Tables 14.2__1.1.1 and 14.2__1.1.2 and Appendices 16.2__6.1.1 and 16.2__6.1.2.1 for Study M97-777.

Medical Officer's Comment

There were no consistent differences in the mean durations of therapeutic improvement between the LD and LD/N treatment groups among either all patients or successful completers in Study M92-878.

Table 17 lists the mean changes from baseline at Post Treatment Month 12 for each of the symptoms/signs of endometriosis assessed by 4-point severity scores in the ITT population. In Study M92-878, all categories were statistically different from baseline at Month 12 and the changes were all in the direction of clinical improvement (i.e., the changes in the severity scores were negative).

The mean changes in severity scores at post treatment Month 12 (improvement from baseline) ranged from –0.6 (dysmenorrhea in the LD group) to –1.3 (pelvic tenderness in the LD/N group).

The mean changes in the severity of signs/symptoms of endometriosis at post treatment Month 12 in the LD/N patients in Study M97-777 were similar to those in Study M92-878.

Table 17 Mean Changes in Clinical Pain – Baseline versus Month 12 of Follow-up

Variable	Study	Treatment Group	Intent-to-Treat Population		
			N	Baseline Mean	Month 12 Mean Change
Dysmenorrhea	M92-878	LD	29	3.1	-0.6*
		LD/N	29	3.0	-0.7*
	M97-777	LD/N	82	3.2	-1.0*
Pelvic Pain	M92-878	LD	22	3.2	-1.2*
		LD/N	26	3.3	-1.0*
	M97-777	LD/N	72	3.3	-1.3*
Deep Dyspareunia	M92-878	LD	15	2.7	-1.2*
		LD/N	15	2.7	-0.9*
	M97-777	LD/N	42	3.0	-1.2*
Pelvic Tenderness	M92-878	LD	22	2.6	-1.0*
		LD/N	25	2.8	-1.3*
	M97-777	LD/N	78	2.9	-1.4*
Pelvic Induration	M92-878	LD	14	2.4	-1.1*
		LD/N	12	2.3	-0.7*
	M97-777	LD/N	55	2.6	-1.3*

* Statistically significant within-group decrease from baseline
Source: Statistical Tables 1.19, 1.20 for Study M92-878 and Statistical Tables 14.2__1.2.1 and 14.2__1.3.1 and Appendices 16.2__6.1.1 and 16.2__6.1.2.1 for Study M97-777.

Medical Officer's Comment

- *There were no consistent differences in the mean changes (degree of therapeutic improvement) between the LD and LD/N treatment groups in Study M92-878 at posttreatment Month 12. The decreases at Month 12 tended to be numerically greater in Study M97-777.*

8.5.2.3 Patients Previously Treated with a GnRH Analog for Endometriosis

The original submission did not specifically assess the clinical response to treatment with LD or LD/N in patients previous treated with a GnRH analog. Since the requested labeling change included removing the restriction against retreatment, the Sponsor was requested to provide a subset analysis comparing clinical responses in patients previously treated with a GnRH analog to those in patients not previously treated. The analysis was limited to patients treated with LD/N in Studies M92-878 and M97-777 because retreatment with LD alone is not under consideration. Forty (40) patients had previously been treated with a GnRH analog (10 in Study M92-878 and 30 in M97-777). Among these patients, the mean (SD) and median duration of prior GnRH treatment was 178.0 (133.12) and 151.0 days (range: 1-667 days).

The proportion (%) of patients with symptoms of endometriosis at baseline, Treatment Weeks 24 and 48, and the Final Treatment Visit in this subset analysis are listed in Table 18. The proportion of patients with each of the symptoms/signs of endometriosis at baseline was similar in the 2 subgroups. The proportion (%) of patients with symptoms was numerically lower at each of the on-treatment assessment times in both subgroups.

Table 18 Proportion (%) of Patients with Symptoms of Endometriosis after Treatment with LD/N (Patients with or without Prior GnRH Treatment)

		Baseline*		Week 24*		Week 48*		Final Visit*	
Variable	Group	N	(%)	N	(%)	N	(%)	N	(%)
Dysmenorrhea	Prior GnRH [1]	40	(100)	28	(0)	26	(0)	39	(3)
	No GnRH [2]	151	(99)	114	(5)	84	(0)	149	(9)
Pelvic Pain	Prior GnRH	40	(98)	28	(71)	26	(65)	39	(69)
	No GnRH	151	(99)	115	(67)	84	(60)	149	(59)
Deep Dyspareunia	Prior GnRH	28	(86)	17	(53)	13	(54)	26	(50)
	No GnRH	117	(90)	84	(56)	60	(45)	127	(51)
Pelvic Tenderness	Prior GnRH	40	(93)	27	(44)	26	(27)	38	(34)
	No GnRH	150	(98)	115	(33)	83	(30)	149	(38)
Pelvic Induration	Prior GnRH	40	(65)	27	(26)	26	(15)	38	(16)
	No GnRH	150	(67)	115	(26)	83	(22)	149	(21)

* Combined data from LD/N treatment groups in Studies M92-878 and M97-777.
[1] Prior GnRH = Patients previously treated with a GnRH analog for endometriosis.
[2] No GnRH = Patients not previously treated with a GnRH analog for endometriosis.
Source: Statistical Table 4.2.1.1, Submission of August 10, 2001.

Medical Officer's Comment

- *There were no consistent numerical differences in the proportion of patients with painful symptoms of endometriosis during treatment with Lupron plus NETA across the prior-GnRH treatment group and the no-prior-GnRH treatment group.*

Mean clinical pain scores at baseline and the changes from baseline at Study Weeks 24 and 48 and the Final Treatment Visit for both subgroups are listed in Table 19. Also listed in Table 19 are average changes in clinical pain scores throughout the treatment period. There were no significant differences between the 2 groups in mean pain scores at baseline for any of the clinical assessments. Statistically significant decreases from baseline values (clinical improvement) were observed in both groups of patients for all parameters at each of the assessment times listed in Table 19.

Table 19 Clinical Pain Severity Scores: Changes from Baseline Values during Treatment with LD/N (Patients with or without Prior GnRH Treatment)

			Baseline	Average	Final	Week 24		Week 48	
Variable	Group [1]	N	Mean	Change*	Change*	N	Change*	N	Change*
Dysmenorrhea	Prior GnRH [2]	39	3.1	-2.1	-2.2	28	-2.2	26	-2.2
	No GnRH [3]	149	3.2	-2.0	-2.1	114	-2.1	84	-2.2
Pelvic Pain	Prior GnRH	39	3.0	-1.0	-1.2	28	-1.2	26	-1.3
	No GnRH	149	3.2	-1.1	-1.2	115	-1.2	84	-1.5
Deep Dyspareunia	Prior GnRH	24	2.5	-0.9	-0.9	16	-0.9	12	-1.1
	No GnRH	112	2.7	-0.8	-0.9	79	-0.9	55	-1.0
Pelvic Tenderness	Prior GnRH	38	2.8	-1.1	-1.4	27	-1.3	26	-1.5
	No GnRH	148	2.8	-1.1	-1.3	115	-1.4	83	-1.5
Pelvic Induration	Prior GnRH	38	2.0	-0.6	-0.8	27	-0.7	26	-0.8
	No GnRH	148	2.0	-0.6	-0.8	115	-0.7	83	-0.7

[1] Data are combined from LD/N treatment groups in Studies M92-878 and M97-777
[2] Prior GnRH = Patients previously treated with a GnRH analog for endometriosis.
[3] No GnRH = Patients not previously treated with a GnRH analog for endometriosis.
* Statistically significant decreases from baseline for all variables.
Source: Statistical Table 4.2.1.2, Submission of August 10, 2001.

Medical Officer's Comments

- *There were no significant numerical differences between the two groups in terms of mean changes from baseline (improvement in symptoms) at Treatment Weeks 24 or 48, at the Final Treatment Visit, or in the average change from baseline for any of the clinical pain scores.*
- *An analysis by the Sponsor (ANOVA) did not show any consistent statistical differences between the clinical responses of the 2 subsets of patients. The small sample size, however, limits the value of the analysis because the statistical power to show a difference was low. However, the numerical data by themselves suggest that retreatment is as effective as primary treatment in relieving painful symptoms of endometriosis in that there were no trends across the 5 assessments of pain in favor of the patients who had not been treated previously with a GnRH analog.*

8.5.3 Secondary Efficacy Assessments

8.5.3.1 Reduction in Serum Estradiol Concentrations

During the treatment period, serum estradiol levels were determined at each protocol scheduled visit. In Study M92-878, the mean serum estradiol levels at baseline were 58.1 pg/mL and 50.5 pg/mL in the LD and LD/N groups, respectively (see Table 20). Statistically significant within-group mean decreases from baseline were noted for both groups at each visit during the Treatment Period. The mean serum estradiol level averaged over the Treatment Period was within the menopausal range (≤ 20 pg/mL) for both treatment groups: 14.5 pg/mL for the LD group and 8.6 pg/mL for LD/N group. In Study M97-777, the mean serum estradiol level for the LD/N group was 48.4 pg/mL at baseline and 8.4 pg/mL averaged over the treatment period.

Table 20 Serum Estradiol Concentrations at Baseline and during the Treatment Period

Treatment Group	Study	Number Patients	Estradiol (pg/mL)	
			Baseline	Treatment [1]
LD	M92-878	45	58.1	14.5
LD/N	M92-878	45	50.5	8.6
LD/N	M97-777	133	48.4	8.4

[1] Average estradiol concentration during the treatment period
Source: Statistical Tables 1.33 and 2.23 of ISE.

Medical Officer's Comment

- *Treatment with LD/N suppressed total serum estradiol concentrations to a statistically significant greater degree than LD alone. In both studies the Sponsor reported only total serum estradiol levels and did not measure serum levels of sex hormone binding globulin (SHBG) or free (biologically active) estradiol. Norethindrone acetate and other androgenic progestins are known to reduce serum concentrations of SHBG. Since approximately 50% of estradiol in serum is bound to SHBG and is therefore not biologically active, it is not known if biologically active levels of estradiol differed in the LD-treated and LD/N-treated patients.*

8.5.3.2 Suppression of Menses

Menstrual bleeding during the prior 28-day interval was summarized at each clinical visit during the treatment period based on the patient's daily diary. Menses was defined as bleeding for 3 or more consecutive days requiring the use of sanitary products. Suppression of menses was defined to be no menses for at least 60 consecutive days during treatment, regardless of whether any bleeding occurred thereafter. Time to suppression was defined as the number of days from the start of treatment to the first day of the last menstrual cycle prior to suppression. Patients who had no bleeding for at least 60 days after the start of study medication were defined as having zero days to suppression. A

summary of menstrual bleeding data for patients who were in the Treatment Period for at least 60 days is presented in Table 21. The percentages of patients who ceased to have menstrual bleeding and who experienced no further menstrual bleeding through the end of treatment were 87% and 84% in the LD and LD/N groups, respectively, in Study M92-878 and 73% in the LD/N group in Study M97-777.

Table 21 Menses Suppression during the Treatment Period

	Study M92-878		Study M97-777
Parameter	LD	LD/N	LD/N
Percent of Patients with Suppression N (%)	47/47 (100)	50/50 (100)	124/127 (98)
Time to Suppression (Days)			
Median	0	0	0
Range	0–146	0–73	0–115
Suppression Maintained to End of Treatment N (%)	41/47 (87)	42/50 (84)	90/124 (73)

Reference: Text Table 3.8a, pg. 78 of ISE

Medical Officer's Comments

- *The Sponsor's definitions for both "suppression of menses" and "maintenance of suppression" were not very stringent. A patient was required to have menstrual bleeding for 3 or more consecutive days before being classified as a failure in terms of suppression of menses.*
- *A third secondary efficacy evaluation was the "patient assessment of pain." Data related to this assessment (in contrast to the primary efficacy assessment of "clinical assessment of pain") were not reviewed by the Medical Officer. The sponsor stated that the relative efficacy of treatment with LD or LD/N based on this secondary assessment was similar to that reported for the primary efficacy assessment.*

8.6 Statistician's Assessment of Efficacy (Protocol-Defined Primary Endpoint)

The FDA Statistician (Ms. K. Meaker) reviewed and confirmed the Sponsor's primary efficacy and safety analyses. Her review did not raise any serious concerns regarding the Sponsor's analyses. Many of the limitations identified by the FDA Statistician regarding the Sponsor's interpretation of these analyses also were noted by the Medical Reviewer and have been incorporated in the Medical Officer's Comments throughout this review.

8.7 Medical Officer's Overall Assessment of Demonstrated Efficacy

8.7.1 Achievement of Protocol-Defined Primary Efficacy Endpoints

Reduction in Painful Symptoms and Signs of Endometriosis.

The primary objective of these supplemental NDAs was a safety endpoint, namely, to demonstrate that treatment with Lupron plus NETA significantly reduced the decrease in bone mineral density that is observed following treatment with Lupron alone. Study M92-878 was a well-designed, randomized, controlled clinical trial, but it was not powered or intended to show statistical equivalence or non-inferiority of Lupron plus NETA compared to Lupron alone in terms of reduction of the symptoms and signs of endometriosis. The planned sample size of 50 patients per treatment group, according to the Sponsor, would provide 80% power to detect a difference between the treatment groups if the true mean of the difference in severity score were at least 0.51. Since the mean decreases from baseline for the clinical pain severity scores (other than dysmenorrhea) did not

exceed 1.5 pain units, the absence of statistical differences should not be interpreted as demonstrating statistical non-inferiority.

Although the small sample size of Study M92-878 and the unblinded, noncomparative design of Study M97-777 limited the statistical assessment of the comparative efficacy of the 2 treatments, the responses to treatment were similar, based on (1) the numerical changes in the 5 clinical pain severity scores and (2) the changes in the proportion of patients with symptoms and signs of endometriosis after 6 and 12 months of treatment. A supplemental analysis requested by the Medical Reviewer of the efficacy data from Study M92-878 supported the Sponsor's claim. In this analysis, the differences between the 2 treatment groups in terms of the percentages of patients who had clinical improvement at their final Treatment Visit was small and ranged [redacted] However, the 95% CIs were wide due to the relatively small sample size.

The original submission did not specifically assess the clinical response to treatment with LD or LD/N in patients previous treated with a GnRH analog. Since the requested labeling change included removing the restriction against retreatment, the Sponsor was requested to provide a subset analysis comparing clinical responses in patients previously treated with a GnRH analog to those in patients not previously treated. The analysis was limited to patients treated with LD/N in Studies M92-878 and M97-777 because retreatment with LD alone is not under consideration. Forty (40) patients had previously been treated with a GnRH analog (10 in Study M92-878 and 30 in M97-777). The responses to treatment in the two groups were similar, based on (1) the mean changes from baseline (improvement in symptoms) and (2) the decrease in the proportion of patients with painful symptoms of endometriosis.

8.7.2 Support of Label Efficacy Claim

Based on the findings in Studies M92-878 and M97-777, revised labeling for Lupron Depot can include a statement that co-treatment with 5 mg norethindrone acetate did not appear to reduce the efficacy of Lupron as assessed by the modified grading system of [redacted]

APPEARS THIS WAY
ON ORIGINAL

9 INTEGRATED REVIEW OF SAFETY

9.1 Extent of Exposure to Study Drugs

In Study M92-878, 32 of 51 patients (63%) randomized into the LD-treatment group and 31 of 55 patients (56%) randomized into the LD/N treatment group received all 13 injections. In Study M97-777, 82 of 136 (60%) patients received all 13 injections. The extent of exposure to Lupron, which was comparable for each treatment group, is presented in Table 22.

Table 22 Extent of Lupron Exposure (% of Patients)

Number of Days	Study M92-878 LD (N= 51)	Study M92-878 LD/N (N =55)	Study M97-777 LD/N (N = 136)
>29	96	98	97
>59	92	91	93
>89	86	84	89
>119	86	82	83
>149	84	76	81
>179	78	75	75
>209	78	71	71
>239	73	67	69
>269	71	62	67
>299	65	60	64
>329	65	56	62
>359	63	56	60

Source: Text Table 3.3a of ISS.

Medical Officer's Comment

- *Both Lupron Depot and Aygestin (NETA) are approved therapies for endometriosis with well known safety profiles. The number of patients treated with Lupron plus NETA and the duration of treatment in Studies M92-878 and M97-777 were sufficient to assess the safety of the combination therapy in the intended population.*

Compliance with daily oral dosing was determined by the study coordinators at each visit via a count of capsules (Study M92-878) or tablets (Study M97-777) from returned bottles. A patient was deemed compliant at a particular study visit if she took 80% to 120%, inclusive, of the prescribed capsules or tablets during the four weeks between visits. The percent of compliant visits for norethindrone acetate 5 mg (Aygestin®) or placebo is presented in Table 23. Patients were assessed as being compliant with NETA dosing 93% (Study M92-878) and 94% (Study M97-777) of the time in the month preceding a clinical visit.

Table 23 Norethindrone Acetate 5 mg (Aygestin®) Compliance

	Study M92-878				Study M97-777	
	LD*		LD/N		LD/N	
Parameter	N	(%)	N	(%)	N	(%)
Compliant Visits	476/520	(92)	499/534	(93)	1293/1374	(94)

*LD group received placebo capsules.
Source: Text Table 3.3d of ISS.

9.2 Protocol Defined Safety Assessments in the Primary Safety Study

9.2.1 Overview of Safety Evaluations

Safety assessments in both studies included collection of adverse events, bone mineral density measurements, general clinical laboratory evaluations, measurements of serum lipids, recording of vital signs and body weight, physical examinations, recording of concomitant medications, and endometrial biopsies (if clinically indicated). Figure 1and Figure 2 (pages 30 and 31) and Table 24 below present overviews of the schedule of safety evaluations that were performed.

Table 24 Summary of Schedule of Safety Evaluations

Safety Evaluation	Prestudy and Treatment Period	Follow-up Period
Adverse Events	Prestudy, Day 0, and every 4 weeks through Week 52	Every month through Month 4, then every 4 months through Month 12
Vasomotor Symptoms [1]	Daily recording in patient diaries with data collection at Day 0 and every 4 weeks through Week 52	Daily recording in patient diaries with data collection every month through Month 4, then Months 8 and 12
Bone Mineral Density	Prestudy, Week 24, and Week 52	Month 8 and 12 [2]
Clinical Laboratory Evaluations	Prestudy, Week 24, and Week 52. Urine pregnancy tests were performed prestudy (within 1 week prior to dosing) and prior to dosing at Week 4.	Lipid profiles only. Study M92-878: every 4 months from Month 8 through Month 24. Study M97-777: every month through Month 4, then every 4 months through Month 12.
Vital Signs and Body Weight	Prestudy, Week 24, and Week 52	Not required per protocol
Physical Examination	Prestudy, Week 24, and Week 52	Not required per protocol
Concomitant Medications	Prestudy, Day 0, and every 4 weeks through Week 52	Every month through Month 4, then every 4 months through Month 12
Endometrial Biopsy	Prestudy (M92-878 only) and only if clinically indicated thereafter (M92-878 and M97-777)	Not required per protocol
Serum Estradiol Levels	Treatment Period data considered efficacy data	At the initial visit after resumption of menses
Menses Resumption	<Not applicable>	Daily recording in patient diaries; data collected through the first post-treatment menstrual cycle

[1] Vasomotor symptoms were assessed in Study M92-878 only.
[2] Study M92-878 allowed for additional assessments at posttreatment Months 16, 20, and 24.

9.2.2 Adverse Events

Adverse event data were obtained by patient report, patient diary, and questioning by the investigator, who rated the severity of the event and its likely relationship to Study Drug. Adverse event data were collected at each clinical visit (scheduled at 28-day intervals during the treatment period).

9.2.3 Clinical Laboratory Measurements

In both studies, patients were to fast overnight prior to collection of blood specimens for laboratory tests. Hematology and chemistry tests were performed during the pre-study period and at Weeks 24 and 52 of the Treatment Period. A baseline pregnancy test was performed within 1 week prior to the first administration of study drug and prior to Week 4 dosing to confirm that the patient was not pregnant. No laboratory measurements, other than serum lipid profiles, were required in the post

treatment follow-up period. The protocol-defined clinical laboratory measurements that were performed are listed in Table 25.

In Study M92-878, general laboratory tests were performed by ——— (formerly known as ——— In Study M97-777 ———, performed all safety-related clinical laboratory measurements.

Table 25 Clinical Laboratory Measurements

Hematology	General Chemistries
Total white blood cell count (WBC)	Glucose
Differential WBC count	Total protein
Red blood cell count (RBC)*	Albumin
Hemoglobin	Total bilirubin
Hematocrit	Aspartate aminotransferase (AST or SGOT)
Platelet count	Alanine aminotransferase (ALT or SGPT)
	Lactate dehydrogenase (LDH)
	Alkaline phosphatase
	Gamma glutamyl transferase (GGT)*
	Blood urea nitrogen (BUN)
Lipids	Creatinine
Total cholesterol	Uric acid
HDL-cholesterol	Sodium*
LDL-cholesterol	Potassium*
Triglycerides	Chloride*
	Bicarbonate*
	Calcium
	Phosphorus

* Measured only in Study M97-777.

9.2.4 Serum Lipid Profiles

During the treatment period, blood samples for the measurement of lipid profiles (total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides) were obtained at pretreatment and Treatment Weeks 24 and 52. In Study M92-878, the measurement of post treatment lipids was not a component of the original protocol. Protocol Amendment No. 2 added the measurement of post treatment lipids. Based on this amendment, blood samples were to be collected beginning at post treatment Month 8 and every 4 months thereafter through the final visit at Month 24 or until lipid values had returned to within the normal range or to baseline values. In Study M97-777, blood samples for the measurement of serum lipids were to obtained at post treatment Months 1, 2, 3, 4, 8, and 12.

9.2.5 Measurement of Bone Mineral Density

Bone mineral density assessments were based on whole vertebral body measurements of L1-L4 that were taken in duplicate by Hologic-trained technicians with Hologic Quantitative Digital Radiography (QDR) machines using dual-energy x-ray absorptiometry (DEXA) methodology. Data from these measurements were processed by ——— were electronically transmitted to TAP Pharmaceutical Products Inc.

Bone mineral density measurements were to be obtained prior to the onset of treatment, at Treatment Weeks 24 and 52 (end of treatment) and at 8 and 12 months after the end of treatment. In Study

M92-878, additional BMD measurements were to be obtained at post treatment Months 16, 20, and 24 if BMD had not returned to pretreatment values.

Medical Officer's Comment

- *Although BMD was measured only at the lumber spine, this does not significantly limit the value or interpretation of the 2 studies submitted in support of this NDA. The lumber spine has a high portion of trabecular bone and is therefore highly susceptible to rapid bone loss in the first few years after the menopause or after induction of hypoestrogenemia by a GnRH analog. Demonstrating that BMD loss was attenuated at this site during treatment with a GnRH analog was appropriate and adequate for the objectives of this study. Measurement of BMD at the hip as well as the spine, however, would have provided additional useful information about possible bone loss at this site.*

9.2.6 Vasomotor Symptoms

In Study M92-878, detailed vasomotor symptom data, based on information recorded in the patient's daily diary, were collected. At the time of each clinical visit, patients reported, base on information in their diaries, whether they had had hot flashes since the previous visit, the total number of days on which hot flashes occurred since the previous visit, and the maximum number of hot flashes that occurred in a 24-hour period since the previous visit. Vasomotor symptoms also were collected and reported as adverse events. In Study M97-777, vasomotor symptoms were reported only as an adverse events.

9.2.7 Vital Signs, Body Weight, and Physical Examinations

Vital signs measurements, consisting of diastolic and systolic blood pressure and pulse rate, and weight measurements were obtained at prestudy, at Treatment Week 24, and at the completion of treatment.

9.3 Patient Disposition and Premature Terminations during Treatment Period

The primary reasons for premature terminations in Studies M92-878 and M97-777 are summarized in Table 26. In Study M92-878, 19 of 51 (37%) LD-treated patients and 24 of 55 (44%) LD/N-treated patients discontinued prematurely from the Treatment Period. The median number of days on treatment for prematurely terminating patients was 174 days for the LD group and 146 days for the LD/N group. Adverse events were the most common primary reason for premature termination in each treatment group, with 9 of 51 (18%) LD-treated patients and 11 of 55 (20%) LD/N patients citing this as the primary reason for premature termination. Requests by patients to discontinue treatment were the second most common primary reason for early withdrawal in each treatment group. Three (6%) of LD-treated patients and 5 (21%) LD/N patients were in this latter category.

Fifty-four (54) of 136 (40%) LD/N patients in Study M97-777 prematurely discontinued during the Treatment Period. The median number of days on treatment for prematurely terminating patients was 162 days. Adverse events, cited by 18 of 136 (13%) patients, were the most common primary reason for termination. Patient requests were again the second most common primary reason, with 14 (10%) patients discontinuing primarily for this reason.

Table 26 Primary Reasons (and Percentages) for Premature Terminations during the Treatment Period

	Study M92-878				Study M97-777	
	LD		LD/N		LD/N	
	N=51		N=55		N=136	
Primary Reason	n	(%)*	n	(%)*	N	(%)*
Bone Mineral Density Out of Range	1	(2)	0	(0)	0	(0)
Patient Request	3	(6)	5	(9)	14	(10)
Worsening of Disease/Symptoms	0	(0)	0	(0)	2	(1)
Therapeutic Failure	0	(0)	2	(4)	0	(0)
Lost to Follow-up	2	(4)	2	(4)	12	(9)
Non-Compliance with Visit Schedule	2	(4)	1	(2)	1	(1)
Adverse Event	9	(18)	11	(20)	18	(13)
Medical Treatment for Endometriosis #	0	(0)	0	(0)	1	(1)
Surgical Treatment for Endometriosis #	0	(0)	0	(0)	3	(2)
Other	2	(4)	3	(5)	3	(2)
Total	**19**	**(37)**	**24**	**(44)**	**54**	**(40)**

* Percent of total number of patients in each treatment group that terminated prematurely.
# Was not listed as a possible reason for premature termination on the Study M92-878 case report form.
Source: Text Table 3.1c of ISS and Statistical Tables 1.3 and 2.3 of ISS.

Medical Officer's Comments

- *The distributions of the reasons for premature termination were very similar in the 2 treatment arms of the randomized and blinded Study (M92-878).*
- *Although co-treatment with NETA decreased vasomotor symptoms (see Section 9.7), it did not increase the overall acceptability of Lupron as a therapy for endometriosis as the premature termination rate in the LD/N treatment group in Study M92-878 was not reduced.*

9.4 Adverse Events

In this review, adverse events are presented and discussed in the following manner. An overview of reported adverse events, based on the numbers of patients reporting adverse events summarized into broad categories, is first presented (Section 9.4.1). This is followed by a summary and discussion of (a) the most commonly reported adverse events (all degrees of severity and all relationships to Study Drugs, Section 9.4.2), (b) the most commonly reported adverse events possibly related to treatment with Study Drugs (Section 9.4.3), (c) adverse events that resulted in withdrawal of patients from the clinical trials (Section 9.4.4), (d) the most commonly reported adverse events of severe intensity (Section 9.4.5), and (e) adverse events that met the regulatory definition of serious (Section 9.4.6).

9.4.1 Overview of Adverse Events (Principal Safety Study)

Table 27 summarizes the number of patients experiencing one or more adverse events in each of the 3 treatment groups as well as in the integrated LD/N group (LD/N patients from Studies M92-878 and M97-777 combined). Fifty (50) of 51 patients (98.0%) in the LD group and 190 of 191 patients (99.5%) treated with LD/N (integrated group) experienced one or more adverse events. A numerically higher percentage of patients in the LD group (80.4%) experienced one or more adverse events rated as severe in intensity compared to patients in either of the LD/N treatment groups (61.8% in Study M92-878 and 27.9% in Study M97-777). A similar percentage of patients experienced treatment-related adverse events in each of the treatment groups, ranging from 94.9% (LD/N group in Study M97-777) to 98.0% (LD group). Patient withdrawals due to adverse events ranged from 13.2% in the LD/N-treated patients in Study M97-777 to 20.0% in the LD/N-treated patients in Study M92-

878. Two (2) patients (1 in each treatment group in Study M92-878) experienced an adverse event that was possibly related to treatment. No deaths were reported in any of the treatment groups.

Table 27. Number and Percentage of Patients Reporting Adverse Events during Treatment

	M92-878				M97-777		Integrated [1]	
	LD N = 51		LD/N N = 55		LD/N N = 136		LD/N N = 191	
	N	(%)	n	(%)	N	(%)	N	(%)
Any Adverse Event	50	(98.0)	55	(100)	135	(99.3)	190	(99.5)
Maximum Intensity of Adverse Event [2]								
Mild	0	–	0	–	4	(2.9)	4	(2.1)
Moderate	9	(18.0)	21	(38.2)	93	(68.4)	114	(60.0)
Severe	41	(80.4)	34	(61.8)	38	(27.9)	72	(37.7)
Treatment-related AE	50	(98.0)	53	(96.4)	129	(94.9)	182	(95.3)
Withdrawal due to AE	9	(18.0)	11	(20.0)	18	(13.2)	29	(15.2)
Serious Adverse Event (SAE)	4	(8.0)	4	(7.3)	4	(2.9)	8	(4.2)
Treatment-related SAE	1	(2.0)	1	(1.8)	0	–	1	(0.5)
AE associated with Death	0	–	0	–	0	–	0	–

[1] LD/N groups from Studies M92-878 and M97-777 combined.
[2] Patient included only once in the category of maximum severity.
Source: Statistical Tables 1.6, 1.7, 1.9, 1.27, 2.5, 3.2, 3.3, and 3.5 of the ISS.

Medical Officer's Comments

- *The proportion of patients with adverse events, as classified in Table 27, was similar in each category with the exception of maximum intensity. The higher proportion of patients with one or more adverse events classified as severe in intensity in the LD group was most likely a result of the high proportion of patients reporting severe hot flashes in this treatment group (see Section 9.4.5).*

9.4.2 Adverse Events (All Intensities and All Relationships to Study Drug)

Adverse events (regardless of intensity or likely relationship to Study Drug) that occurred during the treatment period in at least 10.0% of patients in any of the 3 treatment groups are listed in Table 28. Adverse events in this table are listed by Costart term in decreasing order based on their prevalence in the LD-treatment group. Adverse events were reported for 49 of 51 (98%) patients in the LD group, 55 of 55 (100%) patients in the LD/N group in Study M92-878 and 135 of 136 (99.3%) patients in the LD/N group in Study M97-777. The 2 most frequently reported adverse events in each treatment group were hot flashes and headaches. Hot flashes were reported in 98.0%, 89.1%, and 59.6% of patients in the LD, LD/N (Study M92-878) and LD/N (Study M97-777) treatment groups, respectively. Headaches were reported in 72.5%, 61.8%, and 58.8% of patients in the LD, LD/N (Study M92-878) and LD/N (Study M97-777) treatment groups, respectively.

Table 28 Adverse Events (All Treatment Relationships) Occurring in ≥ 10.0% of Patients

	M92-878		M97-777
	LD (N = 51)	LD/N (N = 55)	LD/N (N=136)
Adverse Event*	n (%)	n (%)	n (%)
Any Adverse Event	49 (98.0)	55 (100.0)	135 (99.3)
Hot flash (vasodilatation)	50 (98.0)	49 (89.1)	81 (59.6)
Headache	37 (72.5)	34 (61.8)	80 (58.8)
Pain	29 (56.9)	18 (32.7)	62 (45.6)
Nausea	22 (43.1)	17 (30.9)	41 (30.1)
Flu Syndrome	19 (37.3)	21 (38.2)	40 (29.4)
Insomnia	18 (35.3)	9 (16.4)	34 (25.0)
Pharyngitis	17 (33.3)	16 (29.1)	34 (25.0)
Vaginitis	14 (27.5)	12 (21.8)	36 (26.5)
Emotional Lability	13 (25.5)	15 (27.3)	38 (27.9)
Asthenia	11 (21.6)	13 (23.6)	27 (19.9)
Constipation	11 (21.6)	7 (12.7)	25 (18.4)
Dizziness	11 (21.6)	10 (18.2)	24 (17.6)
Abdominal Pain	10 (19.6)	11 (20.0)	37 (27.2)
Back Pain	10 (19.6)	11 (20.0)	37 (27.2)
Dyspepsia	10 (19.6)	6 (10.9)	27 (19.9)
Diarrhea	9 (17.6)	8 (14.5)	13 (9.6)
Breast Pain	8 (15.7)	9 (16.4)	11 (8.1)
Accidental Injury	7 (13.7)	6 (10.9)	16 (11.8)
Depression	7 (13.7)	8 (14.5)	34 (25.0)
Migraine	7 (13.7)	4 (7.3)	26 (19.1)
Pelvic Pain	7 (13.7)	7 (12.7)	17 (12.5)
Sinusitis	7 (13.7)	14 (25.5)	19 (14.0)
Amnesia	6 (11.8)	1 (1.8)	4 (2.9)
Infection	6 (11.8)	6 (10.9)	53 (39.0)
Libido Decreased	6 (11.8)	2 (3.6)	10 (7.4)
Rhinitis	6 (11.8)	4 (7.3)	13 (9.6)
Weight Gain	6 (11.8)	11 (20.0)	14 (10.3)
Anxiety	5 (9.8)	0 (0.0.)	16 (11.8)
Flatulence	4 (7.8)	7 (12.7)	8 (5.9)
Nervousness	4 (7.8)	2 (3.6)	21 (15.4)
Vomiting	4 (7.8)	6 (10.9)	11 (8.1)
Acne	3 (5.9)	6 (10.9)	24 (17.6)
Otitis Media	2 (3.9)	7 (12.7)	1 (0.7)
Rash	2 (3.9)	4 (7.3)	15 (11.0)
Urinary Tract Infection	2 (3.9)	10 (18.2)	17 (12.5)
Vaginal Moniliasis	2 (3.9)	7 (12.7)	0 (0.0)
Myalgia	1 (2.0)	8 (14.5)	23 (16.9)
Sweating	1 (2.0)	8 (14.5)	15 (11.0)

* Costart Term

Source: Compiled by Medical Officer from Statistical Tables 1.6 and 3.2 of the ISS.

Medical Officer's Comments

- *In the controlled study, adverse events of any relationship that occurred in a statistically greater proportion of patients in one of the groups were pain (not otherwise specified as to type), insomnia, and anxiety in the LD-treated patients and urinary tract infection, myalgia, and sweating in the LD/N treatment group.*

- *Breast discharge or galactorrhea was reported for 5 patients in the LD/N treatment-groups and for no patients in the LD-treatment group. Four of the 5 cases were assessed as possibly or probably related to Study Drug. The duration of galactorrhea in these patients ranged from 2 hours to 3 months. The sponsor was able to provided serum prolactin values for the 3 patients in Study M97-777. Values from 2 patients were within the normal range while those from the third patient (No. 3204) were elevated during treatment but returned to within the normal range posttreatment. Of the 2 patients with galactorrhea in Study M92-878, one patient (No. 1158) was reported by the Investigator to have had an elevated prolactin and was treated with parlodel.*

9.4.3 Treatment-Related Adverse Events

Treatment-related adverse events that occurred during the treatment period in at least 5.0% of patients in any one of the 3 treatment groups are listed in Table 29. A treatment-related adverse event was defined as an adverse event considered to have an unknown, possible, probable, or definite relationship to Study Drug. Treatment-related adverse events were reported for 50 of 51 (98%) patients in the LD group, 53 of 55 (96%) patients in the LD/N group (Study M92-878) and 129 of 136 (95%) patients in the LD/N group (Study M97-777). Hot flashes and headaches were the most commonly reported treatment-related adverse events. Treatment-related hot flashes were reported in 98%, 89%, and 60% of patients in the LD, LD/N (Study M92-878) and LD/N (Study M97-777) treatment groups, respectively. Treatment-related headaches were reported in 63%, 55%, and 44% of patients in the LD, LD/N (Study M92-878) and LD/N (Study M97-777) treatment groups, respectively.

Table 29. Treatment-Related Adverse Events Occurring in ≥ 5.0 % of Patients

	Study M92-878				Study M97-777		Integrated	
	LD-Only N=51		LD/N N=55		LD/N N=136		LD/N N=191	
Adverse Event*	N	(%)	N	(%)	N	(%)	N	(%)
Any Adverse Event	50	(98)	53	(96)	129	(95)	182	(95)
Hot Flashes	50	(98)	49	(89)	81	(60)	130	(68)
Headache	32	(63)	30	(55)	60	(44)	90	(47)
Insomnia	16	(31)	9	(16)	28	(21)	37	(19)
Nausea	14	(27)	12	(22)	18	(13)	30	(16)
Emotional Lability	12	(24)	14	(25)	34	(25)	48	(25)
Vaginitis	12	(24)	9	(16)	15	(11)	24	(13)
Asthenia	11	(22)	12	(22)	16	(12)	28	(15)
Dizziness	9	(18)	7	(13)	11	(8)	18	(9)
Pain	9	(18)	9	(16)	19	(14)	28	(15)
Depression	7	(14)	7	(13)	29	(21)	36	(19)
Libido Decreased	6	(12)	2	(4)	10	(7)	12	(6)
Migraine	6	(12)	4	(7)	18	(13)	22	(12)
Weight Gain	6	(12)	10	(18)	13	(10)	23	(12)
Breast Pain	5	(10)	7	(13)	10	(7)	17	(9)
Abdominal Pain	4	(8)	5	(9)	14	(10)	19	(10)
Amnesia	4	(8)	1	(2)	3	(2)	4	(2)
Constipation	4	(8)	1	(2)	12	(9)	13	(7)
Nervousness	4	(8)	2	(4)	17	(13)	19	(10)
Anxiety	3	(6)	0	(0)	14	(10)	14	(7)
Chest Pain	3	(6)	2	(4)	2	(2)	4	(2)
Pelvic Pain	3	(6)	2	(4)	7	(5)	9	(5)
Acne	2	(4)	5	(9)	23	(17)	28	(15)
Back Pain	2	(4)	3	(6)	10	(7)	13	(7)
Diarrhea	2	(4)	4	(7)	3	(2)	7	(4)
Dyspepsia	2	(4)	4	(7)	7	(5)	11	(6)
Flatulence	2	(4)	4	(7)	1	(1)	5	(3)
Alopecia	1	(2)	5	(9)	4	(3)	9	(5)
Increased Appetite	1	(2)	0	(0)	8	(6)	8	(4)
Injection Site Pain	1	(2)	4	(7)	4	(3)	8	(4)
Leg Cramps	1	(2)	5	(9)	0	(0)	5	(3)
Paresthesia	1	(2)	3	(6)	3	(2)	6	(3)
Sweating	1	(2)	8	(15)	15	(11)	23	(12)
Vomiting	1	(2)	4	(7)	4	(3)	8	(4)
Generalized Edema	0	(0)	3	(6)	10	(7)	13	(7)
Urinary Tract Infection	0	(0)	3	(6)	1	(1)	4	(2)

Source: Text Table 3.4e of the ISS and Statistical Tables 1.7, 3.3, and 4.3 of the ISS.

Medical Officer's Comments

- *The overall pattern of adverse events in the 2-treatment groups in the controlled study differed to some extent. In the LD/N-treatment groups, there were numerical fewer women reporting adverse events that were possibly related to hypoestrogenemia. These included a reduced proportion of women reporting hot flashes, insomnia, vaginitis, amnesia, and anxiety. Conversely, there were small numerical increases in the proportion of women reporting adverse*

events that were possibly related to androgenic or metabolic effects of NETA including weight gain, acne, and alopecia.

- *When the occurrence of hot flashes was assessed in terms of daily frequency and severity in the 2 treatment groups in Study M92-878 (see Section 9.7), there was a beneficial effect of co-treatment with NETA on reducing vasomotor events.*
- *A higher proportion of women reported sweating, separate from hot flashes, as an adverse event in both of the LD/N treatment groups. It is not possible from the reported data to determine if these events were related to hypoestrogenemia or an action of NETA (e.g., the known thermogenic effect of progesterone).*
- *Depression is a known and potentially serious adverse effect of treatment with high doses of a progestin. There was no difference in the proportion of women reporting treatment-related depression in the LD and LD/N-treatment groups in the controlled study. The proportion of women reporting depression that was possibly related to treatment in Study M97-777 was numerically higher (21%) than in either treatment group in Study M92-878. Depression rated as severe in intensity, however, was reported more frequently in the LD/N-treated patients (see Section 9.4.5).*

9.4.4 Adverse Events Resulting in Patient Withdrawal

Adverse events reported during the treatment period that were associated with patient withdrawal from the study (premature terminations) are listed by preferred terms in Table 30 (Study M92-878) and in Table 31 (Study M97-777). Overall, 9 of 50 (18%) patients in the LD group, 11 of 55 (20%) patients in the LD/N group (Study M92-878) and 18 of 136 (13%) patients in the LD/N group (Study M97-777) withdrew or were withdrawn, at least in part, because of an adverse event. In most instances, the adverse event was assessed as possibly or probably related to treatment with Study Drug.

Medical Officer's Comments

- *In the LD treatment group, the adverse events most frequently associated with premature termination were hot flashes (3 patients) and insomnia (2 patients).*
- *In the LD/N treatment group in Study M92-878, the adverse events most frequently associated with premature termination were hot flashes and emotional lability (each reported for 2 patients).*
- *In Study M97-777, the adverse events most frequently associated with premature termination were depression (5 patients), acne (3 patients), and hirsutism (2 patients, both of whom also withdrew because of acne). These are well known and expected adverse effects associated with the use of relatively high doses of an androgenic progestin such as NETA.*

APPEARS THIS WAY
ON ORIGINAL

Table 30 Adverse Events Associated with Premature Withdrawal (Study M92-878)

Treatment	Patient No.	Adverse Event	Severity	Relationship
LD-Only	1043	Hot Flashes	Mild	Definite
	" "	Insomnia	Severe	Probable
	1088	Personality Disorder	Moderate	Probable
	1093	Hot Flashes	Severe	Definite
	" "	Libido Decreased	Severe	Definite
	1107	Headache	Unknown	Possible
	1162	Anxiety	Moderate	Possible
	" "	Insomnia	Moderate	Possible
	1176	Pelvic Pain	Moderate	Not Related
	" "	Depression	Moderate	Unknown
	1182	Hot Flashes	Severe	Probable
	1192	Emotional Lability	Severe	Definite
	1306	Arthralgia (Rt. hip)	Mild	Possible
LD/N	1022	Emotional Lability	Moderate	Probable
	1032	Hot Flashes	Mild	Probable
	" "	Amnesia	Mild	Possible
	1076	Paresthesia (Rt. leg)	Severe	Possible
	1086	Abdominal Bloating	Moderate	Unknown
	" "	Flatulence	Moderate	Not Related
	1092	Back Pain	Severe	Not Related
	" "	Pain (Lt. leg)	Severe	Unknown
	1096	Libido Decreased	Mild	Probable
	" "	Asthenia	Mild	Possible
	" "	Abdominal Pain	Severe	Not Related
	1108	Flatulence	Moderate	Unknown
	" "	Abdominal Pain	Moderate	Unknown
	" "	Diarrhea	Mild	Possible
	1115	Hot Flashes	Mild	Possible
	1153	Emotional Lability	Severe	Possible
	1164	Unintended Pregnancy	Severe	Not Related
	1235	Chest Pain	Mild	Possible
	1272	Depression	Moderate	Not Related

Source: Text Table 3.9a of the ISS and Statistical Table 1.28 of the ISS.

Table 31 Adverse Events Associated with Premature Withdrawal (Study M97-777)

Treatment	Patient No.	Adverse Event	Severity	Relationship
LD/N	805	Asthenia	Mild	Probable
	1202	Depression	Severe	Possible
	" "	Emotional Lability	Severe	Possible
	1210	Migraine	Severe	Possible
	1304	Acne	Mild	Possible
	" "	Chills	Mild	Probable
	" "	Hirsutism	Mild	Possible
	" "	Sweating	Mild	Probable
	1401	Headache	Severe	Possible
	" "	Vomiting	Severe	Possible
	1501	Emotional Lability	Severe	Probable
	1802	Nausea	Moderate	Possible
	1803	Vaginal Bleeding	Moderate	Probable
	2001	Depression	Moderate	Probable
	2103	Agitation	Moderate	Possible
	" "	Amnesia	Moderate	Possible
	" "	Anxiety	Moderate	Possible
	" "	Depression	Moderate	Possible
	" "	Hostility	Moderate	Possible
	" "	Sweating	Moderate	Probable
	2104	Nervousness	Moderate	Possible
	" "	Hot Flashes	Moderate	Definite
	2203	Acne	Moderate	Probable
	2206	Insomnia	Unknown	Unknown
	2207	Depression	Moderate	Possible
	2804	Acne	Mild	Possible
	" "	Brittle Hair	Mild	Possible
	" "	Hirsutism	Mild	Possible
	2809	Libido Decreased	Mild	Probable
	" "	Depression	Mild	Probable
	" "	Weight Gain	Mild	Probable
	2901	Lymphadenopathy	Moderate	Not Related
	3204	Shoulder Pain	Severe	Possible

Source: Text Table 3.9b of the ISS and Statistical Table 2.6 of the ISS.

9.4.5 Severe Adverse Events

Adverse events rated as severe in intensity that occurred during the treatment period in at least 2.0% of patients in any of the 3 treatment groups are listed in Table 32. Severe adverse events were reported for 41 of 51 (80%) patients in the LD group, 34 of 55 (62%) patients in the LD/N group (Study M92-878) and 38 of 136 (28%) patients in the LD/N group (Study M97-777). Hot flashes were the most commonly reported severe adverse event in Study M92-878, occurring in 67% of patients in the LD group and 25% of patients in the LD/N group. Severe hot flashes, however, were reported by only 1 patient in Study M97-777. Headaches were the second most frequent severe adverse event in Study M92-878, occurring in 12% of LD patients and 11% of LD/N patients. Headaches were the most frequent severe adverse events in Study M97-777, with 13 of 136 (10%) patients reporting them.

Table 32 Severe Adverse Events (All Relationships) Reported by ≥ 2.0% of Patients

Adverse Event	Study M92-878-878				Study M97-777		Integrated	
	LD N = 51		LD/N N = 55		LD/N N = 136		LD/N N = 191	
	N	(%)	N	(%)	N	(%)	N	(%)
Any Adverse Event	*41*	*(80)*	*34*	*(62)*	*38*	*(28)*	*72*	*(38)*
Hot Flashes	34	(67)	14	(25)	1	(1)	15	(8)
Headache	6	(12)	6	(11)	13	(10)	19	(10)
Migraine	5	(10)	2	(4)	5	(4)	7	(4)
Pain	5	(10)	3	(5)	4	(3)	7	(4)
Emotional Lability	3	(6)	2	(4)	2	(1)	4	(2)
Insomnia	2	(4)	0	(0)	0	(0)	0	(0)
Abdominal Pain	2	(4)	4	(7)	3	(2)	7	(4)
Flu Syndrome	2	(4)	0	(0)	0	(0)	0	(0)
Libido Decreased	2	(4)	0	(0)	0	(0)	0	(0)
Asthenia	1	(2)	2	(4)	0	(0)	2	(1)
Accidental Injury	1	(2)	0	(0)	2	(1)	2	(1)
Pelvic Pain	0	(0)	3	(5)	4	(3)	7	(4)
Sweating	0	(0)	3	(5)	0	(0)	3	(2)
Nausea	0	(0)	3	(5)	1	(1)	4	(2)
Urinary Tract Infection	0	(0)	3	(5)	0	(0)	3	(2)
Back Pain	0	(0)	2	(4)	2	(1)	4	(2)
Depression	0	(0)	1	(2)	4	(3)	5	(3)
Dysmenorrhea	0	(0)	0	(0)	3	(2)	3	(2)
Syncope	0	(0)	0	(0)	2	(1)	2	(1)
Constipation	0	(0)	0	(0)	2	(1)	2	(1)
Flatulence	0	(0)	1	(2)	1	(1)	2	(1)
Infection	0	(0)	1	(2)	1	(1)	2	(1)
Bronchitis	0	(0)	1	(2)	1	(1)	2	(1)

Source: Text Table 3.4h of ISS.

Medical Officer's Comments

- *Although adverse events rated as severe in intensity occurred in a significantly greater proportion of patients in the LD-treatment group compared to the integrated LD/N-treatment group (80% vs. 38%), the difference was due largely, or completely, to a greater occurrence of severe hot flashes in the LD patients.*
- *Severe depression was reported by 5 of 191 (3%) LD/N-treated patients and no LD-treated patients.*

9.4.6 Serious Adverse Events

Serious adverse events that were reported during either the treatment period or the post treatment follow-up period are listed by Study and patient in Table 33. In Study M92-878, serious adverse events were reported for 14% of the LD-treated patients and 9% of the LD/N-treated patients. Of these serious adverse events, only 1 in each group was classified as possibly related to treatment with Study Drug. The treatment related serious adverse events were a renal calculus in Patient 1233 (LD group) in the post treatment period and a urinary tract infection in Patient 1234 (LD/N group). In

Study M97-777, serious adverse events were reported for 4 LD/N treated patients. None were classified as related to treatment with Study Drug.

Table 33 Serious Adverse Events in Studies M92-878 and M97-777

Study Drug	Patient Number	Adverse Event	Onset (Study Day)	Severity	Relation to Study Drug	Action Taken (Study Drug)
Study M92-878						
LD	1123	Pylonephritis	356	Severe	NR	None
LD	1362	Adverse Reaction to Imitrex	42	Severe	NR	None
LD/N	1191	Pilonidal Cyst	168	Moderate	NR	None
LD/N	1211	Carcinoma of Ovary	Post Tx	Severe	NR	NA
LD/N	1164	Unintended Pregnancy	29	Severe	NR	Discontinued
LD/N	1234	Urinary Tract Infection	303	Severe	Possible	None
LD	1174	Pelvic Pain	Post Tx	Severe	NR	NA
LD	1202	Asthma	170	Severe	NR	None
LD	1306	Post-Operative Pain	68	Mild	NR	None
LD/N	1305	Infected Renal Cyst	226	Severe	NR	None
LD	1315	Back Injury/Post Op-Infection	Post Tx	Severe	NR	NA
LD	1233	Renal Calculus	Post Tx	Severe	Possible	NA
Study M97-777						
LD/N	1807	Deviated Nasal Septum (Repair)	151	Moderate	NR	None
LD/N	3203	Fracture of Distal Radius	198	Severe	NR	None
LD/N	1905	Drug Overdose (Intentional OD) [1]	314	Severe	NR	None
	" "	Depression	314	Severe	NR	None
	" "	Liver Enzyme Changes 2nd to OD	314	??	??	None
LD/N	1909	Neck Pain/?Ruptured Disc	116	Severe	NR	None

[1] Patient attempted suicide by overdosing with acetaminophen.
Source: Statistical Tables 1.27 and 2.5 of the ISS.

Medical Officer's Comments

- *Few medically serious adverse events were reported in these studies and only 2 were considered to be possibly related to treatment by the Investigators. Both of these events involved the kidney and both were reported by the same Investigator. These events were a serious urinary tract infection in Patient No. 1234 (LD/N treatment group) and a renal calculus in Patient No. 1233 (LD-treatment group, post treatment follow-up period).*
- *Other serious adverse events, with the possible exception of depression and drug overdose in Patient No. 1905 (LD/N-treatment group) were not likely to be related to treatment with Study Drug as assessed by the Investigators.*

9.5 Deaths

No deaths were reported during either the treatment or post treatment follow-up phases.

9.6 Changes in Bone Mineral Density

9.6.1 Overview of Bone Mineral Density Data and Data Presentation

Bone mineral density values and percent changes in BMD values from baseline in the 3 treatment groups are listed in Table 34, Table 35, and Table 36. In each Table, BMD data are presented in the following manner.

Treatment Period. For each treatment group, BMD values (mean, SD, minimum and maximum) at baseline and on-treatment that were obtained at the Week 24, Week 52, and Final Treatment Visits are listed. Also listed are the BMD values obtained closest to 52 weeks after the onset of treatment and falling in the interval of Week 36-64, regardless of the patient's total length of treatment. Mean percent changes from baseline BMD values are also listed for each of these assessment times.

Post Treatment period. Study M92-878 had a 2 year post treatment follow-up period. BMD measurements were to be obtained at post treatment Months 8, 12, 16, 20, and 24. In Table 34 and Table 35, BMD values and percent changes from baseline BMD values for post treatments visits labeled as Month 8, Month 16, and Final are presented. Study M97-777 had a 1 year post treatment follow-up period. BMD measurements were to be obtained at post treatment Month 8 and Month 12. BMD values and percent changes from baseline in BMD values for these visits as well as the Final Posttreatment Visit are listed in Table 36.

9.6.2 Bone Mineral Density Values and Percent Changes from Baseline

9.6.2.1 Study M92-878

BMD values and the percent changes from baseline values for the LD treatment group in Study M92-878 are listed in Table 34. Of the 51 patients who were enrolled into the LD treatment arm, 41 and 29 patients had on-treatment BMD measurements at Week 24 and Week 52 visits, respectively. BMD values decreased from a mean of 1.029 gm/cm^2 at baseline to a mean of 0.964 gm/cm^2 at Week 52. At Week 52, the mean percent change from baseline was -6.3%. The means of the changes from baseline at post treatment Months 8 and 12 and the Final Visit 24 were –3.3%, -2.2%, and –1.9%, respectively. The largest percent decreases from baseline in individual patients reported at post treatment Months 8 and 12 and the Final Visit were -11.7%, -4.8%, and –5.5%, respectively.

Table 34 BMD Values and Percent Changes from Baseline (Study M92-878-LD Group)

Summary Statistic	Baseline	Treatment Period			Week 36-64	Post Treatment Period		
		Week 24	Week 52	Final		Month 8	Month 16	Final
N	51	41	29	41	31	19	16	23
Bone Mineral Density Values (gm/cm^2)								
Mean	1.029	0.997	0.964	0.976	0.964	0.974	0.976	0.986
SD	0.110	0.113	0.097	0.112	0.095	0.082	0.102	0.101
Percent change from baseline								
Mean	NA	-3.2%	-6.3%	-5.3%	-6.4%	-3.3%	-2.2%	-1.9%
SD	NA	1.8%	2.3%	2.8%	2.4%	3.2%	2.1%	2.2%

Source: Statistical Table 14.3.7_5 of the Final Report for Study M92-878.

BMD values and the percent changes from baseline values for the LD/N treatment group in Study M92-878 are listed in Table 35. Of the 55 patients who were enrolled into the LD/N treatment arm, 42 and 32 patients had on-treatment BMD measurements at Week 24 and Week 52 visits, respectively. BMD values changed from a mean of 1.059 gm/cm^2 at baseline to a mean of 1.064 gm/cm^2 at Week 52. At Week 52, the mean percent change from baseline was -1.0%. The means of the changes from baseline at post treatment Months 8 and 12 and the Final Visit 24 were –0.9%, -0.7%, and -0.4%, respectively.

The largest percent decreases from baseline in individual patients reported at post treatment Months 8 and 12 and the Final Visit were -7.3%, -4.3%, and –7.3%, respectively.

Table 35 BMD Values and Percent Changes from Baseline (Study M92-878-LD/N Group)

Summary Statistic	Baseline	Treatment Period			Week 36-64	Post Treatment Period		
		Week 24	Week 52	Final		Month 8	Month 16	Final
N	55	42	32	42	32	23	12	23
Bone Mineral Density Values (gm/cm²)								
Mean	1.059	1.057	1.064	1.050	1.059	1.059	1.042	1.063
SD	0.126	0.130	0.137	0.129	0.138	0.135	0.104	0.131
Percent change from baseline								
Mean	NA	-0.3%	-1.0%	-0.9%	-0.9%	-0.9%	-0.7%	-0.4%
SD	NA	1.9%	2.4%	2.3%	2.4%	2.9%	2.1%	2.6%

Source: Statistical Table 14.3.7_5 of the Final Report for Study M92-878.

Medical Officer's Comments

- *According to the Sponsor, bone mineral density measurements were performed by [redacted] trained technicians utilizing DEXA technology and Quantitative Digital Radiography machines (QDR). All DEXA scans were reviewed [redacted] prior to electronic transmission of data to the Sponsor. DEXA is the current standard methodology for measuring BMD. [redacted] is the manufacturer of the QDR imaging machines that were used to measure BMD. [redacted] QDR machines are widely used both in clinical practice and in clinical trials.*
- *In the LD treatment group in Study M92-878, a total of 6 of 41(15%) patients with BMD measurements after the start of treatment had one or more BMD values that indicated a loss of more than 8.0%. Only one of these decreases was noted by the Week 24 assessment (a change of -8.3%). Treatment was terminated for this patient because of excessive loss of BMD in accordance with Protocol stopping rules. This patient's BMD at baseline was 0.846 gm/cm² and had decreased to 0.776 gm/cm² (-8.3% change) at the Week 24 assessment. Three of these 6 patients had posttreatment follow-up measurements. In 2 of these 3 patients, the decrease in BMD at the final follow-up visit was less than 5% (i.e., -3.0% and –4.3%). No patient in the LD/N-treatment groups was terminated for an excessive decrease in BMD by the Week 24 visit.*
- *In the LD/N treatment group in Study M92-878, 9 of 42 patients (21%) had one or more post baseline BMD measurements with decreases of more than 3% from baseline. Only 3 of these 9 patients had decreases of greater than 3% by the Week 24 visit (changes of -4.7%, -5.3%, and –3.6%, respectively). Two of the 9 patients (5% of the enrolled patients) had one or more post baseline BMD measurements with decreases of more than 5% from baseline. The maximal change in BMD was -8% and was observed in 1 patient (Patient No. 1243). This was the only patient with a final posttreatment follow-up BMD value that was more than 5% lower than baseline (a changes of –7.3% in BMD).*

9.6.2.2 Study M97-777

BMD values and the percent changes from baseline values for the LD/N treatment group in Study M97-777 are listed in Table 36. Of the 136 patients who were enrolled into the study, 115 and

84 patients had treatment period BMD measurements at Week 24 and Week 52 visits, respectively. BMD values changed from a mean of 1.067 gm/cm^2 [redacted] at baseline to a mean of 1.058 gm/cm^2 at Week 52 [redacted]). At Week 52, the mean percent change from baseline was -1.1% (range: -6.9% to 5.3%). The means of the percent changes from baseline at post treatment Months 8 and 12 and the Final Visit were -0.6%, 0.1%, and -0.0%, respectively. The largest percent decreases from baseline in individual patients reported at post treatment Months 8 and 12 and the Final Visit were -7.5%, -4.9%, and -7.5%, respectively.

Table 36 BMD values and Percent Changes from Baseline (Study M97-777)

Summary Statistic	Baseline	Treatment Period				Post Treatment Period		
		Week 24	Week 52	Final	Week 36-64	Month 8	Month 12	Final
N	136	115	84	115	101	89	65	91
Bone Mineral Density Values (gm/cm^2)								
Mean	1.067	1.061	1.058	1.052	1.051	1.057	1.087	1.064
SD	0.123	0.127	0.130	0.125	0.127	0.125	0.130	0.127
Min	[redacted]							
Max								
Percent change from baseline								
Mean	NA	-0.2%	-1.1%	-1.0%	-1.0%	-0.6%	0.1%	-0.0%
SD	NA	2.1%	2.6%	2.5%	2.7%	2.7%	2.5%	2.7%
Min								
Max								

Source: Statistical Table 3.2 of August 10, 2001 submission.

Medical Officer's Comments

- *The magnitude of the BMD changes in Study M97-777 was similar to that in the LD/N treatment arm in Study M92-878.*
- *The post treatment follow-up data in Study M97-777 were more useful than those from Study M92-878 as a higher percentage of patients had such data.*
- *The absence of a control group (e.g., normal volunteers not treated with Study Drug) increases the potential risk that machine drift could obscure small changes in BMD. However, quality control procedures described by the Sponsor (e.g. regular use of calibration phantoms) and the relatively high precision of lumber spine BMD measures (in contrast to hip measurements) minimizes this risk.*
- *Twenty-eight (28) of 115 patients (24%) with BMD measurements after the start of treatment had one or more BMD values that indicated a loss of more than 3.0% from baseline. Eight of these 28 patients had BMD decreases of > 5.0%. The maximum changes in BMD values were –6.4% (Patient No. 404) and –7.5% (Patient No. 3003). These changes were observed at 53 and 33 days, respectively, after completion of 12 months of treatment with LD/N. The times at which these measurements were obtained were likely to have been those at which the maximal decreases in BMD occurred. No further BMD measurements were obtained in either patient to assess posttreatment recovery. The BMD decrease in Patient No. 3003 is clinically significant in that this patient entered the Study with a relatively low BMD of 0.864 gm/cm^2 (83% of the age-matched control value) that decreased to 0.799 gm/cm^2 (76% of the age-matched control value) at the final measurement. At the Week 24 Visit, the change in BMD from baseline was only –1.6% in this patient.*

- *It is noteworthy that at the Week 24 Visit, only 11 of the 115 patients (10%) had a BMD value that indicated a loss of more than 3.0% from baseline. No patient at the Week 24 Visit had a BMD value that indicated a loss of more than 5.0% from baseline.*
- *Ten of the 157 LD/N-treated patients (combined data from Studies M92-8787 and M97-777) who had post baseline BMD measurements had a decrease of >5.0% at one or more assessments. Of these 10 patients, only 1 patient had a decrease of more than 5.0% at the Week 24 Visit (a change from baseline of -5.3% in Patient No. 1234 in Study M92-878).*

9.6.3 Summary of Bone Mineral Density Changes during Treatment with LD or LD/N

9.6.3.1 Primary BMD Analyses

In addition to the descriptive analyses presented in Section 9.6.2, the Sponsor provided additional analyses based in part on requests from DRUDP. These analyses are summarized in Table 37. All of the additional analyses included calculating 2-sided 95% confidence limits (95% CIs) for the percent differences in BMD from baseline at each of the assessment times. Based on a prior agreement with DRUDP, a successful intervention for reducing GnRH-induced bone loss should result in a lower bound for the 95% CI for the difference from baseline of not less than -2.2%. Table 37 lists the mean changes from baseline and the associated 95% CIs at Week 24, Week 52, and the Final Treatment Visit. The lower bound of the 95% CI for the difference from baseline for the LD/N treatment groups in Studies M92-878 and M97-777 was above (i.e., greater than) –2.2% at Weeks 24 and 52 and at the Final Treatment Visit. In contrast, the lower bound of the 95% CI for the difference from baseline for the LD treatment group was below (i.e., less than) –2.2% at each assessment time.

Table 37 Overall Summary of BMD Changes from Baseline during Treatment for Up to 1 Year

Time of Assessment [1]	Study M92-878						Study M97-777		
	LD (n=51)			LD/N(n=55)			LD/N (n=136)		
	N	Percent Change	95% CI	N	Percent Change	95% CI	N	Percent Change	95% CI
Wk 24 (9 month Int.)[2]	41	-3.2	(-3.8, -2.6)	42	-0.3	(-0.8, 0.3)	115	-0.2	(-0.6, 0.2)
Wk 24 (2 month Int.)[3]	38	-3.3	(-3.9, -2.7)	41	-0.2	(-0.9, 0.4)	105	-0.3	(-0.7, 0.1)
Wk 52 (7 month Int.)[4]	29	-6.3	(-7.1, -5.4)	32	-0.9	(-1.9, -0.1)	84	-1.1	(-1.6, -0.5)
Wk 52 (2 month Int.)[5]	23	-6.5	(-7.5, -5.3)	25	-0.8	(-2.0, 0.2)	77	-1.1	(-1.7, -0.5)
Final Visit	41	-5.3	(-6.1, -4.4)	42	-0.9	(-1.7, -0.2)	115	-1.0	(-1.4, -0.5)

[1] Measurements had to be obtained no later than 32 days after a dose of Lupron to be classified as during treatment.
[2] 9 month interval. Includes on-treatment measurements that fell within 2-252 days after the first day of treatment
[3] 2 month interval. Includes on-treatment measurements that fell within 140-196 days after the first day of treatment.
[4] 7 month interval. Includes on-treatment measurements > 252 after the first day of treatment.
[5] 2 month interval. Includes on-treatment measurements that fell within 336-392 days after the first day of treatment.
Source: Statistical Tables 2.7 (ISS), 2.8 (ISS) and 3.1.1 and 3.1.2 (Submission of August 10, 2001).

Medical Officer's Comments

- *The intervals around the target assessments times of Week 24 and Week 52 chosen by the Sponsor were very broad as described in the footnote to Table 37. Use of the intervals defined by the Sponsor might under estimate the extent of bone loss for patients who actually received treatment for a full 24 or 52 weeks. The outcomes of the analyses using tighter intervals that included only patient data from Treatment Days 140-196 for Week 24 and Treatment Days 336-392 for Week 52 were similar to those using the wider intervals.*
- *Results from Study M92-878 and Study M97-777 indicate that co-administration of 5 mg of NETA and 1000 mg of elemental calcium (OsCal with or without added Vitamin D) significantly*

reduced the loss of BMD at both Weeks 24 and 52 that was observed as a result of treatment with Lupron and OsCal alone (i.e., without NETA).

9.6.3.2 Supplemental BMD Analyses

Since it was possible that patients who terminated prematurely and did not have Week 52 measurements may have had a tendency for a greater decrease in BMD, the Sponsor was asked to calculate the mean percent changes from baseline BMD at Week 24 for patients with and without Week 52 BMD data. The results of this analysis are summarized in Table 38. In the LD group, the mean decrease in BMD was approximately 0.4% less at Week 24 in those patients who did not have Week 52 BMD data. In the LD/N groups, however, the mean decrease in BMD was approximately 0.7% greater at Week 24 in those patients who did not have Week 52 BMD data. The differences, according to the Sponsor, were not statistically significant.

Table 38 Mean Percent Changes from Baseline to Week 24 in BMD - Comparison between Patients with Week 52 BMD Data and Patients without Week 52 BMD Data

Study	Treatment Group	Group with Week 52 BMD Data		Group without Week 52 BMD Data	
		N	Mean % Change	N	Mean % Change
M92-878	LD	29	-3.3	12	-2.9
M92-878	LD/N	32	-0.1	10	-0.8
M97-777	LD/N	84	0.0	31	-0.7

Source: Statistical Tables 1.33 and 2.10 of the ISS.

Medical Officer's Comment

- *The decrease in BMD was slightly greater at Week 24 in those patients without Week 52 data. The impact of the loss of these patients on the estimates of BMD changes at Week 52, however, is likely to have been small.*

The Sponsor also performed an additional supplemental analysis to assess further the possible effects of premature withdrawals on the observed changes in BMD at Week 52. In this analysis, the BMD decrease at Week 52 for those patients who did not have Week 52 measurements was assumed to be 2-fold (linear loss) or 3-fold (accelerated loss) the loss observed at Week 24. Table 39 summarizes the imputed Week 52 BMD decreases based on these assumptions.

Table 39 Mean Percent BMD Changes from Baseline and 95% Confidence Intervals at Week 52 (with Imputed Percent Changes at Week 52)

Treatment Group	N	Imputed as 2 Times Week 24 Loss		Imputed as 3 Times Week 24 Loss	
		Mean Loss	95% CI	Mean Loss	95% CI
M97-777 LD/N	115	-1.3%	(-1.8, -0.7)	-1.6%	(-2.2, -0.9)
Integrated LD/N	157	-1.3%	(-1.7, -0.8)	-1.6%	(-2.1, -1.0)

Reference: Statistical Tables 2.11 and 4.16 in ISS.

Medical Officer's Comment

- *Based on these assumptions, the losses in BMD at Week 52 increased from the observed loss of -1.1% to -1.3% and -1.6 % based on imputed losses of 2-fold and 3-fold those observed at Week 24, respectively, for patients without actual Week 52 data. The lower bounds of the 95%*

CIs for these imputed losses from baseline were at or above –2.2%, the agreed upon criteria for a successful BMD sparing intervention.

9.6.4 Recovery of BMD Decreases in the Post Treatment Follow-up Period

The mean percent changes in BMD values, relative to baseline values, for those patients with posttreatment follow-up measurements are summarized in Table 40. Also listed in the Table are the mean end-of-treatment changes from baseline for those patients with posttreatment measurements. In each treatment group, the mean BMD decrease from baseline at the final follow-up BMD measurement was less than that observed at the end of treatment.

Table 40 Mean Percent Changes (Recovery) in BMD in Follow-up Period

	M92-878						M97-777		
	LD-Only			LD/N			LD/N		
Post Treatment Measurement	N	Mean % Change	95% CI (%)	N	Mean % Change	95% CI (%)	N	Mean % Change	95% CI (%) [2]
End of Treatment [1]	23	-5.5	(-6.8, -4.3)	23	-1.2	(-2.4, -0.1)	86	-0.9	(-1.5, -0.4)
Month 8	19	-3.3	(-4.9, -1.8)	23	-0.9	(-2.1, 0.4)	89	-0.6	(-1.2, 0.0)
Month 12	16	-2.2	(-3.3, -1.1)	12	-0.7	(-2.1, 0.6)	65	0.1	(-0.6, 0.7)
Month 16	9	-1.5	(-3.2, 0.2)	7	0.1	(-2.9, 3.2)		ND [3]	
Month 20	7	-1.9	(-3.5, -0.3)	7	0.2	(-2.6, 3.0)		ND	
Month 24	4	-0.3	(-4.1, 3.5)	6	1.6	(-0.4, 3.6)		ND	
Final	23	-1.9	(-2.8, -1.0)	23	-0.4	(-1.6, 0.7)	91	0.0	(-0.6, 0.5)

[1] Patients with post treatment measurements.
[2] 95% CI (2-sided) of percent change in BMD values from baseline.
[3] Study M97-777 had a 1-year follow-up period.
Source: Statistical Tables 3.1.4 (August 10, 2001 submission) and 14.3_7.1.1 (Study M97-777: Final Report-Posttreatment Period).

Medical Officer's Comment

- *For the patients with post treatment follow-up data, there was partial (LD treatment group) or near complete (both LD/N treatment groups) recovery in BMD.*

9.6.5 BMD Changes in Patients Previously Treated with a GnRH Agonist

The original submission did not specifically assess changes in BMD resulting from treatment with LD or LD/N in patients previous treated with a GnRH analog. Since the requested labeling change included removing the restriction against retreatment, the Sponsor was requested to provide a subset analysis comparing BMD changes in patients previously treated with a GnRH analog to those in patients not previously treated. The analysis was limited to patients treated with LD/N in Studies M92-878 and M97-777 because retreatment with LD alone is not recommended. Forty (40) patients had previously been treated with a GnRH analog (10 in Study M92-878 and 30 in M97-777). Among these patients, the mean (SD) and median duration of prior GnRH treatment was 178.0 (133.12) and 151.0 days (range: 1-667 days).

Changes in BMD values for patients treated with LD/N in studies M92-878 or M97-777 are listed in Table 41 according to whether the patient had had prior treatment with a GnRH analog. Mean BMD changes in the group with prior GnRH treatment ranged from –0.483% (Week 24, 2-month interval) to –1.219% (Week 36-64 interval). Mean BMD changes in the group with no prior GnRH treatment ranged from –0.148% (Week 24, 9-month interval) to –1.162% (Week 52, 2 month-interval).

Medical Officer's Comment

- *Although the sample size is small (only 32 and 25 patients with prior GnRH treatment had BMD measurements at Weeks 24 and 52, respectively) there was no suggestion that NETA was significantly less effective in preventing a decrease in BMD in the retreated patients.*

Table 41 Change in BMD in Patients with and Without Prior GnRH Treatment

Time of Measure	Prior GnRH Treatment			No Prior GnRH Treatment		
	N	Baseline (gm/cm^2)	Percent Change from Baseline	N	Baseline (gm/cm^2)	Percent Change from Baseline
9-Month (Week 24) and 7-Month (Week 52) Intervals [1]						
Week 24	32	1.033	-0.515	125	1.069	-0.148
Week 52	25	1.036	-0.786	91	1.081	-1.136
End of Treat.	32	1.033	-0.802	125	1.069	-0.988
Week 36-64 [2]	29	1.031	-1.219	104	1.082	-0.923
2-Month Intervals [3]						
Week 24	30	1.036	-0.483	116	1.076	-0.209
Week 52	22	1.040	-0.789	80	1.084	-1.162
Week 48-56 [2]	24	1.045	-0.797	87	1.082	-1.039

[1] Includes on-treatment measurements that fell within 2-252 days (9-month interval [Week 24]) or > 252 days (7-month interval [Week 52]) after the first day of treatment.
[2] Includes measurements that fell within the indicated interval regardless of whether patient was within 32 days of dosing with Lupron.
[3] Includes on-treatment measurements that fell within 140-196 days (Week 24) or 336-392 days (Week 52) after the first day of treatment.
Source: Statistical Tables 3.3.1, 3.3.2, 3.3.4, and 3.3.4 of August 10, 2001 submission.

9.7 Hot Flashes

In both Studies, data concerning hot flashes were collected on the Adverse Event Case Report Form (CRF). In Study M92-878, more detailed information also was collected based on the patient's daily diary. Comparative information concerning the frequency and severity of hot flashes in the LD and LD/N treatment groups, obtained at the Week 24 and Final Treatment Visit assessments, is provided in Table 42. In the LD/N treatment group, fewer patients reported hot flashes. The number of days with hot flashes and the maximum number of hot flashes in a 24 hour period also were less in the LD/N-treated patients. The findings were similar at the other monthly assessments that are not represented in the Table.

Medical Officer's Comments

- *Study M92-878 was blinded and randomized. The observed differences between the treatment groups are likely to be a result of treatment with NETA.*
- *Comparative data between the LD group in Study M92-878 and the LD/N group in Study M97-777 concerning the proportion of patients reporting hot flashes is of limited value as Study M97-777 was a single arm, unblinded study in which patients were likely told that adjunct treatment with NETA would reduce the frequency and severity of hot flashes.*

Table 42 Vasomotor Symptoms in the Month Prior to the Assessment Visit (Study M92-878)

Assessment Visit	Treatment Group	Number of Patients Reporting Hot Flashes		Number of Days with Hot Flashes		Maximum Number Hot Flashes in 24 Hours	
		N	(%)	N [2]	Mean	N [2]	Mean
Week 24	LD	32/37	87	37	19	36	5.8
	LD/N	22/38	58 [1]	38	7 [1]	38	1.9 [1]
Final Visit	LD	44/50	88	50	21	50	7.0
	LD/N	33/55	60 [1]	55	10 [1]	55	2.7 [1]

[1] Statistically significantly less than the LD group ($p < 0.01$).
[2] Number of patients assessed.
Reference: Statistical Tables 1.21, 1.22, and 1.23. In the ISS

9.8 Vital Signs and Weight

Vital signs (blood pressure and pulse rate) and weight at baseline and at the end-of-treatment are summarized in Table 43. Statistically significant changes from baseline were observed for sitting pulse rate (LD group: mean decrease of 5.14 beats per minute) and weight (mean increase of 6.37 and 4.85 pounds in the in the LD/N treatment groups in Studies M92-878 and M97-777, respectively).

In Study M92-878, hypertension was reported as an adverse events during the treatment period for 0 of 51 (0%) patients in the LD group and for 1 of 55 (1.8%) patients in the LD/N group. The one instance of hypertension was assessed as mild and not related to treatment. In Study M97-777, hypertension was reported as adverse events during the treatment period for 7 of 136 (5.1%) patients. Of the 7 reports of hypertension, 5 and 2 were rated as mild and moderate in severity, respectively. Five of these 7 instances of hypertension were assessed as not related to treatment.

Table 43 Baseline and End-of-Treatment Vital Signs and Weights

Study	Treatment Group	N	Baseline Mean	End of Treatment Mean	Change From Baseline Mean (SE)	P-value
Diastolic Blood Pressure(Mm hg)						
M92-878.	LD	44	69.82	70.50	0.68 (1.51)	0.654
M92-878.	LD/N	42	72.33	71.67	-0.67 (1.50)	0.658
M97-777	LD/N	119	71.58	72.66	1.08 (0.90)	0.233
Systolic Blood Pressure (Mm hg)						
M92-878.	LD	44	113.73	111.86	-1.86 (2.25)	0.413
M92-878.	LD/N	42	116.14	115.67	-0.48 (1.80)	0.793
M97-777	LD/N	119	113.66	114.03	0.36 (1.12)	0.747
Sitting Pulse Rate (Bpm)						
M92-878.	LD	44	76.86	71.73	-5.14 (2.02)	0.015
M92-878.	LD/N	40	72.00	74.35	2.35 (1.48)	0.120
M97-777	LD/N	119	74.93	76.70	1.76 (1.21)	0.147
Body Weight (Lbs)						
M92-878.	LD	45	144.19	147.39	3.19 (2.01)	0.119
M92-878.	LD/N	42	147.64	154.01	6.37 (1.61)	<0.001
M97-777	LD/N	120	151.06	155.92	4.85 (0.96)	<0.001

Source: Statistical Tables 2.17 of the ISS and 1.4 of the August 10, 2001 submission.

Medical Officer's Comments

- *An increase in weight is not unexpected in women taking moderately high doses of an androgenic progestin.*
- *The development of hypertension in 7 of 136 (5.1%) patients in Study M97-777 (although rated as mild in 5 and unrelated to treatment in 5) is of some concern.*

9.9 Laboratory Assessments

9.9.1 Mean Changes in Hematology and Chemistry Values from Baseline

For the purpose of generating summary statistics, data obtained during the Treatment Period were grouped into time intervals as follows: (1) data obtained on Treatment Days 2-252 were mapped to Treatment Week 24 and (2) data obtained after Day 252 were mapped to Treatment Week 52.

Mean changes in hematology and serum chemistry values, other than lipids, during treatment with LD or LD/N are listed in Table 44. Changes in serum lipid values are reviewed in Section 9.9.3. Table 44 lists the following values for each measurement: (1) mean baseline value, (2) mean changes from baseline (in the same units as the baseline value) at Week 24, Week 52, and the Final Treatment Visit, and (3) the p-value (t test statistic) for the change from baseline at the Final Visit. Small but statistically significant changes from baseline values, in one or more treatment groups, were observed for most of the laboratory measurements at the Final Treatment Visit.

Table 44 Mean Changes in Hematology and Serum Chemistry Values from Baseline

Parameter	Study [1]	Group	Baseline	Change from Baseline			P value
				Week 24	Week 52	Final	
Hemoglobin (g/dL)	M92	LD	13.05	0.16	0.34	0.31	0.053
	M92	LD/N	13.15	0.53	0.49	0.51	<0.001
	M97	LD/N	13.33	0.59	0.66	0.64	0.001
Total WBC ($x10^9$/L)	M92	LD	6.79	-1.15	-1.23	-1.23	<0.001
	M92	LD/N	7.11	-0.41	-0.30	-0.37	0.135
	M97	LD/N	6.38	0.11	-0.16	-0.02	0.848
Platelets ($x10^9$/L)	M92	LD	249.06	-11.75	-5.58	7.53	0.320
	M92	LD/N	259.90	12.43	8.66	5.89	0.130
	M97	LD/N	242.54	8.04	22.95	19.04	0.001
Neutrophils (%)	M92	LD	58.97	-7.53	-8.90	-8.50	<0.001
	M92	LD/N	60.37	-4.87	-2.57	-3.29	0.048
	M97	LD/N	58.21	0.17	0.01	0.16	0.833
Lymphocytes (%)	M92	LD	31.31	6.94	7.30	7.39	<0.001
	M92	LD/N	29.17	4.71	3.04	3.12	0.019
	M97	LD/N	32.46	0.01	0.18	-0.10	0.887
Glucose (mg/dL)	M92	LD	88.38	-3.15	-1.29	-0.03	0.990
	M92	LD/N	89.15	1.41	-1.64	0.80	0.792
	M97	LD/N	90.37	-1.56	-1.36	1.64	0.448
Creatinine (mg/dL)	M92	LD	0.98	0.04	0.05	0.03	0.046
	M92	LD/N	1.01	0.10	0.08	0.07	<0.001
	M97	LD/N	0.75	0.08	0.07	0.08	0.001
Calcium (mg/dL)	M92	LD	9.21	0.22	0.21	0.21	0.005
	M92	LD/N	9.23	0.10	0.02	0.03	0.603
	M97	LD/N	9.09	0.34	0.40	0.39	0.001
Phosphorus (mg/dL)	M92	LD	3.53	0.26	0.43	0.34	<0.001
	M92	LD/N	3.47	-0.13	-0.03	-0.01	0.925
	M97	LD/N	3.53	-0.20	-0.06	-0.05	0.452
Bilirubin (mg/dL)	M92	LD	0.41	-0.02	-0.04	-0.01	0.841
	M92	LD/N	0.46	-0.02	0.02	0.01	0.807
	M97	LD/N	0.56	0.01	-0.03	-0.05	0.029
Alkaline Phosphatase (IU/L)	M92	LD	68.63	12.90	23.92	17.35	<0.001
	M92	LD/N	67.37	-5.85	0.14	-0.71	0.754
	M97	LD/N	75.79	-5.50	0.54	-1.23	0.414
SGOT (IU/L)	M92	LD	17.08	3.41	2.17	3.08	<0.001
	M92	LD/N	18.39	0.93	3.64	3.88	0.088
	M97	LD/N	20.69	-0.42	0.34	0.23	0.746
SGPT (IU/L)	M92	LD	14.55	4.44	3.13	4.08	0.004
	M92	LD/N	18.15	1.46	5.07	6.22	0.092
	M97	LD/N	18.53	0.91	3.64	3.08	0.015
LDH (IU/L)	M92	LD	148.90	10.28	19.22	12.00	0.016
	M92	LD/N	150.49	14.85	22.39	19.05	<0.001
	M97	LD/N	153.08	12.69	18.34	18.63	0.001
GGT (IU/L) [2]	M97	LD/N	18.53	5.15	9.01	7.61	0.001

[1] M92 = Study M92-878; M97 = Study M97-777.
[2] Obtained only in Study M97-777.
[3] Based on the change at the Final Visit.
Source: Statistical Tables 1.1.1 of the August 10, 2001 submission and 2.16 of the ISS.

Medical Officer's Comments

- *Mean relative changes from baseline of greater than -10% or +10% at the Final Treatment Visit were observed for the following measurements.*

Measurement	Treatment Group	
	Decrease	Increase
Total WBC	LD (-18%)	
Neutrophils	LD (-14%)	
Lymphocytes		LD (+24%); LD/N-1 [1] (+11%)
Creatinine		LD/N-2 [2] (+11%)
Alk. Phos.		LD (+25%)
SGOT		LD (+18%); LD/N-1 (+21%)
SGPT		LD (+28%); LD/N-1 (+34%); LD/N-2 (+17%)
LDH		LD/N-1 (+13%); LD/N-2 (+12%)
GGT [3]		LD/N-2 (+41%)

[1] LD/N-1 = LD/N group in Study M92-878.
[2] LD/N-2 = LD/N group in Study M97-777.
[3] Measured only in study M97-777.
Source: Prepared by Medical Officer based on information in Table 44.

- *The largest percentage increases from baseline values were observed for liver enzymes (SGOT, SGPT, and GGT). SGOT and SGPT changes of similar magnitude occurred in both the LD and LD/N treatment groups in Study M92-878. GGT levels were measured only in Study M97-777. Hepatic toxicity has not been of clinical concern with this class of drugs.*
- *Increased alkaline phosphatase levels observed only in the LD group were most likely a consequence of increased bone turnover. The absence of an increase in alkaline phosphatase levels in the LD/N-treatment groups is consistent with the minimal decrease in bone mineral density observed in these groups.*

9.9.2 Incidence of Shifts to Low or High Hematology and Chemistry Values

The incidence rates of patients with shifts in hematology or serum chemistry laboratory values to (a) values below the lower limit of the normal range (shift to low) or (b) to values above the upper limit of the normal range (shift to high) are listed in Table 45.

Table 45. Incidence Rates (%) of Patients with Shift to Low or High Laboratory Values at the Final Treatment Visit

Parameter	Shift to Low						Shift to High					
	M92-878 (LD)		M92-878 (LD/N)		M97-777 (LD/N)		M92-878 (LD)		M92-878 (LD/N)		M97-777 (LD/N)	
	N [1]	Percent [2]	N	Percent	N	Percent	N	Percent	N	Percent	N	Percent
Hemoglobin	32	3	37	8	107	0	36	0	41	0	116	0
Hematocrit	27	11	30	10	108	0	36	0	41	2	116	1
White Blood Cells	36	3	41	0	111	5	34	0	37	3	115	0
Platelet Count	35	0	41	0	113	0	36	3	40	0	115	0
Neutrophils	34	3	41	5	112	1	35	0	40	0	115	0
Lymphocytes	35	0	39	0	115	2	34	6	40	5	110	3
Eosinophils	36	0	41	0	115	0	34	9	36	3	111	5
Glucose	39	3	40	10	118	4	39	8	40	5	117	2
Blood Urea Nitrogen	40	0	41	0	118	0	40	3	41	0	118	0
Creatinine	40	0	41	0	118	0	40	0	41	0	118	0
Uric Acid	40	0	41	2	118	0	39	3	37	8	117	1
Calcium	40	3	41	0	117	0	40	0	41	0	118	4
Phosphorus	40	3	39	3	116	1	40	8	40	3	118	3
Total Protein	39	0	41	0	118	0	39	0	41	2	116	1
Albumin	40	0	41	0	118	0	40	0	41	2	115	3
Total Bilirubin	40	0	41	0	118	1	39	3	40	3	113	1
Alkaline Phosphatase	40	0	38	5	118	1	39	10	39	0	114	3
SGOT	40	0	41	0	118	0	40	3	41	5	114	4
SGPT	40	0	41	0	118	2	40	5	40	5	116	8
LDH	37	0	39	3	118	0	38	5	40	10	116	2
GGT [3]	ND		ND		118	0	ND		ND		116	6

[1] Number of patients who did not have an abnormal value at baseline.
2 Percentage of patients who did not have the abnormal value at baseline but had the abnormal value at the final assessment.
[3] GGT was not measured in Study M92-878.
Source: Statistical Tables 1.40 and 3.11 of the ISS.

Medical Officer's Comments

- *Shifts to below the normal range affecting more than 5% of patients in a treatment group were observed for hemoglobin or hematocrit values in Study M92-878 in both the LD and LD/N treatment groups and for glucose in the LD/N group. Shifts to above the normal range affecting more than 5% of patients in a treatment group were observed for the following measurements in the following treatment groups*

Treatment Group	Measurement
LD (M92-878)	Lymphocytes, eosinophils, glucose, phosphorus, and alkaline phosphatase
LD/N (M92-878)	Uric acid and LDH
LD/N (M97-777)	SGPT and GGT

- *Among the hematology and serum chemistries values (other than lipids) that were outside of the normal range, few were more than 20% below the lower limit of the normal range or more than 2-fold above the normal range. Seven patients had one or more serum chemistry values that were ≥ 2-fold above the upper limit of the normal range as summarized below. Six of these 7 patients were treated with Lupron plus NETA.*

Measurement	Study	Tx Group	Pt. No.	Max Value	Tx Day	x ULN	Outcome
Glucose (mg/dL)	M97-777	LD/N	909		367	2.6	Partial resolution post Tx
Bilirubin (mg/dL)	M92-878	LD	1152		170	2.3	SGPT & SGOT nl; Resolved on Tx;
SGOT (IU/L)	M92-878	LD/N	1114		366	2.9	Bilirubin nl; no follow-up data
SGPT (IU/L)	M92-878	LD/N	1114		366	3.8	" "
SGPT (IU/L)	M92-878	LD/N	1272		307	2.7	Bilirubin nl; resolved post Tx
SGPT (IU/L)	M92-878	LD/N	1022		87	2.0	Bilirubin nl; no follow-up data
SGPT (IU/L)	M97-777	LD/N	908		386	3.1	Bilirubin nl; SGPT decreased to 68 IU/L 365 days post Tx
GGT (IU/L)	M97-777	LD/N	909		367	2.9	Bilirubin nl; Lesser elevations of SGPT/SGOT; partial resolution
GGT (IU/L)	M97-777	LD/N	913		398	2.0	Bilirubin, SGPT/SGOT nl; Resolved post Tx

[1] Baseline GGT was elevated (76 IU/L).
Source: Laboratory data listings from Final Reports for Studies M92-878 and M97-777.

- *Of the 6 patients with increased liver enzyme levels, none had elevated serum bilirubin levels. In 5 of these 6 patients, maximal liver enzyme levels were observed after 300 days of treatment with LD/N.*
- *The increase in serum bilirubin level in Patient No. 1152 was not accompanied by an increase in either SGPT or SGOT blood levels. This patient's bilirubin level returned to within the normal range without interruption of Lupron treatment.*

9.9.3 Serum Lipids

The effects of treatment with Lupron alone or Lupron plus 5 mg NETA on serum lipid levels were assessed by the measurement of total cholesterol, HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), and triglycerides at baseline, Treatment Weeks 24 and 52, and the Final Treatment Visit. In Study M97-777, posttreatment lipid levels were determined at Follow-up Months 1, 2, 3, 4, 8, and 12. Only limited posttreatment lipid data were obtained in Study M92-878 and are not discussed in this review.

9.9.3.1 Mean Lipid Values and Changes from Baseline during the Treatment Period

Total Cholesterol

In the LD treatment group, there were small, statistically significant increases in total serum cholesterol concentrations, with changes in mean values ranging from [redacted] (see Table 46). In the LD/N treatment groups, smaller, statistically inconsistent, increases in total cholesterol values, with changes in mean values ranging from [redacted], were observed. The increases at Week 52 in all treatment groups tended to be slightly greater than those at Week 24.

Table 46 Mean Total Serum Cholesterol Levels (mg/dL) (Studies M92-878. and M97-777)

Week	Study	Treatment Group	N	Baseline Mean	Treatment Visit	Mean % change from baseline [1]	P-value*
24	M92-878	LD	39	170.5	185.1	8.6	<.001
	M92-878	LD/N	41	179.3	180.3	0.6	.779
	M97-777	LD/N	117	181.2	184.8	2.0	.124
52	M92-878	LD	23	168.0	184.2	9.6	.002
	M92-878	LD/N	28	176.8	181.9	2.9	.170
	M97-777	LD/N	85	180.3	187.2	3.8	.016
Final	M92-878	LD	40	171.0	184.8	8.1	<.001
	M92-878	LD/N	41	179.3	183.2	2.2	.265
	M97-777	LD/N	118	181.1	186.5	3.0	.029

* Within group change from baseline
[1] Percentage change of mean treatment visit value from baseline.
Source: Statistical Tables 1.1.1 from the August 10, 2001 submission and 2.16 from the ISS.

HDL-Cholesterol

Statistically significant and similar decreases in mean HDL-C concentrations were observed at Weeks 24 and 52 and the Final Treatment Visit in both LD/N treatment groups (see Table 47). The decreases in mean HDL-C values did not change substantially between Week 24 and the Final Treatment Visit and ranged from [redacted]. In the LD treatment group, small increases in mean HDL-C values, ranging from [redacted] were observed.

Table 47 Mean Serum HDL-Cholesterol Levels (mg/dL) (Studies M92-878. and M97-777)

Week	Study	Treatment Group	N	Baseline Mean	Treatment Visit Mean	Mean % change from baseline [1]	P-value*
24	M92-878	LD	39	52.4	56.0	6.9	.017
	M92-878	LD/N	41	51.8	41.5	-19.9	<.001
	M97-777	LD/N	117	51.0	42.6	-16.5	<.001
52	M92-878	LD	23	49.1	50.0	1.8	.512
	M92-878	LD/N	28	51.2	41.6	-18.8	<.001
	M97-777	LD/N	85	51.0	41.9	-17.8	<.001
Final	M92-878	LD	40	52.4	55.2	5.3	.051
	M92-878	LD/N	41	51.8	41.7	-19.5	<.001
	M97-777	LD/N	118	51.1	42.5	-16.8	<.001

* Within group change from baseline
[1] Percentage change of mean treatment visit value from baseline.
Source: Statistical Tables 1.1.1 from the August 10, 2001 submission and 2.16 from the ISS.

Medical Officer's Comments

- *According to the guidelines of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (JAMA 2001; 285(19): 2486-2497), an HDL-C of < 40 mg/dL is a risk factor for coronary heart disease (CHD). In Study M92-878, 15% of patients in the LD group and 41% of patients in the LD/N group had a HDL-C value < 40 mg/dL at their Final Treatment Visit. In Study M97-777, 43% of patients had a HDL-C value < 40 mg/dL at their Final Treatment Visit.*
- *These increases in the proportion of patients with a HDL-C level < 40 mg/dL in the LD/N treated patients are consistent with the mean changes in HDL-C levels summarized in Table 47. They are also consistent with the anticipated effects of high doses of an androgenic progestin.*
- *It is of interest that similar decreases in serum HDL-C were observed in patients treated with Lupron plus 5 mg NETA plus conjugated equine estrogens in Treatment Arms 3 and 4 of Study M92-878. This observation supports the Sponsor's decision to not investigate further estrogen add-back therapy since NETA plus estrogen co-therapy was associated with (1) increased uterine bleeding, (2) a possible decrease in efficacy, and (3) similar decreases in serum HDL levels.*

LDL-Cholesterol

Mean LDL-C levels increased slightly from baseline values in all treatment groups (see Table 48). The increases were not substantially different across the LD and LD/N treatment groups and ranged from [redacted]. The increases at Week 52 were similar to those observed at Week 24.

Table 48 Mean Serum LDL-Cholesterol Levels (mg/dL) (Studies M92-878. and M97-777)

Week	Study	Treatment Group	N	Baseline Mean	Treatment Visit Mean	Mean % change from baseline [1]	P-value*
24	M92-878	LD	39	96.6	105.3	9.0	.023
	M92-878	LD/N	41	101.5	114.7	13.0	.002
	M97-777	LD/N	117	109.1	119.8	9.8	<0.001
52	M92-878	LD	23	95.5	107.7	12.8	.005
	M92-878	LD/N	27	101.8	112.7	10.7	.017
	M97-777	LD/N	83	106.1	120.4	13.5	<0.001
Final	M92-878	LD	40	97.0	104.6	7.8	.018
	M92-878	LD/N	41	101.5	115.1	13.4	<0.001
	M97-777	LD/N	118	109.1	120.4	10.4	<0.001

* Within group change from baseline
[1] Percentage change of mean treatment visit value from baseline.
Source: Statistical Tables 1.1.1 from the August 10, 2001 submission and 2.16 from the ISS.

Medical Officer's Comments

- *As the majority of study patients would be expected to be in the lowest risk category for CHD (without existing CHD and with <2 cardiovascular risk factors), LDL-C levels for these patients should be maintained at <160 mg/dL according to NCEP criteria. In Study M92-878, 3% of patients in the LD treatment group and 7% of patients in the LD/N treatment group had a LDL-C value >160 mg/dL at their Final Treatment Visit. In Study M97-777, 12% of patients had a LDL-C value >160 mg/dL at their Final Treatment Visit.*
- *Treatment with Lupron alone or co-treatment with Lupron plus NETA had minimal effects on serum LDL-C levels. Although the proportion of patients with increased LDL-C levels was greater in each of the LD/N treatment groups, the proportion of patients with increased LDL-C*

levels at baseline also was greater in these groups (5% and 8%) compared to the LD treatment group (0%) as shown in Table 51 on page 76.

LDL/HDL Ratio

Mean LDL/HDL ratios increased significantly in the LD/N treatment groups (see Table 49). The increases ranged form [redacted] The increases at Week 52 were not substantially different from those at Week 24. Small, statistically inconsistent, increases in mean LDL/HDL ratios, ranging from [redacted], were observed in the LD treatment group.

Table 49 Mean Serum LDL/HDL-Ratios (Studies M92-878. and M97-777)

Week	Study	Treatment Group	N	Baseline Mean	Treatment Visit Mean	Mean % change from baseline [1]	P-value*
24	M92-878	LD	39	1.95	2.06	5.6	.129
	M92-878	LD/N	41	2.06	2.86	38.8	<.001
	M97-777	LD/N	117	2.29	3.03	32.3	<.001
52	M92-878	LD	23	2.05	2.34	14.1	.013
	M92-878	LD/N	27	2.10	2.83	34.8	<.001
	M97-777	LD/N	83	2.25	3.15	40.0	<.001
Final	M92-878	LD	40	1.96	2.10	7.1	.067
	M92-878	LD/N	41	2.06	2.89	40.3	<.001
	M97-777	LD/N	118	2.29	3.07	34.1	<.001

* Within group change from baseline
[1] Percentage change of mean treatment visit value from baseline.
Source: Statistical Tables 1.1.1 from the August 10, 2001 submission and 2.16 from the ISS.

Medical Officer's Comment

- *Recent NCEP guidelines do not define a specific value below which the LDL/HDL ratio should be maintained. However, in Study M92-878, 3% and 12% of patients in the LD and LD/N treatment groups had a LDL/HDL ratio >4.0 at their Final Treatment Visit. In Study M97-777, 18% of patients had a LDL/HDL ratio >4.0 at their Final Treatment Visit.*

Triglycerides

Similar changes in triglyceride levels were observed in the LD and LD/N treatment groups (see Table 50). Changes in mean triglyceride levels ranged from [redacted] (LD/N treated patients in Study M97-777 at Week 52) and generally were not statistically significant.

APPEARS THIS WAY
ON ORIGINAL

Table 50 Mean Serum Triglycerides Levels (mg/dL) (Studies M92-878. and M97-777)

Week	Study	Treatment Group	N	Baseline Mean	Treatment Visit Mean	Mean % change from baseline[1]	P-value*
24	M92-878	LD	39	107.8	119.0	10.4	.137
	M92-878	LD/N	41	130.2	120.3	-7.6	.355
	M97-777	LD/N	117	105.4	114.6	8.7	.154
52	M92-878	LD	23	117.1	132.2	12.9	.202
	M92-878	LD/N	28	123.3	142.2	15.3	.180
	M97-777	LD/N	85	104.3	121.0	16.0	.015
Final	M92-878	LD	40	108.5	124.9	15.1	.046
	M92-878	LD/N	41	130.2	136.3	4.7	.577
	M97-777	LD/N	118	104.9	120.0	14.4	.020

* Within group change from baseline
[1] Percentage change of mean treatment visit value from baseline.
Source: Statistical Tables 1.1.1 from the August 10, 2001 submission and 2.16 from the ISS.

9.9.3.2 Percentage of Patients with Abnormal Serum Lipid Values

The percentages of patients with abnormal serum lipid values at baseline, Week 24, and the Final Treatment Visit are listed in Table 51. On-treatment percentages include (1) all patients with abnormal serum lipid values unadjusted for baseline abnormalities (referred to as "All Pts" and (2) only patients who did not have the abnormal value at baseline but an abnormal value at the on-treatment assessment (referred to as "New Pts").

Medical Officer's Comment

- *The potential adverse clinical impact of the observed changes in serum lipid values on cardiovascular risk is discussed in Section 9.10.1.*

9.9.3.3 Serum Lipid Values in the Post Treatment Follow-up Period

Serum lipid values in the post treatment Follow-up Period in Study M97-777 are summarized in Table 52. For those patients having post treatment follow-up measurements, the end-of-treatment serum HDL-C values were statistically lower than baseline and the end of treatment LDL-C values, LDL/HDL ratios, and triglycerides values were statistically higher than at baseline. Mean serum levels of HDL-C, LDL-C, and triglycerides returned to values that were not statistically different than baseline after discontinuation of treatment with LD/N.

Medical Officer's Comment

- *Serum values for LDL-C, HDL-C, and triglycerides were no longer statistically different from baseline by Follow-up Months 4, 8, and 12 , respectively. Although the LDL/HDL ratio at the Month 12 Follow-up visit was statistically different from baseline, the difference was not clinically meaningful.*

Table 51 Percentage of Patients with Abnormal Serum Lipid Values at Week 24 and Final Treatment Visit

	M92-878 (LD)				M92-878 (LD/N)				M97-777 (LD/N)			
	Baseline		On Treatment		Baseline		On Treatment		Baseline		On Treatment	
	N[1]	Percent Abnl	Percent Abnl (All Pts)[2]	Percent Abnl (New Pts)[3]	N	Percent Abnl	Percent Abnl (All Pts)	Percent Abnl (New Pts)	N	Percent Abnl	Percent Abnl (All Pts)	Percent Abnl (New Pts)
Week 24												
Total Cholesterol (>240 mg/dL)	39	15%	23%	15%	41	15%	20%	9%	117	6%	7%	5%
HDL Cholesterol (<40 mg/dL)	39	15%	10%	3%	41	15%	44%	37%	117	15%	41%	32%
LDL Cholesterol (>160 mg/dL)	39	0%	8%	8%	41	5%	7%	3%	117	9%	11%	6%
LDL/HDL RATIO >4.0	39	0%	3%	3%	41	2%	15%	13%	117	7%	21%	17%
Triglycerides (> 200 mg/dL)	39	13%	13%	6%	41	12%	10%	3%	117	5%	9%	7%
Final Visit												
Total Cholesterol (>240 mg/dL)	40	15%	33%	26%	41	15%	27%	17%	118	6%	8%	5%
HDL Cholesterol (<40 mg/dL)	40	15%	15%	6%	41	15%	41%	37%	118	14%	43%	36%
LDL Cholesterol (>160 mg/dL)	40	0%	3%	3%	41	5%	7%	3%	118	8%	12%	6%
LDL/HDL RATIO >4.0	40	0%	3%	3%	41	2%	12%	10%	118	7%	18%	13%
Triglycerides (> 200 mg/dL)	40	13%	15%	6%	41	12%	15%	8%	118	5%	10%	6%

[1] Number of patients with a serum lipid value.

[2] "All Pts." Total percentage of patients with abnormal value at the time of the assessment regardless of baseline value.

[3] "New Pts." Percentage of patients with abnormal value at the time of the assessment who did not have the abnormal value at baseline.

Source: Statistical Tables 3.1, 3.2, 3.3, and 3.4 of September 4, 2001 submission.

Table 52 Serum Lipid Values in the Post treatment Follow-up Period (Study M97-777)

Variable	Final Treatment Visit			Month 4 Follow-up Visit			Month 8 Follow-up Visit			Month 12 Follow-up Visit			Final Follow-up Visit		
	N[1]	Baseline Mean	Visit Mean	N	Baseline Mean	Visit Mean	N	Baseline Mean	Visit Mean	N	Baseline Mean	Visit Mean	N	Baseline Mean	Visit Mean
Cholesterol	97	182.3	186.9	83	182.0	184.0	81	183.1	184.7	70	181.9	184.4	97	182.3	184.3
HDL-Cholesterol	97	51.4	42.1***	83	51.4	49.3*	81	50.9	48.9	70	51.5	49.9	97	51.4	50.3
LDL-Cholesterol	97	109.8	121.6***	83	109.5	111.6	79	111.7	113.0	69	110.1	112.7	97	109.8	110.6
LDL/HDL	97	2.3	3.1***	83	2.3	2.5**	79	2.3	2.5*	69	2.3	2.5*	97	2.3	2.4*
Triglycerides	97	102.0	119.0**	83	101.7	115.6**	81	102.2	125.0**	70	100.7	116.7	97	102.0	122.6**

[1] Only data from patients with data at both baseline and the visit for the corresponding lipid variable are included.

*,**, *** Statistically significantly different from baseline at the 0.05, 0.01, and 0.001 levels, respectively.

Source: Text Tables 12.4b and 12.4c of the Final Report for Study M97-777 (One Year Posttreatment Follow-up)..

APPEARS THIS WAY
ON ORIGINAL

9.10 Safety Consultations

The Division of Metabolic and Endocrine Drug Products (DMEDP) was consulted (1) for an assessment of the likely increase in cardiovascular risk that would be associated with the adverse lipid changes observed in patients treated with Lupron plus 5 mg NETA and (2) an assessment of the adequacy of the clinical data that supported the Sponsor's claim that co-treatment with 5 mg NETA significantly attenuated the decrease in BMD that was observed in the women treated with Lupron alone. Brief summaries of the conclusions/recommendations of these consults are provided below.

9.10.1 Serum Lipid Changes

Dr. Anne Pariser, Medical Officer in DMEDP, noted in her Consultation of August 16, 2001 that HDL-C levels of <40 mg/dL were observed in about 45% of patients in the NETA-exposed groups and were the most significant and consistent lipid-altering effect seen as a consequence of treatment with LD/N. Her conclusions included the following statements.

- *"A decreased HDL-C has been established as a risk factor for CV disease in large epidemiological trials; however, these studies were conducted predominantly in men and post-menopausal women, and in older patients (age >50 years). The significance of short-term, drug-induced reductions in HDL-C in pre-menopausal women at low risk for CV disease has not been determined."*
- *"As most patients likely to be treated with LD/N for endometriosis are at low-risk for CV disease it is unlikely that the small changes seen in total cholesterol, LDL-cholesterol and triglycerides with treatment with NETA would result in a significant change in CV risk status for these patients. This is especially true as treatment is likely to be of a relatively short duration."*

Dr. Pariser recommended that:

1) *Labeling include the effects seen on the lipid profile with treatment with LD plus NETA.*
2) *Labeling include a statement regarding low HDL-C and increased CV risk, although the short-term effect of treatment-induced low HDL-C levels on CV risk in endometriosis patients is unknown.*
3) *Labeling include a recommendation that CV risk assessment be undertaken at baseline, and that management of other CV risk factors, such as smoking, be undertaken.*
4) *The decrease in HDL-C as a function of weight gain should be further explored.*
5) *Consideration should be given to the investigation of other add-back regimens with less effect on HDL-C, such as less androgenic progestins, e.g., medroxyprogesterone.*

Medical Officer's Comment

- *Items 1-3 will be addressed in labeling as suggested by Dr. Pariser. Items 4 and 5 are general suggestions/comments that do not require specific actions at this time.*

9.10.2 Changes In BMD

The supplemental review of the bone mineral density findings by Dr. Bruce Schneider, Medical Officer in DMEDP, supported the conclusions of the primary Medical Reviewer in DRUDP that the Sponsor had adequately demonstrated that co-treatment with 5 mg of NETA attenuated the decrease in BMD observed with Lupron treatment alone. Dr. Schneider also stated in his review that

- *"I believe that the sample size was sufficient for these studies in patients with endometriosis. The methodology for BMD determination was standard and certainly acceptable." However, he also stated that "in osteoporosis prevention studies, BMD changes are always measured at important*

extra-vertebral sites. Thus, the available information does not provide a complete picture of the overall BMD responses to Lupron and Lupron/NETA. This should be a consideration in approval of Lupron plus NETA for prolonged primary treatment or retreatment."

Other comments by Dr. Schneider included the following statements.

- *"We have data on 32 patients previously treated with a GnRH analog, who were given LD/NETA as participants in the above two studies. This subset was analyzed separately. This analysis disclosed that the mean BMD loss in this group at 24 and 52 weeks was –0.515% and –0.786%, respectively. These are in reasonable agreement with the behavior of the group as a whole.... I have no information regarding the time interval between the termination of the first GnRH treatment and the initiation of Lupron therapy. Nonetheless, it appears from the data that patients who have experienced prior GnRH therapy response as well to NETA add-back therapy as do GnRH-naïve individuals."*
- *"In certain individuals who are at high risk of bone loss (by BMD, personal and family history, body weight, etc.), I think that addition of NETA would be helpful in reducing any further BMD decrease at the spine at 6 months. It is likely that some individuals will experience BMD losses of more than 3% during this period, and some patients may not replace these losses."*

10 DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The 3.75-mg monthly dose of Lupron Depot that was used in these Studies is the approved dose for the management of endometriosis. An 11.25-mg dose of Lupron Depot, administered once every 3 months, is also approved for the management of endometriosis. There are no issues concerning the dose of Lupron or the Lupron dosing regimen. A daily dose of 5-15 mg of norethindrone acetate is approved for the treatment of endometriosis. No additional dose-ranging studies with NETA, however, were conducted to determine if a lower dose would have provided adequate bone-protection with less of an adverse effect on serum lipids, particularly HDL-cholesterol.

11 USE IN SPECIAL POPULATIONS

11.1 Women and Children

Endometriosis is a disease that affects primarily reproductive–aged women. It does not affect prepubertal girls. Lupron also is approved for the treatment of precocious puberty.

11.2 Subjects with Renal or Hepatic Impairment

Studies in women with renal or hepatic impairment have not been conducted with Lupron. Present labeling does not address this issue. Norethindrone acetate is contraindicated (present label) in women with "markedly impaired liver function or liver disease."

11.3 Racial Differences in Efficacy and Safety Findings

The total number (percentage) of black women in the 2 studies submitted in support of this application was small, 25 of 243 patients (10%). It was felt that a subset analysis based on race would be of limited value, and consequently it was not performed. The Sponsor, however, conducted subset analyses based on the median age (28 years) of all enrolled patients. The analyses did not reveal any consistent or significant clinical differences in the responses to treatment in women ≤ 28 years of age and those > 28 years of age.

12 PACKAGE INSERT

The Sponsor has proposed extensive revisions to the presently approved package insert for Lupron Depot. These revisions focused largely on the one-year findings in Studies M92-878 and M97-777. Because this Medical Reviewer recommends that both primary treatment and retreatment with Lupron plus NETA be limited to a maximum of 6 months, the proposed label should be extensively revised. Sections on the potential benefits and risks of co-treatment with NETA also will need to be revised. Information regarding which patients are likely to benefit most from NETA co-treatment (e.g., women with known low BMD or other risk factors for the development of osteoporosis) should be added. Conversely, warnings about the use of 5 mg NETA in women with increased cardiovascular risk factors should be added. In addition, contraindications and warnings concerning the use of NETA that are included in the presently approved label for Aygestin also should be added to the Sponsor's proposed label for Lupron Depot.

13 CONCLUSIONS AND RECOMMENDATIONS

13.1 Overall Risk/Benefit Assessment

Benefits of Treatment with Lupron plus NETA

The approved duration of treatment with GnRH agonists for the management of pain due to endometriosis is restricted to 6 months, and retreatment is generally not recommended. These limitations have been imposed because of concern that a longer period of treatment or retreatment would produce clinically significant irreversible bone loss in some women because of prolonged hypoestrogenemia. Symptomatic relief is usually noted by the end of the first month of treatment with GnRH analogs and may continue for many months or even years after completion of 6 months of treatment. However, there are patients for whom retreatment would be desirable because of recurrence of symptoms. In an effort to safely increase the permissible duration of treatment as well as to safely permit retreatment, the Sponsor conducted 2 clinical trials in which women were treated with Lupron plus NETA for up to 1 year. Based on findings from small clinical trials conducted by academic investigators, the Sponsor anticipated that treatment with NETA would attenuate Lupron-induced decrease in BMD, either through a direct action on bone or indirectly through conversion to estrogenic and/or androgenic compounds.

The effects of treatment with Lupron alone or Lupron plus 5 mg NETA on BMD in Studies M92-878 and M97-777 are summarized below in Table 53. The percent decrease in BMD from baseline observed at both Week 24 and Week 52 in patients treated with Lupron plus NETA was reduced in both studies compared to the BMD decrease in patients treated with Lupron alone. Of greater importance in assessing the potential benefit of co-treatment with NETA is the magnitude of the decrease in BMD from baseline. Based in part on discussions with DMEDP, it was agreed that if the mean BMD decrease from baseline in the LD/N treatment group was no greater than –2.2%, co-treatment with NETA would be considered to have had a clinically beneficial effect. This outcome would require that the lower bound of the 2-sided 95% CI for the mean change in BMD from baseline be no less than –2.2%. In both Studies, the lower bound of the CI in the LD/N treated patients was greater than (i.e., above) –2.2% at both the Week 24 and Week 52 assessments.

Table 53 Summary of BMD Changes from Baseline during Treatment for Up to 1 Year

Time of Assessment	Study M92-878						Study M97-777		
	LD (n=51)			LD/N(n=55)			LD/N (n=136)		
	N	Percent Change	95% CI [3]	N	Percent Change	95% CI	N	Percent Change	95% CI
Week 24 [1]	41	-3.2	(-3.8, -2.6)	42	-0.3	(-0.8, 0.3)	115	-0.2	(-0.6, 0.2)
Week 52 [2]	29	-6.3	(-7.1, -5.4)	32	-1.0	(-1.9, -0.1)	84	-1.1	(-1.6, -0.5)

[1] Includes on-treatment measurements that fell within 2-252 days after the first day of treatment.
[2] Includes on-treatment measurements > 252 after the first day of treatment.
[3] Two-sided 95% confidence interval about the mean difference from baseline.
Source: Statistical Tables 3.1.1 (Submission of August 10, 2001) and 2.7 (ISS).

Patients treated with Lupron plus NETA also had fewer and less severe hot flashes than patients treated with Lupron alone. The benefits of NETA therapy on vasomotor symptoms, as shown in Study M92-878, included statistically significant reductions in the number of women reporting hot flashes, the number of days with hot flashes, and the maximum number of hot flashes in a 24-hour period.

Potential Risks of Co-Treatment with Lupron plus NETA.

Because the therapeutic effect of Lupron on the painful symptoms of endometriosis is a consequence of the hypoestrogenic condition produced during treatment, it was possible that co-treatment with NETA would reduce efficacy. Findings from the blinded and controlled clinical study (Study M92-878) did not shown any decrease in efficacy in the LD/N treated patients compared to the LD-treated patients. Clinical improvement was similar in both treatment groups assessed both by decreases in mean clinical pain severity scores and the proportions of patients with clinical improvement in each of the 5 endometriosis symptom categories.

The adverse effects resulting from co-treatment with 5 mg NETA were not unexpected and consisted primarily of (1) adverse changes in serum lipid profiles and (2) an increase in androgenic metabolic effects. Percent changes in mean serum lipid concentrations at the Week 24 and Week 52 treatment visits are summarized below in Table 54. The major impact of treatment with Lupron plus NETA on serum lipid profiles, compared to treatment with Lupron alone, was to significantly (1) decrease serum HDL-cholesterol concentrations and (2) increase the LDL/HDL ratios.

Table 54 Serum Lipid Concentrations: Mean Percent Changes from Baseline

Measurement	Week 24				Week 52			
	LD Gp (n=39)		LD/N Gp (n=158)[1]		LD Gp (n=23)		LD/N Gp (n=113)[1]	
	Baseline mg/dL	Tx Visit % Change	Baseline mg/dL	Tx Visit % Change	Baseline mg/dL	Tx Visit % Change	Baseline mg/dL	Tx Visit % Change
Total Cholesterol	170.5	8.6%	180.7	1.6%	168.0	9.6%	179.4	3.6%
HDL Cholesterol	52.4	6.9%	51.2	-17.4%	49.1	1.8%	51.0	-18.1%
LDL Cholesterol	96.6	9.0%	107.1	10.6%	95.5	12.8%	105.0	12.8%
LDL/HDL Ratio	2.0*	5.6%	2.2*	33.9%	2.1*	14.1%	2.2*	38.8%
Triglycerides	107.8	10.4%	111.8	3.8%	117.1	12.9%	109.0	15.8%

[1] Integrated results from Studies M92-878 and M97-777
* No unit as value is a ratio.
Source: Statistical Tables 1.1.1 and 1.1.2.2 (Submission of August 10, 2001).

Although decreased HDL-cholesterol levels have been identified as a risk factor for cardiovascular disease in large epidemiological trials; these studies were conducted predominantly in men and post-

menopausal women. The significance of short-term, drug-induced reductions in HDL-cholesterol in premenopausal women at low risk for cardiovascular disease has not been determined. Since most patients likely to be treated with Lupron plus NETA for endometriosis are at low-risk for cardiovascular disease and approved treatment is for a relatively short duration (6 months), it is unlikely that the changes in serum lipids would result in a significant change in long-term cardiovascular risk status for these patients.

Other adverse effects of treatment with NETA included androgenic metabolic effects, such as acne, and depression (a known adverse effect of progestins) that were reported in a greater proportion of the LD/N treated patients. Across the 2 studies, depression rated as severe in intensity was reported by 5 of 191 (3%) LD/N-treated patients and no LD-treated patients. Mean weight gains also were numerically greater in the LD/N treatment groups. Hypertension was reported as an adverse event in 8 of 191 (4.3%) LD/N-treated patients and in no LD-treated patients.

Treatment for 6 Months Versus Treatment for 12 Months

Although treatment for 12 continuous months may be of benefit for some patients, the Sponsor did not provide data to show that (1) the clinical response after 12 months of treatment is significantly better than that after 6 months of treatment or (2) the persistence of symptomatic improvement is greater after 12 months of treatment than after 6 months of treatment.

Information in the Figure labeled "Percent of Patients with Sign/Symptoms at Baseline, Final Treatment Visit, and After 6 and 12 Months of Follow-Up" in the presently approved package insert indicates that there is good persistence of relief through Month 12 of follow-up for 4 of the 5 clinical pain categories. The Sponsor was requested to analyze the data from the LD/N-treated patients in Studies M92-878 and M97-777 by the same statistical procedure as used for the Figure in the package insert. The Sponsor chose to perform a similar but not identical analysis. Based on this supplemental analysis and the analyses presented in the original submission, there was no evidence that 12 months of treatment, compared to the 6 months of treatment represented in current labeling, was followed by a longer period of pain relief. It is therefore recommended that the initial treatment period with Lupron continue to be 6 months as in current labeling. For those patients who have a recurrence of symptoms, a single course of retreatment with Lupron plus NETA of up to 6 months duration can be considered.

Summary

Co-treatment with NETA and Lupron should be considered for all patients undergoing initial 6 months of treatment for endometriosis. The decision to include NETA should be based on the benefits of reducing the decrease in BMD and the frequency of vasomotor symptoms balanced against the adverse effect on serum lipids and the increase in other androgenic adverse events. Co-treatment with NETA would be of most benefit for women with increased risk factors for osteoporosis and those in whom retreatment is a likely possibility. Conversely, co-treatment with NETA should be avoided in women with increased cardiovascular risk factors. Patients for whom retreatment is contemplated should have their BMD measured prior to retreatment. Based on presently available data only a single 6-month course of retreatment with Lupron Depot plus 5 mg NETA can be recommended. Patients should not be retreated with Lupron alone.

13.2 Approvability

13.2.1 Recommendations Regarding Approval

The following recommendations apply to both NDA 20-011/s021 and NDA 20-708/s011:

1. Information about the benefits and potential risks of co-treatment with Lupron plus 5 mg norethindrone acetate (NETA) can be added to labeling for both Lupron Depot 3.75 mg and Lupron Depot 3 Month 11.75 mg. Information also should be added to labeling as to which patients are most likely to benefit from co-treatment with NETA and which patients should not receive co-treatment with NETA.
2. A single course of retreatment with Lupron plus NETA, not to exceed 6 months, can be permitted based on the information provided in this application. The present restriction concerning retreatment should be modified accordingly in the label. Lupron alone should not be used for retreatment.
3. The maximum duration of a single course of treatment with Lupron (or Lupron plus NETA) should continue to be 6 months. The Sponsor's request to extend a single course of treatment for up to 12 months should not be approved. The Sponsor has not demonstrated that there would be significant and additional long-lasting clinical benefit if a single course of treatment were to be extended beyond 6 months.

13.2.2 Specific Recommendations to the Sponsor

1. Specific recommendations concerning revisions to the proposed labels were communicated to the Sponsor on September 14, 2001.
2. If the Sponsor wishes to obtain a labeling change supporting 1 year of continuous co-treatment with Lupron plus NETA, the Sponsor will need to submit new clinical data showing that there is additional and sustained long-lasting clinical benefit resulting from the longer treatment period.
3. If the Sponsor wishes to obtain a labeling change permitting more than one 6-month course of retreatment, the Sponsor will need to submit new clinical data supporting the safety and efficacy of repeated courses of retreatment.

Scott E. Monroe MD
Medical Officer, DRUDP

Addendum

Final revised package inserts and patient package inserts for Lupron Depot 3.75 mg and Lupron Depot 11.25 mg were received from the Sponsor on September 21, 2001. They were reviewed and found to be acceptable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Scott Monroe
9/21/01 02:26:32 PM
MEDICAL OFFICER

Dena Hixon
9/21/01 02:33:09 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMO TO FILE:	20-Aug-2001
Medical Reviewer:	Anne Pariser, M.D.
NDA#:	20-011/S-021
	20-708/S-11
Consult Date:	16-Aug-2001
Sponsor:	TAP Pharmaceutical Products, Inc.
Drug:	Lupron Depot 3.75 mg
	Lupron Depot-3 Month 11.25 mg
Subject:	Correction to Consult dated 16-August-2001

Correction: Page 4, third paragraph (correction in ***bold underlined italics***), as follows:

Despite the lack of clinical evidence that hormonal drug treatment with estrogen and progesterone can affect CV risk in pre-menopausal women, low HDL-C as a risk factor for CV disease has been firmly established by large epidemiologic trials[i]. Four large prospective epidemiologic studies have been performed in the United States that related levels of HDL-C and the incidence of CHD. These studies were: the Framingham Heart Study (FHS)[ii], Lipid Research Clinics Prevalence Mortality Follow-up study (LRCF)[iii], the Lipid Research Clinics Coronary Prevention Trial (CPPT)[iv], and the Multiple Risk Factor Intervention Trial (MRFIT)[v]. These trials have evaluated older, predominantly male, higher-risk patients, and only FHS and LRCF included women. The FHS included men and women between the ages of 50 and 69, and LRCF included men and women ages 30-69. The results from these studies were generally consistent in demonstrating that a 1 mg/dL increment in HDL-C was associated with ***a decreased*** risk of CHD and total CVD mortality of about 2%. The results in women in the LRCF were even more striking, with a 1 mg/dL increment in HDL-C associated with an approximately 4% decrease in CHD and total CV mortality. The relationship of HDL-C to all-cause mortality was weak however, and there were no differences in overall mortality observed between patients with different HDL-C levels. As these trials were performed in predominantly male, higher risk patients, it is not known if similar results would be obtained in a population of pre-menopausal female patients at low-risk of CHD, with secondarily induced (i.e., drug induced) low HDL-C.

---

[i] Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, Jacobs DR, Bangdiwala S, Tyroler HA. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989;79(1):460-466.

[ii] Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease: The Framingham Study. Am J Med 1977;62:707-714.

[iii] Jacobs DR for the Lipid Research Clinics follow-up study. High density lipoprotein cholesterol and coronary heart disease, cardiovascular disease, and all-cause mortality. Circulation 1985;72(suppl III):III-85.

[iv] Gordon DJ, Knoke J, Probstfield JL, Superko R, Tyroler HA for the Lipid Research Clinics Program. High-density lipoprotein cholesterol and coronary heart disease in hypercholesterolemic men: The Lipid Research Clinics Coronary Primary Prevention Trial. Circulation 1986;74:1217-1225.

[v] Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial: Risk factor changes and mortality results. JAMA 1982;248:1465-1477.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Anne Pariser
8/20/01 12:00:45 PM
MEDICAL OFFICER

Mary Parks
8/27/01 01:33:06 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Consult from the Division of Metabolic and Endocrine Drug Products

Division Requesting Consult:	Division of Reproductive and Urologic Drug Products, HFD-580
Drug Name:	Lupron Depot 3.75 mg Lupron Depot-3 Month 11.25 mg
Duration:	12 Months
Sponsor:	TAP Pharmaceutical Products, Inc.
NDA #:	20-011/S-021 20-708/S-11
Consult Date:	16-August, 2001
Author:	Anne R. Pariser, M.D. Division of Metabolic and Endocrine Drug Products, HFD-510

A. Consult Request

The Division of Reproductive and Urologic Drug Products (DRUDP) has requested an assessment of the level of risk associated with the adverse effects on the serum lipid profile seen in women when norethindrone acetate (NETA) 5 mg daily is added to Lupron for the treatment of endometriosis. The duration of treatment will be 6 to 12 months, or initial treatment will be for 6 months followed by retreatment for additional 6 month periods. The following questions are to be addressed:

1. Has the sponsor submitted sufficient data to permit a meaningful assessment of the effects of 6 and 12 months of treatment with 5 mg of NETA per day on lipids?
   A) Is the sample size adequate?
   B) Are the laboratory measurements appropriate and adequate?

2. What is the assessment of the risk(s) associated with the changes in lipids that were observed after 6 and 12 months of treatment with 5 mg of NETA per day?

3. Are these lipid-related risks likely to be significantly greater in women treated with Lupron plus NETA than those in women treated with Lupron alone?

4. If DRUDP were to extend the recommended treatment period with Lupron from 6 months to a maximum of 12 months for patients who also receive 5 mg NETA per day, what additional warnings or precautions would be included in labeling?

B. Background

Lupron Depot (LD) plus norethindrone acetate (NETA) "add-back" therapy is being evaluated by the DRUDP for the treatment of women with endometriosis. Lupron (leuprolide acetate), a gonadotropin-releasing hormone (GnRH) agonist, is currently approved for the treatment of pain associated with endometriosis. Treatment with Lupron or other GnRH agonists for longer than 6-months, or retreatment after the initial 6 months of therapy, is currently not recommended due to the hypoestrogenic effects of

treatment, particularly the loss of bone mineral density (BMD). Patient tolerance to treatment has also been limited, most commonly due to vasomotor symptoms. Investigators have attempted to decrease these side-effects and to allow treatment with GnRH agonists for longer than 6 months with the use of "add-back" therapies, which add-back sex-hormones to the GnRH agonist treatment[1]. Several small clinical trials have investigated the use of GnRH agonists with add-back therapies, usually either progestins alone or progestins plus estrogens, for up to one year. Add-back therapies, with progestins however, have been noted to have adverse effects, most notably unfavorable effects on the lipid profile.

NETA, a 19-nortestosterone derived progestin, is currently approved for the treatment of endometriosis, secondary amenorrhea, and abnormal uterine bleeding. NETA was selected for use as add-back therapy with Lupron based on previous research with norethindrone (NET). NET has been used with Lupron in doses of 0.35 to 3.5 mg per day (mean 2.04 per day), and NET has been used in combination with other GnRH agonists at doses of 1.4-10 mg per day. NET is not commercially available in the United States, and NETA was used instead as it has similar properties to NET. NETA is thought to be about ½ as potent as NET.

NETA and the other C-19-nortestosterone derived progestins possess androgenic activity, and have been associated with decreases in high density lipoprotein cholesterol (HDL-C), increases in low density lipoprotein cholesterol (LDL-C), and increases in the LDL/HDL ratio. The lipid effects appear to be dose-related. The adverse effects of NET on the lipid profile have been demonstrated in two small clinical studies that administered NET in combination with Lupron or nafarelin (another GnRH agonist). In one open-label, randomized, 48-week study by Surrey et al[2], 19 female patients with endometriosis were treated with LD plus sodium etidronate cycled with calcium carbonate and NET 2.5 mg daily (Group 1), or LD plus NET 10 mg daily (Group 2). Results showed that patients receiving both doses of NET experienced some decrease in HDL-C. Group 2 experienced larger decreases in HDL-C than Group 1, -37% vs -12% respectively, after 48 weeks of treatment. Persistent increases in LDL-C (+27 in Group 2, and +14% in Group 1) were also noted. Increases in the LDL/HDL ratio, and decreases in apo AI were also seen in Group 2. Both groups experienced some weight gain over the course of treatment, with Group 2 experiencing a significantly greater weight gain than Group 1 (7.7 ± 1.7 kg vs 3.4 ± 1.0 kg respectively). The primary differences between the two groups were in the greater lipid changes and weight gain associated with the higher doses of NET.

In another study by Riis et al[3], women with endometriosis were treated with nafarelin (n=9), or nafarelin plus NET 1.2 mg per day for 6 months (n = 17). Lipid results for the nafarelin plus NET group were notable for significant decreases in HDL-C of -10 to -15% during treatment, and for significant decreases in total cholesterol [TC] (-3 to –9%) and LDL-C (0 to –12%) during treatment and in the follow up period. Nafarelin alone significantly increased TC (+14 to +20%), and LDL-C (+5 to +20%) during treatment and follow up, and significantly decreased HDL-C (-9%) at 12 months in the follow up period.

Similar effects on the lipid profile have been demonstrated when NET and other progestins are used alone as contraceptive agents. In a study by Enk et al[4], depot injections of NET and depot-medroxyprogesterone (DMPA) [a 17-alpha-hydroxyprogesteone derivative] were administered for one year. NET showed persistent decreases in HDL-C of about –30% at 13 months of treatment compared to baseline. DMPA showed decreases in HDL-C and total cholesterol (TC) of about 10-20%. Another study by McEwan et al[5] evaluated the effects of long-term use (2-5 years, or >5 years) of depot-norethisterone enanthate (Nor-en) on serum lipids. Nor-en produced no differences from baseline in triglyceride (TG), TC, LDL-C and very low density lipoprotein cholesterol (VLDL-C). Decreases in HDL-C of -16% were seen in women who used Nor-en for 2-5 years, and decreases in HDL of -12% were seen in women who used Nor-en for >5 years. Similar decreases in HDL-C to those seen with NET and Nor-en have also been seen with other 19-nortestosterone derivatives administered orally (e.g. levonorgestrel)[6]. Effects on serum lipids for DMPA have been variable however, with some studies showing no effect on the lipid profile, and others showing mild increases in TC and LDL-C, and 10-20% decreases in HDL-C.

The effect on the lipid profile of GnRH agonists alone has also been studied[7,8]. The effect on the lipid profile has generally been mild, with either small increases in LDL-C and TC levels and little to no effect on HDL-C, or no effect on the lipid profile. These findings are consistent with the hypoestrogenic and hypoandrogenic effects of GnRH agonist treatment.

The effect of Danazol, another treatment for endometriosis, has also been studied. Danazol possesses strong androgenic activity and was compared to nafarelin in a study by Valimake et al[9] in patients with endometriosis (nafarelin n = 12, danazol n = 6). Both groups had decreases in TG and mild increases in TC. Danazol produced decreases in HDL-C and increases in LDL-C that recovered in the post treatment period. Nafarelin had no significant effects on HDL-C or LDL-C. These results suggest that the androgenic effects of treatment may be the predominant factor effecting serum lipids.

Although the effects of progestins on the serum lipids in women treated for endometriosis have been well documented in clinical trials, the long-term effects of these drugs on coronary heart disease (CHD) and cardiovascular (CV) morbidity and mortality have not been determined. Studies investigating the long-term effects of progesterone and estrogen administration on CV disease have been performed almost exclusively in users of oral contraceptive (OC) agents. The results of these studies have been conflicting, particularly as earlier studies investigated the effects of the older, higher-dose estrogen/progesterone combination OC agents that carried a higher risk of CV complications. More recent studies however, have found no increased risk of myocardial infarction (MI) in current users of low-dose OC agents[10], and other studies have shown an increased risk of MI only in OC users who are heavy smokers (>25 cigarettes per day)[11]. Results of the WHO Collaborative Study of Cardiovascular Disease and Steroid Contraception[12] found that OCs and heavy smoking together greatly increased the risk of MI, especially in combination with OCs containing 50 mcg of estrogen or more. These

results suggest a thrombotic rather than an atherogenic mechanism is involved in OC-related CV disease. The data from these studies however, did not allow for a firm conclusion about the possibility that progestin-containing OCs might affect the risk of MI in current users[13].

Past users of OCs have also been found to be at no greater risk of experiencing an MI than women who have never used OCs. A case-control study in women experiencing their first MI found that there was no increased risk of MI in former OC-users, whether use had ceased in the distant past or more recently[14]. These results suggest no prolonged effect on atherosclerotic CHD associated with OC agents in women; however it is not known if these findings would also apply to women treated with hormonal add-back therapy for endometriosis.

Despite the lack of clinical evidence that hormonal drug treatment with estrogen and progesterone can affect CV risk in pre-menopausal women, low HDL-C as a risk factor for CV disease has been firmly established by large epidemiologic trials[15]. Four large prospective epidemiologic studies have been performed in the United States that related levels of HDL-C and the incidence of CHD. These studies were: the Framingham Heart Study (FHS)[16], Lipid Research Clinics Prevalence Mortality Follow-up study (LRCF)[17], the Lipid Research Clinics Coronary Prevention Trial (CPPT)[18], and the Multiple Risk Factor Intervention Trial (MRFIT)[19]. These trials have evaluated older, predominantly male, higher-risk patients, and only FHS and LRCF included women. The FHS included men and women between the ages of 50 and 69, and LRCF included men and women ages 30-69. The results from these studies were generally consistent in demonstrating that a 1 mg/dL increment in HDL-C was associated with an increased risk of CHD and total CVD mortality of about 2%. The results in women in the LRCF were even more striking, with a 1 mg/dL increment in HDL-C associated with an approximately 4% decrease in CHD and total CV mortality. The relationship of HDL-C to all-cause mortality was weak however, and there were no differences in overall mortality observed between patients with different HDL-C levels. As these trials were performed in predominantly male, higher risk patients, it is not known if similar results would be obtained in a population of pre-menopausal female patients at low-risk of CHD, with secondarily induced (i.e., drug induced) low HDL-C.

Finally, the unfavorable effects on the lipid profile by progestin therapy must also be considered in the context of the patient's overall CV risk profile. The Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults presented updated clinical guidelines for cholesterol testing and management in May 2001[20]. The panel recommended that CV risk assessment and the intensity of risk-reduction therapy be adjusted to a person's absolute risk of CV disease. Risk determinants include the presence or absence of CHD, level of LDL-C and the major risk factors. The major risk factors are summarized in the following table:

Table 1: Major Risk Factors (Exclusive of LDL-C) That Modify LDL Goals*
Cigarette Smoking
Hypertension
Low HDL-C (<40 mg/dL)**
Family history of premature CHD (CHD in male first-degree relative, 55years; CHD in female first-degree relative <65 years)
Age (men ≥45 years; women ≥55 years)

*Diabetes is regarded as a CHD risk equivalent.
(HDL-C ≥60 mg/dL counts as a "negative" risk factor,; its presence removes 1 risk factor from the total count)

The panel identified LDL-C as the primary target of cholesterol-lowering therapy and recommended CHD risk status as a guide to the type and intensity of cholesterol-lowering therapy. HDL-C and TG are secondary targets for risk reduction, after the primary target of LDL-C. LDL-C treatment goals are based on risk status, and intervention with therapeutic lifestyle changes (TLC) and drug treatment are recommended as follows:

Table 2: NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for TLC and Drug Therapy in Different Risk Categories

Risk Category	LDL goal (mg/dL)	LDL Level at Which to Initiate TLC (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
With CHD or CHD risk equivalents (10-year risk >20%)	≤100	≥100	≥130 (100-129: drug optional)*
Without CHD and with ≥2 risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10-20%: ≥130 10-year risk <10%: ≥160
Without CHD and with <2 risk factors**	<160	≥160	≥190 (160-189: LDL-lowering optional)

*Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
**Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

C. Studies Under Review

To support labeling changes to include treatment with Lupron for up to one year, or for retreatment after the initial 6 months of Lupron therapy, the sponsor has submitted 2 clinical studies in women with endometriosis who were treated with monthly Lupron plus add-back therapy. In one study, M92-878, women were treatment with Lupron alone, (Group 1), Lupron plus NETA 5 mg per day (Group 2), Lupron plus NETA plus conjugated equine estrogen (CEE) 0.625 mg per day (Group 3), or Lupron plus NETA plus CEE 1.25 mg per day (Group 4). In the other study, M97-777, all women were treated with Lupron plus NETA 5 mg per day for one year. As treatment with NETA was anticipated to cause adverse effects on the serum lipid profile, safety monitoring included evaluation of the effects of NETA on serum lipids.

1. Study M92-878

a) Study Design

Study M92-878 was a double-blind, randomized, parallel-group, multi-center study in 201 female patients with endometriosis accompanied by pain. Patients with cardiovascular disease or stroke were excluded from study participation. There were four treatment groups:
Group 1: Lupron Depot (LD) alone
Group 2: LD in combination with NETA 5 mg per day
Group 3: LD in combination with NETA and CEE 0.625 mg per day
Group 4: LD in combination with NETA and CEE 1.25 mg per day

All treatments were for a period of one year followed by a two-year post-treatment follow-up. All patients received LD 3.75 mg IM at four-week intervals for 52 weeks, and calcium supplements twice daily throughout the treatment and follow-up periods.

The primary efficacy outcome was improvement during treatment in pain. Suppression of estradiol (E2) and menses were used as efficacy markers. Safety was assessed by adverse events, and changes from baseline in vital signs, physical exam, BMD and laboratory tests. Serum lipid measurements for TC, LDL-C, HDL-C, and TG were obtained at baseline, at treatment Weeks 24 and 52, and during post-treatment follow-up.

Study visits and procedures are summarized in the following tables:

Table 3: M92-878 Study Visits and Procedures, Prestudy and Treatment Periods

Procedure	Prestudy		Treatment Period				
	Within 12 months of entry	Within 1 month of entry	Day 0	Weeks 4, 8, 12, 16, 20	Week 24	Weeks 28, 32, 36, 40, 44, 48	Week 52
Surgical Diagnosis Endometriosis	X						
Informed Consent		X					
Start Barrier Contraception		X					
Pregnancy Test		X*		X**			
Endometriosis/Fertility/ Menstrual History		X					
Medical History		X					
Endometrial Biopsy		X					
Clinical Evaluation Symptoms/Pelvic Exam		X	X	X	X	X	X
Pain Evaluation		X	X	X	X	X	X
Menstrual Record/ Daily Log		X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X
Blood Draw for E2			X	X	X	X	X
Bone Mineral Density		X			X		X
Physical Examination		X			X		X
Clinical Laboratory (including lipids)		X			X		X
Injection/Dispense Oral Medications			X	X	X	X	

*Within one week of entry
**Urine pregnancy test Week 4 only

Table 4: M92-878 Study Visits and Procedures, Post-Treatment Period

Procedure	Months Post-Treatment								
	Month 1	Month 2	Month 3	Month 4	Month 8	Month 12	Month 16	Month 20	Month 24
Clinical Evaluation Symptoms/Pelvic Exam	X	X	X	X	X	X			
Pain Evaluation	X	X	X	X	X	X			
Menstrual Record/ Daily Log	X	X	X	X	X	X			
Blood Draw for E2	X	X	X	X					
Calcium Supplementation	X	X	X	X	X	X	X	X	
Bone Mineral Density					X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Lipid Profile*					X	X	X	X	X

*Repeat until WNL or at baseline if baseline had been abnormal

b) Patient Disposition

Two-hundred and one (201) patients were randomized into the four treatment groups, and 120 patients (60%) completed one year of the study. Lipid results in the follow-up (post-treatment) period were available in only a small number of patients. Patient disposition is summarized in the following table:

Table 5: M92-878 Disposition of Patients

		Treatment			
	All	LD	LD/N	LD/N/CEE.625	LD/N/CEE1.25
Randomized, n (%)	201	51	55	47	48
Completed treatment, n(%)	120	32 (63)	31 (56)	33 (70)	24 (50)
Entered f/u Year 1, n(%)	62	39 (76)	39 (71)	35 (74)	26 (54)
Completed f/u Year 1, n(%)	50	14 (36)	10 (26)	14 (30)	12 (25)
Completed f/u Year 2, n(%)	16	4 (22)	6 (46)	5 (11)	4 (8)

c) Lipid Results

Total Cholesterol

Results of serum lipid analyses at Week 24 and Week 52 show a significant increase from baseline in TC for the LD-alone and LD/N/CEE1.25 groups. In both these groups, TC increased by about 10% from baseline, with similar results at Weeks 24 and 52. There were no significant changes in the LD/N and LD/N/CEE.625 groups. TC results by treatment group are summarized in the following table:

Table 6: M92-878 Total Cholesterol Results

Week	Treatment Group	n	Baseline	After Treatment	Mean % change from baseline	P-value*
24	LD-only	39	170.5	187.6	10	.001
	LD/N	41	179.3	174.8	-3	.722
	LD/N/CEE.625	42	172.2	180.0	5	.116
	LD/N/CEE1.25	38	170.4	187.6	10	.002
52	LD-only	23	168.0	187.7	12	.001
	LD/N	28	176.8	177.2	<1	.211
	LD/N/CEE.625	29	171.9	173.8	1	.632
	LD/N/CEE1.25	23	169.3	185.8	10	.004
Final	LD-only	40	171.0	186.9	9	<.001
	LD/N	41	179.3	177.8	-1	.231
	LD/N/CEE.625	42	172.2	177.9	3	.212
	LD/N/CEE1.25	39	170.7	190.2	11	<.001

*Within group change from baseline

HDL-C

Decreases in HDL-C from baseline at Weeks 24 and 52 were seen for the 3 NETA exposed groups, LD/N (-19% to –18% at Weeks 24 and 52 respectively), LD/N/CEE.625 (-25% to –28%), and LD/N/CEE1.25 (-11% to –16%). The HDL-C decreases did not change substantially between Week 24 and Week 52 for any group. There was no significant change in HDL-C for the LD-alone group. The HDL-C results are summarized in the following table:

Table 7: M92-878 HDL-C Results

Week	Treatment Group	n	Baseline	After Treatment	Mean % change from baseline	P-value*
24	LD-only	39	52.5	56.0	7	.024
	LD/N	41	51.8	41.9	-19	<.001
	LD/N/CEE.625	42	55.4	41.5	-25	<.001
	LD/N/CEE1.25	38	50.2	44.5	-11	<.001
52	LD-only	23	49.1	51.6	5	.798
	LD/N	28	51.2	42.1	-18	<.001
	LD/N/CEE.625	29	57.0	40.8	-28	<.001
	LD/N/CEE1.25	23	50.2	42.3	-16	<.001
Final	LD-only	40	52.4	55.3	6	.080
	LD/N	41	51.8	42.1	-19	<.001
	LD/N/CEE.625	42	55.4	41.8	-25	<.001
	LD/N/CEE1.25	39	50.0	45.4	-9	<.001

*Within group change from baseline

By NCEP guidelines (see Background) an HDL-C of <40 mg/dL is a risk factor for CHD. By these criteria, 75 patients (37%) had clinically relevant HDL-C decreases (HDL-C of <40 mg/dL) at any time during study drug treatment. Decreases in HDL-C to <40 mg/dL were more common in patients exposed to NETA (45-52% of patients) than in the LD-alone group (14%). HDL-C decreases to <40 mg/dL overall and by treatment group are summarized in the following table:

Table 8: M92-878 Patients with HDL-C Decreases to <40 mg/dL During Study Treatment

		Treatment			
	All	LD	LD/N	LD/N/CEE.625	LD/N/CEE1.25
Randomized patients, n (%)	201	51	55	47	48
Patients with HDL decreases, n (%)	75 (37)	7 (14)	23 (45)	20 (43)	25 (52)

HDL-C results in the post-treatment period were available in only a few patients per group, and appeared to return to baseline values in most patients (see Appendix).

LDL-C

LDL-C increased from baseline by +8 to +17% in all 4 treatment groups at Weeks 24 and 52, with similar results for all 4 groups at each time point. The LDL-C results are summarized in the following table:

Table 9: M92-878 LDL-C Results

Week	Treatment Group	n	Baseline	After Treatment	Mean % change from baseline	P-value*
24	LD-only	39	96.6	107.9	11	.034
	LD/N	41	101.5	113.2	12	<.001
	LD/N/CEE.625	41	98.1	114.4	17	<.001
	LD/N/CEE1.25	38	102.5	118.1	15	<.001
52	LD-only	23	95.5	110.1	15	.017
	LD/N	27	101.8	110.3	8	.009
	LD/N/CEE.625	29	96.4	112.0	16	.002
	LD/N/CEE1.25	23	100.9	116.1	15	<.001
Final	LD-only	40	97.0	106.8	10	.052
	LD/N	41	101.5	113.6	12	<.001
	LD/N/CEE.625	41	98.1	112.8	15	<.001
	LD/N/CEE1.25	39	102.4	117.2	14	<.001

*Within group change from baseline

As the majority of study patients would be expected to be in the lowest risk category for CHD (without CHD and with <2 risk factors), the LDL-C goal by NCEP criteria for these patients would be <160 mg/dL. Also by NCEP criteria, LDL-C levels that would require intervention other than lifestyle modification, such as drug treatment, would be levels >190 mg/dL. There were 17 patients (8%) who had an increased LDL-C ≥160 during the study. There were slightly more patients in the LD/N/CEE1.25 group who had an LDL-C ≥160 mg/dL; however as the number of patients were small overall, no conclusions will be generated from this. LDL-C increases to ≥160 mg/dL overall and by treatment group are summarized in the following table:

Table 10: M92-878 Patients with LDL-C Increases to ≥160 mg/dL During Study Treatment

		Treatment			
	All	LD	LD/N	LD/N/CEE.625	LD/N/CEE1.25
Randomized patients, n (%)	201	51	55	47	48
Patients with HDL decreases, n (%)	17 (8)	3 (6)	3 (5)	3 (6)	8 (17)

There were 4 patients (2%) with elevations in LDL-C to ≥190 mg/dL that occurred at any time during the study. These increases overall and by treatment group are summarized in the following table:

Table 11: M92-878 Patients LDL-C Increases to ≥190 mg/dL During Study Treatment

		Treatment			
	All	LD	LD/N	LD/N/CEE.625	LD/N/CEE1.25
Randomized patients, n (%)	201	51	55	47	48
Patients with LDL increases, n (%)	4 (2)	1 (2)	2 (4)	1 (2)	0

LDL/HDL Ratio

The LDL/HDL ratio increased significantly from baseline in the 3 NETA exposed group at Weeks 24 and 52, and the LD-alone group showed no significant change from baseline. Increases were relatively small however, and the majority of patients remained in a below average to average risk group for CHD. The LDL/HDL results are summarized in the following table:

Table 12: M92-878 LDL/HDL Results

Week	Treatment Group	n	Baseline	After Treatment	P-value*
24	LD-only	39	1.95	2.14	.322
	LD/N	41	2.06	2.82	<.001
	LD/N/CEE.625	41	1.92	2.95	<.001
	LD/N/CEE1.25	38	2.17	2.85	<.001
52	LD-only	23	2.05	2.32	.088
	LD/N	27	2.10	2.77	<.001
	LD/N/CEE.625	29	1.90	2.99	<.001
	LD/N/CEE1.25	23	2.14	3.04	<.001
Final	LD-only	40	1.96	2.18	.233
	LD/N	41	2.06	2.85	<.001
	LD/N/CEE.625	41	1.92	2.89	<.001
	LD/N/CEE1.25	39	2.17	2.82	<.001

*Within group change from baseline

TG

Increases from baseline in TG were seen in the LD/N/CEE.625, and LD/N/CEE1.25 groups at Week 24, and in the LD/N/CEE1.25 groups at Week 52. There was a statistically significant but clinically mild increase from baseline in TG in the LD/N group of 4% at Week 52, and a non-significant decrease from baseline in TG in the LD/N group at Week 24. The LD-alone group had no significant change from baseline in TG. The TG results are summarized in the following table:

Table 13: M92-878 Triglyceride Results

Week	Treatment Group	n	Baseline	After Treatment	Mean % change from baseline	P-value*
24	LD-only	39	107.8	117.9	9	.155
	LD/N	41	130.2	102.3	-21	.61
	LD/N/CEE.625	42	96.6	126.0	30	.012
	LD/N/CEE1.25	38	90.2	120.4	33	.089
52	LD-only	23	117.1	123.6	6	.127
	LD/N	28	123.3	128.8	4	.031
	LD/N/CEE.625	29	91.4	112.5	23	.517
	LD/N/CEE1.25	23	91.2	132.8	46	.022
Final	LD-only	40	108.5	123.5	14	.052
	LD/N	41	130.2	117.4	-10	.213
	LD/N/CEE.625	42	96.6	122.0	26	.07
	LD/N/CEE1.25	39	91.6	135.2	48	.001

*Within group change from baseline

In the short-term, TG elevations >500-600 mg/dL could be considered as clinically significant, mainly as a risk factor for pancreatitis rather than CHD. Three patients had

clinically significant elevations in TG (>500 mg/dL) during study drug treatment. Only 1 patient had a TG >600 mg/dL, patient 1158 (treatment group LD/N), who had a TG of 666 mg/dL at Day –7 prior to study drug treatment, which will not be considered as study related. Patients with TG elevations >500 mg/dL are summarized in the following table:

Table 14: M92-878 Clinically Significant Changes in TG

Patient Number	Treatment	Study Day	Days Post Treatment	Lab Value
1072	LD/N	1	-	493
1072		168	-	297
1072		365	0	583
1158	LD/N	-7	-	666
1158		187	-	491
1321	LD/N/CEE.625	-4	-	387
1321		176	-	517
1321		548	173	504

In the long-term by NCEP criteria, TG levels <200 mg/dL are desirable. Thirty-four (34) patients (17%) had TG elevations that were ≥200 mg/dL at any time during the study, and these were about equally distributed in the treatment groups, as follows:

Table 15: M92-878 Patients with TG Increases to ≥200 mg/dL During Study Treatment

		Treatment			
	All	LD	LD/N	LD/N/CEE.625	LD/N/CEE1.25
Randomized patients, n (%)	201	51	55	47	48
Patients with TG Increases, n (%)	34 (17)	9 (18)	11 (22)	7 (15)	7 (15)

d) Other Significant Results

Body weight changes can affect lipid levels, and have been shown to increase TC, LDL-C and decrease HDL-C. Mean body weight at the final treatment visit compared to baseline increased in all treatment groups. Comparisons of mean baseline weight to mean final treatment visit weight by treatment group are as follows:

Table 16: M92-878 Body Weights (lbs)

Treatment Group	n	Baseline	After Treatment	P-value*
LD-only	45	144.2	150.7	.056
LD/N	42	147.6	153.7	<.001
LD/N/CEE.625	41	145.4	155.8	<.001
LD/N/CEE1.25	42	152.2	152.8	.003

2. Study M97-777

a) Study Design

Study M97-777 was an open-label, single-arm, multi-center study in 136 female patients with endometriosis accompanied by pain. All patients received LD 3.75 mg at four-week intervals, and NETA 5 mg per day for 52 weeks. Patients received post-treatment follow-up for one year. All patients also received calcium supplements twice daily throughout the treatment and follow-up periods.

The primary and secondary efficacy endpoints were change from baseline for endometriosis-related pain parameters at each visit, change from baseline in estradiol levels, and suppression of menses. Safety endpoints included percent change from baseline in BMD at the final treatment visit (primary safety endpoint), percent change from baseline in BMD at Week 24 and Week 52, adverse events, and changes from baseline in vital signs, weight, physical examination, and laboratory tests. Serum lipid measurements for TC, LDL-C, HDL-C, and TG were obtained at baseline, at treatment Weeks 24 and 52, and during post-treatment follow-up Months 1, 2, 3, 4, 8, and 12.

Study visits and procedures are summarized in the following table:

Table 17: M97-777 Study Visits and Procedures

Procedure	Prestudy	Treatment Period						Follow-up Period		
	Days -28 to -1	Day 0	Week 4	Weeks 8, 12, 16, 20	Week 24	Weeks 28, 32, 36, 40, 44, 48	Week 52	Months 1, 2, 3, 4	Month 8	Month 12
Surgical Diagnosis of Endometriosis*	X									
Start Barrier Contraception	X									
Informed Consent	X									
Pregnancy Test	X**		X							
Physical Exam	X				X		X			
Laboratory Tests	X				X		X			
Lipid Profile	X				X		X	X	X	X
Pain Evaluation	X	X	X	X	X	X	X	X	X	X
Clinical Evaluation Symptoms/Pelvic Exam	X	X	X	X	X	X	X	X	X	X
Bone Mineral Density	X				X		X		X	X
Blood Draw for E2	X	X	X	X	X	X	X	X	X	X
Endometriosis/Menstrual/ Fertility History	X									
Medical History	X									
Review Entry Criteria	X									
Study Medication Administration		X	X	X	X	X				
Endometrial Biopsy	If clinically indicated									

*Within 12 months of entry
**Within 1 week of dosing

b) Patients Disposition

One hundred thirty-six (136) patients were entered into the study, and 82 patients (60%) completed 1 year of treatment. The disposition of patients is summarized in the following table:

Table 18: M97-777 Patient Disposition

	LD/N
Randomized, n (%)	136
Completed treatment, n (%)	82 (60)
Entered f/u Year 1, n (%)	119 (88)
Completed f/u Year 1, n (%)	64 (47)

c) Lipid results

There were mild increases in TC of +1 to +3%, and mild increases in TG (+9 to +19%). The LDL-C increased by +8 to +12%. HDL-C decreased by –16 to –18%. The results are summarized in the following table:

Table 19: M97-777 Lipid Results

		n	Baseline	After Treatment	Mean % Change from Baseline
TC					
	Week 24	117	181.2	182.6	1
	Week 52	85	180.3	185.0	3
	Final	118	181.1	184.4	2
TG					
	Week 24	117	105.4	115.1	9
	Week 52	85	104.3	123.7	19
	Final	118	104.9	120.7	15
HDL-C					
	Week 24	117	51.0	42.8	-16
	Week 52	85	51.0	41.7	-18
	Final	118	51.1	42.8	-16
LDL-C					
	Week 24	117	109.1	117.4	8
	Week 52	83	106.1	118.6	12
	Final	118	109.1	117.9	8
LDL/HDL					
	Week 24	117	2.29	2.94	-
	Week 52	83	2.25	3.10	-
	Final	118	2.29	2.98	-

The results were also analyzed by patients who completed the 52 weeks of treatment and had lipid results at the final treatment visit. These results were similar to the results overall (in Table 19) and showed increases from baseline in TC of +3%, LDL-C of +11%, TG of +17%, and an increase in the LDL/HDL ratio. HDL-C decreased from baseline by –18%. The results are summarized in the following table:

Table 20: M97-777 Mean Lipid Values at Baseline and Final Treatment Visits for LD/N Patients with Follow-up Lipid Data

Variable	n	Baseline Mean (mg/dL)	Final Treatment Mean (mg/dL)	Mean % Change from Baseline
TC	97	182.3	186.9	+3
LDL-C	97	109.8	121.6**	+11
HDL-C	97	51.4	42.1**	-18
LDL/HDL	97	2.3	3.1**	
TG	97	102.0	119.0***	+17

** = p<.001
*** = p<.01

By NCEP criteria, 64 patients (47%) had clinically significant decreases in HDL-C to <40 mg/dL that occurred during study drug treatment or during the post-treatment period. Twenty-four (24) patients (18%) had an LDL-C increase to ≥160 mg/dL, and 8 patients (6%) had increases in LDL-C to ≥190 mg/dL during study drug treatment. Four (4) of these patients (patients 803, 1805, 1908, and 1909) experienced LDL-C elevations to ≥190 mg/dL during the post-treatment period. Thirty (30) patients (22%) had elevations in TG to ≥200 mg/dL during the study, and 5 patients had TG elevations ≥500 mg/dL. Only 1 of these patients (patient 1203) experienced a TG elevation ≥500 mg/dL during study drug treatment. Two patients had elevations ≥500 mg/dL in the pre-study period prior to starting study drug (patients 909 and 2208). Patient 909 also had a TG ≥500 mg/dL in the post-treatment phase. Two additional patients (1805 and 1905) experienced TG elevations ≥500 mg/dL during the post-treatment phase.

d) Other

Mean weight at the final treatment visit significantly increased from baseline by 4.8 lbs.

Table 21: M97-777 Weight Changes Baseline to Final Treatment

n	Baseline Mean (lbs)	Treatment Mean (lbs)	p-value*
120	151.1	155.9	<.001

*Within group change from baseline

D. Discussion

The changes in the lipid profile seen with treatment with LD/N in both studies showed mean decreases in HDL-C of −16 to −19%, mean increases in LDL-C of +8 to +12%, and little effect on TC. The changes in TG were non-significant and variable. These lipid results were similar to those observed in the double-blind and open-label studies, and were consistent with results seen in previous clinical trials with 17-nortestosterone derived-progestins. As most patients likely to be treated with LD/N for endometriosis are at low-risk for CV disease, it is unlikely that the small changes seen in TC, LDL-C and TG with treatment with NETA would result in a significant change in CV risk status for these patients. This is especially true as treatment is likely to be of a relatively short duration.

The HDL-C changes, however, resulted in an HDL-C of <40 mg/dL in about 45% of patients in the NETA-exposed groups and were the most significant and consistent lipid-altering effect seen with treatment with LD/N. A decreased HDL-C has been established as a risk factor for CV disease in large epidemiologic trials; however, these studies were conducted predominantly in men and post-menopausal women, and in older patients (age >50 years). The significance of short-term, drug-induced reductions in HDL-C in pre-menopausal women at low risk for CV disease has not been determined. Studies in pre-menopausal women with OC agent use have indicated that CV events are predominantly thrombotic, not atherogenic, in nature and most strongly related to higher doses of estrogen (>50 mcg per day) and smoking. The association with the progestin type and use has not been determined. In studies of women experiencing CV events with a past history of OC use vs never-users, suggested no sustained risk for CHD after OC agents were discontinued. This suggests no lasting CV effects from estrogen/progesterone exposure. It should be kept in mind however, that no definitive studies on the long-term use of progestins or LD/N have been performed and the CV risk of 6-12 months of use (or intermittent use for 6 month periods with retreatment) is unknown.

Per NCEP guidelines, the unfavorable effects on the lipid profile must also be considered as part of overall CV risk assessment. It is reasonable to assume then, that patients with established CV risk factors at baseline, such as smoking, may be at greater risk of treatment with progestins, and should be assessed for risk factor management if treatment with LD/N is necessary and prolonged.

E. Conclusion

Questions from the consult request:

1) Has the sponsor submitted sufficient data to permit a meaningful assessment of the effects of 6 and 12 months of treatment with 5 mg of NETA per day on lipids?
   a) Is the sample size adequate?
   b) Are the laboratory measurements appropriate and adequate?

Yes, the data are sufficient, sample size was adequate, and laboratory measurements were appropriate. It can be concluded that LD/N produces decreases in HDL-C, increases in LDL-C and increases in the LDL/HDL ratio. Changes in these lipid parameters improved in the follow-up period, but did not completely return to baseline. These results were consistent between the two studies and consistent with historical data from previous clinical trials. It is also noted that the addition of CEE did not mitigate the effects on HDL-C, and that the effect on HDL-C as a function of weight gain needs to be further explored.

2) What is the assessment of the risk(s) associated with the changes in lipids that were observed after 6 and 12 months of treatment with 5 mg of NETA per day?

The absolute risk is unknown, but is likely to be small (see Discussion section).

3) Are these lipid-related risks likely to be significantly greater in women treated with Lupron plus NETA than those in women treated with Lupron alone?

It is possible that there may be some increased risk with the adverse effects of NETA on the lipid profile, but it is unlikely that women treated with LD plus NETA would be at significantly higher risk of CV disease than women treated with LD alone. The theoretical risk for CV disease needs to be balanced against the greater loss of BMD seen in women treated with LD alone.

4) If DRUDP were to extend the recommended treatment period with Lupron from 6 months to a maximum of 12 months for patients who also receive 5 mg of NETA per day, what additional warnings or precautions would be included in labeling?

It is recommended that labeling include the specific effects on the lipid profile seen with treatment with LD plus NETA. It is recommended that this include percent changes in lipid parameters, especially for HDL-C. It would also be recommended that a statement regarding low HDL-C and the increased risk of CV disease be included, although the risk in this low-risk population is not known. Women should also have a CV risk assessment (by NCEP criteria) done at baseline, and that management of other CV risk factors, such as smoking cessation, be undertaken if applicable.

F. Recommendations

It is recommended that:

1) Labeling include the effects seen on the lipid profile with treatment with LD plus NETA.
2) Labeling include a statement regarding low HDL-C and increased CV risk, although the short-term effect of treatment-induced low HDL-C levels on CV risk in endometriosis patients is unknown.
3) Labeling include a recommendation that CV risk assessment be undertaken at baseline, and that management of other CV risk factors, such as smoking, be undertaken.
4) The decrease in HDL-C as a function of weight gain should be further explored.
5) Consideration should be given to the investigation of other add-back regimens with less effect on HDL-C, such as less androgenic progestins, e.g., medroxyprogesterone.

G. Appendices

1. Study M92-878

a) Patients with LDL-C ≥160 mg/dL During the Study

Table22: M92-878 Patients With LDL-C ≥160 mg/dL During Study

Treatment	Patient Number	Treatment Day	Days Post-Treatment	LDL-C Value
LD	1233	-14	-379	
		170	-196	
		198	-168	
		366	0	
		709	343	
	1335	-8	-394	
		171	-216	
		408	21	
		668	281	
	1362	-2	-364	
		165	-198	
		358	-5	
		910	547	
LD/N	1022	-8	-94	
		87	0	
	1272	-21	-275	
		171	-84	
		307	52	
		363	108	
	1301	-7	-372	
		177	-189	
		370	4	
LD/N/CEE.625	1155	-11	-395	
		185	-200	
		385	0	
	1203	-30	-401	
		169	-203	
		375	3	
	1291	-8	-413	
		197	-209	
		406	0	
		977	571	
		1025	619	
LD/N/CEE/1.25	1044	-14	-323	
		188	-122	
		325	15	
	1085	-23	-378	
		1	-355	
		160	-196	
		356	0	
		937	581	
	1095	-20	-355	
		170	-166	
		338	2	
	1106	-29	-420	
		189	-203	

Table22: M92-878 Patients With LDL-C ≥160 mg/dL During Study				
Treatment	Patient Number	Treatment Day	Days Post-Treatment	LDL-C Value
		398	6	
	1113	-23	-79	
		71	14	
	1186	-4	-374	
		167	-204	
		371	0	
	1293	-4	-212	
		188	-21	
		218	9	
	1297	-17	-405	
		183	-206	
		386	-3	
		872	483	
		1007	618	
		1119	730	

b) Patients with LDL-C ≥190 mg/dL During the Study

Table 25: M92-878 Patients with LDL ≥190 at any time during the study				
Treatment	Patient Number	Treatment Day	Days Post-treatment	Lab Value
LD	1233	-14	-379	
		170	-196	
		198	-168	
		366	0	
		709	343	
LD/N	1272	-21	-275	
		171	-84	
		307	52	
		363	108	
	1301	-7	-372	
		177	-189	
		370	4	
LD/N/CEE.625	1291	-8	-413	
		197	-209	
		406	0	
		977	571	
		1025	619	

c) Patients With HDL-C <40 mg/dL During the Study

Table 23: M-92-878 Patients with HDL<40 mg/dL During the Study				
Treatment	Patient Number	Treatment Day	Days Post-Treatment	Lab Value
LD	1093	-21	-80	
		60	0	
	1111	-3	-375	
		180	-193	
		368	-5	
	1123	1	-367	
		172	-196	
		403	35	
	1157	-20	-420	
		190	-211	
		402	1	
		1060	659	

Table 23: M-92-878 Patients with HDL<40 mg/dL During the Study				
Treatment	Patient Number	Treatment Day	Days Post-Treatment	Lab Value
		1137	736	
	1295	208	-224	
		432	0	
		680	248	
		952	520	
	1315	-1	-380	
		178	-202	
		380	0	
		771	391	
	1362	-2	-364	
		165	-198	
		358	-5	
		910	547	
LD/N	1003	1	-377	
		175	-203	
		378	0	
		776	398	
	1006	-5	-377	
		177	-196	
		373	0	
	1013	-17	-387	
		173	-198	
		378	7	
	1018	-47	-418	
		-4	-375	
		169	-203	
		372	0	
	1025	-12	-391	
		172	-208	
		379	-1	
	1032	-9	-129	
		142	21	
	1038	-7	-384	
		173	-205	
		376	-2	
		834	456	
		971	593	
	1042	-8	-372	
		169	-196	
		364	-1	
	1072	1	-364	
		168	-197	
		365	0	
	1084	-25	-400	
		173	-203	
		375	-1	
	1096	-10	-235	
		170	-56	
		209	-17	
	1115	-8	-93	
		86	0	
	1132	-11	-270	
		172	-88	

Table 23: M-92-878 Patients with HDL<40 mg/dL During the Study				
Treatment	Patient Number	Treatment Day	Days Post-Treatment	Lab Value
	1145	1	-365	
		169	-197	
		367	1	
	1158	-7	-319	
		187	-126	
	1173	-21	-385	
		169	-196	
		365	0	
		1016	651	
	1191	-26	-392	
		171	-196	
		367	0	
	1204	-33	-398	
		170	-196	
		366	0	
	1246	-14	-412	
		183	-216	
		402	3	
		688	289	
	1251	-6	-264	
		177	-82	
	1292	-3	-403	
		190	-211	
		402	1	
	1371	186	-221	
		410	3	
		898	491	
		996	589	
		1038	631	
	1383	-28	-395	
		169	-199	
		373	5	
LD/N/CEE.625	1004	-4	-404	
		183	-218	
		410	9	
	1024	-138	-462	
		-5	-329	
		176	-149	
		337	12	
	1033	-11	-339	
		175	-154	
		328	-1	
	1073	1	-363	
		167	-197	
		363	-1	
	1077	-3	-366	
		169	-195	
		196	-168	
	1102	-13	-369	
		175	-182	
		357	0	
	1112	-14	-378	
		169	-196	

Table 23: M-92-878 Patients with HDL<40 mg/dL During the Study				
Treatment	Patient Number	Treatment Day	Days Post-Treatment	Lab Value
		362	-3	
	1117	-6	-375	
		170	-200	
		373	3	
		849	479	
	1131	-14	-336	
		179	-144	
	1155	-11	-395	
		185	-200	
		385	0	
	1171	-20	-385	
		170	-196	
		366	0	
	1216	-6	-397	
		191	-201	
		219	-173	
		308	-84	
		393	1	
	1248	-7	-392	
		186	-200	
		382	-4	
		627	241	
		736	350	
	1271	-9	-378	
		170	-200	
	1291	-8	-413	
		197	-209	
		406	0	
		977	571	
		1025	619	
	1298	-11	-388	
		183	-195	
		379	1	
	1303	-20	-387	
		170	-198	
		367	-1	
	1308	-5	-385	
		171	-210	
		381	0	
	1321	-4	-378	
		176	-199	
		548	173	
	1374	-4	-180	
		178	1	
LD/N/CEE1.25	1002	-5	-372	
		171	-197	
		368	0	
	1014	-32	-378	
		-3	-349	
		155	-192	
		347	0	
	1023	-71	-427	
		-32	-388	

Table 23: M-92-878 Patients with HDL<40 mg/dL During the Study				
Treatment	Patient Number	Treatment Day	Days Post-Treatment	Lab Value
		169	-188	
		358	1	
	1034	-7	-406	
		177	-223	
		400	0	
	1044	-14	-323	
		188	-122	
		325	15	
	1094	-34	-204	
		18	-153	
		173	2	
		173	2	
		214	43	
		247	76	
	1104	-22	-403	
		180	-202	
		382	0	
	1106	-29	-420	
		189	-203	
		398	6	
	1113	-23	-79	
		71	14	
	1124	-4	-370	
		170	-197	
		379	12	
	1127	-18	-375	
		163	-195	
		358	0	
	1142	-17	-393	
		172	-205	
		377	0	
	1147	-18	-238	
		162	-59	
		221	0	
	1151	-20	-413	
		184	-210	
		450	56	
	1186	-4	-374	
		167	-204	
		371	0	
	1195	-20	-245	
		170	-56	
	1201	158	-203	
		361	0	
	1232	167	-196	
		251	-112	
		363	0	
	1293	-4	-212	
		188	-21	
		218	9	
	1297	-17	-405	
		183	-206	
		386	-3	

Table 23: M-92-878 Patients with HDL<40 mg/dL During the Study				
Treatment	Patient Number	Treatment Day	Days Post-Treatment	Lab Value
		872	483	
		1007	618	
		1119	730	
	1307	-46	-190	
		16	-129	
	1313	-13	-392	
		177	-203	
		380	0	
	1322	1	-372	
		93	-280	
		178	-195	
		374	1	
		1033	660	
	1331	-3	-430	
		165	-263	
		431	3	
	1361	-66	-121	
		7	-49	

d) Patients with TG ≥200 mg/dL During the Study

Table 24: M92-878 Patients with TG ≥200 During the Study				
Treatment	Patient Number	Treatment Day	Days Post-treatment	Lab Value
LD	1093	-21	-80	
		60	0	
	1107	-22	-239	
		190	-28	
		240	22	
	1123	1	-367	
		172	-196	
		403	35	
	1157	-20	-420	
		190	-211	
		402	1	
		1060	659	
		1137	736	
	1295	208	-224	
		432	0	
		680	248	
		952	520	
	1315	-1	-380	
		178	-202	
		380	0	
		771	391	
	1362	-2	-364	
		165	-198	
		358	-5	
		910	547	
LD/N	1032	-9	-129	
		142	21	
	1038	-7	-384	
		173	-205	

Table 24: M92-878 Patients with TG >200 During the Study				
Treatment	Patient Number	Treatment Day	Days Post-treatment	Lal Value
		376	-2	
		834	456	
		971	593	
	1072	1	-364	
		168	-197	
		365	0	
	1084	-25	-400	
		173	-203	
		375	-1	
	1158	-7	-319	
		187	-126	
	1204	-33	-398	
		170	-196	
		366	0	
	1246	-14	-412	
		183	-216	
		402	3	
		688	289	
	1301	-7	-372	
		177	-189	
		370	4	
	1371	186	-221	
		410	3	
		898	491	
		996	589	
		1038	631	
LD/N/CEE.625	1004	-4	-404	
		183	-218	
		410	9	
	1041	-26	-110	
		67	-18	
	1105	213	-221	
		442	8	
	1291	-8	-413	
		197	-209	
		406	0	
		977	571	
		1025	619	
	1303	-20	-387	
		170	-198	
		367	-1	
	1308	-5	-385	
		171	-210	
		381	0	
	1321	-4	-378	
		176	-199	
		548	173	
LD/N/CEE1.25	1094	-34	-204	
		18	-153	
		173	2	
		173	2	
		214	43	
		247	76	

Table 24: M92-878 Patients with TG ≥200 During the Study				
Treatment	Patient Number	Treatment Day	Days Post-treatment	Lab Value
	1106	-29	-420	
		189	-203	
		398	6	
	1127	-18	-375	
		163	-195	
		358	0	
	1142	-17	-393	
		172	-205	
		377	0	
	1194	-23	-389	
		381	14	

2. Study M97-777

a) Patients with LDL-C ≥190 mg/dL During the Study

Table 25: M97-777 Patients with LDL≥190 During the Study			
Patient number	Treatment Day	Days Post treatment	Lab value
803	-19	-132	
	114	0	
	149	35	
	170	56	
	202	88	
	231	117	
	360	246	
	506	392	
805	-10	-122	
	118	5	
	146	33	
	174	61	
	202	89	
	230	117	
	378	265	
1303	-21	-388	
	169	-199	
	366	-2	
	403	35	
	431	63	
	459	91	
	487	119	
	611	243	
1805	-39	-403	
	177	-188	
	364	-1	
	421	56	
	458	93	
	494	129	
1908	-28	-393	
	170	-196	
	366	0	
	393	27	
	423	57	

Table 25: M97-777 Patients with LDL>190 During the Study			
Patient number	Treatment Day	Days Post treatment	Lab value
	450	84	
	478	112	
	626	260	
1909	-18	-384	
	171	-196	
	368	1	
	400	33	
	423	56	
	451	84	
	479	112	
	606	239	
2209	-7	-371	
	171	-194	
	395	30	
	423	58	
	452	87	
	480	115	
2805	-24	-387	
	168	-196	
	365	1	
	392	28	
	420	56	
	453	89	
	483	119	
	606	242	

b) Patients with TG >500 mg/dL During the Study

Table 26: M97-777 TG>500 mg/dL During the Study			
Patient number	Treatment Day	Days Post-treatment	Lab Value
909	-22	-387	
	-15	-380	
	-7	-372	
	164	-202	
	303	-63	
	367	1	
	450	84	
	485	119	
	609	243	
1203	-14	-397	
	169	-215	
	197	-187	
	252	-132	
	383	-1	
	420	36	
1805	-39	-403	
	177	-188	
	364	-1	
	396	31	
	421	56	
	458	93	
	494	129	
1907	-15	-376	
	167	-195	

	363	1
	391	29
	419	57
	447	85
	475	113
	587	225
	616	254
2208	-47	-330
	-2	-285
	175	-109

H. References

[1] Olive DL, Pritts EA. Treatment of endometriosis. N Engl J Med 2001;345(4):266-275.
[2] Surrey ES, Voigt B, Fournet N, Judd HL. Prolonged gonadotropin-releasing hormone agonist treatment of symptomatic endometriosis: The role of cyclic sodium etidronate and low-dose norethindrone "add-back" therapy. Fertil Steril 1995;63:747-755.
[3] Riis BJ, Christiansen C, Johansen JS, Jacobson J. Is it possible to prevent bone loss in young women treated with luteinizing hormone-releasing hormone agonists? J Clin Endocrinol Metab 1990;70:920-942.
[4] Enk L, Landgren BM, Lindberg U, Silfverstolpe G, Crona N. A prospective, one-year study on the effects of two long acting injectable contraceptives (depot-medroxyprogesterone acetate and norethisterone oenanthate) on serum and lipoprotein lipids. Horm Metab Res 1992;24:85-89.
[5] McEwan JA, Griffin M, Fotherby K, Trayner I. Long-term use of depot-norethisterone enanthate: Effect on blood lipid fractions. Contraception 1992;46:49-60.
[6] Ball MJ, Ashwell E, Gillmer MDG. Progestagen-only contraceptives: Comparison of the metabolic effects of levonorgestrel and norethisterone. Contraception 1991;44(3):223-233.
[7] Crook D, Gardner R, Worthington M, Nolan J, Stevenson JC, Shaw RW. Zoladex versus danazol in the treatment of pelvic endometriosis: Effects on plasma lipid risk factors. Horm Res 1989;32 Suppl 1:157-160.
[8] Farish E, Fletcher CD, Barnes JF, Mack A, Gary CE, Hart DM. Reversible menopause induced by the GnRH analogue buserelin: Effects on lipoprotein metabolism. Acta Endocrinol (Copenh) 1992;127(2):123-126.
[9] Valimaki M, Nilsson CG, Roine R, Ylikorkala O. Comparison between the effects of nafarelin and danazol on serum lipids and lipoproteins in patients with endometriosis. J Clin Endocrinol Metab 1989;69:1097-1103.
[10] Sidney S, Siscovick DS, Petitti DB, Schwartz SM, Quesenberry CP, Psaty BM, Raghunathan TE, Kelaghan J, Koepsell TD. Myocardial infarction and use of low-dose oral contraceptives: A pooled analysis of 2 US studies. Circulation 1998;98(11):1058-1063.
[11] Rosenberg L, Palmer JR, Rao RS, Shapiro S. Low-dose oral contraceptive use and the risk of myocardial infarction. Arch Intern Med 2001;161:1065-1070.
[12] WHO Collaborative Study of Cardiovascular Disease and Steroid Contraception. Acute myocardial infarction and combined oral contraceptives: Results of an international multicenter case-control study. Lancet 1997;349:1202-1209.
[13] Petitti DB, Sidney S, Quesenberry CP. Oral contraceptive use and myocardial infarction. Contraception 1998;57(3):143-155.
[14] Rosenberg L, Palmer JR, Lesko SM, Shapiro S. Oral contraceptive use and the risk of myocardial infarction. Am J Epidemiol 1990;131(6):1009-1016.
[15] Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, Jacobs DR, Bangdiwala S, Tyroler HA. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989;79(1):460-466.

[16] Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease: The Framingham Study. Am J Med 1977;62:707-714.

[17] Jacobs DR for the Lipid Research Clinics follow-up study. High density lipoprotein cholesterol and coronary heart disease, cardiovascular disease, and all-cause mortality. Circulation 1985;72(suppl III):III-85.

[18] Gordon DJ, Knoke J, Probstfield JL, Superko R, Tyroler HA for the Lipid Research Clinics Program. High-density lipoprotein cholesterol and coronary heart disease in hypercholesterolemic men: The Lipid Research Clinics Coronary Primary Prevention Trial. Circulation 1986;74:1217-1225.

[19] Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial: Risk factor changes and mortality results. JAMA 1982;248:1465-1477.

[20] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285(19):2486-2497.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Anne Pariser
8/17/01 10:04:30 AM
MEDICAL OFFICER

Mary Parks
8/17/01 11:55:44 AM
MEDICAL OFFICER
acting for Dr. Orloff

APPEARS THIS WAY
ON ORIGINAL

August 13, 2001

MEMORANDUM

To: Jeanine Best, MSN, RN, Project Manager; Scott Monroe, MD, Medical Officer, DRUDP, HFD-580
From: Bruce S. Schneider, MD, DMEDP, HFD-510
Through: David Orloff, MD

Subject: NDA 20-011/S-021 and 20-708/S-11 (TAP Pharmaceutical Products, Inc). Consultation regarding efficacy of norethindrone acetate (NETA, Aygestin® 5 mg tablets daily) in prevention of loss of bone mineral in women treated with Lupron® (Depot 3.75 mg IM monthly or Depot 11.25 mg IM every 3 months) for endometriosis for one year.

Background: Lupron® (leuprolide acetate) is a GnRH agonist that is approved for the treatment of pain associated with endometriosis. The hypoestrogenic state that is induced by Lupron® results in atrophic changes in the ectopic endometrial tissue, with a consequent reduction in painful symptoms. Associated with the reduction in circulating estrogens is loss of bone mineral; because of this, Lupron® treatment has been restricted to six months. Many patients are relieved of painful symptoms within a few months of treatment. Following withdrawal of the medication, some patients relapse, while others experience prolonged remissions.

One strategy for countering the loss of bone mineral that accompanies GnRH therapy is to add progestins or progestins plus estrogen to the regimen ("add-back" therapy). To permit treatment of endometriosis for up to one year, the sponsor conducted two clinical trials designed to evaluate the efficacy of "add-back" therapy in prevention of loss of bone mineral in Lupron®-treated patients. Descriptions of the two studies are presented in the consult request and in the sponsor's submission.

Study M92-878, was a randomized, double-blind, 4-arm (Lupron alone, Lupron plus NETA 5 mg/day, Lupron + NETA + CEE 0.625 mg, and Lupron + NETA + CEE 0.125 mg) trial that lasted for one year, followed by an additional 24-month period in which observational data were collected. There were approximately 50 pre-menopausal women in each study arm. Study M97-777 was an open-label, single-arm study with a 52-week treatment period followed by a 12-month observational period. All (N=136) patients received Lupron plus NETA 5 mg. The same inclusion/exclusion criteria were used for both studies. Patients were supplemented with 500 mg elemental calcium/day, without vitamin D. Thus a total of 191 patients had planned exposure to Lupron + NETA for one year. It was agreed that criteria for acceptance of efficacy were that the lower boundary of the

95 % confidence interval of the % change from baseline be > -2.2 (i.e., that the lower boundary of the 95% CI fall above –2.2).

The sponsor has conducted no dose-finding studies for NETA; dose selection was based on a prior publication that studied the efficacy of 5 mg daily. Complete descriptions of endpoints, methods of data collection and management, patient characteristics, and other parameters are included in the submission. This consultation will focus on assessment of BMD. The sponsor measured BMD at the lumbar spine (L1-L4) using DEXA. Duplicate measurements were taken with Hologic Quantitative Digital Radiography (QDR) and processed centrally by the sponsor. BMD evaluations were performed at baseline, Week 24, and Week 52. During follow-up periods BMD evaluations were planned for every four months through Month 24. There were no bone marker studies, nor were there BMD measurements made at other skeletal sites.

Results: In the following table, I have summarized patient disposition for the LD-only (Lupron alone) and LD/NETA group for M92-878 and LD/NETA for M97-777.

	STUDY M92-878		STUDY M97-777
	LD ONLY	LD/NETA	LD/NETA
Randomized	51	55	136
Completed treatment period	32 (63%)	31 (56%)	82 (60%)

The sponsor presents listings and summaries of discontinuations, including reasons for discontinuation. Apparently, the dropout rates did not differ significantly between the two treatment groups in the first study.

BMD Results of Study M92-878: BMD analyses were performed on two sets of Week 52 data. One set included only Week 52 scans of patients on therapy. The other included all week 52 scans, regardless of whether a patient was on therapy. Other analyses were performed, based on defined intervals. In addition, the sponsor carried out "Week 52 imputation analyses," in which Week 52 data were imputed for patients lacking on-treatment measurements at that time point. These used two slightly different models.

The results of these analyses are presented in the sponsor's Table 3.10a. Data are presented only for the LD-Only and LD/NETA treatment groups. The CEE groups are not presented. In the LD-Only group, there were statistically significant ($p<0.001$) declines from baseline in spinal BMD of 3.2-3.3% at 24 weeks, depending on method of calculation. At 52 weeks, the mean lumbar spine BMD had declined by about 6.3% from baseline (significant change from baseline, $p<0.001$), again depending on method of calculation and data set used. In contrast, the LD/NETA group showed mean declines from baseline of 0.2-0.3% at 6 months (within-group change from baseline NS; difference from LD-Only group $p<0.001$). At 52 weeks, the mean decline from baseline was about

0.9%. Most within-group comparisons of BMD changes from baseline at 52 weeks in the LD/NETA group were not statistically significant. The imputed analyses showed declines of 1.1%, which were statistically significant. All comparisons (using all analytical approaches) between the two treatment groups were statistically significant ($p<0.001$) at both time points. The percent changes for BMD values were quite stable across all analytical approaches.

Thus the data demonstrate that, in the LD-Only group, there was a mean loss of spinal BMD of about 3.3% at six months and 6.3% at 12 months. Patients treated with LD + NETA experienced losses of about 0.3% at six months and 0.9% at 12 months. Differences from baseline were not statistically significant in this treatment group. Between-treatment group differences were statistically significant at both time points. The data show that patients treated with LD-Only experience substantial declines in lumbar spinal BMD. These losses in spinal BMD are potentially clinically meaningful if there is no recovery when Lupron treatment is interrupted (these pre-menopausal patients are for the most part estrogen-sufficient in the absence of Lupron). The magnitude of the losses is not unexpected, given the responses of trabecular bone to estrogen withdrawal. The data also demonstrate that the BMD losses can be prevented by addition of NETA 5 mg/day.

Results of Study M97-777: The sponsor presents the results of the second study (M97-777) in several statistical tables.

One hundred thirty-six patients entered the study, and 82 (60%) completed the year of treatment. Patients without a Week 52 DEXA scan had results of their latest Treatment Period scan carried forward and included in the analysis. Other analyses included the percent changes from baseline at the Week 24 and Week 52 visits.

Irrespective of whether imputed values were used, the results were essentially the same across analyses. There were small reductions of about 0.2% from baseline at 24 weeks; these were not statistically significant. At 52 weeks, there were statistically significant ($p<0.001$) reductions from baseline of about 1.0-1.2%, depending on analytical approach to the data. In each case (Table 3.10b of the submission), the lower boundary of the 95% CI was well above –2.2. For example, for the Week 52 data collected at 7-month interval, the mean % BMD change was –1.1 (-1.6, -0.5). The data set with the greatest change, Week 52 (imputation), had a mean of –1.2% (-1.7, -0.8).

In answer to specific questions:

1. *Are the reductions in loss of BMD that are associated with NETA appropriate surrogates for maintenance of bone strength?*

NETA is a progestational agent. There are no preclinical studies that indicate that NETA increases or maintains bone strength in ovariectomized animals. Therefore, BMD changes in association with NETA therapy could not be used as a surrogate for bone quality. According to our current guidelines, NETA could not be approved for the prevention of post-menopausal osteoporosis in the absence of such studies. I recognize that this compound is likely working via an estrogenic and/or androgenic pathway in bone, and that there is little reason to believe that these effects are not associated with maintenance of bone quality. Certainly there is even less reason to suspect that bone quality is harmed by this sex steroid. Nonetheless, our guidelines would mandate the performance of these studies for prevention indication for postmenopausal osteoporosis.

In addition, the sponsor has not performed adequate (or any) dose-ranging studies. These are always required for drug approval.

In the present, rather unusual circumstance, one might consider that NETA is being used to counteract the adverse effects of an approved drug. This consideration might play a role in a regulatory decision.

Finally, NETA will be used for relatively short periods, as opposed to prevention therapies for postmenopausal osteoporosis.

2. *Is the measure of BMD at only one site (lumbar spine) in the context of the submitted studies sufficient to assess the effects of 6 and 12 months of treatment with Lupron/NETA on bone integrity?*

Loss of trabecular bone predominates in estrogen-deficient states. Thus BMD loss is most prominent at the lumbar spine. However, following estrogen withdrawal, loss of bone also occurs at the hip, wrist, and other skeletal sites. In osteoporosis prevention studies, BMD changes are always measured at important extra-vertebral sites. Thus the available information does not provide a complete picture of the overall BMD responses to Lupron and Lupron/NETA.

3. *Is the methodology (including sample size, laboratory measurements) adequate?*

I believe that the sample size was sufficient for these studies in patients with endometriosis. The duration of the trials was certainly adequate. I leave it to the medical officer in HFD-580 to decide whether the trial population was sufficiently representative. In my opinion, it was probably adequately representative. The methodology for BMD determination was standard and certainly acceptable.

4. *What is your assessment of the comparative adverse effect on bone of 12 months of treatment with Lupron + NETA, compared to 6 months of treatment with Lupron alone?*

The changes are about 1% loss at one year with LD/NETA, vs about 3% at 6 months with Lupron alone. Based on these changes alone, there is certainly no increase in bone adverse effect at one year with combination therapy, over that which is seen with standard treatment.

5. *Do you recommend adding NETA to Lupron treatment for 6 months?*

In certain individuals who are at high risk of bone loss (by BMD, personal and family history, body weight, etc.), I think that addition of NETA would be helpful in reducing any further BMD decrease at the spine at 6 months. It is likely that some individuals will experience BMD losses of more than 3% during this period, and some patients may not replace these losses. This is a medical opinion, and it should be taken in the context of the regulatory and scientific issues discussed above in Question 1.

6. *Is there any reason to believe that, in patients previously treated with a GnRH analog, re-treatment with Lupron/NETA will result in greater bone loss than in patients who had not previously been treated with a GnRH analog?*

We have data on 32 patients previously treated with a GnRH analog, who were given LD/NETA as participants in wither of the above two studies. This subset was analyzed separately. This analysis disclosed that the mean BMD loss in this group at 24 and 52 weeks was –0.515% and –0.786%, respectively. These are in reasonable agreement with the behavior of the group as a whole. Of interest, the GnRH-naïve subset lost –0.148% at 6 months and –1.136% at 52 weeks. I have no information regarding the time interval between the termination of the first GnRH treatment and the initiation of Lupron therapy. Nonetheless, it appears from the data that patients who have experienced prior GnRH therapy response as well to NETA add-back therapy as do GnRH-naïve individuals.

I hope that this consult has been helpful. If I can be of further assistance, please do not hesitate to contact me.

Bruce S. Schneider, MD
DMEDP, HFD-510

Cc Dr. Colman,

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bruce Schneider
8/22/01 02:57:07 PM
MEDICAL OFFICER

signed for D.Orloff

Eric Colman
8/22/01 03:03:42 PM
MEDICAL OFFICER
Eric Colman for David Orloff

NDA 20-011/S-021
Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Safety Update Review – See Page 22 of the Medical Officer's Review.

/S/

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 020011
Trade Name: LUPRON DEPOT 3.75 mg
Generic Name: LEUPROLIDE ACETATE
Supplement Number: 021 **Supplement Type**: SE1
Dosage Form:
Regulatory Action: AP **Action Date**: 9/21/01
COMIS Indication: TREATMENT OF ENDOMETRIOSIS

Indication #1: Lupron Depot 3.75 is indicated for management of endometriosis, including pain relief and reduction of endometric lesions. Lupron depot monthly with norenthindrone acetate 5 mg daily is also indicated for initial management of endometriosis and for management of recurrence of symptoms. Duration of initial treatment or retreatment should be limited to 6 months.
Label Adequacy: Does not apply
Formulation Needed: No new formulation is needed
Comments (if any)

Lower Range	Upper Range	Status	Date
Adult	Adult	Waived	9/21/01

Comments: Endometriosis is not a condition found in the pediatric population.

This page was last edited on 9/21/01

/S/ 9/21/01

Signature Date

APPEARS THIS WAY
ON ORIGINAL

NDA 20-011, S-021
NDA 20-708, S-011
Lupron Depot 3.75 mg or 3-Month 11.25 mg with norethindrone acetate 5 mg for 12 months in the management of endometriosis.

Request for waiver for pediatric drug development.

Pursuant to 21 CFR § 314.55(c)(2)(iii), TAP Pharmaceutical Products Inc. requests for full waiver of the requirements of § 314.55(a) for pediatric use information.

These supplemental applications are for use of Lupron Depot 3.75 mg or Lupron Depot – 3 Month 11.25 mg with norethindrone acetate 5 mg daily for the management of endometriosis for 12 months.

Endometriosis is not a condition that is found in the pediatric population. As such Lupron Depot and norethindrone acetate regimen is expected to be ineffective for this indication in any pediatric age group, and qualifies for a full waiver under 21 CFR § 314.55(c)(2)(iii).

The safety and efficacy of Lupron Depot 7.5 mg, 11.25 mg and 15 mg has been evaluated in the pediatric population for the management of central precocious puberty and these strengths of Lupron Depot are approved for this indication under NDA 20-263.