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 from –4% to +9%. 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 Biberoglu and Behrman.

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 [redacted] In Study M97-777, [redacted] 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 [redacted]-trained technicians with [redacted] Quantitative Digital Radiography (QDR) machines using dual-energy x-ray absorptiometry (DEXA) methodology. Data from these measurements were processed by [redacted]) and 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.

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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.*

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 (range: 0.823 to 1.348) at baseline to a mean of 0.964 gm/cm^2 at Week 52 (range:). At Week 52, the mean percent change from baseline was -6.3% (range:). 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				Post Treatment Period		
		Week 24	Week 52	Final	Week 36-64	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
Min								
Max								
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%
Min								
Max								

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 (range:) at baseline to a mean of 1.064 gm/cm^2 at Week 52 (range:). At Week 52, the mean percent change from baseline was -1.0% (range:). 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				Post Treatment Period		
		Week 24	Week 52	Final	Week 36-64	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
Min								
Max								
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%
Min								
Max								

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 ——— trained technicians utilizing DEXA technology and Quantitative Digital Radiography machines (QDR). All DEXA scans were reviewed by ! ——— prior to electronic transmission of data to the Sponsor. 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.*
- *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 (range: [redacted]) at baseline to a mean of 1.058 gm/cm^2 at Week 52 (range: [redacted]). At Week 52, the mean percent change from baseline was -1.1% ([redacted]). 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	[redacted]							

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 f _____ _____ . Mean BMD changes in the group with no prior GnRH treatment ranged from _____

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

			Baseline	End of Treatment	Change From Baseline	
Study	Treatment Group	N	Mean	Mean	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.

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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	0.03	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
In the LD/N treatment groups, smaller, statistically inconsistent, increases in total cholesterol values, with changes in mean values ranging , 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 . In the LD treatment group, small increases in mean HDL-C values, ranging from 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 7.8% to 13.5%. 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 32.3% to 40.0%. 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 5.6% to 14.1%, 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 –7.65% (LD/N treated patients in Study M92-878 at Week 24) to 16.0% (LD/N treated patients in Study M97-777 at Week 52) and generally were not statistically significant.

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.

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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)..

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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