CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-886/S-013

MEDICAL REVIEW(S)

Medical Officer's Review
(Supplemental NDA)

DEC 22 1998

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Sponsor: G. D. Searle & Company
4901 Searle Parkway
Skokie, Il 60077

Drug(s):

Generic: Nafarelin acetate
Leuprolide acetate

Trade: Synarel
Lupron

Chemical: Synarel: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-3- (2-naphthyl) -D-alanyl-L-leucyl-L-arginyl-L-prolyl-glycinamide acetate
Lupron: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl—N-ethyl-L-prolinamide acetate

Pharmacologic Category: Long acting Gonadotropin Releasing Hormone Agonists

Route: Intranasal (nafarelin)
intramuscular (leuprolide)

Dose: Nafarelin: 200 micrograms twice daily. The solution is a 2mg/ml solution of the free base, given in a primed unit which delivers 100 µl of nafarelin with each spray.

Leuprolide: 3.75 milligrams monthly

Proposed Indication: Endometriosis

Related INDs: IND

Related NDAs NDA 19, 886 Synarel - marketed product by G.D. Searle
NDA 19, 943 Lupron - marketed product by Tap Pharmaceuticals

Medical Officer's Review

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1.0 Resume

This submission is a labeling revision for the marketed product Synarel to allow comparison claims between this product and Lupron for the treatment of endometriosis. The submission included only one trial LAB/NAF 610/USA, RS-94991. The study was a single blind, placebo-controlled, parallel, randomized design of 200 women conducted in the United States at 20 centers. Patients were randomly assigned at a ratio of 1:1 to receive either nafarelin 200 µg BID or leuprolide 3.75 mg i.m. monthly for six months of treatment. Subsequent to the 6 month treatment period, there was a 6 month follow-up. Women were included who were diagnosed with endometriosis by previous laparoscopy or laparotomy and were presently symptomatic from this disorder but otherwise in general good health. Recent use of hormonal medications and certain concurrent illnesses were reasons for exclusion. Study participants were between years of age (mean 31) and were predominantly Caucasian (85%)

A total of 236 patients were enrolled and of these 208 (nafarelin-105 and leuprolide-103) received study drug and were included in the safety analysis. A total of 168 completed the 6 month treatment period and 117 patients completed the entire 12 months of treatment and follow-up.

Twenty patients (nafarelin-7 and leuprolide-13) discontinued the study medications because of adverse events, however, their data were included in both safety and efficacy analysis. A total of 6 patients (evenly distributed at 3-nafarelin and 3- leuprolide) discontinued because the treatment was ineffective.

The principle measures of efficacy and safety were changes in the signs and symptoms of endometriosis, estradiol levels, hypoestrogenic symptoms secondary to GnRH treatment and bone density. Secondary measures of efficacy which were performed at selected sites were progesterone levels and objective hot flash measurements. Safety was evaluated through the assessment of adverse events and laboratory parameters.

Nafarelin at the dose studied was clinically comparable to leuprolide for the treatment of the symptoms of endometriosis (dysmenorrhea, dyspareunia and pelvic pain). Patients on both leuprolide and nafarelin, experience bone mineral loss as the result of their treatment. At the 200µg BID dose of Synarel, patients experienced less bone loss at the end of 6 months of treatment than did those treated with 3.75 mg Depot form of leuprolide. Hypoestrogenic symptoms were experienced by nearly all of the patients on leuprolide and nafarelin. Patients on nafarelin experienced a median 66% of days with hot flushes as opposed to 91% of days for patients on leuprolide acetate . The median percent days with bleeding was 8% on nafarelin acetate and 6% on leuprolide acetate. During the treatment phase, 89% of patients reported adverse events (nafarelin-90% and leuprolide-88%) Twenty patients (10%) terminated the study medications early because of adverse events (nafarelin-7% and leuprolide-13%).

Based on the results of this single trial, the sponsor of nafarelin acetate would like to make the claim of equivalency to leuprolide on the treatment of the signs and symptoms of endometriosis and a superiority claim with respect to the safety effects on bone and hypoestrogenic side effect of hot flushes. The supportive evidence which supports these claims, and concerns about these claims will be discussed in detail in this review.

2.0 Background

Endometriosis is a progressive and invasive, non-malignant disease which causes pelvic pain, painful menstrual periods, pain during intercourse and infertility. Widely varying figures for the prevalence of endometriosis have been presented in the published literature, and a rough estimate is that between 3-10% of women of reproductive age (1) have endometriosis. Among women with pelvic pain or infertility, the reported incidence ranges from 20 -90 % (2). About 4 per 1,000 women age 15 - 64 are hospitalized with endometriosis each year, slightly more than those admitted with breast cancer (3). Endometriosis should be suspected in any women complaining of infertility and the suspicion is heightened when there are also complaints of dysmenorrhea and dyspareunia (3) Symptoms can range from none to severe. The fact that women with minimal endometriotic lesions on surgical evaluation often present with the most severe symptoms emphasized the paradoxical, perplexing nature of the disease.

Although the precise etiology of endometriosis is unknown, several well respected theories have been put forth including retrograde menstruation proposed by Sampson in the 1920's, vascular or lymphatic transport of endometrial fragments and coelomic metaplasia. All of these mechanisms may contribute to the clinical problem in an individual patient, and the degree of contribution for each probably varies from patient to patient. The progression of the disease may be influenced by the individual's immune system.

Surgical removal of endometrial implants was the mainstay of treatment for many years, however, some woman failed to achieve complete pain relief either because of incomplete implant excision or post-operative disease recurrence. Implants of endometriosis react to steroid hormones in a manner somewhat, but not exactly, similar to normally stimulated endometrium. However, endometriotic tissue displays histologic differences and biochemical differences, including enzyme activity and receptor levels which differ in concentration and response compared to normal endometrium (3). Estrogens stimulate the growth of endometriotic implants. The discovery of the down-regulatory properties of the natural gonadotrophin-releasing hormone (GnRH) and its synthetic, nonsteroidal agonistic (and now antagonistic) analogs has made it possible to create a reversible hypoestrogenic state. GnRH therapy, as with all hormonal treatment for endometriosis, must be considered suppressive rather than curative.

In the United States, three GnRH agonists (leuprolide acetate, nafarelin acetate and goserelin acetate) are currently approved for the treatment of endometriosis . The three compounds have an initial agonist or stimulatory effect on pituitary gonadotrophs resulting in release of gonadotropins and gonadal steroids followed by down-regulation and desensitization of the pituitary resulting in hypogonadotroic hypogonadal state. Nafarelin acetate is administered intranasally on a daily basis. Leuprolide depot is administered intramuscularly and monthly. Goserelin consists of a small biodegradable cylinder which is inserted subcutaneously and monthly using a prepackaged syringe.

A long acting GnRH agonist can create a pseudomenopause for the treatment of endometriosis (4,5). At the end of 2-4 weeks of daily exposure (administration) of the agonist, estrogen levels will decrease to those found in oophorectomized women. Dosage can be adjusted by monitoring serum estradiol levels: the best therapeutic effect is associated with a range of pg/ml (pmol/l).

The objective of this NDA , study 610, was to compare leuprolide acetate and nafarelin with respect to measures of efficacy and safety.

2.1 Regulatory history

Synarel

NDA 19,886 for Synarel (nafarelin acetate) for the treatment of endometriosis was submitted on November 11, 1988. On April 28, 1989, the Fertility and Maternal Health Advisory Committee recommended approval of nafarelin for relief of pain associated with endometriosis. The NDA was approved on February 13, 1990.

The agency received a new protocol amendment to IND
It was reviewed by Vanaja V. Ragavan on 10/28/91 and the study was allowed to proceed. It was a Phase IV study which called for a 12 month single blind study of safety and efficacy in 240 women (120 women per arm) at 20 sites who were to receive a six month treatment with nafarelin or leuprolide and six months of follow-up. Women were to be included who had the clinical signs and symptoms of endometriosis including pelvic tenderness, induration, dysmenorrhea, dyspareunia and pelvic pain. The primary endpoints were to be symptom relief, estradiol level, bone density and hypoestrogenic symptoms. The secondary variables, in subsets of patients at selected sites, were progesterone levels and objective hot flash measurements. The reviewer found no clinical deficiencies.

2.2 Preclinical Studies

The non-clinical section of this NDA is included by cross reference to the same in the original NDA 19,886.

2.3 Human Pharmacology studies

No new studies were submitted for review under this NDA.

2.4 International Marketing Experience

Synarel (nafarelin acetate) is approved for marketing in 46 foreign markets for the indications of endometriosis, IVF, uterine fibroids and precocious puberty. It is approved in the US only for endometriosis and precocious puberty.

3.0 Protocol ICM LAB/NAF 610: COMPARISON OF NAFARELIN INTRANASAL vs. LEUPROLIDE DEPOT INTRAMUSCULAR IN PATIENTS WITH ENDOMETRIOSIS

3.1 Objective

The objective of this study was to compare in 200 women, nafarelin intranasal and leuprolide depot for symptom relief, bone mineral loss, hypoestrogenic effects, and adverse events while on treatment.

3.2 Design

This was a single-blind, double placebo, parallel randomized study conducted in 20 centers in the United States Patients were treated for six months with an active and a placebo medication and then followed for an additional 6 months to termination of the study. Pregnancy surveillance continued for 6 months after study termination in those patients who indicated a desire to become pregnant.

3.3 Study population, inclusion/exclusion criteria

To be admitted to the study, women had to have been generally healthy, between 18 and 46 years of age with menstrual cycles in the preceding three months ranging from 24-36 days. The woman must have had a diagnosis of endometriosis made by laparoscopy or laparotomy within the prior 18 months and at time of study enrollment have clinical signs or symptoms consistent with endometriosis including induration, pelvic tenderness, dysmenorrhea, dyspareunia, dyschezia or other pelvic discomforts. Women could have a complaint of infertility, but infertility alone was insufficient for entry into the study. The women had to be willing to give informed consent and undergo all study procedures, use barrier contraception (if non-sterilized) throughout the six months of active treatment and 6 months of follow-up. Women were

excluded: if they were pregnant; breastfeeding; had bone mineral densities greater than 2 standard deviations below the normal mean for age; had any disease that would interfere with the conduct or analysis of the study (including any history of malignancy other than basal cell carcinoma which was ≤ 5 years in remission, moderate to severe cervical dysplasia, cerebral vascular accidents, coronary heart disease, untreated thyroid disease or treated thyroid disease if the woman was not euthyroid, active liver disease, active gallbladder disease, uncontrolled hypertension, diabetes mellitus and kidney stones); who had a clinically significant laboratory abnormality on screening. Women were also excluded: who received Danazol in the prior 6 moths; GnRH agonist in the prior 12 months; oral contraceptives, short-acting estrogens or progestins within 30 days of starting study drug medication; who were known or suspected substance abusers and who were likely to be noncompliant with the drug regimen or other study requirements.

3.4 Procedures, blinding and randomization

At screening woman were assessed for their eligibility by inclusion/exclusion criteria, general and gynecologic histories were taken. A patient assessment of quality of life related to endometriosis was obtained. General and gynecologic (including Pap) examinations were performed and the sign and symptom severity profile completed. Blood was obtained for hematology, chemistry profile , lipid profile (fasting). Pregnancy testing was performed on either a urine or serum sample and urinalysis was done. At sites designated as A (subset of 80 patients total) and A+ (subset of 20 patients total), one follicular phase (day 7-14) sample of estradiol and one luteal phase (day 15-26) sample of progesterone was obtained. All laboratory analyses were performed by a central laboratory. Baseline bone densitometry with DEXA of L1-L4 was obtained prior to start of treatment. Informed consent was obtained and instructions were given for the completion of the nightly diary and a 2 month supply of the diary given.

Reviewer's comment:
The rationale for obtaining the baseline estradiol determinations in the mid-late follicular phase of the cycle when these values are most variable is unclear to me. The Sponsor would have obtained more uniform results if all baseline values had been obtained in the early follicular phase of the cycle (e.g. a day 3 value). Interpretation of baseline estradiol values is clearly hampered in this regard.

Randomization was done on a 1:1 basis. Randomization numbers were assigned sequentially without interruption. Participants were to remain blinded throughout the study. If possible, a third person (other than the study coordinator or investigator) prepared and administered the injections.

If eligible, the volunteers began their study drug within 4 days of the onset of the following menses (ie by cycle day 4). Each patient received two boxes of medication. Patients randomized to nafarelin received one box containing 6 bottles of nafarelin and spray adaptors and another box containing 6 vials of sterile normal saline solution for injection. Patients randomized to leuprolide received one box containing 6 bottles of leuprolide with 6 bottles of diluent and the other box containing 6 bottles of placebo nasal spray.

Women were seen on a monthly basis to be administered their injectable medication, to obtain additional nasal spray and to report on their current status. A menstrual pattern and severity profile were assessed at each monthly visit. Patient diaries were reviewed and adverse events recorded on adverse event reporting forms. A patient assessment form was completed by the patient. Concomitant medications were reviewed. During the study, women were prohibited from taking Danazol, any other GnRH agonist, systemic glucocorticoids, oral contraceptives, estrogens and progestins, and ovulation induction drugs. Pelvic examinations were required only at months 1, 2, 3 and 6. Hematology, chemistry profile, lipid profile (fasting) and urinalysis was obtained on all patients at visit 7. A single DEXA scan (L1-L4) was obtained within 2 weeks of visit 7. Urine pregnancy testing was obtained prior to the DEXA scan. At subset sites A, estradiol levels (two samples, one prior to the administration of medication at that visit and one 7-10 days later before medications administration) were obtained at visits 4 and 7 and at subset sites A+, estradiol determinations were made at visits 3, 4, 5, 6, and 7 (again samples were obtained before the

medication at that visit and 7-10 days later before any medication was taken). At subset site B, objective hot flash measurements were performed between visits 3 and 4 and between visits 5 and 6.

Following the end of the 6 month treatment period, each patient was seen at 7.5 months, 9 months and 12 months. Endometriosis symptom and pelvic exam assessment of the signs were performed. Adverse events were recorded, review of the nightly patient diary (collected at visit 9) and concomitant medications were performed and patient assessment of quality of life was made. A Pap smear was performed at 7.5 months. A DEXA scan (L1-L4) was performed at 12 months.. Site A participants had estradiol and progesterone analyzed at 7.5 and 9 months. Site A+ participants had estradiol and progesterone assayed weekly following the last nasal spray administration for a total of 8 weeks. During the 6 month post-treatment follow-up, the only restrictions on medication were no use of oral contraceptives, GnRH analogs or danazol.

Patients who completed the study and indicated that they intended to attempt conception were contacted 12 months after treatment was ended to determine whether or not a pregnancy was achieved.

3.5 Endpoints

Signs and Symptom Severity:
At baseline and monthly visits 1, 2, 3, 4, 5, 6, 7.5, 9 and 12, patients were asked to fill out a menstrual pattern and symptom severity report form. The patient report of the symptoms of dysmenorrhea, dyspareunia and pelvic pain were rated as follows:

Dysmenorrhea

Absent	No discomfort
Mild	Some loss of work efficiency; mild analgesics help
Moderate	Occasional loss of work efficiency; moderate analgesics
Severe	Incapacitation; strong analgesics
Not applicable	Amenorrhea since prior visit

Dyspareunia

Absent	No difficulty or pain
Mild	Tolerated discomfort
Moderate	Intercourse painful to the point of interruption of intercourse
Severe	Avoids intercourse because of pain
Not applicable	Not sexually active. Prefers not to answer

Pelvic Pain

Absent	No discomfort
Mild	Occasional pelvic discomfort or pain
Moderate	Noticeable discomfort or pain for most of cycle
Severe	Requires strong analgesic. Persistent pain other than during menses

At baseline and months 1, 2, 3, 6, 7.5, 9 and 12 pelvic exams were performed to assess the signs of endometriosis, inudration and pelvic tenderness. The physician evaluated ratings of induration and pelvic tenderness were as follows:

Induration

Absent	No induration
Mild	Uterus freely mobile, induration in the cul-de-sac

Moderate	Thickened and indurated adnexa and cul-de-sac, restricted uterine mobility
Severe	Nodular adnexa and cul-de-sac, uterus frequently frozen

Pelvic Tenderness

Absent	No tenderness
Mild	Minimal tenderness on palpation
Moderate	Extensive tenderness on palpation
Severe	Unable to palpate because of tenderness

Reviewer's Comments: These are the same criteria as used in the original NDA 19,886 to establish efficacy of Synarel for the treatment of endometriosis. These are also consistent with other validated measures as used in the NDA for the approval of Lupron.

Estradiol Level
Estradiol measurements were performed in a subset of 80 patients. Samples were obtained once during the follicular phase at baseline and, thereafter, two samples (pre- and post-drug administration) were taken at months 3 and 6 on treatment and a single sample at post-treatment visits at 7.5 and 9 months. Monthly estradiol determinations were made in a subset of 20 participants beginning at month two through month 6. Following the end of treatment, weekly samples of estradiol were collected from these participants for 8 weeks and then a single sample at the month 9 visit.

Bone Mineral Density
At baseline, all participants had two bone mineral density evaluations performed using DEXA of L1-L4. The average BMD value for each scan was recorded. A single DEXA scan of L1-L4 was performed within two weeks of the 6 month visit and at the post-treatment visit at month 12.

Hypoestrogenic Symptoms
Participants began recording of hypoestrogenic symptoms on their daily diary at baseline and nightly entries into the diary were continued through month 9 in the post-treatment follow-up period. Diaries were collected for the final time at the month 9 visit.

Safety
Adverse events (AEs), changes in physical exam, bone mineral density determination and lab results and pregnancy were reviewed to evaluate safety. Pelvic examinations and laboratory studies were done as clinically indicated. Description of events included duration, severity (mild, moderate, or severe) and the investigator's opinion as to the relationship to the trial medication (probably related, possibly, related, probably not related. If not related, the investigator was to report on whether the event was present before the study, or due to the primary disease, concomitant medications, intercurrent illness, or another reason.

3.6 Patient Disposition

Two Hundred Thirty Six (236) participants were enrolled in the study.
Two Hundred Eight participants took study drug (105-Nafarelin and 103-Leuprolide)
One Hundred Forty Seven (147) women took study drug for 6 months.
One Hundred Seventeen (117) women completed the entire 12 month study.

Reviewer's Comments: There were 28 patients who enrolled but were not randomized to study medications; these included 26 screening failures and two patients who were lost to follow-up. Eighty one percent (81%) of participants who were randomized to study medications completed six months of treatment. Fifty Six percent (56 %) of the patients who were randomized, completed the entire study (six months of treatment and six months of follow-up). This is a high attrition rate for the entire study, but it may be difficult to retain participants in a study after they are no longer receiving study medication.

3.7 Discontinuations

Table 1
REASONS FOR DISCONTINUATION[1]
All Subjects Treated Group

Reason for discontinuation	During 6 months of treatment[2]		During 6 months post-treatment follow-up		Total
	Nafarelin	Leuprolide	Nafarelin	Leuprolide	
Adverse Events	7	13	3	3	26
Ineffectiveness of study medication	3	3	N/A	N/A	6
Lost to follow-up	1[3]	5	6[4]	3	15
Study Administration Problems	2	0	5	3	10
Became pregnant	0[5]	0	12	5	13
Death	1[6]	0	0	0	1
Other	2	4	5	5	17
Total discontinued	16[7]	25	31	19	91
Total entered	105	103			208

1 Table was constructed from Table 5 page 55 and Figure 2 page 115, volume 1.
2 These figures include patients who stopped medication during the treatment period, but remained in the post-treatment follow-up. These patients included who were randomized to nafarelin and who were randomized to leuprolide.
3 Correction of the data from Table 5 Page 55 and Figure 2 page 115. Patient was lost to follow-up after visit 5 where she would have gotten the placebo injection, however, date of the last nasal spray was listed as unknown on Form 16, " End of Treatment" CRF.
4 See footnote #3.
5 One patient, , became pregnant shortly after enrollment but before randomization. She had a termination procedure and rejoined the study and was randomized to treatment.
6 Patient who had randomized to nafarelin died during an accidental house fire.
7 See footnote #3

Reviewer's comment: The most common reason for discontinuation during study medication treatment was adverse events. Adverse events accounted for 49 % of discontinuation during treatment and 12 % of discontinuation during the post-treatment period. There were more discontinuations for adverse events during active treatment with leuprolide (n=13) vs. nafarelin (n=7).

3.8 Compliance

Only two patients were excluded during the treatment phase for non-compliance while 4 patients were excluded for non-compliance during the post-treatment follow-up. Four additional patients were excluded in the post-treatment phase because of a need for medications which were excluded by protocol. An evaluation of the drug delivery method for both placebo and active drug revealed that a total of 22 patients missed the nasal spray dose for more than 3 consecutive days during the treatment period, as compared to 21 patients who failed to keep the injection schedule within the specified treatment window. All but 4 of these, were included in the efficacy analyses (see efficacy analyses below).
Ten patients in the nafarelin group missed their intranasal dose for more than 3 consecutive days (only patients were excluded from the efficacy analyses-see below). Eight patients in the leuprolide group failed to maintain the injection schedule within the treatment window (all eight were included in the efficacy analyses).

Reviewer's Comments: Study drug compliance was quite good, with only 5% of patients who were randomized to treatment actually excluded for non-compliance.

3.9 Baseline characteristics

The study population was predominantly (85%) Caucasian, had a mean age of 31 (nafarelin-30 and leuprolide-31) and an average weight of 64 kg. The background characteristics of race, height, weight, blood pressure, medication history, diet and exercise pattern, caffeine and alcohol usage were similar in the two treatment groups. The only baseline imbalance was in the percentage of current smokers; patients treated with nafarelin were more likely to be current smokers than patients given leuprolide (nafarelin-37%, leuprolide 18%: p=0.002). Treatment groups were balanced at baseline with respect to gynecologic and endometriosis history. The average age at menarche was 13 years; and the typical cycle length was 28 days. The chief complaints secondary to endometriosis were pain (93%), infertility (23%), both infertility and pain (19%) and "other". Thirty nine percent of patients had prior hormonal therapy. The baseline laparoscopic scores according to the AFS classification were: 58 (28%)-Stage I (minimal); 66 (32%)-Stage II (mild); 49 (24%)-Stage III (moderate); and 35 (17%) Stage IV (severe).

Reviewer's Comments: The imbalance in percentage of current smokers should have no impact on study drug metabolism. GnRH agonists are metabolized by peptidase and not cytochrome P-450 enzymes (which might be increased in smokers). In addition, the biopharmacology reviewer felt that there would not be any significant effect on nasal absorption in smokers vs. non-smokers.

3.10 Efficacy Analyses

Table 2
Exclusions from Primary Efficacy Analyses

REASON FOR EXCLUSION	PATIENT NUMBER	STUDY DRUG
Patient Reliability		nafarelin
Protocol violations		nafarelin
Patient received less than 3 injections and/or less than 3 months nasal spray		nafarelin
		nafarelin
		nafarelin
		nafarelin
		leuprolide
		leuprolide
		leuprolide
		leuprolide
		leuprolide
		leuprolide
		leuprolide
		leuprolide
		leuprolide
		leuprolide

There were 16 patients excluded from the efficacy analyses. Fourteen of the patients were excluded for being on study drug for less than 3 months while 2 were excluded for protocol violations. Patient used oral contraceptives (Ortho Novum) during the treatment period. Patient was administered both nafarelin and leuprolide because of an error in drug administration and dispensing.. In addition, there were 13 patients who took steroid/hormonal medications during the post-treatment phase of the study (nafarelin-

7, leuprolide 6) which resulted in the partial exclusion of symptom, bone mineral density, estradiol or progesterone data. Three patients on nafarelin and one patient on leuprolide took medications for the recurrence of endometriosis and were considered as no improvement in the post-treatment symptom severity analyses.

Reviewers comments: There was no language in the protocol which pre-specified that patients with less than three month of drug treatment would be excluded from the efficacy analyses. The protocol states that patients who miss two visits and do not maintain their diary should be considered for termination from the study as non-compliant. The protocol further states that if the patient receives less than 90 days of treatment, schedule a post-treatment follow-up for 6 weeks and do all procedures listed for termination. Again there is no statement that patients with less than three months of drug treatment would be excluded from the efficacy analyses, yet the sponsor removed 14 patients from the analyses for this reason. This reviewer, however, agrees that it is reasonable to exclude from the efficacy analyses, patients who have completed less than three months of treatment in a 6 month study of active treatment.

Sign and Symptom Severity

Table 3 is the Sponsor's clinical equivalence analysis at the end of 6 months of treatment.

Table 3[1]
ESTABLISHMENT OF TREATMENT EQUIVALENCE BETWEEN NAFARELIN AND LEUPROLID BASED ON THE IMPROVEMENT RATE[2] OF TOTAL SIGN AND SYMPTOM SEVERITY AT THE END OF ACTIVE TREATMENT
ALL EFFICACY PATIENTS

PATIENT POPULATION[3]	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVEMENT RATE	CONFIDENCE BOUND[4] ON TREATMENT DIFFERENCE (NAF-LEU)	P-VALUE[5]
Pretreatment Severity						
Mild (1-2)	nafarelin 400mcg	1	1	100%		
	leuprolide 3.75 mg	3	3	100%	-[6]	-[6]
Moderate (3-5)	nafarelin 400 mcg	23	19	83%		
	leuprolide 3.75mg	20	14	70%	-0.13	0.016
Severe (6-10)	nafarelin 400 mcg	57	50	88%		
	leuprolide 3.75mg	58	56	97%	-0.19	0.030
Very Severe (11-15)	nafarelin 400mcg	18	17	94%		
	leuprolide 3.75mg	9	8	89%	-0.22	0.063
All Severity	nafarelin 400mcg	99	87	88%		
	leuprolide 3.75 mg	90	81	90%	-0.11	<0.001

Missing data were replaced through interpolation/extrapolation from baseline. Total sign and symptom is the sum of patient-assessed and investigator-assessed scores.

Nafarelin is considered to be clinically equivalent to leuprolide if the population improvement rate of nafarelin (Rnaf) is not lower than that of leuprolide (Rleu) by 20% or more.

1. Reproduction of Table 25, p81 volume 1.

2. Proportion of patients whose pretreatment total sign and symptom severity score is larger than the end of treatment score. Amenorrhea patients included in the analysis of dysmenorrhea with a score of 0. Patients for whom dyspareunia was 'not applicable' were recorded as a missing value.
3. Only patients with a pretreatment symptom severity score > 0 were included.
4. This is the lower limit of 95% 1-sided confidence interval of Rnaf - Rleu. It defines the strictest criterion of clinical equivalence which is statistically supported by the observed data.
5. The p-value tests the null hypothesis H_0: Rnaf - Rleu ≤ 20%. Treatment equivalence is concluded when $p<0.05$.
6. Confidence bound and p-value given only when the sample size of each treatment group is no less than 5.

Reviewer's Comments: The analysis performed by the Sponsor presents a lower limit of a 1-sided 95% confidence interval for the difference in percentage of improved patients which is -11%. This difference is not greater than -20% and the Sponsor concludes statistical equivalence to leuprolide. When this same analysis is done using a 97.5% one-sided lower confidence bound was -12 %. The Sponsor created a *post hoc* scoring system of 0, 1, 2, and 3 for the signs and symptoms severity ratings of absent, mild, moderate and severe, respectively. The Sponsor then took a total of these scores over the 5 symptoms/signs and created the *post hoc* severity categories of 0 (none), 1-2 (mild), 3-5 (moderate), 6-10 (severe) and 11-15 (very severe). The numbers and percentages in Table 3 above are not based on the *post hoc* categories but on the number of patients who improved with respect to the total score itself. The original statistical plan submitted in the protocol of 10/2/91 states that clinical equivalence between nafarelin and leuprolide will be evaluated for the proportion of patients improving at least one category for each symptom severity. The protocol further delineates that clinical equivalence to leuprolide is defined to be an improvement rate within 20% of the improvement rate of leuprolide or higher. Therefore, the analysis submitted by the Sponsor differs substantially from that submitted in the original protocol.

Because of this discrepancy, the Sponsor was asked to perform two equivalency analysis for each of the individual signs and symptoms; one analysis using extrapolated/interpolated data and one using only data which was collected, i.e. no extrapolation or interpolated data was to be included. Improvement was to be defined as an improvement of 1 category or more from baseline to end of treatment. Improvement rate is the proportion of patients whose pretreatment symptom severity score is larger that the end of treatment score. The Sponsor was asked to use a 97.5% one-sided confidence bound. All efficacy patients not included in the tables were to be listed. The following ten tables are reproductions of the efficacy analyses subsequently submitted by the Sponsor. Each table addresses one of the five signs and symptoms of endometriosis as follows:

Table 4 - Pelvic Tenderness- All Efficacy Patients
Table 5 - Pelvic Tenderness -All Efficacy Patients (data without extrapolation or interpolation)
Table 6 - Pelvic Induration- All Efficacy Patients
Table 7 - Pelvic Induration- All Efficacy Patients (data without extrapolation or interpolation)
Table 8 - Dysmenorrhea- All Efficacy Patients
Table 9 - Dysmenorrhea- All Efficacy Patients (data without extrapolation or interpolation)
Table 10 - Dyspareunia- All Efficacy Patients
Table 11 - Dyspareunia- All Efficacy Patients (data without extrapolation or interpolation)
Table 12 - Pelvic Pain- All Efficacy Patients
Table 13- Pelvic Pain- All Efficacy Patients (data without extrapolation or interpolation)

Table 4
Establishment of Treatment Equivalence Between Nafarelin and Leuprolide Based on the Improvement Rate of Pelvic Tenderness at End of Active Treatment for All Efficacy Patients

PATIENT POPULATION[1]	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVEMENT RATE	CONFIDENCE BOUND ON THE TREATMENT DIFFERENCE (NAF- LEU)[2]	P-VALUE[3]
Pretreatment Severity						
Mild	nafarelin 400mcg	35	19	54%		
	leuprolide 3.75 mg	37	23	62%	-0.33	0.211
Moderate	nafarelin 400mcg	51	40	78%		
	leuprolide 3.75 mg	40	36	90%	-0.28	0.210
Severe	nafarelin 400mcg	4	4	100%		
	leuprolide 3.75 mg	2	1	50%	-[4]	-[4]
All Severity	nafarelin 400mcg	90	63	70%		
	leuprolide 3.75 mg	79	60	76%	-0.20	0.030

Missing date were replaced through interpolation/extrapolation from the baseline. Patients used concomitant medication due to endometriosis/pelvic pain and were counted as no improvement.

Nafarelin is considered to be clinically equivalent to leuprolide if the population improvement rate of nafarelin (Rnaf) is not lower than that of leuprolide (Rleu) by 20% or more. Improvement rate is the proportion of patients whose pretreatment symptom severity score is larger that the end of treatment score.

1. Only patients with pretreatment symptom severity score > 0 were included. Twenty three patients (9-nafarelin, 14-leuprolide) were excluded from the efficacy analyses because they were not experiencing pelvic tenderness at baseline.
2. This is the lower limit of 97.5 % 1-sided confidence interval of Rnaf - Rleu. It defined the strictest criterion of clinical equivalence which is statistically supported by the observed data.
3. The p-value tests the null hypothesis H_o: Rnaf-Rleu $\leq$ -20%. Treatment equivalence is concluded when $p < 0.025$.
4. Confidence bound and p-value were given only when the sample size of each treatment group is no less than 5.

Table 5
Establishment of Treatment Equivalence Between Nafarelin and Leuprolide Based on the Improvement Rate of Pelvic Tenderness at the End of Treatment for All Efficacy Patients, Based on Data without Extrapolation or Interpolation

PATIENT POPULATION[1]	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVE-MENT RATE	CONFIDENCE BOUND ON THE TREAMENT DIFFERENCE (NAF-LEU)[2]	P-VALUE[3]
Pretreatment Severity						
Mild	nafarelin 400mcg	30	18	60%	—	
	leuprolide 3.75 mg	35	23	66%	-0.32	0.176
Moderate	nafarelin 400mcg	51	42	82%		
	leuprolide 3.75 mg	38	36	95%	-0.27	0.218
Severe	nafarelin 400mcg	4	4	100%		
	leuprolide 3.75 mg	1	1	100%	-[4]	-[4]
All Severity	nafarelin 400mcg	85	64	75%		
	leuprolide 3.75 mg	74	60	81%	-0.20	0.024

Patients [illegible] used concomitant medication due to endometriosis/pelvic pain and were counted as no improvement.

Nafarelin is considered to be clinically equivalent to leuprolide if the population improvement rate of nafarelin (Rnaf) is not lower than that of leuprolide (Rleu) by 20% or more. Improvement rate is the proportion of patients whose pretreatment symptom severity score is larger than the end of treatment score.

1. Only patients with pretreatment symptom severity score > 0 were included. Thirty Three patients were excluded from the efficacy analyses. Of these, 23 (9-nafarelin, 14-leuprolide) were not experiencing pelvic pain at baseline. In addition, 5-nafarelin and 5-leuprolide patients were missing data for pelvic tenderness at the end of treatment.
2. This is the lower limit of the 97.5% 1-sided confidence interval of Rnaf-Rleu. It defines the strictest criterion of clinical equivalence which is statistically supported by the observed data.
3. The p-value test the null hypothesis H_o: Rnaf - Rleu $\leq$ 20%. Treatment equivalence is concluded when $p < 0.025$.
4. The confidence bound and p-value were given only when the sample size of each treatment groups is no less than 5.

Table 6
Establishment of Treatment Equivalence Between Nafarelin and Leuprolide Based on the Improvement Rate of Induration at the End of Active Treatment for All Efficacy Patients

PATIENT POPULATION[1]	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVE-MENT RATE	CONFIDENCE BOUND ON THE TREATMENT DIFFERENCE (NAF-LEU)[2]	P-VALUE[3]
Pretreatment Severity						
Mild	nafarelin 400 mcg	34	19	56%		
	leuprolide 3.75 mg	24	19	79%	-0.50	0.509
Moderate	nafarelin 400mcg	19	18	95%		
	leuprolide 3.75 mg	24	23	96%	-0.19	0.015
Severe	nafarelin 400 mcg	4	4	100%		
	leuprolide 3.75 mg	2	2	100%	-[4]	-[4]
All Severity	nafarelin 400 mcg	57	41	72%		
	leuprolide 3.75mg	50	44	88%	-0.33	0.396

Missing data were replaced through interpolation/extrapolation from baseline. Patients used concomitant medication due to endometriosis/pelvic pain and were counted as no improvement.

Nafarelin is considered to be clinically equivalent to leuprolide if the population improvement rate of nafarelin (Rnaf) is not lower than that of leuprolide (Rleu) by 20% or more. Improvement rate is the proportion of patients whose pretreatment symptom severity score is larger than the end of treatment score.

1. Only patients with pretreatment symptom severity score > 0 were included. Eight five patients were excluded from the efficacy analyses. Of these, 83 (42-nafarelin, 41-leuprolide) were not experiencing induration at baseline. In addition, two patients on leuprolide (7702 and 6502) were missing data on induration at baseline.
2. This is the lower limit of the 97.5% 1-sided confidence interval of Rnaf-Rleu. It defines the strictest criterion of clinical equivalence which is statistically supported by the observed data.
3. The p-value test the null hypothesis H_0: Rnaf - Rleu $\leq$ 20%. Treatment equivalence is concluded when $p < 0.025$.
4. The confidence bound and p-value were given only when the sample size of each treatment groups is no less than 5.

Table 7

Establishment of Treatment Equivalence Between Nafarelin and Leuprolide Based on the Improvement Rate of Pelvic Induration at the End of Treatment for All Efficacy Patients, Based on Data without Extrapolation of Interpolation

PATIENT POPULATION	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVEMENT RATE	CONFIDENCE BOUND ON THE TREATMENT DIFFERENCE (NAF-LEU)[2]	P-VALUE[3]
Pretreatment Severity						
Mild	nafarelin 400 mcg	31	19	61%		
	leuprolide 3.75 mg	23	19	83%	-0.48	0.579
Moderate	nafarelin 400 mcg	19	18	95%		
	leuprolide 3.75mg	21	21	100%	-0.20	0.028
Severe	nafarelin 400mcg	4	4	76%		
	leuprolide 3.75 mg	2	2	91%	-[4]	-[4]
All Severity	nafarelin 400 mcg	54	41	76%		
	leuprolide 3.75 mg	46	42	91%	-0.31	0.363

Patients used concomitant medication due to endometriosis/pelvic pain and were counted as no improvement.

Nafarelin is considered to be clinically equivalent to leuprolide if the population improvement rate of nafarelin (Rnaf) is not lower than that of leuprolide (Rleu) by 20% or more. Improvement rate is the proportion of patients whose pretreatment symptom severity score is larger than the end of treatment score.

1. Only patients with pretreatment symptom severity score > 0 were included. Ninety two patients were excluded from the efficacy analyses. Of these, 83 (42-nafarelin, 41-leuprolide) were not experiencing induration at baseline. Two leuprolide patients were missing data on induration at baseline. In addition, 7 patients on (3-nafarelin, 4-leuprolide) were missing data on induration at the end of treatment.
2. This is the lower limit of the 97.5% 1-sided confidence interval of Rnaf-Rleu. It defines the strictest criterion of clinical equivalence which is statistically supported by the observed data.
3. The p-value test the null hypothesis H_0: Rnaf - Rleu $\leq$ 20%. Treatment equivalence is concluded when $p < 0.025$.
4. The confidence bound and p-value were given only when the sample size of each treatment groups is no less than 5.

Table 8
Establishment of Treatment Equivalence Between Nafarelin and Leuprolide Based on the Improvement Rate of Dysmenorrhea at the End of Active Treatment for all Efficacy Patients

PATIENT POPULATION[1]	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVE-MENT RATE	CONFIDENCE BOUND ON THE TREATMENT DIFFERENCE (NAF-LEU)[2]	P-VALUE[3]
Pretreatment Severity						
Mild	nafarelin 400 mcg	23	20	87%		
	leuprolide 3.75 mg	20	19	95%	-0.29	0.203
Moderate	nafarelin 400mcg	44	38	86%		
	leuprolide 3.75mg	41	40	98%	-0.25	0.137
Severe	nafarelin 400mcg	31	27	87%		
	leuprolide 3.75mg	29	22	76%	-0.12	0.003
All Severity	nafarelin 400mcg	98	85	87		
	leuprolide 3.75 mg	90	81	90	-0.13	<0.001

Missing data were replaced through interpolation/extrapolation from baseline. Patients used concomitant medication due to endometriosis/pelvic pain and were counted as no improvement.

Nafarelin is considered to be clinically equivalent to leuprolide if the population improvement rate of nafarelin (Rnaf) is not lower than that of leuprolide (Rleu) by 20% or more. Improvement rate is the proportion of patients whose pretreatment symptom severity score is larger than the end of treatment score. Amenorrhea patients were included in the analysis of dysmenorrhea with a score of 0.

1. Only patients with pretreatment symptom severity score > 0 were included. Four patients (1-Nafarelin, 3-leuprolide) were excluded from the efficacy analyses because they were not experiencing dysmenorrhea at baseline.
2. This is the lower limit of the 97.5% 1-sided confidence interval of Rnaf-Rleu. It defines the strictest criterion of clinical equivalence which is statistically supported by the observed data.
3. The p-value test the null hypothesis H_0: Rnaf - Rleu ≤ 20%. Treatment equivalence is concluded when $p < 0.025$.

Table 9
Establishment of Treatment Equivalence Between Nafarelin and Leuprolide Based on the Improvement Rate of Dysmenorrhea at the End of Active Treatment for all Efficacy Patients, Based on Data without Extrapolation of Interpolation

PATIENT POPULATION[1]	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVEMENT RATE	CONFIDENCE BOUND ON THE TREATMENT DIFFERENCE (NAF-LEU)[2]	P-VALUE [3]
Pretreatment Severity						
Mild	nafarelin 400 mcg	23	22	96%		
	leuprolide 3.75 mg	20	20	100%	-0.17	0.007
Moderate	nafarelin 400mcg	44	41	93%		
	leuprolide 3.75mg	41	41	100%	-0.17	0.003
Severe	nafarelin 400mcg	31	29	94%		
	leuprolide 3.75mg	28	27	96%	-0.17	0.008
All Severity	nafarelin 400mcg	98	92	94		
	leuprolide 3.75 mg	89	88	99	-0.11	<0.001

Patients used concomitant medication due to endometriosis/pelvic pain and were counted as no improvement.

Nafarelin is considered to be clinically equivalent to leuprolide if the population improvement rate of nafarelin (Rnaf) is not lower than that of leuprolide (Rleu) by 20% or more. Improvement rate is the proportion of patients whose pretreatment symptom severity score is larger than the end of treatment score. Amenorrhea patients were included in the analysis of dysmenorrhea with a score of 0.

1. Only patients with pretreatment symptom severity score > 0 were included. Five patients (1-Nafarelin, 4-leuprolide) were excluded from the efficacy analyses. Of these, 4 patients (1-nafarelin, 3-leuprolide) were not experiencing dysmenorrhea at baseline. One leuprolide patient was missing dysmenorrhea data at the end of treatment.
2. This is the lower limit of the 97.5% 1-sided confidence interval of Rnaf-Rleu. It defines the strictest criterion of clinical equivalence which is statistically supported by the observed data.
3. The p-value test the null hypothesis H_0: Rnaf - Rleu $\leq$ 20%. Treatment equivalence is concluded when $p < 0.025$.

Table 10
Establishment of Treatment Equivalence Between Nafarelin and Leuprolide Based on Improvement Rate of Dyspareunia at the End of Active Treatment for All Efficacy Patients

PATIENT POPULATION[1]	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVEMENT RATE	CONFIDENCE BOUND ON THE TREATMENT DIFFERENCE (NAF -LEU)[2]	P-VALUE[3]
Pretreatment Severity						
Mild	nafarelin 400mcg	26	18	69%		
	leuprolide 3.75 mg	32	20	63%	-0.21	0.032
Moderate	nafarelin 400 mcg	20	10	50%		
	leuprolide 3.75mg	18	12	67%	-0.53	0.548
Severe	nafarelin 400 mcg	17	15	88%		
	leuprolide 3.75mg	10	7	70%	-0.22	0.031
All Severity	nafarelin 400 mcg	63	43	68%		
	leuprolide 3.75mg	60	39	65%	-0.15	0.006

Missing data were replaced through interpolation/extrapolation from baseline. Patients used concomitant medication due to endometriosis/pelvic pain and were counted as no improvement.

Nafarelin is considered to be clinically equivalent to leuprolide if the population improvement rate of nafarelin (Rnaf) is not lower than that of leuprolide (Rleu) by 20% or more. Improvement rate is the proportion of patients whose pretreatment symptom severity score is larger than the end of treatment score. Patients for whom dyspareunia was "not applicable' were recorded as dyspareunia missing.

1. Only patients with pretreatment symptom severity score > 0 were included. Sixty Nine patients (36-nafarelin, 33-leuprolide) were excluded from the efficacy analyses. Of these, 43 (23-nafarelin, 20 leuprolide) were not experiencing dyspareunia at baseline. In addition, 26 patients had dyspareunia data which was missing or 'not applicable' at baseline.
2. This is the lower limit of the 97.5% 1-sided confidence interval of Rnaf-Rleu. It defines the strictest criterion of clinical equivalence which is statistically supported by the observed data.
3. The p-value test the null hypothesis H_0: Rnaf - Rleu ≤ 20%. Treatment equivalence is concluded when $p < 0.025$.

Table 11

Establishment of Treatment Equivalence Between Nafarelin and Leuprolide Based on Improvement Rate of Dyspareunia at the End of Active Treatment for All Efficacy Patients, Based on Data without Extrapolation or Interpolation

PATIENT POPULATION[1]	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVEMENT RATE	CONFIDENCE BOUND ON THE TREATMENT DIFFERENCE (NAF -LEU)[2]	P-VALUE[3]
Pretreatment Severity						
Mild	nafarelin 400mcg	23	18	78%		
	leuprolide 3.75 mg	28	18	64%	0.14	0.009
Moderate	nafarelin 400 mcg	17	12	71%		
	leuprolide 3.75mg	15	11	73%	0.40	0.245
Severe	nafarelin 400 mcg	14	14	100%		
	leuprolide 3.75mg	10	8	80%	-0.13	0.006
All Severity	nafarelin 400 mcg	54	44	81%		
	leuprolide 3.75mg	53	37	70%	-0.06	<0.001

Patients used concomitant medication due to endometriosis/pelvic pain and were counted as no improvement.

Nafarelin is considered to be clinically equivalent to leuprolide if the population improvement rate of nafarelin (Rnaf) is not lower than that of leuprolide (Rleu) by 20% or more. Improvement rate is the proportion of patients whose pretreatment symptom severity score is larger than the end of treatment score. Patients for whom dyspareunia was "not applicable' were recorded as dyspareunia missing.

1. Only patients with pretreatment symptom severity score > 0 were included. Eighty five (45-nafarelin, 40 leuprolide) patients were excluded from the efficacy analyses. Of these, 43 (23-nafarelin, 20 leuprolide) were not experiencing dyspareunia at baseline. Fourty two patients had dyspareunia dat data that was either missing or 'not applicable' at baseline or at the end of treatment.
2. This is the lower limit of the 97.5% 1-sided confidence interval of Rnaf-Rleu. It defines the strictest criterion of clinical equivalence which is statistically supported by the observed data.
3. The p-value test the null hypothesis H_0: Rnaf - Rleu $\leq$ 20%. Treatment equivalence is concluded when $p < 0.025$.

Table 12
Establishment of Treatment Equivalence Between Nafarelin and Leuprolide Based on the Improvement Rate of Pelvic Pain at the End of Active Treatment for All Efficacy Patients

PATIENT POPULATION[1]	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVEMENT RATE	CONFIDENCE BOUND ON THE TREATMENT DIFFERENCE (NAF -LEU)[2]	P-VALUE[3]
Pretreatment Severity						
Mild	nafarelin 400mcg	28	22	79%		
	leuprolide 3.75 mg	36	21	58%	-0.05	0.001
Moderate	nafarelin 400 mcg	40	28	70%		
	leuprolide 3.75mg	35	28	80%	-0.32	0.233
Severe	nafarelin 400 mcg	20	16	80%		
	leuprolide 3.75mg	16	11	69%	-0.23	0.040
All Severity	nafarelin 400 mcg	88	66	75%		
	leuprolide 3.75mg	87	60	69%	-0.08	<0.001

Missing data were replaced through interpolation/extrapolation from baseline. Patients used concomitant medication due to endometriosis/pelvic pain and were counted as no improvement.

Nafarelin is considered to be clinically equivalent to leuprolide if the population improvement rate of nafarelin (Rnaf) is not lower than that of leuprolide (Rleu) by 20% or more. Improvement rate is the proportion of patients whose pretreatment symptom severity score is larger than the end of treatment score.

1. Only patients with pretreatment symptom severity score > 0 were included. Seventeen patients (11-nafarelin, 6-leuprolide) were excluded from the efficacy analysis because they were not experiencing pelvic pain at baseline.
2. This is the lower limit of the 97.5% 1-sided confidence interval of Rnaf-Rleu. It defines the strictest criterion of clinical equivalence which is statistically supported by the observed data.
3. The p-value test the null hypothesis H_o: Rnaf - Rleu ≤ 20%. Treatment equivalence is concluded when $p < 0.025$.

Table 13

Establishment of Treatment Equivalence Between Nafarelin and Leuprolide Based on the Improvement Rate of Pelvic Pain at the End of Active Treatment for All Efficacy Patients, Based on Data without Extrapolation or Interpolation

PATIENT POPULATION[1]	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVEMENT RATE	CONFIDENCE BOUND ON THE TREATMENT DIFFERENCE (NAF -LEU)[2]	P-VALUE[3]
Pretreatment Severity						
Mild	nafarelin 400mcg	28	22	79%		
	leuprolide 3.75 mg	36	21	58%	-0.05	0.001
Moderate	nafarelin 400 mcg	40	30	75%		
	leuprolide 3.75mg	35	31	89%	-0.33	0.337
Severe	nafarelin 400 mcg	20	17	85%		
	leuprolide 3.75mg	15	15	100%	-0..36	0.537
All Severity	nafarelin 400 mcg	88	69	78%		
	leuprolide 3.75mg	86	67	78%	-0.13	0.001

Patients used concomitant medication due to endometriosis/pelvic pain and were counted as no improvement.

Nafarelin is considered to be clinically equivalent to leuprolide if the population improvement rate of nafarelin (Rnaf) is not lower than that of leuprolide (Rleu) by 20% or more. Improvement rate is the proportion of patients whose pretreatment symptom severity score is larger than the end of treatment score.

1. Only patients with pretreatment symptom severity score > 0 were included. Eighteen patients (11-nafarelin, 7-leuprolide) were excluded from the efficacy analysis because they were not experiencing pelvic pain at baseline. In addition, 1 leuprolide patient was missing pelvic pain data at the end of treatment.
2. This is the lower limit of the 97.5% 1-sided confidence interval of Rnaf-Rleu. It defines the strictest criterion of clinical equivalence which is statistically supported by the observed data.
3. The p-value test the null hypothesis H_o: Rnaf - Rleu $\leq$ 20%. Treatment equivalence is concluded when $p < 0.025$.

Reviewers Comments: The analyses for equivalency performed as specified in the original protocol on each sign and symptom, with and without the use of extrapolated/interpolated data, demonstrate equivalency of nafarelin 400 mcg and leuprolide 3.75 mg in the treatment of the subjective symptoms of dysmenorrhea, dyspareunia and pelvic pain. Equivalency between nafarelin 400 mcg and

leuprolide 3.75 mg was not demonstrated for the investigator-determined sign of induration. Equivalency between nafarelin 400 mcg and leuprolide 3.75 mg was not demonstrated using extrapolated/interpolated data for the investigator-determined sign of pelvic tenderness, however, when non-extrapolated/interpolated data was used (Table 5) statistical significance was just met with p=0.024.

At six months post-treatment, the improvement rate as measured by total severity symptom score (*post hoc analysis)* for both nafarelin and leuprolide significantly fell with rates of 35% and 40 %, respectively for nafarelin and leuprolide (lower limit of 95% 1-sided confidence interval of Rnaf-Rleu = -0.17; p=0.021).

Estradiol level

Figure 1

LAB/NAFA810/USA
INVESTIGATOR: MULTIPLE

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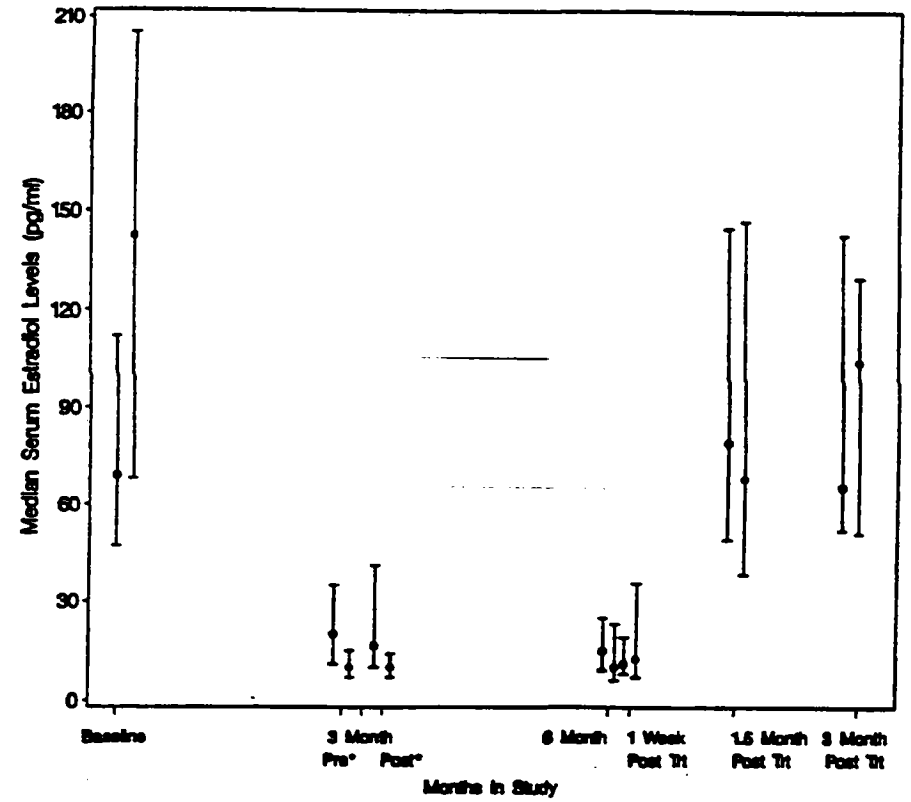
FIGURE 14

Serum Estradiol Levels During Treatment and Post Treatment
by Month for A and A+ Sites Efficacy Patients



	Number of Patients					
o o o	20	47	46	43	35	38	28
• • •	22	37	35	41	36	36	17

o o o N: 6 months Nafarelin 200 mcg bid
• • • L: 6 months Leuprolide 3.75 mg/month

The plot represents the sample median at each time point, with the bottom and top edges indicating the lower and upper quartiles, respectively (i.e., the 25th and 75th percentiles).
All estradiol levels <6 pg/ml. were recorded as 5 pg/mL.
* During the treatment phase, two specimens were drawn, one prior to the injection (pre), the other 7 to 10 days later (post).

SOURCE: ESTRAD.SAS (30SEP94,12:14)

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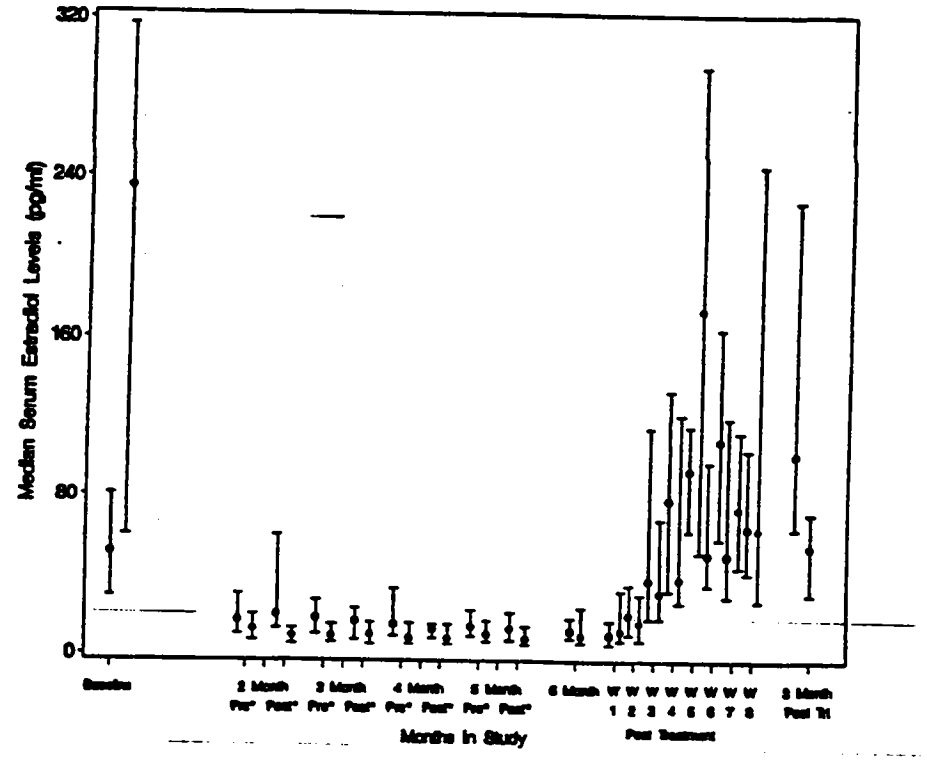
Figure 14, Page 127 volume (reproduced above as Figure 1) presents the Sponsor's analyses of mean serum estradiol levels by month for efficacy patients in the A and A+ sites. The Figure depicts that there were significant differences between the two treatments at baseline with respect to median serum estradiol: estradiol levels were higher among patients randomized to leuprolide than among patients in the nafarelin group. However, there were no significant treatment group differences in the proportion of patients with follicular phase estradiol in the normal range.

Reviewer's comments: The explanation for the difference in baseline estradiol between the two treatment is not clear. However, as stated previously baseline estradiol levels were performed in the mid-late follicular phase when there is a great degree of variability of the normal levels. The original protocol suggested a subset sample size of 80 patients (Site A) who would undergo comparative estradiol measurements during the treatment phase. A large number of baseline estradiol values were discarded because the levels were drawn outside of the specified window. This left a relatively small subset sample size of approximately 20 patients per arm, with wide variability noted between subjects and between treatment arms. Nevertheless, the baseline estradiol levels were in the normal range for both treatment groups.

LAB/NAFA610/USA
INVESTIGATOR: MULTIPLE

FIGURE 15A

Serum Estradiol Levels During Treatment and Post Treatment
by Month for A+ Sites Efficacy Patients



		Number of Patients																
∘ ∘ ∘	7	22	19	23	22	19	18	19	19	21	17	15	15	13	17	15	15	11
• • •	8	22	21	20	18	20	18	20	18	20	17	13	12	14	8	13	14	5

∘ ∘ ∘ N: 6 months Nafarelin 200 mcg bid
• • • L: 6 months Leuprolide 3.75 mg/month

The plot represents the sample median at each time point, with the bottom and top edges indicating the lower and upper quartiles, respectively (i.e., the 25th and 75th percentiles).
All estradiol levels <6 pg/mL were recorded as 5 pg/mL.
* During the treatment phase, two specimens were drawn, one prior to the injection (pre), the other 7 to 10 days later (post).

SOURCE: ESTRAD1.SAS (30SEP94,13:33)

As estradiol levels from patients at sites A and A+ were analyzed at 3 months and 6 months (Fig 15 A, page130 volume 1), both patients on nafarelin 400 mcg and leuprolide 3.75 mg demonstrated a marked decline in estradiol levels. During treatment, patients in the nafarelin group had consistently higher median

serum estradiol levels than those in the leuprolide group; nafarelin range 12-20 pg/ml, leuprolide 8-12.5pg/ml-Figure 2 (reproduction of Figure 15 A).

Reviewer's Comments: Nafarelin acetate is approved for the treatment of endometriosis at a dosage strength which is titratable from 200 mcg bid to 400 mcg bid. The label states that the recommended initial daily dose is 200 mcg, bid, but in an occasional patient, this dose may not produce amenorrhea. For patients with persistent regular menstruation after 2 months of treatment, the dose of nafarelin acetate may be increased to 400 mcg bid. Leuprolide Acetate Depot is approved at a single dose of 3.75 mg monthly. This study compared the lowest approved dose of nafarelin acetate with the only approved dose of leuprolide depot. It is likely that had the higher dose of nafarelin also been studied, the degree of suppression in estradiol levels would have been greater.

Bone Mineral Density.

Review of bone mineral density data was consulted to HFD-510. The mean baseline BMD values were comparable; 1.15-nafarelin and 1.14-leuprolide. The mean percent changes in BMD from baseline to the end of treatment were -3.2% and -4.5 % for the nafarelin and leuprolide subjects, respectively (p=0.002). The mean percent changes in BMD from end of treatment (at 6 months) to end of study (at 12 months) were -1.5% and -2.5%, respectively (p=0.07). The results of the analyses were similar when the patients without bone density correction factors were excluded and when age was introduced as covariant. The HFD-510 medical officer commented that the data from the study indicated that BMD decreased to a lesser degree following 6 months of treatment with 400 mcg/day of nafarelin compared with 3.75 mg/ month of leuprolide in women with endometriosis. The reviewer further states that data from a subset of women suggest that the changes in BMD may have been due to a greater reduction in estradiol levels in the women receiving leuprolide compared with nafarelin.

Reviewer's comment: The fact that the mean baseline BMD values were comparable argues against any clinically meaningful differences in the baseline estradiol levels. Again this trial compared the lowest approved dose of nafarelin acetate with the only approved dose of leuprolide depot. It is likely that had the higher dose of nafarelin acetate been studied, the resultant estradiol levels during treatment would have been lower and the small differences in bone mineral density loss may have been negated. Also one must question the clinical significance of the -3.2 versus -4.5 difference between nafarelin 400 mcg and leuprolide depot 3.75 mg when these agents are used (as currently labeled) for a single treatment course. In fact, six months following treatment, the changes in BMD between the treatment arms were not significantly different. The treatment difference could, however, take on more significance when these agents are used in women with previous compromised bone mineral density or if used on repeated occasions.