MEDICAL OFFICER REVIEW

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NDA 19-943
Sponsor: TAP Pharmaceuticals Inc.

Date of submission: 3-31-94
Date of transfer to MO: 10-27-94
Date of review: 2-15-95

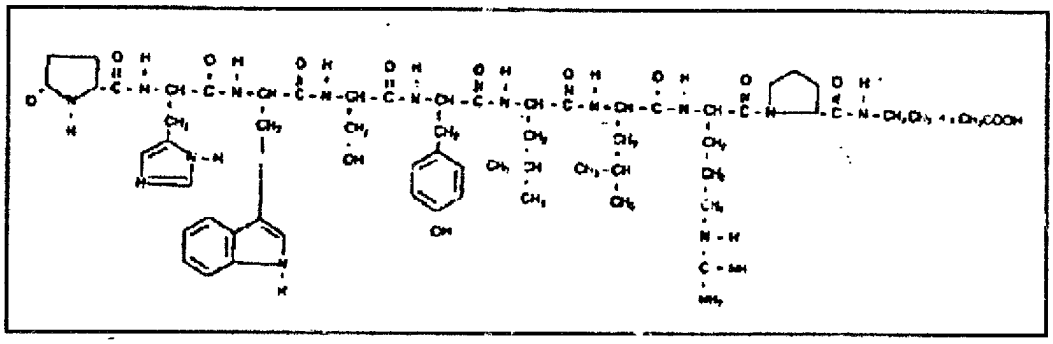
MAR 13 1995

1. General Information:

a. Name of drug:

(1)	**Generic:**	Leuprolide acetate
(2)	**Proposed trade name:**	Lupron Depot
(3)	**Chemical name:**	5-oxo-L-propyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) .

Leuprolide acetate has the following chemical structure:



b. Pharmacologic Category: Long acting gonadotropin releasing hormone agonist

c. Proposed indications: Pre-operative management of uterine leiomyomata to improve hematologic status and to reduce uterine/myoma volume and associated symptoms when surgery is delayed.

d. Dosage form (s) and routes of administration: 3.75 mg in purified gelatin (0.65mg), D,L-lactic and glycolic acids copolymer (33.1 mg), and D-mannitol (6.6 mg). The accompanying ampule of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75mg), polysorbate 80 (1.5 mg), and water for injection USP, and acetic acid, NF to control pH. Each vial of 3.75 mg lupron depot is mixed with diluent and given intramuscularly (IM) once a month.

e. Related drugs: Other GnRH analogues.

2. Manufacturing Controls: Please see Chemistry review of the original NDA application for Lupron Depot.

3. Pharmacology Review: Please see Pharmacology review of toxicity studies.

4. Pharmacodynamics and Pharmacokinetics: Please see Biopharm review

Clinical Background:

Background:

Uterine leiomyomas are the most common pelvic tumors in women and occur in 20-25% of all women, and can result in pelvic pain, infertility, abnormal uterine bleeding, and spontaneous abortions.[4] Leiomyomas or uterine fibroids are neoplasms of smooth muscle. Although they are the most common solid tumor of the female genital tract, they are benign. Thus therapeutic intervention is not required for all women with uterine fibroids. Indications for the treatment of uterine myomas include menorrhagia with iron deficiency anemia, uterine pressure or pain, rapidly increasing fibroid size, recurrent abortion with endometrial cavity distortion, and infertility with endometrial cavity distortion.[1] Unexplained or refractory infertility may also be an indication for myomectomy. Management of patients with symptoms of uterine myomas has traditionally been surgical, ranging from myomectomy to hysterectomy. Of the 650,000 hysterectomies performed annually in the United States, approximately 27% or 175,000 are performed for uterine myomas. Myomectomy is performed in about 18,000 patients per year. Myomectomy has a recurrence rate of 15% (range, 4% to 59%) and a repeat operation rate of 10% (range, 3% to 21%), and subsequent hysterectomy is required in an additional 1% to 5% of patients. [2]

Why these tumors form is unknown. One view is the presence of a gene encoding for fibroid development, as there is often a positive family history of fibroids in patients who develop these tumors.[3] Fibroids occur and increase in size during the reproductive years and may regress after the menopause. Continuous estradiol secretion, uninterrupted by pregnancy and lactation, is thought to be an underlying risk factor in the development of these tumors.[3,10,19] The supporting evidence for this includes the association between nulliparity and fibroids, the relative risk of fibroids decreasing with each additional term pregnancy, and the risk being reduced to one-fifth in women with five term pregnancies compared with nulliparous women. Oral contraceptives reduce the risk of fibroids by approximately 17% with each five years of usage, and so does cigarette smoking. Obesity increases the risk with a 21% increase for each 10 kg weight gain. This is probably due to the peripheral conversion by fat aromatase of circulating androgens to estrogen.[3]

Possible growth factors influencing fibroid growth: estrogen and progesterone and polypeptide growth factors which seem to stimulate cell proliferation by binding specific high affinity cell membrane receptor. These factors include epidermal growth factor, transforming growth factor alpha, insulin like growth factors and fibroblast growth factor.[6,14]

Approximately 30% of women with fibroids have been reported to have menstrual abnormalities, most often menorrhagia; but this figure is controversial as 50% of women who complain of menorrhagia do not have excessive menstrual loss when measured objectively.[3] Menorrhagia may occur when the uterine cavity surface is expanded by submucous fibroids. The increased bleeding may be due to either increased vascularity of the uterus or

anovulatory cycles but this has not been substantiated .[3] Farrer-Brown et al (1970,1971) showed that fibroids arising at various sites in the uterus could cause congestion and dilatation of endometrial venous plexuses by impinging and obstructing veins in the myometrium playing a role in enhanced uterine bleeding.[3]

Chronic backache may be present when the fibroid is of moderate size in a retroverted uterus; and acute pain may be present with red degeneration, necrosis, and with torsion of a pedunculated fibroid.[3]

The role of fibroids as a causal factor in infertility remains controversial.[3,24] It is obvious that obstruction of both uterine tubes by fibroids or gross uterine cavity distortion could contribute to infertility. However, fibroids are common and certainly occur in both normally fertile and infertile women and there is no clear evidence that the mere presence of fibroids is causally linked to infertility.[3] Though in a select group of patients who underwent myomectomy, abortion rates were found to be about 41%, with reduction to 19% after myomectomy.[3]

Surgery remains the treatment of choice of uterine fibroids. Several different procedures are appropriate including myomectomy by either laparoscopy, laparotomy, or hysteroscopy or hysterectomy by various surgical approaches. The choice of therapy will depend on the surgical aspects of treatment, but also on the size and number of myomata, the age of the patient, and the desire to preserve fertility and uterine function.[2]

Clinicians have long recognized that fibroids are dependent on estrogen for maintaining their growth and size; and therefore if a state of reduced estrogen secretion could be induced, this could result in the reduction in growth of fibroids and even their regression. The continued administration of gonadotropin releasing hormone (GnRH) agonist analogues can effectively reduce circulating estrogen levels by suppressing the pituitary-ovarian function. Several studies have shown the effectiveness of GnRH agonists in the treatment of conditions believed to be dependent on ovarian steroid production, such as endometriosis (Matta & Shaw 1987), precocious puberty (Comite et al. 1984) and ovarian hyperandrogenism (Chang et al. 1983).[4,19] There are multiple reports in the literature on the use of analogues to reduce the size of fibroid tumors. (see list of references). If well controlled randomized studies can show in patients with myoma associated menorrhagia a reduction in transfusion requirement, increase autologous blood deposit, conversion of hysterectomy from emergency to elective surgery and/ or increase the feasibility of a vaginal procedure then a course of a GnRH agonist could be proposed before hysterectomy in these patients.[14] In addition, the correlation of clinical examination, ultrasonographic volume determinations, and uterine weights in individual patients might provide valuable information for the clinician who is trying to determine which patient with leiomyomas is a candidate for a vaginal hysterectomy.[15]

History of NDA 19-943: In 1989 the NDA was voluntarily withdrawn and the following deficiencies were recorded:

a. There was no data for surgical facilitation with the use of Lupron.
b. There was no data for peri-menopausal use in women, especially given the variability in the time to reach menopause and the dangers to bone loss in this susceptible group of women with the use of Lupron for longer than six months.
c. The data in the NDA for the use of Lupron in women with severe menorrhagia and anemia was limited and failed to include iron therapy.
d. The bone mineral measurements were not conducted in a large enough population of women.

The following is the list of recommendations made by the advisory committee October 26-27, 1989 to sponsor. It was noted that during the advisory committee meeting the sponsor changed the indication to read: "Lupron Depot is indicated in the temporary, symptomatic relief of leiomyoma uteri (uterine fibroids) for a period of up to six months, especially in patients where reduction in uterine volume and or improvement in hematologic parameter is important. Treatment may be prior to surgery or when surgery is not desirable."

Recommendations: (Transcribed from review of original submission of NDA 19-943 November 27, 1989)

1. The sponsor should not use an open-ended phrase such as "when surgery is not desirable" in their indication.
2. If reduction in blood loss during surgery is a desired outcome, such a primary efficacy parameter should be appropriately studies. Such studies would be double-blinded, randomized and supported by enough patients to show statistical significance.
3. The surgeon performing the studies should be completely blinded and the number of surgeons used in the overall protocol should be greatly reduced, in order to obtain as homogenous a data source as possible. The larger the number of surgeons, especially within a single center, the larger the variability will be.
4. Studies on improvement in hematocrit should include iron replacement therapy for both groups of patients, Lupron and placebo treated women. If this indication is sought, there should be enough patients included in the study who would benefit from the treatment and show statistically significant improvements.
5. Data should be stratified with regard to those women who will both obtain a less hematologically risky surgical preparation and will be able to bank their own blood for possible use during surgery. Women in whom complicated surgery can be anticipated, such as those with multiple tumors or very large uteri may also be included in the latter group.
6. Data on bone safety during treatment and especially in the recovery period should be conducted in enough patients to obtain adequate statistical power. The present NDA (1989 submission) was lacking in adequate follow-up data.

Consideration should be given to provide normal standards of care to both Lupron treated and placebo treated patients such as adequate calcium supplementation, etc.

7. Reduction in uterine volume alone is an inadequate end point. Reduction in uterine volume should be tied to such important surgical outcomes such as route of myomectomy or hysterectomy, difference in planes of dissection, intra-operative blood loss, etc.
8. A more careful consideration of the appropriate period of treatment should be included. If the data suggest three months of therapy is adequate, why continue for six months when three months of treatment is adequate to provide maximal reduction?
9. To quantitate the degree of hypermenorrhea and improvement in this outcome, would be important. And to quantitate improvement in days and amount of bleeding with treatment would be very important.
10. Placebo-controlled studies to determine the usefulness of analogue therapy in the hysteroscopic removal of submucous myomas might be considered. There was a single case presented and committee felt it needed further study.
11. Inclusion of all the following cells (and possibly others) in the study design: which of the women with fibroids and anemia will or will not respond; treatment with or without calcium treatment; and with or without iron.
12. Women should not, in the middle of the trial, switch to a treatment or placebo arm. Drop outs should be taken into consideration in the trial and treated as such.
13. Placebo should be included, but both treated and placebo groups should receive "standard care", such standard to be determined at the time of institution of trial.
14. If surgical facilitation is a desirable outcome, only those patients in whom surgery will be performed as usual standard of care should be included. These would then include women with larger fibroids than those included in the NDA (submission of 1989).
15. If surgery is the only desirable outcome in some patients and anemia and other symptoms are not important, a sub group could be studied, where immediate surgery versus Lupron + surgery could be compared for various surgical outcomes such as type of surgery, blood loss, surgical facilitation etc.

The committee's response to the question: "Should leuprolide be used to treat leiomyomata uteri as the sponsor suggests in its revised indication?" Five committee members voted no, and two voted yes.

A letter was sent to TAP on August 29, 1991 which stated that "the entry criterion should include patients with hemoglobin readings less than or equal to ten grams and efficacy should be determined by an increase to at least twelve grams."

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6. Clinical studies:

Overview of the NDA:

The NDA consists of four well controlled trials, of which there are three identical studies which were conducted to evaluate the role of Lupron in the treatment of leiomyomas. These studies were submitted in the 1989 application that was voluntarily withdrawn. These studies are resubmitted with minor changes as noted by sponsor. These changes are noted in Vol. 1.5 and are as follows: Costart terms version changed from 2 to 3; package inserts in Appendix A replaced from Lupron injection to lupron depot 3.75 mg., statistical analysis system were re-run and HDL/LDL ratio has changed to LDL/HDL ratio.The studies were identical in nature except for the type of diagnostic testing used to evaluate the size of the myomas and bone mineral content diagnostic tests. These three studies are labelled M86-034 (which used Accuson ultrasound); M86-049 (which used magnetic resonance imaging: MRI) and M86-062 (which used both ultrasound and MRI) . All three studies were randomized, double-blind, placebo-controlled studies conducted at a total of 13 investigative centers, each with a planned sample size of 40 patients (20 in each treatment group). Each study consisted of a 24 week treatment period during which patients received six depot injections of lupron or placebo, one at each visit every four weeks, for 20 weeks. In the aforementioned clinical trials, enrollment was not based on hematologic status. These protocols will be describe in this review.

The fourth trial labeled M90-411, is a phase III stratified, randomized double-blind parallel group multicenter study with twelve week treatment and six month no treatment follow-up for patients with iron deficiency anemia presumed secondary to prolonged or excessive bleeding associated with uterine leiomyomas.

In addition there are two open uncontrolled studies labeled M86-048 and 86-043. M86-048 enrolled patients from studies M86-034, M86-049 and M86-062 who had not demonstrated improvement (> 25% reduction in uterine volume) and had been initially assigned to placebo. M86-043 enrolled patients from studies 034, 049 and 062 who had a clinical response (>25% reduction in uterine volume) during the controlled study on Lupron Depot therapy. Patients were evaluated to determine post-treatment effects on efficacy and safety parameters following a six month course of Lupron.

a. Controlled study M90-411:

(1) Investigators and Study Centers:

Name	Place	# of patients
Norman Assad	Albuquerque, NM	1
Guy Benrubi	Jacksonville, Fl	6
Richard Blake	Washington, DC	17
William Butler	Charleston, SC	7
Bruce Carr	Dallas, Tx	4
Ashwin Chatwani	Philadelphia, PA	17
P. Ronald Clisham	New Orleans, LA	2
Charles Coddington	Norfolk, Va	8
Robert Collins	Cleveland, OH	12
Ponjola Coney	Tucson, Az	3
Christine Cook	Louisville, Ky	5
Rosa Cruz	Santurce, PR	2
Alexander Dlugi	Troy, MI	3
Frank Deleon	Fort Worth, Tx	1
Maxin Dorin	Albuquerque, NM	5
Heber Dunaway	Metairie, LA	4
David Feldman	Fresno, CA	5
Peter Gillett	Montreal, Canada	11
Neil Gladstone	Riverdale, GA	2
Gilbert Hass	Oklahoma City, OK	3
Richard Hansell	Indianapolis, IN	6
Terry Hung	Miami, Fl	3
W. Glenn Hurt	Richmond ,VA	1
Francis Gutchins	Bala Cynwyd, PA	4
Allan Jacobs	N.Y., N.Y.	7
Walid Kassem	Minneapolis, MN	2
Amalia Kelly	N.Y., N.Y.	2
L. Micheal Keltel	San Diego, CA	4
Muhammed Khan	Chicago, IL	2
Oscar Kletzky	Torrance, CA	23
Abner Korn	San Francisco, CA	9
Abraham Litchtmacher	unavailable	3
Maclin	unavailable	4
Rachel McConnell	Las Vegas, NV	2
Gene McNeely	Detroit, MI	13
Michael Miller	Little Rock, AR	1
Ozgul Muneyyirci	Brooklyn, N.Y.	18
David Olive	New Haven, CT	2
Subir Roy	Los Angeles, CA	9
Scott	unavailable	2
Kaylen Silverberg	San Antonio, Tx	13
Emil Steinberger	Houston, Tx	6

Andrea Stephens	St. Louis, MO	9
Thomas Stovall	Winston-Salem, NC	3
Robert Summitt	Memphis, TN	15
Michael Trierweiler	Denver, CO	1
Rafael Valle	Chicago, IL	12
Robert Weiss	Boston, MA	10
Hyungkoo Yun	Jersey City, N.J.	1
Nezaam Zamah	Kansas City, MO	4
Total		309

(2) Objective of the study

There were three objectives of this study: 1) to determine whether Lupron Depot plus iron was more effective than iron alone in the preoperative treatment of anemia due to prolonged or excessive bleeding associated with uterine leiomyomas, 2) to determine if these patients could be improved surgical candidates by decreasing surgical risk and by increasing the possibility of autologous blood donation, and 3) to compare the efficacy of Lupron Depot 3.75 mg with the 7.5 mg dosage strength for this treatment. The principal criteria for efficacy were changes in hematologic status; changes in uterine bleeding were used as corroborative data; changes in uterine and leiomyoma size and clinical symptomatology were also assessed. The safety profile of Lupron Depot in uterine leiomyoma patients was also evaluated.

(3) Rationale for the study

The rationale for the study is the known estrogen sensitivity of uterine fibroids. Lupron Depot by rendering women hypogonadal and hypoestrogenic, will decrease uterine bleeding and decrease the size of fibroid tumors.

(4) Experimental design:

(a) Patient Population

Demography

i. Number : Total of 309 patients were randomized into one of two strata based on pre-study hematocrit
ii. Age : At least eighteen years of age and premenopausal
iii. Sex: Female

(b) Clinical characteristics for inclusion:

1. The patient must have had a pelvic mass consistent with uterine leiomyoma established by history, pelvic examination ultrasound and or MRI
2. If only a single leiomyoma was present, one dimension had to have been at least 3 cm. The leiomyoma (s) must not have been extensively calcified.
3. The patient must have been non-pregnant and non-lactating with a history of prolonged or excessive uterine bleeding for at least three cycles or three months prior

to initiation of treatment. If the patient had received previous therapy for uterine leiomyomas, had been using oral contraceptives or other steroid hormonal preparation, or had previously been pregnant, she had to have resumed her normal menses for at least two cycles prior to study entry.

4. The patient was naive to treatment with leuprolide acetate and other GnRH analogs; and had not been treated medically or surgically for uterine leiomyomas within three months prior to study entry.

5. Hemoglobin $\leq$10.2 g/dl and serum iron $\leq$ 60 mcg/dl

6. The patient was a candidate for surgery (hysterectomy, myomectomy, or endometrial ablation) for prolonged/excessive uterine bleeding and iron-deficiency anemia secondary to uterine leiomyomas.

7. Endometrial biopsy, performed (if possible) seven or more days after the last day of menstrual bleeding, must have shown secretory (sponsor probably means proliferative) endometrium, unless:

i. there was documentation that prior treatment with progesterone had not been efficacious in reducing uterine bleeding and the patient remained a surgical candidate, or

ii. ovulation was demonstrated with either another biopsy, elevated serum progesterone, a biphasic basal body temperature graph, or a positive ovulation predictor kit, or

iii. the investigator attested that the use of progesterone was not clinically indicated in the patient and reason was to have been documented.

8. The patient was not pregnant at study entry and agreed to use barrier contraception during the study and for six weeks after the final study drug injection.

9. Free of osteoporosis and prestudy bone density measurement at least 80% of the mean bone density of age-matched controls.

(b) Exclusion criteria:

1. Pregnancy and lactation
2. Gynecologic malignancy
3. Thalassemia, sickle cell anemia, folic acid deficiency, abnormal serum folate level, abnormal partial thromboplastin time, and/or abnormal prothrombin time
4. Non menstrual bleeding disorders
5. Concomitant disease with the potential for producing bleeding/or hemorrhage resulting in iron deficiency anemia.
5. Donation of blood within two weeks prior to the pre-treatment blood draw for hemoglobin and hematocrit determinations.
6. Osteoporosis/ or pre-study bone density measurement less than 80% of the mean bone density of age matched controls.
7. Use of drugs that interfere with platelet function less than two weeks prior to study entry and during treatment period.
8. Patient not a surgical candidate.
9. Insufficient evidence to document the presence of uterine leiomyomas
10. Pretreatment surgery for leiomyomas performed within three months of receiving the first dose of study drug.

11. Use of non-steroidal anti-inflammatory drugs and prostaglandin synthetase inhibitors after day one of menstrual cycle or throughout the treatment period.

(5) Procedure

(a) Specific formulations used in the study, including the control drug:

Intramuscular injection of Lupron Depot 7.5 mg; Lupron Depot 3.75 mg; or placebo at each visit every four weeks. The study drug was supplied as a two part package: a single-dose vial containing lyophilized powder, which consisted of leuprolide acetate incorporated in a biodegradable copolymer and a 1.5 diluent.

(b) Type of experimental controls, study design, measures to eliminate bias, etc.:

In this study, there was a placebo group. The study was double-blind and randomized. However, it is difficult to blind those subjects receiving active drug, since the drug causes hot flashes in over 90% of cases while the placebo will have no such effect, inducing inevitable bias.

Multiple problems can exist in accurate measurement of the uterus, especially by ultrasound and especially uteri that have many fibroids. The most common measurement used was the ellipsoid, which required measurement of height, width and depth. Such measurements are often not accurate in a normal uterus, and can create major problems in uteri with irregular shapes. Volume is a cubed measurement. Thus inaccurate measurements of uterine dimensions are amplified during calculation for volume.

(c) Dosage schedule: As above

(d) Concomitant medication: ferrous sulfate as 525 mg (105 mg elemental iron) two times daily or ferrous gluconate 324 mg (37.5 mg elemental iron) three times daily. And calcium carbonate 1250 mg (500 mg elemental calcium) two times daily.

(e) Clinical procedures

1. Pre-study: Procedures and evaluations which were performed prior to the initial injection included the following: medical and gynecologic history, pelvic examination, physical examination, anemia laboratory profile [CBC, reticulocyte count, serum folate, ferritin, iron, total iron binding capacity (TIBC), unsaturated iron binding capacity (UIBC), hemoglobin electrophoresis], routine chemistries, pelvic ultrasound or MRI examination, abdominal roentgenogram (if necessary to document calcification), endometrial biopsy, clinical evaluation of disease symptoms, quality of life evaluation, documentation of intended surgical approach for treatment of the uterine leiomyomas if surgery would have been performed prior to initiation of study treatment, serum estradiol (E2) and FSH determinations, and determination of bone

density by Hologic Quantitative Digital Radiography (QDR) equipment for dual energy x-ray absorptiometry (DEXA).

2. At each visit: Evaluations of disease and treatment related signs and symptoms, menstrual record, record of non-menstrual bleeding, quality of life assessment, and E2 determinations. In addition monthly CBC, ferritin, iron, TIBC, and UIBC.

3. In general: Pelvic examination, physical examination, pelvic ultrasound or MRI, endometrial biopsy, and routine chemistries were repeated at Week 12. Pelvic ultrasound or MRI was performed within two weeks following the last day of treatment. Repeat bone mineral density determinations were performed at Weeks 8 and 12 if performed pre-study. If the bone mineral density decreased by greater than 1% during the treatment period, the bone mineral density determinations were also performed at three and six months following the last day of treatment. Patients were followed for six months post-treatment to assess surgical data and outcome, menstrual and hormonal pattern, hematologic status, fertility, bone density changes, quality of life, and general clinical status.

(6) Safety considerations

(a) Clinical studies:

Adverse reactions were monitored and severity noted and recorded, including their relationship to study drug.

(b) Laboratory studies:

i. The battery of hematological tests performed at prestudy (except for serum folate, hemoglobin electrophoresis, and reticulocyte count) were repeated at each monthly visit through the study. Reticulocyte counts were repeated on Day 4 and Week 2. Routine chemistries were repeated at Week 12.

ii. Special studies: Determination of bone density by dual energy x-ray absorptiometry (DEXA) was performed only if access to DEXA existed. Repeat bone mineral content determinations was performed at Week 12 and at three and six months post-treatment if performed prestudy. BUN, glucose, creatinine, calcium, phosphorus, albumin, total protein, total bilirubin, uric acid, alkaline phosphatase, prothrombin time (PT), partial thrombosplastin time (PTT), SGOT, SGPT, LDH, total cholesterol, HDL cholesterol, and LDL cholesterol were performed.

(c) Indications for removing a patient from the study:

If worsening of the disease occurred, and or the severity or frequency of symptoms increased to an intolerable level for the patient, or imparted additional medical risk to the patient, the investigator had the option of terminating the patient from the study and treating the patient surgically.

(7) Efficacy considerations

(a) Clinical and lab measurements:

1. The primary efficacy endpoint in study M90-411 was the change in hematologic status. A significant response had been defined by the agency as an increase in hemoglobin of 2gm/dl. The calculation of change in these parameters were based on the difference between the prestudy values and the final values obtained prior to autologous blood donation, transfusion or the end of the treatment. Patients were enrolled into one of two strata, based on the pretreatment hematocrit values $\leq$ 28% and $\geq$ 28%. The proportion of responders in the treatment groups were compared by pairwise Fisher's Exact tests within each stratum and by Cochran-Mantel-Haenzsel tests for the combined strata. In addition, mean changes from baseline in the hematologic parameters were compared among treatment groups within each stratum and for the combined strata using one-way and two-way analyses of variance, respectively.

2. Secondary efficacy measurements or supportive data were the clinical evaluation of symptoms. This data was analyzed by assigning scores of 1, 2, 3, or 4 to grades of none, mild moderate, or severe, respectively. Cochran-Mantel-Haenzsel methods were used to compare these scores between treatment groups, with baseline severity level as the stratification variable. Mean changes from baseline in leiomyoma and uterine volume and mean changes from baseline in an overall quality of life score were compared among treatment groups using analysis of variance or analysis of covariance.

3. Percent changes from baseline in bone mineral density measurements and changes from baseline in initial signs, body weight, and clinical laboratory determinations were compared using one-way analysis of variance or covariance.

4. Summary statistics for hormone levels and bleeding status were shown for each measurement time, for each treatment group.

(b) Degree of difference for significance: All p-values were based on two-tailed tests. Tests resulting in p-values less than or equal to 0.050 were reported as "significant" .

(c) · Were the endpoints appropriate?

1. The primary efficacy endpoint in this study was the change in hematologic status, an increase of 2 gm/dl.
This reviewer was not present at the Agency in 1991 when these standards were established and I have doubts about this standard for the following reasons:
More effort should have been undertaken to ascertain whether or not iron plus Lupron was clinically better than iron alone in raising the hemoglobin level. This would be consistent with what Dr. Price (medical officer) states he intended at the September 17, 1991 meeting with the sponsor: to see a 2gm difference between groups (Lupron + iron vs iron alone).

The study included iron replacement therapy for both groups of anemic (Hgb $\leq$ 10 g/dl) patients: drug and placebo and enough patients were included in the study who would benefit from treatment to show a statistically significant improvement. This is consistent with one of the Advisory Committee recommendations in 1989 for proper studies for this indication. This approach would allow a woman with anemia which places her at serious surgical risk, to improve her anemia and allow her to place blood in the blood bank for autologous transfusion if a transfusion were needed.

2. The secondary efficacy parameters included reduction in uterine and myoma volume, change in disease- related symptoms, effects of hormonal suppression and the change in quality of life. The reduction in uterine and myoma volume endpoint is not precise because there is no evidence that uterine volume measured by ultrasonography can be translated into estimates of uterine weights or gestational size. It is likely that the irregular contours of some uteri do not correspond to any single geometric formula for volume determination: therefore, use of a single formula might produce an overestimation of true uterine volume, particularly in women with leiomyomas.(ref. #9 Clinical Background)

Furthermore, the inclusion criteria includes fibroids with the longest diameter as small as 3 cm. A fibroid of this size may not require treatment and this requirement is not consistent with the usual gynecological practice of treating only large fibroids which cause symptoms.

8. Statistical Consultation: (Please see Statistical Review and Evaluation of Study M90-411).

9. Results of study M90-411:

9.1 Demographic data:

For evaluable patients, within each stratum, mean age, height, and weight did not differ significantly across treatment groups. Mean age was 39 years (range 23-52) mean height was 64 inches (range 52-71) and mean weight was 166 pounds (range 102-350).

9.2 Evaluable patients:

Two hundred sixty-five of the 309 (86%) patients enrolled were considered eligible for efficacy analysis.

	Treatment Group		
Number of Patients	Lupron Depot 7.5	Lupron Depot 3.75	Iron
Entered	107	104	98
Evaluable	99 (93%)	89 (86%)	77 (79%)
Stratum A	36	32	29
Stratum B	63	57	48
Excluded from efficacy analysis	8	15	21

The reasons for total exclusion from the efficacy analysis include the following: insufficient washout from previous treatments (18), other causes for bleeding and/or anemia not eliminated (19) , did not qualify hematologically (9), patient not a surgical candidate (1), evidence of malignancy (2), received salicylates (2), insufficient evidence of myoma (2), no data after treatment (2), and excessive uterine bleeding not documented (1). Patients who had more than one reason are included in each reason. (Data from table 2 Vol. 1.5)

There were partial efficacy data exclusions for 113 additional patients (41 Lupron Depot 7.5 mg, 40 Lupron 3.75 mg, and 32 placebo) due to non compliance with intended study procedures or dosing regimens..

Twenty-eight patients discontinued from the study prematurely. A summary of discontinuations by treatment group and stratum follows.

	Treatment Group		
Number of Patients	Lupron Depot 7.5	Lupron Depot 3.75	Iron
Entered	107	104	98
Premature terminations	3 (3%)	11 (11%)	14 (14%)
Stratum A	2	8	9
Stratum B	1	3	5

Primary reasons for discontinuation in study M 90-411:

Reason for Premature Termination	Number of Patients			
	Lupron Depot 7.5	Lupron Depot 3.75	Iron	Total
Prestudy criteria not met	1	4	3	8
Adverse event	1	3	1	5
Worsening of the disease	0	1	2	3
Early surgery of the leiomyomas	0	0	2	2
Patient request	0	0	2	2
Loss to follow-up	1	1	2	4
Study blind broken	0	1	1	2
Non-compliance with visit schedule	0	1	1	2
Total	3	11	14	28

9.3 Changes in Hematologic Status:

The following table shows the response rate at all time points for the combined strata analysis using the response definition of $\geq$ 2gm/dl increase in Hgb. This table evaluates responses within group from baseline to final visit. It shows that in the combined stratum 81% of patients in Lupron Depot 3.75 group and 53% in the iron group increased Hgb $\geq$2 g/dl and had $\geq$6% increase in Hct and this result is statistically significantly different. Interestingly it shows at four weeks of therapy the response rate seems to be obtained as a result of iron in both groups. This could possibly indicate that patients who are going to respond to iron will demonstrate this in the first four weeks of therapy and this group of responders would not be candidates for additional therapy? In addition, 53% of patients would have achieved this endpoint with iron alone; but would have been exposed to a drug with significant adverse effects.

Percentage of Patients with Increase of > = 2 g/dl Hgb and > = 6% Hct
(N = Total Evaluable Patients)

Treatment Group	4 Weeks		8 Weeks		12 Weeks		Final Visit	
	N	%	N	%	N	%	N	%
Combined Strata								
Combined Lupron Depot	172	67*	169	80	142	79	181	80
Lupron Depot 7.5	91	66	91	76*	81	80*	97	78*
Lupron Depot 3.75	81	69*	78	85*	61	77*	84	81*
Iron	69	54	67	55	59	58	72	53
Stratum A								
Combined Lupron Depot	60	83	59	88	47	100*	63	94*
Lupron Depot 7.5	32	84	33	85	29	100*	35	94#
Lupron Depot 3.75	28	82	26	92	18	100	28	93
Iron	24	71	19	89	18	83	24	75
Stratum B								
Combined Lupron Depot	112	59	110	75*	95	68*	118	72*
Lupron Depot 7.5	59	56	58	71*	52	69*	62	69*
Lupron Depot 3.75	53	62	52	81*	43	67#	56	75*
Iron	45	44	48	42	41	46	48	42

*Significantly greater ($p <= 0.05$) than placebo response
Marginally significantly greater ($0.05 < p <= 0.10$) than placebo response

Percent of patients with increase of 2g/dl in Hgb and/or 6%in Hct

	Lupron 3.75 mg + iron	Iron	Difference in responder rate
Stratum A (Hct <28%)	34/35 (97.1%)	32/35 (91.4%)	5.7%
Stratum B (Hct >28%)	55/60 (91.7%)#	48/60 (80.0%)	11.7%
Total	89/95 (93.7%)*	80/95 (84.2%)	9.5%

#p <.10 in favor of Lupron + iron over iron alone
*p <.05 in favor of Lupron + iron over iron alone

Percent of patients attaining Hgb level of at least 12g/dl and/or Hct of at least 36%

	Lupron 3.75 mg +iron	Iron	Difference in responder rate
Stratum A (Hct <28)	29/35 (82.9%)***	17/35 (48.6%)	34.3%
Stratum B (Hct >28)	52/60 (86.7%)*	41/60 (68.3%)	18.4%
Total	81/95 (85.3%)***	58/95 (61.1%)	24.2%

*p <.05 in favor Lupron +iron over iron alone
***p <.001 in favor of Lupron + iron over iron alone

Clearly responder rates are not what is considered by a surgeon when making a decision about a patient's Hgb prior to performing a surgical procedure. A responder rate can not tell that a patient would be at a serious surgical risk hematologically.

I feel that responder rate data can be misleading when mean Hgb changes are not considered or evaluated. It would be worthwhile to evaluate final mean Hgb and note whether there was a greater than 2 g/dl increase between the two groups, (Lupron + iron group and iron alone group). Just how far apart were the actual therapies in obtaining the goal of 12 g/dl Hgb would be interesting to know. From the table below looking at the mean change in Hgb shows that iron alone therapy was only 1.1-1.2g/dl different from the Lupron + iron treatment group.

The analysis of changes in Hgb from baseline follows for the stratum combined:

		N	Baseline Mean	Treatment Mean	Within group change from baseline
Final	Lupron 7.5 mg	97	8.2 g/dl	12.7g/dl	4.3*
	Lupron 3.75 mg	84	8.2 g/dl	12.6g/dl	4.2*
	Iron	72	8.0g/dl	11.5g/dl	3.1

* Significantly greater ($p < = 0.01$) than iron

Mean Hgb levels for Strata

Stratum A (Hct<28)	Lupron 3.75mg +iron	Iron	Difference
N	35	35	
Baseline	7.1	7.0	.1
Increase	5.3***	3.9	1.4
Stratum B (Hct>28)			
N	60	60	
Baseline	9.2	9.1	.1
Increase	3.8***	2.9	0.9

***p<.001 in favor of Lupron + iron over iron alone

The active treatment group (Lupron) shows statistically significant improvement within group, (within group change from baseline, Lupron: 4.2 g/dl and iron: 3.1 g/dl). The Lupron group does not show enhanced activity; and this is evident by the failure of the Lupron group to beat iron by more than 2 g/dl of Hgb at the end of the study (mean difference 1.1-1.2 g/dl; and when divided into stratum mean difference at most 1.4 with the smallest difference .9 in stratum B Hct >28).
Clinically there is really little difference in a hemoglobin of 11.5g/ dl or 12.6 -12.7g/dl in terms of a serious surgical risk at either value. Either one of these values would allow a surgical patient to donate autologous blood prior to surgery if they so chose.

9.4 Uterine Volume data (tables 32 and 33 vol.1.5):

In this study the median percent change in uterine volume from baseline to final visit for patients in the combine strata was -31%, -39% and +10% for the Lupron Depot 7.5 mg, Lupron Depot 3.75 mg and placebo groups, respectively. There are extremely wide ranges of results.

Uterine Volume Percent Changes for Efficacy Evaluable Patients

	Lupron Depot 7.5 mg				Lupron Depot 3.75 mg				Iron			
	N	Mean	Median	Range	N	Mean	Median	Range	N	Mean	Median	Range
Baseline	72	685	473	65-3434	60	752	451	88-3438	47	667	487	177-2268
Final	72	492	380	36-1972	60	515	290	47-3040	47	750	520	119-3200
Final % Change	72	-24	-31	-78- 72	60	-30	-39	-83- 122	47	20	10	-64- 546

Within treatment groups, the uterine volume changes were very variable, with some patients showing large decreases and others showing somewhat smaller decreases and some patients only showed a single measurement of uterine volume. For example, Lupron Depot 3.75mg treatment group patient #1025 Rx day -17 uterine volume 417 cm 3, at Rx day 79 volume 87 cm3, patient #1047 Rx day -34 uterine volume 1659.65 cm3, at Rx day 86 volume 1582.56 and patient # 438 had only one volume recorded for Rx day -13 647 cm3. (appendix D. 6)

9.5 Gestational Weeks data: (tables 35 and 36):

The gestational weeks data for strata combined show the following changes from baseline to treatment means: Lupron Depot 7.5 mg: 15.30 wks baseline to 13.7 wks, Lupron Depot 3.75 mg: 16.0 wks baseline to 13.3 wks and placebo: 15.7 wks baseline to 15.6 wks.
There appears to be little correlation of the gestational weeks data with uterine volume. For example stratum B Lupron Depot 7.5 mg patient #1250 uterine volume measured 240.55 cm3 and corresponded to 12 wks gestation. In stratum B Lupron Depot 7.5 mg patients 630 and 1087 had gestational weeks of 12 and uterine volume was recorded as 167.05 and 816.40 cm3 respectively.

9.6 Summary of clinical signs and symptoms (table 37)

The sponsor states "Lupron Depot was significantly superior to placebo in reducing the prevalence of bleeding at weeks 8, 12, and the final visit, for both strata, individually and combined". This is expected in light of the hypoestrogenic effect and suppression of menses that results from treatment with a GnRH agonist; but as stated above I question the clinical value of this effect.
In terms of symptoms, there appears to be a trend for Lupron to have a more favorable outcome. Specifically, a decrease in prevalence of symptoms from baseline to final visit is demonstrated in regard to menorrhagia, pelvic pain and bloating and these were statistically significant. The iron treatment was also shown to decrease some prevalence of symptoms.

Prevalence of Clinical Symptoms at Baseline and the Final Visit for Evaluable Patients M90-411

Variable	Treatment Group	Baseline		Final	
		N	%	N	%
Bleeding					
	Lupron Depot 7.5	84	99	84	14*
	Lupron Depot 3.75	76	96	76	16*
	Iron	57	96	56	64
Bloating	Lupron Depot 7.5	84	74	84	45*
	Lupron Depot 3.75	76	75	76	50
	Iron	57	75	56	66
Pelvic Pain	Lupron Depot 7.5	84	69	84	33*
	Lupron Depot 3.75	76	71	76	42*
	Iron	57	65	56	63
Pressure	Lupron Depot 7.5	84	61	84	33
	Lupron Depot 3.75	76	59	76	37
*($p \leq 0.05$)	Iron	57	54	56	45

9.7 Suppression of estradiol (table 41):

The mean estradiol levels decreased significantly within each Lupron Depot group by week 4 and remained so throughout the treatment period.

9.8 Iron consumption:

At the final visit, for the combined strata, the median number of iron tablets consumed was 58 for the Lupron Depot 7.5 mg group, 57 for the Lupron Depot 3.75 group and 59 for the placebo group.

9.9 Donations and transfusions:

Forty evaluable patients donated blood. The percent of patients who donated blood in the combined strata were 14%, 21% and 9% in the Lupron Depot 7.5 mg, Lupron Depot 3.75 mg and placebo treatment groups respectively.

Percent of Patients Who Donated Blood (study M90-411)

Treatment group	n/N	%
Lupron Depot 7.5	14/99	14
Lupron Depot 3.75	19/89	21
Iron	7/77	9

Overall the percentage among all groups was small; and only a total of 40 evaluable patients donated blood. Because of these small numbers it is difficult to make an assessment of the clinical relevance.

Thirty-seven evaluable patients received blood transfusion: 13 from stratum A and 24 from stratum B. The percent of patients who received blood transfusions in the combined strata for Lupron Depot 7.5 mg, Lupron 3.75 mg and placebo treatment groups were 17%, 9%, and 16% respectively.

Percent of Patients Who Received Blood Transfusion (study M90-411)

Treatment group	n/N	%
Lupron Depot 7.5	17/99	17
Lupron Depot 3.75	8/89	9
Iron	12/77	16

Again, the numbers are small for patients who received blood transfusion, only 37 evaluable patients received blood; and according to sponsor data analysis was precluded secondary to confounding variables.

Because there was no standardization regarding transfusion guidelines or surgical procedures across or within the 50 investigative sites, detailed analyses of these data are precluded.

9.10 Vital signs data:

There was a trend for mean increase in body weight from baseline to the final visit for the Lupron Depot 3.75 mg group (+1.6 lbs) and for the placebo group (1.7 lbs). Four patients in the Lupron Depot 7.5 mg treatment group had clinically significant changes in body weight. Three experienced a weight gain of more than 20 pounds during the treatment period: patients #1060, #408 and #1223; and one patient (# 496) experienced a weight loss of more than 20 pounds.
Some of the mean changes in vital signs from baseline were statistically significant, but were not clinically meaningful; and when compared to placebo the differences were not significant. No patient in the treatment and one patient in the placebo group had a mean change in B/P greater than 125/80. This patient, #695 had a baseline B/P of 120/78 and at week 12 B/P of 230/130. The patient was treated with apresoline in addition to other antihypertensive medications.

9.11 Bone density data:

Bone mineral density measurements were carried out using dual energy x-ray absorptiometry (DEXA). At the final visit the mean percent changes from baseline were -1.4%, -2.7% and 0% for Lupron Depot 7.5 mg, Lupron Depot 3.75 mg and placebo, respectively. The change from baseline in both Lupron Depot groups was statistically significant and the decrease in Lupron depot 3.75 mg group was significantly greater than in the placebo group.
The updated safety data at the end of six months from the clinical study M90-411 showed that one patient (#429) in the Lupron Depot 7.5 treatment group experienced a 10% decrease in spinal BMD from baseline at the end of treatment and an additional 2% loss at the end of follow-up. No further information or follow-up for this patient was available.
The safety update data show there was also an increasing decrement in BMD loss over time in follow-up seen in the placebo group and this can not be explained. A statistically significant mean decrease from baseline in both Lupron Depot dosage groups was still observed at follow-up month 3 ($p < .01$), which was not significantly different from the decrease noted in the iron group. In all three treatment groups

there was a small number of patients for whom data were available (ie: Lupron Depot 7.5 N= 9, Lupron 3.75 N=11 and placebo N=8).

Mean Percent Changes in BMD from Baseline at Final Treatment and Each Follow-up Visit (Using Hologic QDR) for Patients with Follow-up Data

	Lupron Depot 7.5 N=9	Lupron Depot 3.75 N=11	Iron N=8
End of Double-Blind Mean % Change	- 2.9	- 3.2*	- 0.4
Month 3 Mean % Change	- 3.7	- 3.1 (N =10)	- 1.5
Month 6 Mean % Change	- 2.6	- 1.5 (N= 8)	- 3.1 (N = 4)
Final Post-Treatment Mean % Change	- 2.5	- 1.8 (N = 11)	- 2.1 (N = 8)

* Statistically significant at $p <= 0.05$ compared to iron

9.12 Laboratory data:

There were several parameters for which the mean changes from baseline in the Lupron Depot groups were statistically significantly different from those of placebo. These included mean decreases in WBC at week 4, in platelet count at weeks 8, 12 and final visit, and in neutrophils weeks 4, 8, 12 and final; and mean increases in lymphocytes, esoinophils and basophils.
The final mean platelet counts for each treatment group were within the range of normal.
In addition, BUN, glucose, uric acid, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, LDH, calcium and phosphorus showed increases from baseline in one or both of the Lupron Depot treated groups and were statistically significantly different from those of the placebo group. None of these mean changes appeared to be clinically significant.

Nevertheless, the following individual changes should be noted:

One Lupron Depot 3.75 mg patient had an LDH that increased to 2220U/l at week 12, four patients had increases in SGPT or SGOT from baseline to week 12. The safety update data indicates that two of the four had no further follow-up data, one had return to baseline and the other showed downward trend toward baseline. In addition there where clinically significant elevation not previously reported: Three Lupron Depot 3.75 mg patients had increases. Two of the three had no further follow-up data and the 3rd had decreased but had not returned to pre-treatment baseline.

Two patients had increases in glucose of 101 to 440 mg/dl and from 102 to 296 mg/dl from baseline to week 12 respectively. One patient showed recovery at follow-up the latter had no follow-up data; and no history of diabetes was recorded for either.

Two patients had clinically significant changes in prothrombin time, these values were increased greater than twice normal. No follow-up recovery data was available .

None of these increases were associated with symptoms according to sponsor. There was no recording of nausea, vomiting or jaundice. The patient with the elevated LDH was thought to have a B12 deficiency and her recruitment into the study was not valid, this patient was lost to follow-up and had no recovery data.

These changes in SGOT, SGPT, LDH, and prothrombin time are all referable to the liver and should not be ignored. Patients with history of liver disease or with elevated liver function parameters may experience worsening of these parameters. Perhaps, pre and post assessments of these parameters should be performed and all elevations followed until normalization to baseline is demonstrated.

9.13 Cholesterol and lipids:

The mean changes in LDL cholesterol (mg/dl) from baseline to final visit were: 18.5, 21.9, and 10.6 for Lupron Depot 7.5 mg, Lupron Depot 3.75 mg and placebo respectively, these differences are statistically significant. Mean changes in the LDL/HDL ratio from baseline to the final visit were: 0.45, 0.50 and 0.19 for the Lupron Depot 7.5 mg, Lupron 3.75 mg and placebo treatment groups respectively and these were statistically significant. The safety update data shows that three Lupron 7.5 patients had elevated triglyceride levels during treatment. One returned to normal at month 6, one had no further data, and one was still elevated. Two Lupron 3.75 patients had elevated values; one remained elevated at follow-up and the other had no follow-up data. Two iron therapy patients had elevation of triglycerides during therapy. One remained elevated at month 6, and the other was still elevated at month 3. Two patients had elevations not previously reported: One Lupron 3.75 and one iron therapy patient. A Lupron patient at month 3 follow-up was discovered to be pregnant and one iron therapy patient had an elevation at month 3 of follow-up.

9.14 Adverse events:

Adverse events that were reported significantly more often for Lupron Depot treated patients than for placebo treated patients were vasodilatation and vaginitis for both dosage groups, and dizziness, depression, arthralgia, and abdominal pain for Lupron Depot 7.5 mg only. Four patients in the Lupron Depot groups terminated due to adverse events.

10. Discussion of study M90-411:

Sponsor:

The sponsors states in conclusion that Lupron Depot, both 7.5 mg and 3.75 mg, with iron was shown to be more effective than iron alone in treating the anemia of patients with uterine leiomyomas. Lupron Depot and iron was also more effective than iron alone in reducing uterine /myoma volume, and in alleviating bleeding and other leiomyoma related symptoms.

Reviewer:

Even though the sponsor has shown a statistically significant response rate, I do not believe that the clinical implication of these findings has been adequately addressed. Indeed, the findings suggest that iron therapy alone was quite effective in the preoperative treatment of anemia in patients with uterine leiomyomas.

The advantage of suppression of menses secondary to the hypoestrogenic effect of GnRH agonist therapy, should have demonstrated a greater increase in the final treatment mean Hgb, (final treatment mean Hgb: Lupron 12.7 g/dl and placebo 11.5 g/dl). The sponsor also stated that "Lupron Depot was significantly superior to placebo in reducing the prevalence of bleeding at weeks 8, 12, and the final visit, for both strata, individually and combined". Sixty-four percent of iron alone patients had bleeding vs 14-16% of the Lupron+ plus iron treatment group at the final visit (see table p. 20). Despite the increase percentage of bleeding in placebo (iron alone), this group was still able to come fairly close to the final visit mean Hgb of the Lupron Depot treatment groups.
Treatment with GnRH agonist is not benign. A 1.1 to 1.2g/dl of mean Hgb gained by using Lupron plus iron vs iron alone, does not appear to me to justify subjecting pre-menopausal women to any amount of bone mineral density loss, statistically significant cholesterol, lipid or liver function changes; (see laboratory data) or the other adverse events that were reported more often for the Lupron Depot treated patients, (vasodilatation, vaginitis, etc.). For bone mineral density loss, it was shown that the change from baseline in both Lupron Depot groups was statistically significant and the decrease in Lupron Depot 3.75 mg group was significantly greater than in the placebo group.

If one looks at the second alternative clinical response suggested by the FDA, achieving a Hgb $\geq$ 12g/dl, the proportion of efficacy evaluable patients who attained Hgb of $\geq$ 12 g/dl at the final visit when analyzed for patients with Hgb >7 and $\leq$10.2 Lupron Depot shows a statistically significant proportion of patients reaching 12 g/dl Hgb at final visit versus placebo 76% versus 53%, (see table below). This data can be misleading if the risk- benefit ratio of capturing an additional 23% of patients is not assessed, in light of the actual clinical mean gain of 1.1- 1.2 g/dl of Hgb. In terms of a serious surgical risk, clinically there is little difference in a Hgb of 12.6-12.7g/dl and 11.5 g/dl. Any patient with a Hgb in the range of 11.5 and 12.7 g/dl would be a candidate for autologous transfusion prior to surgery. The mean value of 11.5 g/dl was obtained in the iron alone group, and with a prevalence of 64% rate of bleeding at the final visit.

Proportion of Efficacy Evaluable Patients Who Attained Hemoglobin of > =12g/dl at the Final Visit

Baseline Hgb g/dl	Lupron Depot 7.5 mg	Lupron Depot 3.75 mg	Iron	Combined Lupron Depot
*≤7	9/13 (69%)	9/12 (75%)	5/13 (38%)	18/25 (72%)
@> 7 and ≤ 10.2	62/83 (75%)**	56/72 (78%)***	31/59 (53%)	118/155 (76%)****

*Small sample size
@Large sample size for significance
, * , ****, Statistically significant at P = 0.006, 0.002, .001 Compared to Iron alone

The above table can be further stratified in terms of baseline Hgb values of: <7, ≥7 to <8, ≥8to 9 and ≥9g/dl. No statistical significance is note for Hgb ≥7 to 8g/dl or ≥ 9g/dl (see table below).

Percent of Patients With Hemoglobin (Hgb) > = 12 g/dl at Final Visit (Efficacy Evaluable)

Baseline Hgb	7.5 mg	3.75mg	Combined Lupron	Iron alone	Combined vs Iron alone
<7	77%(10/13)	82% (9/11)	79% (19/24)	45% (5/11)	+
≥7 to < 8	71% (10/14)	55% (6/11)	64% (16/25)	42% (5/12)	NS
≥ 8 to <9	70% (21/30)	70% (16/23)	70% (37/53)	43% (10/23)	*
> = 9	77% (30/39)	85%(33/39)	81% (63/78)	65% (17/26)	NS

*, + Statistically significant at P = 0.05 and 0.01 levels, respectively
NS- Not statistically significant

The above data might suggest that patients with Hgb ≥9g/dl would not receive any added advantage of the addition of GnRH to iron therapy.

Further analysis of Mean Hgb levels at final visit for efficacy evaluable patients shows that at the final visit the final mean Hgb between Lupron plus iron vs iron alone differs by at most 1.3 g/dl (see table).

Analysis of Mean Hemoglobin (g/dl) Levels at Final Visit (Efficacy Evaluable Patients)

Baseline Hgb	7.5	3.75	Combined Lupron	Iron	Combined vs Iron
<7	12.2	12.5	12.4	11.1	+
≥ 7 to < 8	12.9	12.5	12.7	11.7	+
≥ 8 to < 9	12.7	12.4	12.5	11.5	**
≥ 9	12.8	13.1	12.9	12.0	***

***, **, *, + Statistically significant at P = 0.001, 0.01, 0.05, 0.10 levels, respectively.

The above tables were two of the six tables that were requested of sponsor after meeting with Dr. Rarick and the reviewing statistician Dan Marticello on February 8, 1995. Specifically, the sponsor was asked to provided tables displaying the changes in hemoglobin levels (stratified to four groups by baseline levels-- <7, 7-7.9, 8-8.9, and ≥9g/dl) by responder according to the criterion of 2 g/dl increases in hemoglobin, achieving hemoglobin level of ≥12g/dl and by analysis of mean hemoglobin levels (baseline to end of treatment) for each group. Both "intent to treat" and efficacy

evaluable" patients by comparison of Lupron 7.5 plus iron, Lupron 3.75 plus iron and Lupron plus iron combined versus iron alone were to be analyzed. After review of this data, my conclusions remain unchanged and the additional tables do not provide any new information.

It is still unclear to me what role if any reduction in uterine volume is playing. The uterine volume data showed changes that were very variable within treatment groups and correlated poorly with gestational weeks data. It was not shown to enhance overall increase in treatment mean Hgb.

It has been documented in literature and in this study that GnRH agonist reduce uterine and myoma size; but the unanswered question is the clinical utility of this effect. The literature also has shown that uterine volume will return to 88% of pretreatment level by three months after discontinuation of GnRH therapy.(ref. #16 Clinical Background)

Potential advantages of a reduction in uterine and myoma size by GnRH agonist therapy, less operative blood loss, increase autologous blood donation, change in planned operative procedure, vaginal hysterectomy instead of abdominal or myomectomy vs hysterectomy etc. were not demonstrated.

Final Conclusions of M90-411:

The advantage of suppression of menses secondary to the hypoestrogenic effect of GnRH agonist therapy:

Expected: Lupron vs Placebo (L vs P)	-1. Greater increase in the final treatment mean Hgb.
	-2. Decreased bleeding.
	-3. Greater proportion of patients attaining Hgb of $\geq$12g/dl.
	-4. Clinically significant decrease in number of patients requiring blood transfusion.
	-5. Clinically significant increase in number of patients who donated blood.
Observed: L vs P	-1. Statistically significant proportion of patients reaching Hgb $\geq$ 12. Final treatment means: 12.6-12.7 g/dl in the Lupron group versus 11.5g/dl in the iron alone group. (Clinically there is little difference in a hemoglobin of 11.5 g/dl and 12.6-12.7 g/dl in terms of a serious surgical risk at either value.)

-2. Fifty percent less bleeding at the final visit Lupron treatment group.

-3. According to the sponsor, because there was no standardization regarding transfusion guidelines across or within the fifty investigative sites, detailed analyses of this data was precluded.
In addition, this reviewer feels that the small numbers in the provided data and lack of standardization makes assessment of clinical relevance difficult to determine.

Actual gain:

-1. The actual gain in mean Hgb is 1.1-1.2 g/dl Lupron group vs iron alone. Further stratification to four groups by baseline hemoglobin levels revealed at most a 1.3 g/dl difference.

-2. Percent of patients attaining Hgb level of at least 12g/dl and/or Hct of at least 36%: 85.3% Lupron 3.75 mg +iron and 61.1% iron alone.

-3. The data did not show that there was a clinically significant decrease in number of patients requiring blood transfusion (lack of standardization of data that was presented).

-4. The data did not show a clinically significant increase in number of patients who donated blood (lack of standardization of data that was presented).

b. Controlled study M86-034:

(1) Investigators and Study Centers:

The only center used in this study was the Brigham and Women's Hospital in Boston, MA. The investigators were Andrew Friedman , M.D. and Isaac Schiff, M.D.

(2) Objective of the study:

The objective of the study was to evaluate the safety and efficacy of Lupron Depot vs placebo in the treatment of uterine fibroids. Efficacy was assessed by measuring changes in uterine volume and size and fibroid tumor size by ultrasound and changes in uterine size by pelvic examination. Changes in severity and frequency of pelvic pain and uterine bleeding was used as corroborative data.

(3) Rationale for the study:

Similar to previous study, (M90-411).

(4) Experimental design:

(a) Patient Population

Demography

i. **Number:** Total of 40, 20 in each arm.
ii. **Age:** At least 20 years of age and premenopausal.
iii. **Sex:** Female

(b) Clinical characteristics for inclusion

1. The patient had pelvic masses consistent with uterine fibroids established by history, ultrasound and pelvic examination.
2. Endometrial biopsy was performed if menometrorrhagia was present.
3. Multiple and single tumors may be present, but at least one dimension should be > 3 cm.
4. The patient was normally menstruating for at least two cycles prior to start of therapy.
5. Pregnancy test was negative, performed one week prior to start of therapy.
6. Infertility evaluation provided for those desiring pregnancy after completion of trial.

(c) Exclusion criteria:

1. History of exposure to any analogues for any reason and history of surgery or medication for fibroids.
2. Evidence of gyn malignancy.
3. Extensive calcification of the fibroid.
4. Nursing mothers and/ or positive pregnancy test.

(5) Procedure:

(a) Specific formulations used in the study, including the control drug:

3.75 mg of Lupron Depot was given IM once every four weeks. The placebo contained no active drug. The drug was placed with a biodegradable copolymer. Both placebo and drug were lyophilized and dissolved in diluent prior to administration.

(b) Type of experimental controls, study design, measures to eliminate bias, etc. :

In all three studies, there was a placebo group. The studies were double-blinded and randomized. As noted, (M90-411) , it was difficult to blind those subjects receiving active drug, since the drug causes hot flashes in over 90% of cases while placebo will have no such effect (see M90-411).

(c) Dosage schedule: As above.

(d) Concomitant medication: None

(e) Clinical procedure:

1. Within three months prior to start of therapy, patients had pelvic ultrasound to establish the presence and size of fibroids. Uterine volume, extent of calcification, and size of the largest tumor was determined by ultrasound. If calcification was found, an abdominal flat plate was performed to determine extent of calcification. Pelvic ultrasound was repeated at 12, 18 and 24 weeks.

2. History of fibroids, menstrual, fertility and other medical history will be recorded.

3. Baseline estradiol (E2) and progesterone (P) levels were determined during the luteal phase. These studies were repeated at 12 and 24 weeks.

4. Pelvic exam to determine size of uterus in "weeks". Pelvic exam was repeated at 12 and 24 weeks.

5. Physical exam at the start and at 24 weeks.

6. Baseline blood test, including hemoglobin, cholesterol, etc. A hematocrit was repeated at 12 weeks. All lab tests were repeated at 24 weeks. A pregnancy test was performed within one week prior to entry into the study.

7. Clinical baseline evaluation of bleeding patterns and extent of bleeding, abdominal discomfort, dyspareunia, urinary disorders, constipation, etc. was performed. Symptoms were rated as none, mild, moderate or severe. Symptoms were rated again during each clinical visit 4 weeks apart.

8. Record of menstruation was started and monitored during each monthly clinical visit.

9. Radiological evaluation of bone mineral content was assessed prior to start of therapy and at 24 weeks, as well as dual photon and CT scan of the spine to assess trabecular bone.

10. If menometrorrhagia was severe (no criteria is give for severity), endometrial biopsy was done.

11. Patients who completed this study were followed-up under protocol number M86-043.

(6) Safety considerations: As in M90-411

(a) Clinical studies:

As in M90-411

(b) Laboratory studies:

i. Routine CBC was performed to monitor changes in hemoglobin at the start, 12 and 24 weeks. Cholesterol and other routine lab tests were performed at the beginning and at 24 weeks. Pregnancy test was performed at the beginning and prior to start of therapy.

ii. Special studies: Radiological evaluation of bone mineral content assessed prior to start of therapy and at 24 weeks. Dual photon or CT scan of the spine to assess trabecular bone was performed, as well as single photon of the wrist and the hip bones.

(c) Indications for removing a patient from the study:

Patients were dropped at any time during the study, and were not replaced. If a patient was dropped, clinical lab tests and physical exam were completed.

(7) Efficacy considerations:

(a) Clinical and lab measurements:

1. The primary efficacy measurement was the change in uterine volume as determined by ultrasound. A response was a reduction in size by 25% or more. Comparison of Lupron and placebo was made by Fisher's exact test of the proportion of responders in each group. Percent change in volume was also analyzed by parametric (ANOVA) and or non-parametric (Wilcoxon rank-sum) tests.

2. The secondary efficacy measurement was the change in levels of symptoms (menorrhagia, menometrorrhagia, abdominal discomfort, urinary disorders, and constipation). These changes were analyzed using procedures appropriate for

ordinal categorical data. Baseline levels were included as covariates as necessary.

3. Changes from baseline to final visit in bone mineral content were analyzed by parametric and/or non-parametric methods.

4. Summary statistics were provided by treatment group for clinical evaluation of signs and symptoms and hormonal lab test.

(b) **Degree of difference for significance:** All p-values were based on two tailed test. Tests resulting in p-values less than or equal to 0.050 were reported as significant.

(c) **Were the endpoints appropriate?**

1. The primary endpoint in this study was reduction in uterine volume of 25% or greater. This endpoint has been shown to be problematic (see comments M90-411). In addition to previously mentioned problems, overall uterine volume provides no information on the changes in individual fibroids which may be responsible for the women's symptoms. The Fertility and Maternal Health Drugs Advisory Committee concluded in October of 1989 that reduction in uterine volume alone is an inadequate endpoint. Reduction in uterine volume should be tied to " important surgical outcomes", for example: shortened surgical time, conversion of a potential abdominal hysterectomy into a vaginal hysterectomy by decreasing size, conversion of a potential hysterectomy to a myomectomy, thus preserving the uterus in a young woman who desires pregnancy, differences in planes of dissection, or less intraoperative blood loss. The clinical significance of isolated decreased in uterine volume in the face of regrowth to original size after analogue is discontinued remains to be elucidated.

In addition some investigators have been concerned that myomas may be reduced to an undetectable size by pre-operative GnRH agonist; and small myomas may be missed at the time of surgery. [17]

In all three studies labeled M86-034, M86-049 and M86-062 the sponsor has failed to provide data that has tied reduction in uterine volume to "important surgical outcomes" (see clinical background).

The inclusion criteria as in M90-411, states that fibroids will be included if the longest diameter measures at least 3cm. Therefore, my comments are the same as for M90-411.

(8) **Statistical consultation:** (Statistical Review was completed as part of the review of the original submission).

(9) Results of the study # M86-034 (Refer vol. 1.16 of the NDA submission)

Evaluable patients:

Twenty patients were included in the study for each group. However, only 37 patients were evaluated at the end of the study. Two Lupron and one placebo patient received less than three injections. In addition, data from two Lupron patients and one placebo patient was excluded due to late (> 35days) injection periods. Data from the next visit was dropped for these patients. The following is a summary of evaluable patients:

	Treated	Placebo
Complete evaluations	15	17
Partial evaluation	2	3
Dropouts	3	3

Demographic data:

There is little difference between the two groups in terms of mean age, height and weight, but the ranges are very wide. The age range is from 29-53 years for Lupron (l) and 29-49 for placebo (p). The weight also varies greatly from 112-282 (l) and 99-263 (p).

Uterine Volume data:

In this study, there is a mean 41% decrease in uterine volume after 24 weeks of therapy, but by 12 weeks, there was already a 39.6% decrease. There appears to be no further decrease after the 12th week of therapy. The placebo group in this study had a consistent 4% increase in uterine volume for both times of evaluation. It is not known whether ultrasound can detect such a small difference as a 4% increase. The range of percentage changes remain wide as outlined below.

	Week 12	Week 18	Week 24	Final
Lurpon	12% to -67%	Not avail.	-10% to -68%	-10%to -68%
Mean	-39%	"	-41%	-39.5%
n	16	"	16	17
Placebo	+50% to -22%	"	+35% to -21%	-21% to +35%
Mean	+4.1%	"	+3.7%	+4%
n	20	"	8	20

The uterine volume changes in the treatment group showed the same variability that was noted in M90-411.

Gestational weeks data:

The gestational weeks data show a significant change from baseline when compared to placebo. Lupron administration reduced the size of the uterus from 16

weeks to 8.9 weeks at the final visit, while with placebo, the mean uterine size changed from 18 to 15.6 weeks at the final visit, which was not significantly different. Correlation with uterine volume and gestational weeks does not appear to be 100%(as was noted in M90-411). There were many patients who had similar gestational weeks on exam, but had very different volume data. For instance, Lupron patients 101, 103 and 105 were examined at 14 weeks, but their ultrasound volumes were 518, 154 and 423 cm3 respectively. This type of data highlights the difficulty in interpreting uterine volume data and determining the clinical significance of this data.

Summary of clinical signs and symptoms:

The numbers for each category for each sign or symptom (worse, no change or improved) are small, since all patients did not have all symptoms. Lupron appears to result in a favorable outcome only with regard to menorrhagia and bloating; but placebo treatment also quite often improved symptoms. This was also noted in study M90-411.

The percentage changes from 12-24 weeks in general correlate well, but the numbers were conflicting. For example in placebo treated patients, 53% showed no change at 12 weeks, while 80% showed no change at 24 weeks to complaints of urinary disorder (the statistical significance to this data is not provided).

Suppression of menses and estradiol:

The majority of patients taking Lupron showed suppression of menses, with only one patient who did not suppress till the fourth month. All placebo patients except four (107, 122, 127, and 140) continued to menstruate.

Estradiol levels were suppressed in the majority of patients who received Lupron, but not in the placebo. An occasional patient had levels of 4-5ng/dl in the Lupron treated group.

Progesterone levels were also suppressed in patients who received Lupron. The progesterone data is difficult to analyze, since the levels in placebo patients varied according to the phase of the cycle.

Hematocrit data:

The hematocrit data appears similar to the uterine volume data in that some patients showed an improvement in hematocrit while others showed worsening with both Lupron and placebo, although the mean values showed no change from baseline for Lupron treated patients.
None of the mean values are found in the range which would be considered to be a low hematocrit ($\leq$ 30%). Two Lupron patients had low hematocrits (31 and 32%). At the final visit their hematocrits were 46 and 39%. In one patient (#128), the hematocrit went from 42 to 35%, even though she was treated with Lupron, had a 42% decrease in uterine volume and was amenorrheic throughout the study.

Vital signs data:

No trends are seen with regard to changes in body weight. Placebo patients were found to have a slight drop in blood pressure.

Bone density data (table 16):

The bone density studies were performed by single photon analysis of the wrist, using both trabecular and cortical bone analysis. The wrist measurements are not found to be useful for hormone dependant bone changes. However, the studies showed no significant change in patients treated with lupron or placebo with regard to trabecular bone, while cortical bone decreased significantly in both groups, with a 6% decrease in patients treated with Lupron and a 3.7% decrease in those treated with placebo. No recovery data are available. These values are significant at p=.001 (Lupron) and p=.05 (placebo).

Laboratory data:

Alkaline phosphatase and phosphorus are elevated in a few patients, similar to that seen with other analogues and probably due to bone turnover. As noted under hematocrit data, hemoglobin and hematocrit rose in four patients and decreased in three patients.

Statistical comparison of Lupron and placebo reveals the following statistically different lab values:

i. Hemoglobin rose from 12.6 g/dl to 13.0 g/dl in the treated group, while it fell from 12.3 to 11.7 g/dl in the placebo treated group. There was a 1.3 g/dl difference between the two groups, with significance at the 0.033 level. However, neither treatment resulted in a statistically significant difference from baseline. The hematocrit values show no statistical difference, again implying very little overall change in this study.
There appears to be no clinical significance to this data.

ii. Uric acid increased with Lupron treatment, but was significant from baseline only at the 0.047 level. The clinical significance of a rise in uric acid from 4.4 to 4.8 mg/dl is not apparent at this time.

iii. Alkaline phosphatase, phosphorus and calcium rose significantly in the treated group, which was probably due to increased bone turnover. There is no follow-up data to demonstrate a return to baseline.

iv. Total cholesterol rose from 200 to 221, HDL fell from 59 to 54.7, LDL rose from a mean of about 124 to 136 and triglycerides rose from 110 to 153. Only the changes from baseline for triglycerides and total cholesterol are statistically significant.

Adverse events:

Adverse events were reported by 100% of Lupron patients and 35% of placebo. Most frequently reported adverse event was hot flushes. 100% of Lupron patients reported it while 15% of placebo (<0.001). In addition to hot flushes, the most frequently reported adverse events in the Lupron group were edema (30%),headache (20%) asthenia (20%) depression (20%), and insomnia (20%). All these events have been noted before and are probably due to the hypoestrogenic state.
With the exception of hot flushes, there were no significant differences between the treatment groups as to the incidence of reporting of these adverse events.

c. Controlled study M86-049:

(1) Investigators and Study Centers

Five centers were used in this study:

Name	Place	Number of patients
Randall Barnes	Chicago, IL	12
Bruce Carr	Dallas, TX	7
W. Paul Dmowski	Chicago, IL	6
William Schlaff	Baltimore, MD	11
Bobby Webster	Wichita, KS	8
	Total	44

(2) Objective of the study:

Same as M86-034

(3) Rationale for this study:

Same as M86-034

(4) Experimental design:

(a) Patient population

Demography

i. Number: 42, 22 in each treatment arm.
ii. Age: At least 20 years of age and premenopausal.
iii. Sex: Female

(b) Clinical characteristics for inclusion, and exclusion:

Same as M86-034

(5) Procedure:

Same as M86-034, except for the use of Magnetic Resonance Imaging rather than Accuson ultrasound as measure of uterine volume.

(6) Safety Considerations:

Same as M86-034

(7) Efficacy considerations:

Same as M86-034

(8) Statistical consultation: (Statistical Review completed with original submission).

(9) Results of the study M86-049 (Tables and figures referred to in the results can be found in vol. 1.18 of the NDA submission) :

Evaluable Patients (Table 1) :

Twenty two patients were evaluated in each group. One placebo patient was excluded from the efficacy analysis, since she received less than three injections. For a further ten patients, partial efficacy data exclusions were due to noncompliance with intended study procedures and dosing regimen. The following is a summary of evaluable patients:

	Treated	Placebo
Complete evaluations	20	14
Partial evaluations	2	8
Dropouts	2 (ADR, other)	12 (no efficacy)

Demographic Data (Table 2) :

Similar to the previous study, the range in age for both groups are very wide: 25-47 for lupron and 28-45 for placebo. Also as before, the weights are extremely variable: 113-202 for lupron and 102-240 for placebo.

Uterine Volume Data (Tables 6,7,8,9) :

In this study, there is again a mean 47.7% decrease in uterine volume after 24 weeks of therapy. But unlike the previous study, there was only a 29.5% decrease at the end of 12 weeks, and 42.0% at 18 weeks. The placebo group had highly fluctuant values for uterine volume. At 12 weeks, there was 12.1% increase in volume, at 18 weeks, with only 9 evaluable patients (compared to 19 at 12 weeks) , there was a 21.6% increase in volume; but at 24 weeks there was only a 2.9% increase. Even though a more precise method of testing was used here, namely, MRI, the variability brings the validity of the testing method into question once again.

The range of percentage changes remain as wide as the previous study, as outlined below:

	Week 12	Week 18	Week 24	Final
Lupron	+45% to - 73%	+4% to - 85%	- 4% to -85%	+45% to - 85%
Mean	-29.5%	-42%	-47.7%	- 40%
n	21	19	18	
Placebo	+137 to - 71%	+92% to - 14%	+55% to - 33%	+137 to -71%
Mean	+12.1%	+21.6%	+2.9%	+14.7%
n	19	9	8	

In terms of significant differences using the sponsor's 25% volume reduction criteria, the sponsor has shown in this study that a significantly greater proportion of patients treated with Lupron had a greater than 25% decrease in volume compared to placebo group, to the significance of $p = 0.003$ at 24 weeks and $p < 0.001$ at the final visit.

At the final visit 3/19 evaluable placebo treated patients showed at least a 25% reduction in volume, while 17/21 evaluable patients showed at least a 25% reduction in volume (Table 4 of vol. 1.18).

Fibroid Volume Data:

Since MRI was used in this study, the sponsor has generated data on fibroid volume (largest discrete tumor) for the two groups.

	Week 12	Week 18	Week 24	Final
Lupron	+5% to 90%	+7% to - 96%	+2% to- 85%	+2% to- 85%
Mean	-32%	-43.7%	-46.1%	-46.1%
Placebo	-20% to +96%	-18% to +93%	-52% to 107%	-52% to +107%
Mean	+10.8%	+28.2%	+13.9%	+12.3%

The data looks very similar to the changes seen in the uterine volume data. In the final visit 16/21 of 76% of patients showed at least a 25% change in volume in the lupron treated group while only 3/19 or 16% showed a greater than 25% change in the placebo treated group.

Gestational Dates data:

Decrease in baseline was 2.3 weeks at week 12 and 3.6 weeks at 24 weeks, while placebo group showed mean +0.1 at week and +0.6 at week 24. Although this is statistically significant, the clinical change of two weeks may be difficult to discern on clinical exam. In fact, 7/21 patients had uterine size at gestational weeks 12 or less and 11/21 patients had 13-16 week gestational size while only 3/21 patients had > 16 week size uteri. A similar distribution was found in the placebo group.

Clinical Signs and Symptoms:

The numbers of patients are again small, similar to the previous study, and the clinical response variable. Menorrhagia, pelvic pressure, and urinary disorders improved in the Lupron group, while menometrorrhagia, bloating, dyspareunia, pelvic pain and constipation improved in both groups to the same extent. There were very few subjects who reported some of the symptoms, for instance, only one patient in the Lupron group and five in the placebo group complained of urinary disorders.

Suppression of menses and estradiol:

None of the Lupron patients demonstrated menstruation after the third month. 4/21 patients in the placebo group experienced amenorrhea for > 35 days from last menses to end of the study.

Estradiol levels showed suppression at 24 weeks.

Hematocrit data:

Hematocrit data appears very similar to the previous study tin that the mean hematocrit values were similar in both groups. The mean hematocrit values do not show a group of patients at significant surgical risk due to anemia in either group.

Vital Signs data:

No significant change are seen in the vital signs.

Bone Density data:

The bone density data were performed at the end of the study using spine dual photon, spine CT, wrist-trabecular single photon, and hip-femoral neck. Spine dual photon showed a 2.2% decrease from baseline while spine CT scan showed a 13.5%decrease, with a highly significant difference (Lupron > iron alone).

Laboratory data:

1) [Hematocrit values do show a significant difference when changed from baseline are compared to placebo.] However, hemoglobin did not show significant changes. This is different from the previous study, where just the opposite was found, with hemoglobin not hematocrit values showing statistical difference.

2) Uric acid did not show an increase as it did in the previous study.

3) Alkaline phosphatase showed a significant rise when compared to baseline, as did phosphorus. Calcium showed no change.

4) Total cholesterol rose as in the previous study, from 193 to 201. Most of the rise seems to derive its significance from a rise in triglycerides.

5) The slight rise in SGOT, and SGPT levels seen in previous studies were not noticed.

Adverse events:

Adverse events were reported by 91% of Lupron patients and 45% of placebo ($p < 0.05$). Most frequently reported, hot flushes occurred in 64% of Lupron patients and none in placebo patients. Aside from hot flushes the only significant difference in incidence of adverse events between treatment groups was for arthralgia ($p < 0.05$).

d. Controlled study M86-062:

(1) Investigators and Study Centers

Seven centers were used in this study:

Name	Place	Number of subjects
Richard Blackewell	Birmingham, Al	4
Florence Comite	New Haven CT	16
Alexander Dlugi	Boston, MA	4
David Guzick	Pittsburgh, PA	4
David Hoffman	Chicago, IL	7
William Le Maire	Miami, FL	7
A. Loucopoulos	New York, NY	2
	Total	44

(2) Objective of the study:

Same as M86-034

(3) Rationale for the study:

Same as M86-034

(4) Experimental design:

(a) Patient population

Demography

i. Number: 44, 21 Lupron, 23 placebo.
ii. Age: At least 20 years of age and premenopausal.
iii. Sex: Female

(b) Clinical characteristics for inclusion, and exclusion:

Same as M86-034, except for the use of Magnetic Resonance Imaging and ultrasound as measure of uterine volume.

(5) Procedure:

Same as M86-034, except for the use of both Magnetic Resonance Imaging and Accuson ultrasound to measure uterine volume.

(6) Safety considerations:

Same as M86-034

(7) Efficacy considerations:

Same as M86-034

(8) Statistical consultation: (Statistical Review was completed with the original submission.

(9) Results of the study M86-062:(Tables from vol. 1.20)

Evaluable Patients:

Twenty one patients in the Lupron and 23 in the placebo group were evaluated in each group. All patients were considered eligible for efficacy analysis, since all received at least three injections. Partial efficacy analysis was excluded for seventeen patients due to noncompliance with study procedures. Following is a summary of evaluable patients:

	Treated	Placebo
Complete evaluations	21	23
Partial evaluations	7	10

Demographic Data:

Similar to the previous study, the range in age for both groups is very wide: 28-47 for lupron and 20-44 for placebo. Also as before, the weight is variable, but not as variable in the previous study, 110-177 pounds for Lupron and 102-212 pounds for placebo.

Uterine Volume Data:

In this study, there is a mean 45.2% decrease in uterine volume after 24 weeks of therapy, which is very close to the two previous studies. The results at 12 and 18 weeks are similar to the first study, M86-034, with a similar decrease at those times as

with 24 weeks of 39.2 and 39.6 respectively. The actual individual values were fluctuant for both groups. There were only 7/19 evaluable patients at the end of 18 and 24 weeks in the placebo group. As in the previous study, there was only a 8.4% increase at the end of 24 weeks, although at 12 weeks there was a 31.3% increase. Even though a more precise method of testing was used here, namely MRI, the variability brings the validity of the testing method into question. According to the sponsor the low number of evaluable patients at the end of the study in the placebo group is due to dropouts due to symptom worsening.

The range of percentage changes remain as wide as previously noted, as outlined below:

	Week 12	Week 18	Week 24	Final
Lupron	+3% to - 57%	+11% to - 83%	+9% to - 71%	+9% to -71%
Mean	-39.2%	-39.6%	- 45.2%	-42.4%
n	14	14	15	18
Placebo	- 20% to +277%	-25% to + 61%	- 27% to +808	- 27% to +277%
Mean	+31.3%	+18.7%	+8.4%	+24.4%
n	16	7	7	19

In terms of significant differences using the sponsor's 25% volume reduction criteria, the sponsor has shown in this study that a significantly greater proportion of patients treated with Lupron had a greater than 25% decrease in volume compared to placebo group, to the significance of $p < 0.001$ at 24 weeks and at the final visit.

At the final visit (which was 24 or 18 weeks), 2/19 evaluable placebo treated patients showed at least a 25% reduction in volume, while 15/18 Lupron treated evaluable patients showed at least a 25% reduction in volume.

Fibroid Volume Data:

Since MRI was used in this study, the sponsor has generated data on fibroid volume (largest discrete tumor) for the two groups.

	Week 12	Week 18	Week 24	Final
Lupron	+6 to -55%	+8 % to - 70%	+11% to - 77%	+11% to - 77%
Mean	-26.5%	-30.5%	-31.4%	-27.5%
n	12	12	13	15
Placebo	+80% to -32%	+44% to - 34%	+116% to -39%	+116% to - 39%
Mean	+2.7%	- 6.6%	+7.0%	+4.8%
n	15	6	6	17

The data looks very similar to the changes seen in the uterine volume data. In the final visit 9/15 or 60% of patients showed at least a 25% change in volume in the Lupron treated group while only 3/17 or 18% showed a greater than 25% change in the placebo treated group.

Gestational Weeks data: (Table 12-13)

In the placebo group gestational weeks data changed for only one patient, and this change was no greater than two weeks at the end of the study. In the Lupron group the largest change from baseline to final visit was noted in patient # 319. This patient went from a 20 week size to 8 week size at final visit. But in general changes range from -7 weeks to zero, (patient # 305 had no change at the final visit).

Clinical Signs and Symptoms:

Similar to the previous studies, menorrhagia, pelvic pressure and urinary disorders are most improved, while menometrorrhagia and other symptoms remain the same between the two groups at 12 and 24 weeks (no statistical significance given).

Suppression of menses and estradiol:

Only one of the Lupron patients had ongoing menstrual cycles while on treatment. This patient also had the smallest percentage estradiol drop while on treatment. Two patients had irregular periods while they were on placebo treatment. Hormone levels were consistent with suppression.

Hematocrit data:

Only one patient in the Lupron treated group and two patients in the placebo treated group had hematocrits of less than 36%. Only a single patient in the entire study had a very low hematocrit of 24%, and this patient's hematocrit did not improve with treatment. According to the menstrual data, this patient was completely amenorrheic. The mean data shows no statistical significance between the two treatment groups in this study.

Vital Signs data:

No significant changes are seen in the vital signs.

Bone Density data:

The number of patients in this study was very small, similar to the previous studies. Peripheral bone mineral density measurements of the wrist including single photon and QCT cortical/trabecular measurements were not sensitive to pick up any changes with Lupron or placebo treatment. In this study, the spinal dual photon showed a 5.3% decrease from baseline, which was highly significant ($p < 0.001$). Hip analysis showed that the femoral neck was not affected, while trochanteric measurements were decreased by 8.8%. No placebo patients were studied and the numbers of patients in the Lupron group were very small.

Laboratory data:

Since the number of patients in the study is small, it is hard to determine clinical significance of statistically significant differences.

1) Hematocrit and hemoglobin values increased slightly in the treated group (by 1.8% and 0.6 g/dl), which is at the 0.05 significance level.

2) Uric acid did not show an significant increase as it did in the first study (M86-034).

3) Alkaline phosphatase again showed a significant rise when compared to baseline, as did phosphorus. In this study, unlike the previous studies, calcium also showed a significant rise. Increase in phosphatase enzyme have been reported previously in patients treated with other GnRH agonist.

4) Total cholesterol did not rise in this study, unlike the two previous studies. All subfractions remained unchanged, except for a rise in triglycerides, but only in the placebo group.

5) The slight rise in SGOT, and SGPT levels seen previously are not noted.

6) WBC counts fell slightly, although not significantly.

7) BUN rose slightly in the treated group, but this observation is not consistently found in all studies.

The mechanisms by which calcium, albumin, phosphate, SGOT and alkaline phosphatase increase during GnRH agonist therapy are unknown.

Adverse events:

Adverse events were reported by 95% of Lupron patients and 43% of placebo ($p < 0.05$). The most frequently reported adverse event: hot flushes--86% of Lupron patients and 9% of placebo. Aside from hot flushes, the only significant difference in incidence of adverse events between the treatment groups was for vaginitis ($p < 0.05$).

Conclusions of Studies: M86-034, M86-049 and M86-062

Uterine volume data: Mean percent change of uterine volume data in patients treated with Lupron was significantly different from those patients treated with placebo. The Table below summarizes the data derived from the evaluable patients from all three studies:

Table 1

Uterine Volume Mean Percent Reductions Final Visit

Treatment	Lupron	Placebo
N (combined)	58	58
% change	-40.6%	14.3%
Baseline volume (cm3)	521.7	492.2
Final volume (cm3)	316.6	546.6
Starting diameter **	10 cm	9.8 cm
Final diameter **	8.4 cm	10.2 cm
Diameter change **	- 1.6 cm	+ 0.4 cm

*

**Assuming a sphere

Final visit varied from 12 to 24 weeks

This table demonstrates a statistically significant difference in volume reduction between the two groups, with volume reduction found with Lupron therapy, but not with placebo therapy. This volume reduction does not appear to be linked to a dramatic reduction in the diameter of the uterus. However volume is a cubed measure, thus a greater than 40% decrease in volume translates into a 1.6 cm overall decrease in diameter. The data is this NDA did not demonstrate that such a decrease in diameter makes a significant difference to surgery.

In a few patients (n = 26), who were followed up at the end of the study, the tumors grew back to their original size, but the sponsors claim that none of the tumors grew to a larger size than pre-treatment. The patients had only one post-treatment measurement, varying from 2 to 13 months (mean of 6 months post-treatment). The findings are consistent with published studies that have shown that the fibroids do grow back within 3-6 months after cessation of treatment.

Fibroid Volume and Gestational Weeks Data:

Information on individual fibroid volume data was available in two of the three studies. Since the protocol called for inclusion of fibroids if they were 3 cm or greater, the starting diameter in the majority of the patients were close to 3 cm, as seen in the table below.

Table 2

Fibroid Volume Mean Percent Reductions: Final Visit

Treatment	Lupron	Placebo
N (combined)	34	35
% change	- 36.8	+ 8.5
Baseline volume (cm3)	142.9	206.0
Final volume	104.5	206.0
Starting diameter	3.2 cm	3.6 cm
Final diameter	2.9 cm	3.6 cm
Diameter change **	- 0.3 cm	0 cm

**Assuming a sphere

It can be seen that the reduction in the diameter of these very small fibroids were indeed very small. It is highly unlikely that such small fibroids would have been

operated on in the first place. Reduction in diameter in diameter of the fibroids was 0.3 cm . Similar to the objections noted in the uterine data above, it is unlikely that such small difference would have had a significant effect on surgery.

Gestational weeks data showed a significant decrease of 4.3 weeks in gestational week size of the uterus, starting from a baseline of 13.8 weeks. These were not large uteri or large myomas; and observation alone or myomectomy may have been indicated in this group of patients.

Variability in response to treatment:

Further analyses of the data shows that there was a great deal of variability in the response of individual patients. Many placebo patients showed reduction in uterine volume, while many Lupron treated patients showed increases in uterine volume while on treatment. Twenty-five percent of Lupron-treated patients did not show a response to treatment, while in two out of three of the studies, 16% and 10% of placebo treated patients showed a decrease in volume (see table below).

Uterine Volume Mean Percent Reductions+
Final Visit

Study	Lupron	Placebo
M86-034	39.5	-4.0
M86-049	40.0	-14.7
M86-062	42.4	-24.4

Uterine Volume
Responder Proportions ++
Final Visit

Study	Lupron	Placebo
M86-034	13/17 (76.5%)	0/20
M86-049	16/21 (76.2%)	3/19 (15.8%)
M86-062	14/18 (77.8%)	2/19 (10.5%)

\+ Mean of individual percent reductions. Negative value indicates an increase from baseline.

++ A patient is considered to be a responder if her uterine volume decreased at least 25% from baseline.

This variability demonstrates that:

1) Not all tumors respond equally well to a hypoestrogenic state.
2) Other growth factors such as growth hormone, epidermal growth factors, etc. may play a role in the growth of these tumors, along with or independent of estrogenic stimulation.
3) The natural history of these tumors, in terms of growth periods and quiescent periods, appear to be variable.
4) There remain unknown and unanswered questions with regard to factors which do and do not influence the growth of leiomyomas.

Based on the above observations it is not clear if one can predict the response of individual patients to the induced hypoestrogenism and the question remains whether the risk of bone loss is worth an uncertain benefit.

Symptomatic Improvement data:

The following summary statement for symptomatic improvement is taken from the statistical review (July 28, 1989). "It was the opinion of the statistical reviewer that there were not enough patients at baseline in each of the three studies for all symptoms except menorrhagia and bloating to show statistically significant decrease after treatment. A shift in favor of Lupron occurred over placebo with regard to frequency and severity of menorrhagia in that the treatment groups were comparable at baseline but not at final visit. The change seen with bloating was not as significant as with menorrhagia. In each of the individual studies, menometrorrhagia, pelvic pain, pressure dyspareunia, urinary disorders and constipation were absent for the majority of the patients".

Prevalence of Bleeding and Bloating at Baseline and Final Visit for Evaluable Patient

Variable	Treatment Group	Baseline		Final	
		N	%	N	%
Bleeding	Lupron	38	63	4	7 *
	Placebo	37	59	26	41
Bloating	Lupron	42	70	20	33*
	Placebo	44	70	40	63

* $p \leq 0.05$

Hematocrit data:

None of the subjects received iron supplementation. Overall, Lupron treated patients showed a one percent increase in hematocrit. Those patients who had menorrhagia present at the beginning of the trial showed a 1. 5% mean increase in hematocrit; but in those patients that did not have menorrhagia at the beginning of the study there was no significant rise in hematocrit. Placebo treated patients showed no change. In the last three studies it was not clear whether such improvements would have occurred with iron replacement alone. Many patients had menorrhagia at the start of the study, (Lupron 35 , placebo 28). It was not shown that they were at increased risk for surgery, since their hematocrits were not substantially low, that is thirty-seven of sixty-nine patients had hematocrits of > 36% in the treatment group. This raises the question of whether it is important to define clearly the population of patients that would benefit from therapy. Is it the menorrhagic patient with iron deficiency anemia or a patient who is menorrhagic without iron deficiency or patients that have objectively demonstrated that they bleed heavily at menses that would benefit?
16/32 patients in treatment group had hematocrits $\leq$ to 36%. There was no delineation of the number that were anemic by traditional definition (hematocrit $\leq$30%). These patients showed within group mean change from baseline of 3.7%. This increase should be viewed with caution in light of the inability to determine the percent that were actually anemic.

Bone studies:

In the three studies (M86-034, M86-049, & M86-062), many different techniques were used and the number of subjects in each group of studies is very small and

therefore statistical validity of conclusions must be questioned. According to the sponsor, " In general, meaningful analyses were precluded due to the variety of methodologies used to measure bone density, small sample sizes, technical errors, and unexpected losses (mean and individual) in placebo patients." .
The largest site-by-method category for combined studies was spinal bone density measured by DPA (24 Lupron Depot and 12 placebo patients). Patients in the Lupron Depot group incurred a mean loss of 3.8% and placebo patients had a mean loss of 0.2%. This difference was statistically significant. Data from the no treatment follow-up trended toward recovery. Changes in spinal bone density measured by QCT showed a significantly greater mean loss (13.5%) in the Lupron Depot group (N=7), compared to the mean loss (2.8%) in the placebo group (N=3). QCT is the most sensitive system for detecting early bone loss. DPA is now obsolete and has been replaced completely by DEXA.

Concluding remarks about the entire NDA:

i. In study M90-411, the hemoglobin efficacy endpoints and clinical response parameters established in 1991 were met. The difference in responder rate for percent of patients with increase of 2g/dl in Hgb for Lupron 3.75 + iron vs iron alone for: stratum A (Hct <28): 5.7%, stratum B (Hct >28): 11.7% and total (combined strata) 9.5%. The difference in responder rate for percent of patients attaining Hgb level of at least 12g/dl, for Lupron 3.75 +iron vs iron alone were: Stratum A, 34.5%, stratum B, 18.4% and total, 24.2%.

ii. A responder rate is not what is generally considered by a surgeon when making a decision concerning the adequacy of a patient's Hgb, prior to performing a surgical procedure.

iii. It appears that in the first 4 weeks of therapy, Lupron + iron and iron alone responder rates are due to the presence of iron in both groups. After this point (4 weeks) iron alone therapy does not show any additional improvement where as the Lupron + iron does.

iv. For the patients with baseline Hgb $\geq$9g/dl, when analysis of mean Hgb levels at final visit were evaluated for percent of patients that reached Hgb $\geq$12g/d, no statistical significance was noted between final values for Lupron + iron vs iron alone. Final values 13.1 vs 12.9 respectively.

v. Overall, the suppression of menses secondary to the hypoestrogenic effect of GnRH agonist therapy plus iron resulted in a final mean gain of Hgb of 1.1-1.2 g/dl over iron therapy alone. The values of 12.6-12.7 g/dl in the treatment group vs 11.5 g/dl in the placebo group clinically appear quite similar and neither of the values represents a value that could be considered a serious surgical risk. From this data it would appear that preoperative treatment with iron alone would enable anemic women with leiomyomata who require surgery to increase their hemoglobin concentrations and allow them to donate autologous blood for potential transfusion.

vi. The data in study M90-411 did not show that there was a clinically significant decrease in the number of patients requiring blood transfusion in the GnRH treatment group.

vii. Study M90-411 did not show a clinically significant increase in the number of patients who donated autologous blood in the GnRH treatment group. Studies M86-034, M86-049 and M86-062 did not contain blood donation or transfusion data.

viii. GnRH agonist therapy is not benign; and it results in statistically significant loss of bone mineral density, statistically significant cholesterol, lipid and liver function changes; and other adverse events: vasodilatation (hot flushes) and vaginitis, dizziness, depression, arthralgia, and abdominal pain.

ix. Mean shrinkage with Lupron on average in all four studies ranges from 42.4% to 24%. This reduction is consistent with the literature. This reduction in volume, however, did not result in fewer abdominal hysterectomies; or in fewer hysterectomies and more myomectomies in patients who desired maintaining their reproductive capacity.

x. There was no evidence that uterine volume measured by ultrasonography or MRI can be translated into estimates of uterine weight or gestational size. Therefore it is unclear clinically as to the significance of ultrasonographically determined uterine volume.

xi. Maximal shrinkage of uterine volume occurs in the first 12 weeks of therapy. Additional therapy does not result in any significant additional shrinkage.

xii. Analysis of individual data points revealed that changes in uterine volume was unpredictable and quite variable. For example, in the last three studies four Lupron patients showed a 1 to 25% decrease in size, while seven placebo patients showed the same trend. Eight Lupron patients showed a 25-50% decrease in volume, with only three showing a greater than 50% decrease (compared to placebo).

xiii. The data presented in the NDA and data reported in the literature show that the reduction in volume is only temporary and the tumors grow back to their original size within 3-6 months, with some papers reporting an increase to greater than original size in some patients. The use of analogues does not appear to represent a cure, but only a temporary suppression.

xiv. Additional open uncontrolled domestic (M86-048 and M86-043) and foreign studies submitted, did not provide any additional information.

Deficiencies/Problems:

The sponsor has demonstrated statistically significant responder rate for increase of Hgb $\geq$2g/dl and or $\geq$6% increase in Hct and statistically significant responder rate for reaching $\geq$12g/dl Hgb. The differences in responder rates between groups

(Lupron 3.75 + iron vs iron), varied depending upon whether percent of patients with increase of 2g/dl in Hgb was evaluated vs percent of patients attaining Hgb $\geq$12g/dl. (Reference tables page 19 of review for actual numbers).

I don't believe that the drug should be approved for the following reasons:

i. The data did not demonstrate a clinically significant gain in Hgb with Lupron plus iron over iron therapy alone. The actual gain was 1.1-1.2g/dl Hgb in the Lupron group, which I do not consider to be clinically significant. A difference of 2g/dl between groups would have been impressive.

ii. The perceived benefits do not outweigh the risks of exposing pre-menopausal women to bone mineral density loss, significant cholesterol, lipid and liver function changes, as well as other adverse events that were reported more often for Lupron Depot treated patients than for iron only treated patients.

iii. In the study that provided blood donation and transfusion data: It was not shown that there was a clinically significant decrease in number of Lupron treated patients requiring blood transfusion. Nor was it shown that there was a clinically significant increase in number of Lupron treated patients who were suitable to provide autologous blood for their surgery.

iv. There was no additional data provided that linked any of the other Advisory Committee Recommendations to benefits of GnRH agonist therapy.

Recommendations:

Non-approval for the indications sought.

(Annette Bey)
Annette Bey, MD

cc: NDA Arch
HFD 510
HFD 510/A.Bey/ ft/ 3-10-95/ 19-943a.nda/P.Corfman

NDA 19-943
Lupron® Depot (leuprolide acetate)
TAP Pharmaceuticals, Inc.

Division Director's Memo

This NDA will be signed off at the Division level. No memo is required.

Memorandum

Date 30 March 1995

From Supervisory Medical Officer
Fertility and Maternal Health Drugs Group/HFD-510

Subject NDA 19-943

To The Record

I have studied the review of this NDA by Dr. Annette Bey, the Medical Officer, dated March 13, 1995, and the Consultation by Dr. Bruce Stadel, dated March 16, 1995. Although I share the view of other gynecologists in this Group that Dr. Bey demonstrates good clinical judgement in establishing a conservative stance concerning the use of Lupron Depot for the treatment of women with leiomyomata, Dr. Stadel's analysis makes it clear that the sponsor has achieved the standards for approval established in 1991, before Dr. Bey began work at the Agency.

Dr. Stadel has also established that the data demonstrate that iron therapy alone is sufficient for a large number of subjects. Therefore I recommend approval of the NDA, with the following indications:

INDICATIONS AND USAGE

Experience with LUPRON DEPOT in females has been limited to women 18 years of age and older.

Endometriosis

LUPRON DEPOT 3.75 mg is indicated for the management of endometriosis, including pain relief and reduction of endometriotic lesions, for no more than 6 months.

Uterine Leiomyomata (Fibroids)

Iron therapy for one month is first line preoperative treatment of patients with anemia caused by uterine leiomyomata. Lupron Depot 3.75 mg plus iron is second line treatment for women who fail to improve on iron alone but should not be provided for more than 3 months.

Finally, I recommend that a patient package insert be provided.

Philip A. Corfman

Philip A. Corfman, MD

NDA 19-943
Lupron® Depot (leuprolide acetate)
TAP Pharmaceuticals, Inc.

Pediatric Page

This is not an NME, therefore, no information is required.

Label Recommendations: NDA 19-943

Name of drug: Lupron Depot

Sponsor: TAP

Indication: "Lupron Depot 3.75 is indicated for three months of therapy in the preoperative management of uterione leiomyomata to improve hematologic status and for up to six months to reduce uterine/myoma volume and associated symptoms when surgery is delayed."

Comments:

The sponsor has requested for three to six months of therapy for the indication throughout the submitted proposed labeling. The sponsor needs to delete all reference in label that states duration of administration to up to six months.

The protocol for change in hematologic status was for three months, there is no six month data. The uterine volume decrease is referenced in the label, calling for three to six months of therapy. But their three studies of uterine volume showed maximum reduction in three months. In the label they refer to additional gain at six months, but this gain was not statistically significant.

The protocol for change in hematologic status called for iron + Lupron, will the approved label call for iron?

The proposed label is submitted as combined labeling for the two indications ie. endometriosis and uterine leiomyomata. I feel that the labeling should be separated. Once separated they can refer specifically to information that came out of the studies for uterine leiomyomata.

The studies were not designed to correlate reduction in uterine and myoma volume with relief of clinical symptoms. The statistical review stated that there were not enough patients at baseline in each of the three studies for all symptoms except for menorrhagia and bloating to show statistically significant decrease after treatment. Therefore any reference to improvement of other symptoms (pelvic pain or pressure) can not be substantiated.

Annette Bey, MD

cc: NDA Arch
HFD 510
HFD 510/ABey/PCorfman

Philip J. Corfman 3-13-95

I separate memo from me states that although I agree with Dr. Bey's clinical judgment in this matter, I recommend approval with more conservative labeling.

I N T E R O F F I C E M E M O R A N D U M

DATE: February 1995

FROM: Bruce V. Stadel, MD, MPH
Medical Officer/Epidemiology

Bruce V Stadel

SUBJECT: NDA 19-943
Leuprolide acetate for depot suspension
(Lupron Depot®, TAP Pharmaceuticals, Inc.)
Study M90-411

TO: Annette Bey, MD
Medical Officer/Fertility & Maternal Health Drugs Group

This replies to your request for consultation regarding the study referred to above. For convenience, I will use the term "Lupron" to mean Lupron Depot, and will refer to intramuscular doses of 3.75 mg/month and 7.5 mg/month as "Lupron 3.75" and "Lupron 7.5," respectively. "Placebo" will mean an intramuscular injection of placebo, and "Iron" will mean a daily oral dose of either two tablets of ferrous sulfate, 525 mg/tablet, or three tablets of ferrous gluconate, 324 mg/tablet.

This study was a stratified, randomized, double-blind, parallel group clinical trial, carried out at 50 centers in the United States. The study compared the efficacy of Iron+Lupron 3.75 mg, Iron+Lupron 7.5 mg, and Iron+Placebo for the preoperative treatment of anemia due to bleeding associated with uterine leiomyomas. Criteria for enrolling women in the study were developed in response to a 29 August 1991 letter from the Division to the Sponsor which states that:

(1) the study should "evaluate the patient's hemoglobin rather than her hematocrit,"

(2) the study should enroll patients with "hemoglobin readings less than or equal to 10 grams," and

(3) "efficacy should be determined by an increase to at least 12 grams." (Attachment 1)

The Division letter was based upon recommendations from the 26-27 October 1989 meeting of the Metabolic-Endocrine Drug Products Advisory committee, which are discussed on page 4-5 of your NDA review, and was elaborated upon in a meeting between the Division and the Sponsor on 17 September 1991; minutes of that meeting are attached (Attachment 2).

The NDA (vol 1.5, pp 53-71), your review, and the statistical review by Mr. Marticello provide good documentation that the study was appropriate with regard to: the study design and criteria for selection of patients; the drug supplies, dosage schedule, and criteria for use of concomitant medications; the schedule and procedures for collecting data in the pre-trial, trial, and post-trial periods; the procedures for evaluating efficacy, safety, and data quality; the criteria for removing patients from the study or analysis; and the methods of analysis and data presentation. Therefore, I will focus in this Memo on:

(1) accounting for the flow of patients through the study,

(2) description of the findings -- in general, and according to the criterion of efficacy in the 29 August 1991 letter from the Division to the Sponsor,

(3) discussion of the implications, for defining the treatment indication, of the findings at four weeks after the first (baseline) injection, compared to the findings at eight weeks (four weeks after the second injection), and at twelve weeks (four weeks after the final injection).

1. Accounting for patients

A total of 309 women with hemoglobin levels of 3-10 g/dl were enrolled in the study, and stratified into two groups according to baseline hematocrit. Of the 309 women, the 120 (38.8%) with hematocrit $\leq$ 28% formed "Stratum A," and the 189 (61.2%) with hematocrit > 28% (Stratum B). Women in the two strata were randomized separately to treatment with Iron+Lupron 7.5 mg, Iron+Lupron 3.75 mg, or Iron+Placebo. Thus, there were six treatment groups in total.

Attachment 3, page 1, shows, for each of the six treatment groups:

(1) the number of women randomized,

(2) the number excluded from all of the Sponsor's analyses according to the study protocol (NDA vol 1.5, pp 70-71),

(3) the number evaluable for at least one study outcome,

(4) the number with the specific outcome of a final visit increase, over baseline, of both $\geq$ 2 g/dl hemoglobin and $\geq$ 6% hematocrit,

(5) the number evaluable for the specific outcome above,

(6) efficacy by analysis of all patients randomized, ("intent-to-treat" analysis), and

(7) efficacy by analysis of patients evaluable for the specific outcome referred to above ("evaluable patient" analysis).

2. Description of findings

2.1 In general

Attachment 3 page 1, shows greater efficacy in both Stratum A and Stratum B for both Iron+Lupron 7.5 mg and Iron+Lupron 3.75 mg, compared to Iron+Placebo, in all analyses. Therefore, the two strata are combined on Page 2. Page 2 shows that efficacy was not meaningfully different for Iron+Lupron 7.5 mg compared to Iron+Lupron 3.75 mg. Therefore, the two doses are combined in the analyses on Page 3, and in the remainder of this Memo.

Page 3 shows 29% greater efficacy for Iron+Lupron versus Iron+Placebo in the intent-to-treat analyses, and 27% greater efficacy in the evaluable patient analysis. Both of these findings are statistically significant ($p < 0.05$, two-sided).

2.2 According to Division criterion of efficacy

Attachment 4 demonstrates efficacy for Iron+Lupron compared to Iron+Placebo according to the criterion of efficacy in the 29 August 1991 letter from the Division to the Sponsor.

The analyses of "Efficacy Evaluable Patients" in Attachment 4 use the same approach for defining numerators and denominators as the analyses in Attachment 3 of "Efficacy as % of N evaluable for this outcome," and are therefore similar in meaning.

The analyses of "All Patients" in Attachment 4 evidently use the last-value-carried-forward approach for defining numerators and denominators, which is a common and legitimate method, but which is not related directly to the intent-to-treat analyses in Attachment 3, of "Efficacy as % of N randomized". However, if the Attachment 4 numerators for "Efficacy Evaluable Patients" are divided by the Attachment 3 denominators for "N randomized," the results are similar to the intent-to-treat analyses in Attachment 3. Using this approach, 64% (135/211) of the women randomized to Iron+Lupron achieved a final visit hemoglobin $\geq$ 12 g/dl, versus 38% (37/98) of the women randomized to Iron+Placebo. The 26% greater efficacy for Iron+Lupron is statistically significant ($p < 0.05$, two-sided). (I do not have the precise "N randomized" denominators to do this separately for baseline hemoglobin < 8 g/dl versus $\geq$ 8 g/dl, but am confident the results would be similar to those shown in Attachment 4.)

3. Implications if findings at 4 weeks compared to 8 and 12 weeks

Attachment 5, page 1 shows the treatment effect of Iron+Lupron and Iron+Placebo at four weeks after the first (baseline) injection. Pages 2-4 show that, compared to the 4-week effect, there is not much further increase in treatment effect, for either Iron+Lupron or Iron+Placebo, at eight weeks (four weeks after the second injection), twelve weeks (four weeks after the final injection), or in the final,last-value-carried-forward analysis.

I think the above findings support two conclusions:

1) A patient's response to iron alone can be evaluated with a treatment course of one month, and many patients will achieve a clinically adequate response to iron alone within this interval.

2) For patients who do not achieve a clinically adequate response to iron alone, iron+Lupron for one month will achieve most of the response that can be expected with longer treatment, although the longer t atment may be needed to maintain the response if the patient is not taken to surgery.

Addendum: Attachment 6 shows mean values of hemoglobin and the percent distribution of patients by hemoglobin categories, at four weeks, for Iron+Placebo (page 1) and Iron+Lupron (page 2).

Comparing the two pages shows that the categories provide more information than the means about differences in effect for the two treatments.

Thus, in Figure 1 (page 1) about 25% of patients have "high-risk" hemoglobin < 10 g/dl and only about 22% have "low risk" hemoglobin ≥ 12 g/dl, whereas in Figure 2 (page 2) only about 11% have hemoglobin < 10 g/dl and about 40% have hemoglobin ≥ 12 g/dl -- with only a 0.8 g/dl increase in the mean. The reason is that the mean is insensitive to changes at the "high-risk" and "low-risk" ends of the distribution, because it is heavily weighted by the percentage of patients "in the middle."

Similar findings are present in many other analyses of data from the study.

cc:
Arch NDA 19-943
HFD 510 Sobel/Corfman/Stadel/Pauls

IND

AUG 29 1991

TAP Pharmaceuticals
Attention: Mr. Dean Sundberg
Director, Regulatory Affairs
2355 Waukegan Road
Deerfield, IL 60015

Dear Mr. Sundberg:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Lupron (leuprolide acetate) Depot, IND

We also refer to your submission dated June 27, 1991, which contains a new protocol designed to study the effect of two different strengths of Lupron Depot plus an iron supplement in the treatment of hypermenorrhea-induced anemia in patients with uterine fibroids.

We also refer to the August 12, 1991 telephone conversation between you and Ms. Lois Simmons of this Division regarding our request that you withhold clinical studies based on this protocol under this IND. The reason for the clinical hold is that the protocol is deficient under 21 CFR 312.42(b)(2)(i) and (ii). The specific deficiencies which justify placing this IND on clinical hold are detailed below:

1. Although the primary inclusion criteria is anemia, women admitted to the study should also present with a large fibroid. The inclusion criterion to admit women with a single 3 cm fibroid is not reasonable because a fibroid of this dimension is not likely to be clinically significant. In addition, women should be included only if the uterus is of 12 week gestational size or greater, confirmed by at least two independent physicians. Evaluation of uterine size is more appropriate clinically than volume measurements made by ultrasound, due to the possibility of distortions of uterine or fibroid volume resulting from abnormally shaped fibroids.

2. The endometrial biopsy should show secretory endometrium as conformation of normal ovulatory cycles. Women with biopsy evidence of hyperplasia and irregular shedding should be excluded.

3. Women admitted to the study should also have documented hypermenorrhea for at least 3 cycles.

4. The technique used to demonstrate hypermenorrhea should be adequately validated.

5. We suggest that you measure serum osteocalcin, and urinary calcium, creatinine, pyridinoline and deoxypyridinoline at baseline, 8 and 12 weeks to monitor bone turnover while patients are on Lupron therapy.

6. The efficacy parameter and entry criteria should be revised to evaluate the patient's hemoglobin rather than her hematocrit. Accordingly, the entry criterion included patients with hemoglobin readings less than or equal to 10 grams, and efficacy should be determined by an increase to at least 12 grams. The number of patients in the study should be revised accordingly.

7. Uterine weight should be documented in those patients who go to surgery.

8. A copy of the informed consent document should be submitted for review.

Until you have submitted the additional required information and we notify you that it is safe to initiate the studies, you may not proceed with the proposed study.

Should you have any questions regarding this IND, please contact Ms. Lois Simmons at 301-443-3510.

Your cooperation is appreciated.

Sincerely yours,

8/27/91

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

cc: IND Orig
HFD-510
HFD-510/VRagavan/PCorfman
HFD-511/LSimmons/8.12.91/ft/kso/8.27.91/ .ch
Concurrences:JShort/8.20.91/VRagavan/PCorfman/8.26.91

PARTIAL CLINICAL HOLD

Simmons 27 aug 91

IND
Lupron (leuprolide acetate) Depot
TAP Pharmaceuticals

September 17, 1991

Memorandum of Meeting

TAP Representatives:

B. Brownelller, Clinical Research Manager
J. Lancaster, Ph.D., Biostatistician
J. Miller, M.D., Medical Director
J. Seely, Ph.D., Vice President, Research and Development
D. Sundberg, Director, Regulatory Affairs

Attending for TAP:

T. Stovall M.D., Ass't Professor/Director of Gynecology, Univ of Tenn.

FDA Staff:

Dr. Sobel
Dr. Troendle
Dr. Corfman
Dr. Ragavan
Dr. Bennett
Dr. Price
Dr. Rarick
Ms. Simmons

Purpose: TAP requested the meeting to discuss the specific deficiencies leading to the clinical hold that had been imposed on a new protocol submitted to their IND to study the effect of two different strengths of Lupron Depot plus an iron supplement in the treatment of hypermenorrhea-induced anemia in women with uterine fibroids. The firm was particularly interested in obtaining the Division's input regarding the best means of resolving these issues.

Discussion and Conclusions: Dr. Miller opened the meeting for TAP by stating that he would address the deficiencies listed in the clinical hold letter individually and noted that the firm was especially eager to obtain closure on each of the problem issues. A copy of the clinical hold letter is attached for ease of reference.

Item 1--Dr. Ragavan observed that the firm has complicated the study by trying to include too many endpoints. The focus of the study should be limited to the improvement of anemia in the hypermenorrhea patients. Both the firm and the Division agreed that the acceptable study patient is a pre-surgical candidate showing evidence of significant anemia, significant fibroids (either as a single large fibroid or as a number of smaller growths), and hypermenorrhea. The firm acknowledged that they

would seek to include a claim for improvement of hematologic status in their labeling if results of the study are favorable.

Item 2--TAP agreed to precisely define the target population by ruling out all other causes of anemia and excessive bleeding through exhaustive medical management, including use of progestins, if indicated, before any patient is included in the study.

Items 3 and 4--The Division believed that the firm was attempting to become too sophisticated if they were to do chemical extractions of tampons and pads to validate the history of excessive blood loss. It will be sufficient to use documentation of past bleeding history, decreased hematocrit and evidence of anemia to categorize these patients.

Item 5--The firm indicated that, at this time, they prefer to monitor bone loss using the DEXA technology due to the limited availability of reference sites performing the assays requested in this item. Dr. Ragavan acknowledged that this list was included as analytical parameters which she would like to see documented but agreed that it was probably wishful on her part to expect the firm to provide this information. She agreed to provide the firm with the names of locations providing this type of testing in the event that the firm is interested in monitoring these parameters on a limited basis. The Division indicated that the DEXA technology is adequate to determine bone loss, and it will not be necessary for the firm to satisfy this assay requirement before the revised protocol can be approved.

Item 6--The discussion of this point centered on adequately defining a clinically significant response while on treatment in this study. Dr. Price indicated that it is commonly accepted to demonstrate a 2 gram improvement in the hemoglobin to characterize a clinically meaningful response. After much debate, it was agreed that the treatment would be considered effective if the results showed a 2 gram increase in the hemoglobin within each individual study group, and that the comparison between groups showed an improvement in the hematocrit of at least 3 percentage points.

Items 7 and 8--Both the firm and the Division agreed that these items were straightforward requests and did not warrant discussion.

As the end of the meeting, Dr. Miller remarked that TAP had come into possession of a protocol for treating uterine fibroids submitted by a competitor, and it appeared that TAP was being held to more strict investigative requirements than the other firm. Dr. Ragavan briefly addressed this issue. She also has included a memo on the subject along with the TAP generated comparison between the two fibroid protocols which are attached and will become part of the documented meeting minutes.

The meeting concluded with the TAP representatives expressing their appreciation for the opportunity to meet with the FDA and for the input and suggestions made by the Agency during the discussion.

Lois Simmons, CSO

Attachments (3)
FDA's clinical hold letter of August 29, 1991, to TAP
Dr. Ragavan's memo of September 18, 1991
"Comparison of Major Features of TAP and Competitor Uterine Leiomyomata Protocols"

cc: IND Arch.
HFD-510
Attendees
HFD-511/LSimmons/9.18.91/FT/MMM/10/3/91/ .mts
Concurrences:JShort/9/22/VRagavan/9/25/PCorfman/RBennett/PPrice9/26/LRarick

NDA 19-943
Study M90-411

TOTAL N = 309

	Stratum A (Hct ≤ 28%) N = 120			Stratum B (Hct > 28%) N = 189		
	Iron & Lupron (mg) 7.5	3.75	Iron & Placebo	Iron & Lupron (mg) 7.5	3.75	Iron & Placebo
N randomized	41	42	37	66	62	61
N excluded	5	10	8	3	5	13
N evaluable for at least one outcome	36	32	29	63	57	48
N with final visit increase of ≥ 2 g/dl Hgb & ≥ 6% HCt	33	26	18	43	42	20
N evaluable for this outcome	35	28	24	62	56	48
Efficacy						
as % of N randomized	81	62	49	65	68	33
as % of N evaluable for this outcome	94	93	75	69	75	42

Strata A & B Combined

	Iron & Lupron (mg) 7.5	3.75	Iron & Placebo
N randomized	107	104	98
N excluded	8	15	21
N evaluable for at least one outcome	99	89	77
N with final visit increase of ≥ 2 g/dl Hgb & ≥ 6% Hct	76	68	38
N evaluable for this outcome	97	84	72
Efficacy			
as % of N randomized	71	65	39
as % of N evaluable for this outcome	78	81	53

	Lupron Doses Combined	
	Iron & Lupron	Iron & Placebo
N randomized	211	98
N excluded	23	21
N evaluable for at least one outcome	188	77
N with final visit increase of 2 g/dl Hgb & $\geq$ 6% Hct	144	38
N evaluable for this outcome	181	72
Efficacy		
as % of N randomized	68	39
as % of N evaluable for this outcome	80	53

Numbers of Exclusions by Reasons

	Stratum A (Hct ≤ 28%)			Stratum B (Hct > 28%)		
	Iron & Lupron (mg) 7.5	3.75	Iron & Placebo	Iron & Lupron (mg) 7.5	3.75	Iron & Placebo
Prior medication within 3 months of first dose	4	3	2		1	5
No efficacy data after baseline		2	1			
Other causes for bleeding not eliminated	1	2	2	1	1	
Excessive bleeding not documented pre-dosing						1
Insufficient evidence of leiomyoma uteri					1	1
Not surgical candidate		1				
Surgery performed late					1	
Prohibited concomitant medication			1			
Prestudy P & PTT > 1.5 x upper limit of normal			1			1
Anemia profile > 60 days before first dose			1	1		
Serum folate < 2 5		2	1	1		1
Did not qualify hematologically			1		1	3
Adverse event indicating cancer						1

Percent of Patients With Hemoglobin (Hgb) ≥ 12 g/dL at Final Visit

Efficacy Evaluable Patients

Baseline Hgb	7.5 mg	3.75 mg	Combined Lupron	Placebo	Combined vs. Placebo
<8	74% (20/27)	68% (15/22)	71% (35/49)	43% (10/23)	*
≥8	74% (51/69)	79% (49/62)	76% (100/131)	55% (27/49)	**

All Patients

Baseline Hgb	7.5 mg	3.75 mg	Combined Lupron	Placebo	Combined vs. Placebo
<8	76% (25/33)	64% (18/28)	70% (43/61)	34% (11/32)	***
≥8	75% (55/73)	79% (53/67)	77% (108/140)	59% (37/63)	*

***, **, *, + Statistically significant at P=0.001, 0.01, 0.05, 0.10 levels, respectively
NS - Not statistically significant