CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-708

MEDICAL REVIEW(S)

MEDICAL OFFICER'S REVIEW OF NDA 20-708

1. General information

1.1. Medical Officer's review

1.1.1. NDA 20-708
1.1.2. Submission dated 7 March 1996
1.1.3. Submission transferred to this medical reviewer 27 September 1996
1.1.4. Review completed 17 January 1997

1.2 Drug names

1.2.1. Generic name:
Leuprolide acetate for depot suspension
1.2.2. Proposed trade name:
Lupron Depot-3 month 11.25 mg
1.2.3. Chemical name:
5-oxo-L-prolyl-L-histidyl-L-seryl-L-tyrosyl-D-leucyl-L-arginyl-N-prolinamide acetate

1.3 Sponsor

TAP Holdings, Inc
Deerfield IL

1.4 Pharmacological category

Long acting gonadotropin releasing hormone agonist

1.5 Proposed indications

Treatment of endometriosis and preoperative hematologic improvement of anemia caused by leiomyomata uteri.

1.6 Dosage form and route of administration (taken from proposed labeling)

1.7 **NDA drug classification**

S

1.8 **Related drugs**

Leuprolide acetate (Lupron) is currently approved in several formulations for the treatment of endometriosis, leiomyomata uteri, prostatic cancer, and precocious puberty.

Other drugs in this class of GnRH agonists include **nafarelin acetate** (approved for endometriosis and precocious puberty), **histrelin acetate** (approved for precocious puberty), and **gosarelin acetate** (approved for endometriosis, prostatic cancer, and breast cancer). There is a 3-month formulation of goserelin approved for treatment of prostatic cancer. (This application is also for a 3 month formulation.) To date, no GnRH drug product other that leuprolide is approved for the treatment of leiomyomata uteri.

2. **Material reviewed and background information**

2.1. NDA 19-943 (First submission)

NDA 19-943, submitted for the treatment of leiomyomata uteri, was not recommended for approval by the reviewing medical officer in her review of November 27, 1989. Her recommendation was supported by the Advisory Committee for Fertility and Maternal Health Drugs at its meeting of October 27, 1989.

By the time of the meeting, the sponsor had limited the indication to "..the temporary, symptomatic relief of leiomyoma [sic] uteri (uterine fibroids) for a period of up to 6 months, especially in patients where reduction in uterine volume and/or improvement in hematologic parameters is important. Treatment

may be prior to surgery or when surgery is not desirable." Nevertheless, the Committee voted 5 to 2 against approval of this revised indication, with several comments, including the following, quoted from the Summary Minutes of the meeting:

- "It was agreed that the sponsor had demonstrated a statistically significant decrease in uterine volume with Lupron therapy, but the Committee expressed doubt whether this is a clinically relevant endpoint in itself."

- "The Committee was not convinced that up to 6 months of therapy would be required.."

- "If the sponsor wishes to include prevention of blood-loss and/or anemia as an indication, future clinical trials should be designed to compare Lupron treatment with use of iron..."

As a result of these actions and recommendations, the sponsor withdrew the NDA, and submitted an IND for the treatment of anemia secondary to bleeding from leiomyomata uteri, to be used prior to surgery.

2.2. NDA 20-011

NDA 20-011, submitted for treatment of endometriosis, was recommended for approval by the medical officer on February 15, 1990.

2.3. NDA 19-943 (Resubmission)

Subsequent to the recommendations of staff and the Advisory Committee, the sponsor undertook appropriate studies and resubmitted the NDA. The NDA was approved in 1995 to be used with iron therapy for the relief of fibroid-induced anemia prior to surgery.

2.4. NDA 20-708 (The current NDA)

This NDA provides details of a PK/PD study comparing the 11.25 formulation of the drug to

the 3.75 (approved) formulation. It contains no clinical studies.

2.5. Information supplementary to NDA 20-708, provided by the sponsor at the request of the medical officer.

3. **Chemistry/manufacturing controls**

Please see chemistry review

4. **Animal Pharmacology/Toxicology**

Please see pharmacology/toxicology reviews.

5. **Human Pharmacology, Pharmacokinetics, Pharmacodynamics**

See the Biopharmaceutics review. Clinical aspects of these studies are reviewed in section 6.

6. **Clinical aspects of the PK/PD studies**

6.1. **Background**

Lupron Depot 3.75 mg, administered monthly for the treatment of endometriosis and for the preoperative treatment of anemia secondary to uterine fibroids, was approved as safe and effective under NDA 20-011, (for endometriosis) and NDA 19-943 (for fibroids). The drug is not recommended for use for more than 6 months due to the risk of osteoporosis from the patient's drug-induced hypoestrogenic state.

6.2. **Summary of study design**

The study, Protocol M94-139, entitled "Pharmacokinetic and hormonal response study of a three-month depot formulation of leuprolide (11.25 mg) in female subjects", was undertaken by John Cavanaugh, MD, PhD at the Abbott Clinical Pharmacology Research Unit in Waukegan IL from October 1994 through August 1995. It was a "single center, open-label, single-dose, Pharmacokinetic and

hormonal response study in twenty healthy female subjects with normal ovarian function".

The 20 subjects (15 Caucasian, 5 Hispanic) were aged 21-39 (mean 33), body weight 98-182 pounds (mean 138), and height 61 to 72 inches (mean 66). The source of the subjects is not provided. Standard exclusion criteria were applied, including pregnancy or the likelihood of becoming pregnant, lactation, malignancy, surgery affecting reproductive endocrinology, abnormal vaginal bleeding, and use of steroid or gonadotropin 90 days prior to injection. Four weeks prior to dosing, the subjects underwent a history and physical and pre-study blood was drawn. The subjects were seen "on Days 0, 1, 2, 4, 7, and twice a week during Weeks 1.5 through 16 and then weekly through Week 20". Week 20 is termed "End of Study" and there is no discussion whether the subjects were seen after week 20.

The blood collection schedule is displayed in **Appendix 1**, taken from the submission. It provides an overview of the timing of the study.

6.3. **Study findings**

On request, the sponsor provided **Figure 2.1** in **Appendix 2** which displays the leuprolide levels after administration of the 3.75 formulation. These data were transferred to **Figure 2.2**, to facilitate comparison of leuprolide concentrations induced by the two formulations. The biopharmacology review will provide more details concerning this issue, but the levels appear to be roughly comparable.

Nevertheless, it is important to note that in response to a request for comparable figures for 3 month continuous dosing with the 3.75 formulation, the sponsor stated:

6.4. Safety concerns

As discussed above, a major safety concern with the use of these drug products is osteoporosis induced by the hypoestrogenic state caused by the drugs. Patients are also frequently disturbed by attendant vasomotor symptoms, but the osteoporosis hazard is a more serious risk and is the reason the current label recommends limiting continuous dosing to 6 months.

It is therefore instructive to examine **Figure 3.1.** and **Figure 3.2** in **Appendix 3**, requested from the sponsor, which display serum estradiol levels after administration of the 11.25 and the 3.75 formulations. The estradiol levels tend to return to normal by the end of the treatment period. However, **Figure 3.3** and **Figure 3.4**, also provided on request, are disturbing in that they demonstrate that continuous dosing with the 3.75 formulation for 3 months for both endometriosis and fibroids markedly depresses estradiol levels, with no apparent return to normal at the end of the treatment period.

In response to a request for data on repeated use of the 11.25 formulation, the sponsor reported that

6.4.1. The endometriosis indication

As reflected in labeling, GnRH drug products have important and potentially serious side effects due to the suppression of estrogen to menopausal levels. Many patients experience vasomotor symptoms and are at risk of developing osteoporosis. This is the basis of labeling for the endometriosis indication that the

However, since endometriosis is a chronic condition, and approval is "..**for..pain relief and reduction of endometriotic lesions..**", it is acceptable to approve this NDA for use in such patients, with the condition that the limitation of treatment to 6 months be retained and emphasized.

6.4.2. **The leiomyomata uteri indication**

Following the recommendations of its Advisory Committee, the Agency restricted its approval of NDA-19943 for the treatment of leiomyomata uteri to be use

Studies in support of NDA 19-943 for the leiomyomata uteri indication demonstrated that the relief of anemia secondary to blood loss from leiomyomata uteri occurred relatively quickly. **Appendix 4**, taken from the medical review of NDA 19-943, is important in this regard. One need only focus on the percentage increases in hemoglobin and hematocrit levels for Lupron Depot 3.75 and iron alone (in the box), to discover that:

- a significant number of subjects improved on iron alone,
- significantly more subjects improved on the drug,
- but since maximum improvement occurred with the second dose, the third dose of Lupron 3.75 was not needed for the approved indication.

Therefore, since the indication noted above is to be retained, there is no justification for approving a 3 month formulation.

6.4.3. **Use of the drug more than 6 months**

For reasons cited above, there are reasons to be concerned about the prolonged hypoestrogenic state induced by long-term treatment with this drug, and such data are not scheduled to be available until March 1998. I therefore recommend that the statement the

currently appearing in the PRECAUTIONS section be revised to state

and be moved to the WARNINGS section and be printed in bold. The patient package insert should be amended accordingly.

7. **Clinical studies**

There were no clinical studies undertaken for this NDA other than the PK/PD study discussed in section 6.

8. **Recommendations**

8.1. Assuming that the supporting PK/PD studies are acceptable to the Biopharmaceutics reviewers, this NDA is:
- o approvable for the treatment of endometriosis, but
- o not approvable for the pre-operative treatment of anemia due to leiomyomata uteri.

8.2. The labeling should be amended accordingly.

Philip A. Corfman, MD
Medical Reviewer

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15.0 SUMMARY OF BLOOD COLLECTION SCHEDULE

Purpose	Quantity (Whole Blood)	Plasma/Serum	Schedule
A. Routine hematology, chemistries, urinalysis (local lab)	Per local lab	Per local lab	1. Prestudy (within 4 wks) 2. Wk 12 3. Wk 20 4. Early termination
B. Leuprolide level (analysis by Abbott; submit at end of study)	7 mL	Plasma	1. Day 0 (pre– & 4 hrs post–inj.) 2. Days 1, 2, 4, 7 3. Q half wk for Wks 1.5–16 4. Q wk for Wks 17–20
C. FSH, LH, estradiol, progesterone (analysis by Endocrine Sciences; submit weekly)	15 mL	Serum	1. Prestudy (mid–luteal) 2. Day 4 3. Q wk for Wks 1–10 4. Q half wk for Wks 10.5–12 5. Q wk for Wks 13–20*
D. β–HCG	Per local lab	Per local lab	1. Prestudy (within one week). 2. Wk 4

Prestudy	Day 0	Day 1	Day 2	Day 4	Day 7	Week 1½	Week 2	Week 2½	Week 3	Week 3½	Week 4	Week 4½	Week 5	Week 5½	Week 6	Week 6½	Week 7	Week 7½	Week 8
ACD	B**	B	B	BC	BC	B	BC	B	BC	B	BCD	B	BC	B	BC	B	BC	B	BC

Week 8½	Week 9	Week 9½	Week 10	Week 10½	Week 11	Week 11½	Week 12	Week 12½	Week 13	Week 13½	Week 14	Week 14½	Week 15	Week 15½	Week 16	Week 17	Week 18	Week 19	Week 20
B	BC	B	BC	BC	BC	BC	ABC	B	BC	B	BC	B	BC	B	BC	BC	BC	BC	ABC*

* Samples should be obtained __beyond__ Week 20 (at weekly intervals) if ovarian function (euhormonal state) has not resumed by Week 20. (See Section 7.2.1 for criteria).

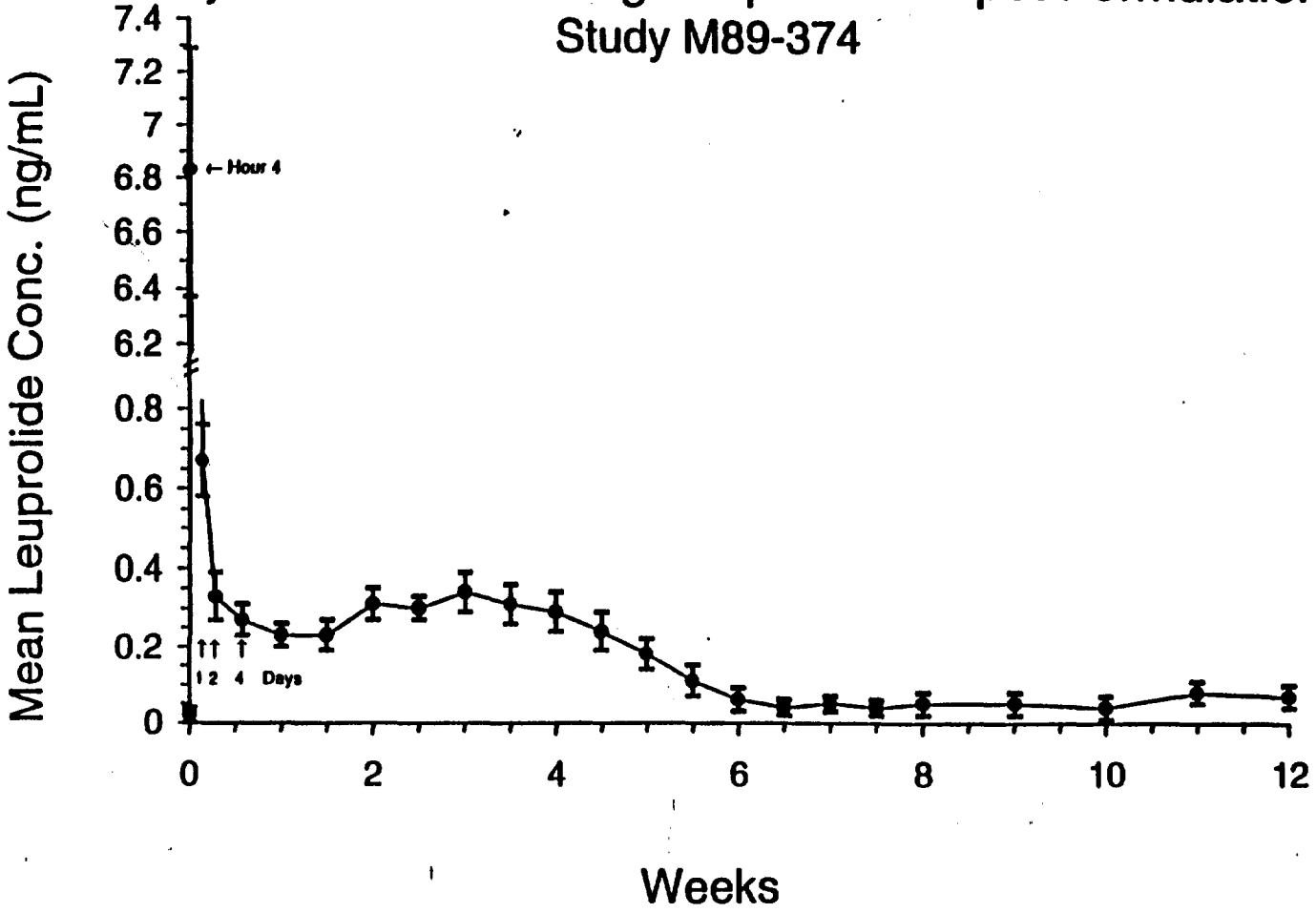
** Pre– and 4–hrs post depot injection

Appendix 1.
(One page)

Figure 2

Mean (± S.E.) Plasma Leuprolide Concentrations Following a Single Intramuscular Injection of a 3.75 mg Leuprolide Depot Formulation In Women

Study M89-374

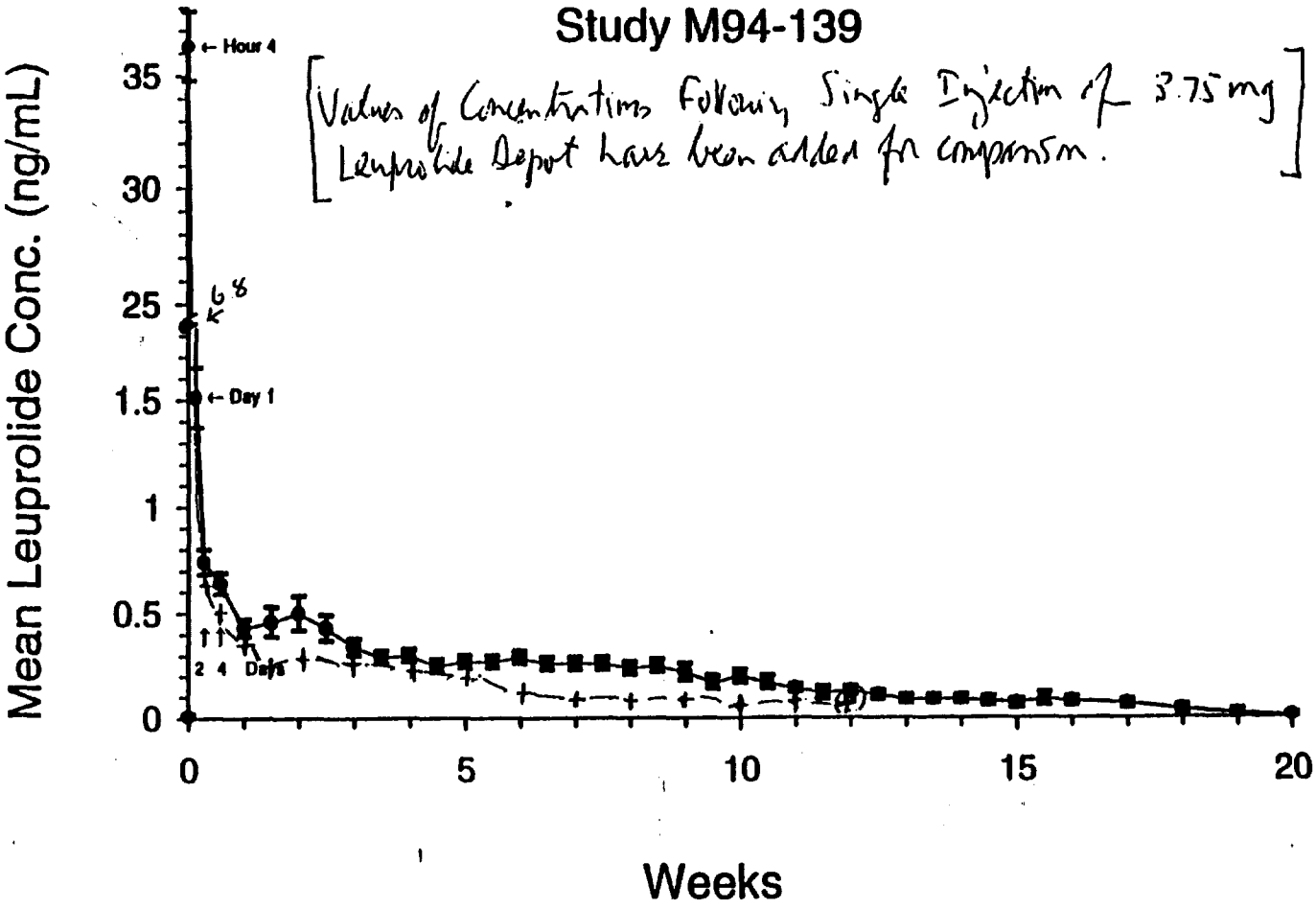


Appendix 2.
Figure 2.1.

Figure 1

Mean (± S.E.) Plasma Leuprolide Concentrations Following a Single Intramuscular Injection of a 11.25 mg Leuprolide Depot Formulation In Women

Study M94-139



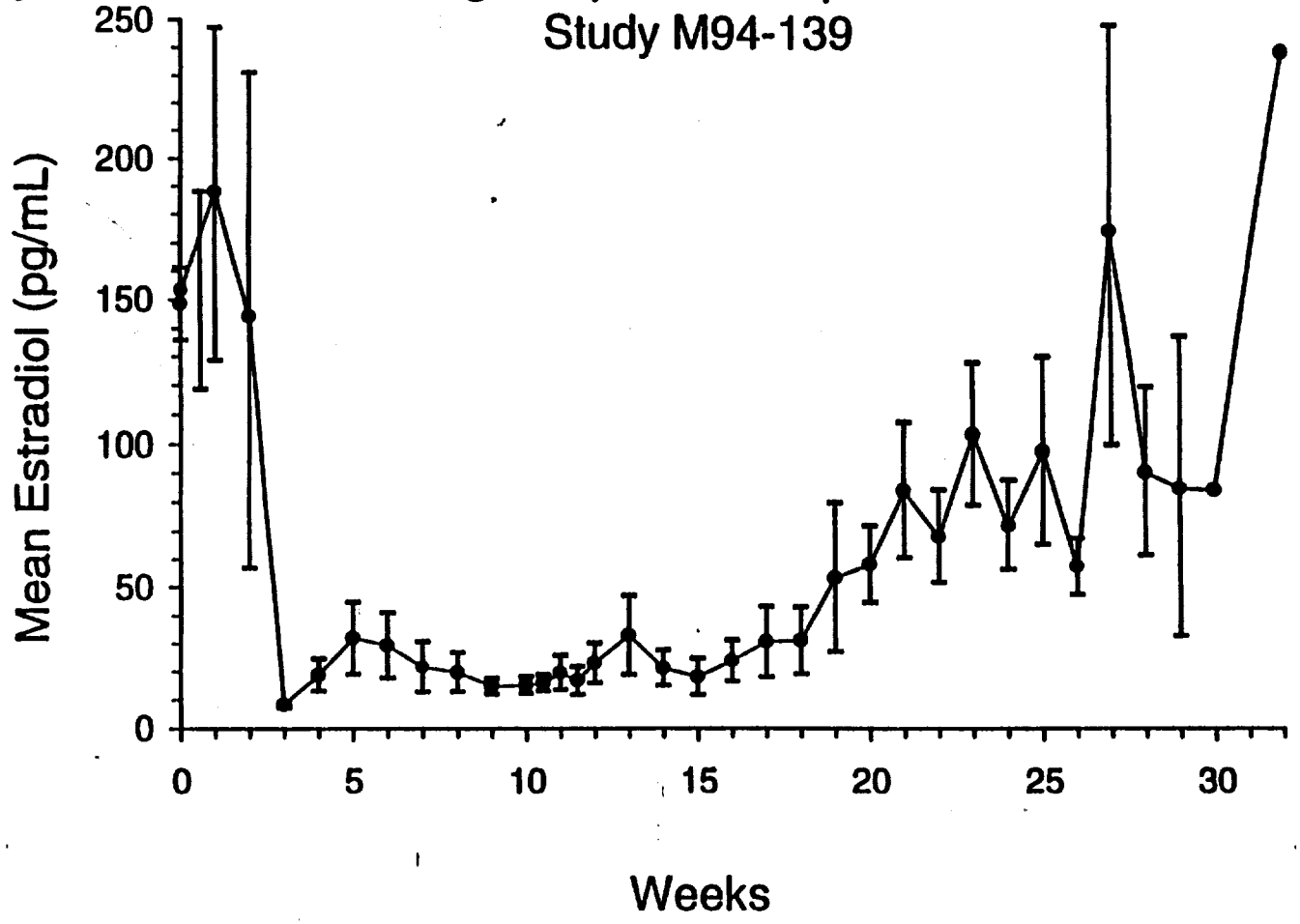
[Values of Concentrations Following Single Injection of 3.75 mg Leuprolide Depot have been added for comparison.]

Appendix 2.
Figure 2.2.

Figure 3a

Mean (± S.E.) Serum Estradiol Following a Single Intramuscular Injection of a 11.25 mg Leuprolide Depot Formulation In Women

Study M94-139

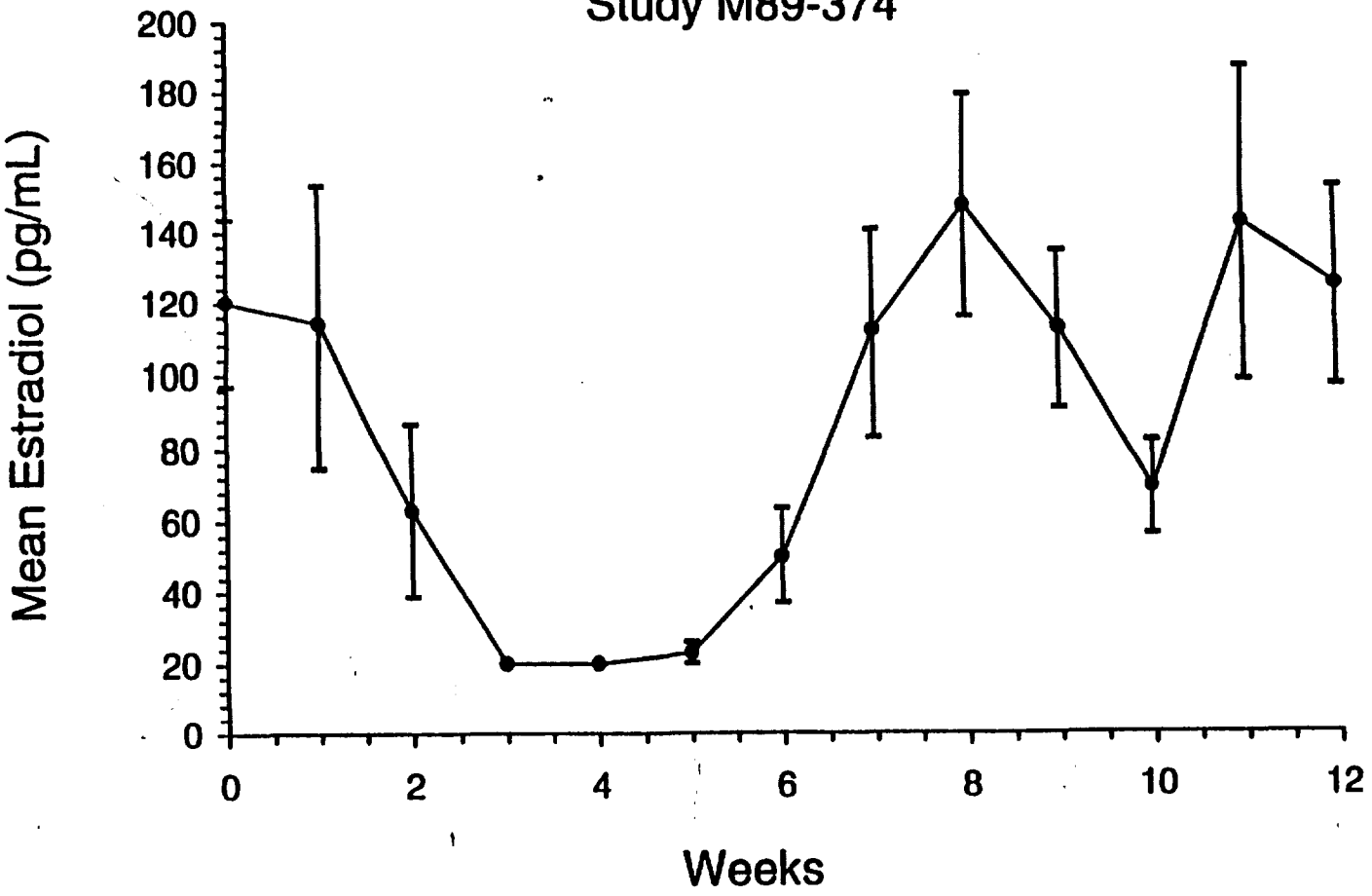


Appendix 3.
Figure 3.1.

Figure 7

Mean (± S.E.) Serum Estradiol Following a Single Intramuscular Injection of a 3.75 mg Leuprolide Depot Formulation In Women

Study M89-374



Appendix 3.
Figure 3.2.

Figure 12
Mean (± S.E.) Serum Estradiol in Endometriosis Patients During Treatment With 3 Monthly Injections of a 3.75 mg Leuprolide Depot Formulation
Study M86-031

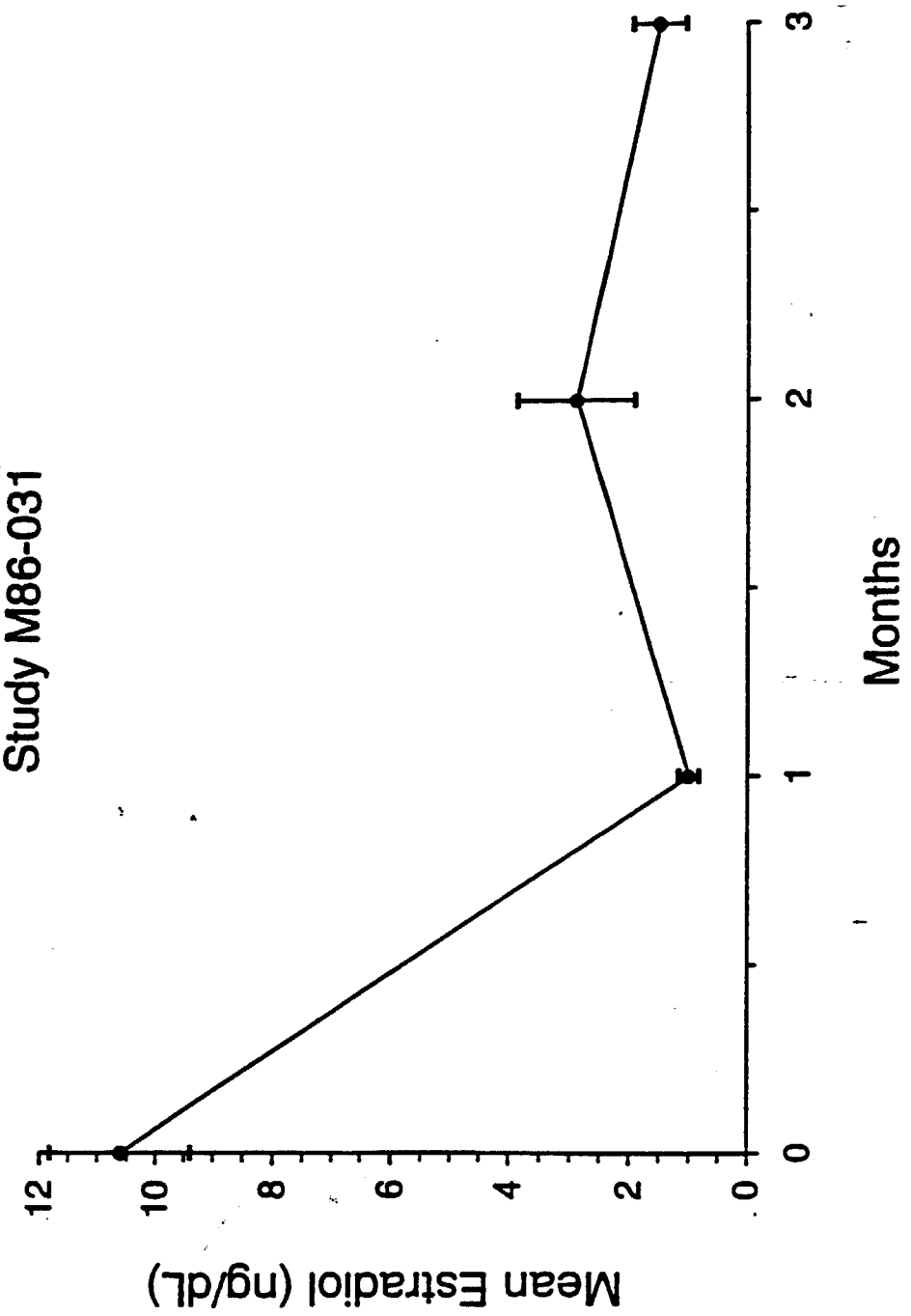
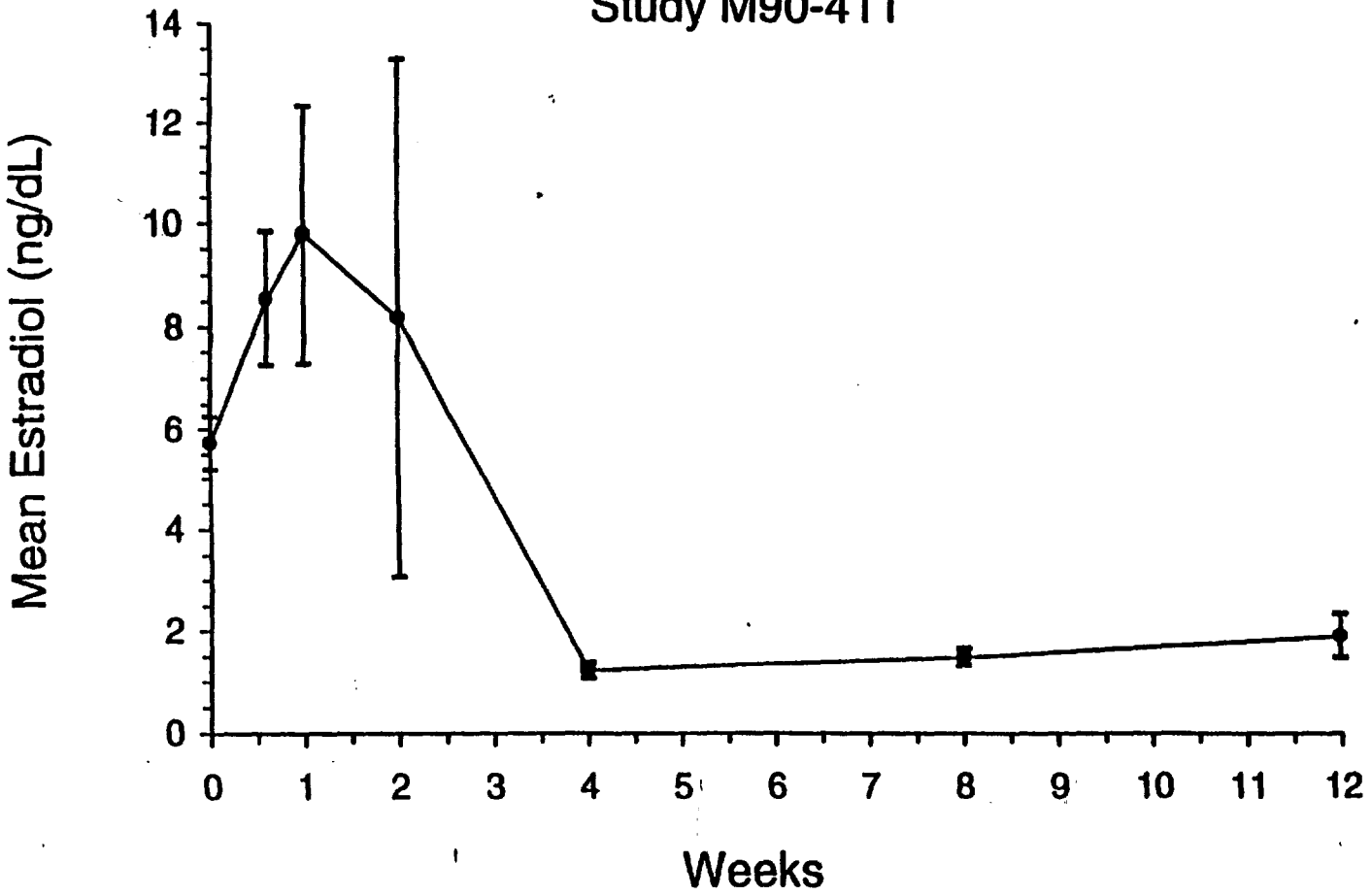


Figure 11

Mean (± S.E.) Serum Estradiol In Uterine Fibroids Patients During Treatment With 3 Monthly Injections of a 3.75 mg Leuprolide Depot Formulation

Study M90-411



Appendix 3.
Figure 3.4.