NDA

19010

AP LTR

NDA 19-018

TAP Pharmaceuticals, Inc.
Attention: Mr. Dean Sundberg
Abbo · Park
North .hicago, Illinois 60064

Gentlemen:

Reference is made to your new drug application dated December 20, 1983 submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for the preparat..n Lupron (leuprolide acetate) Injection, and to your resubmission dated May 4, 1984.

We also refer to your additional communications dated April 15, July 8, and December 22, 1983, February 1, March 7, April 23, May 30, September 20, October 5 and 24, and November 1 and 8, 1984.

We also acknowledge receipt of your submission dated December 19, 1984, that included a clinical safety update, the initial promotional material, and final printed labeling which, as requested by this Agency, deletes the Pediatric Use section.

The application was filed on December 19, 1984.

We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved, contingent upon your commitment to resolve in a timely manner the outstanding deficiencies with regard to the bioavailability data submitted for this product.

With regard to parts (8) and (9) of the application, we reserve comment as to the adequacy of the analytical methods proposed for the drug until the results of our laboratory tests on the samples submitted are available and have been evaluated. In this regard, it is understood from the telephone conversation on January 4, 1985 between your representative Mr. Dean Sundberg and Mr. Helmut Nunn of this Administration, that if these results indicate some modifications of the proposed methods are necessary before they can be accepted, or additional samples are required, you will submit such revised methods and/or samples if requested by the Administration.

The enclosures summarize the conditions relating to the approval of this application.

Please submit one market package of the drug when available.

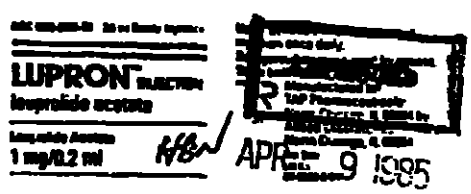
Sincerely yours,

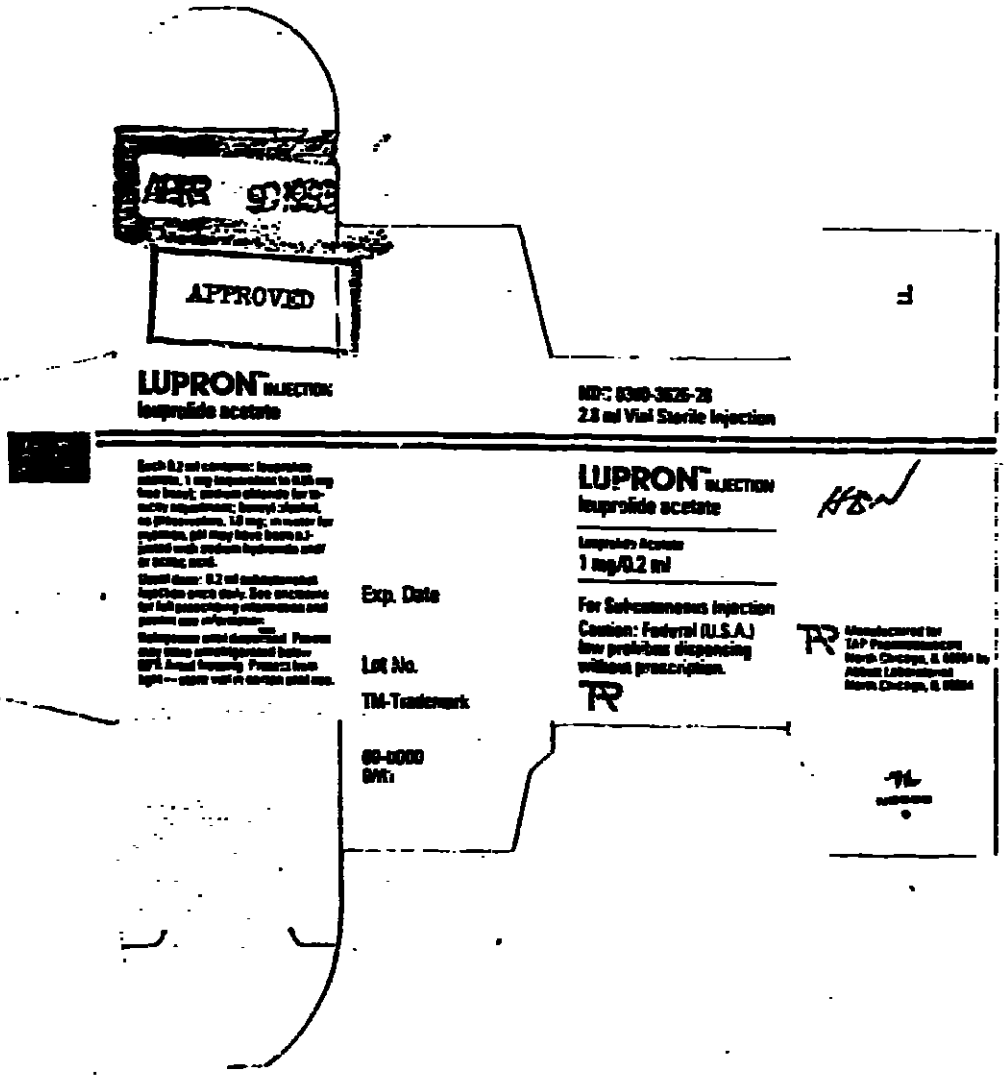
Elaine C. Esber, M.D.
Acting Director,
Office of Biologics Research and Review
Center for Drugs and Biologics

Enclosures: Records and Reports Requirement (Reg. 310.300)
Conditions of Approval of NDA

APPROVAL

LBLING


LUPRON
leuprolide acetate
1 mg/0.2 ml
APR 9 1985


APPROVED
LUPRON INJECTION
leuprolide acetate
NDC: 0300-3625-28
2.8 ml Vial Sterile Injection
LUPRON INJECTION
leuprolide acetate
1 mg/0.2 ml
For Subcutaneous Injection
Caution: Federal (U.S.A.) law prohibits dispensing without prescription.
Exp. Date
Lot No.
TM-Trademark
69-0000
BMI:

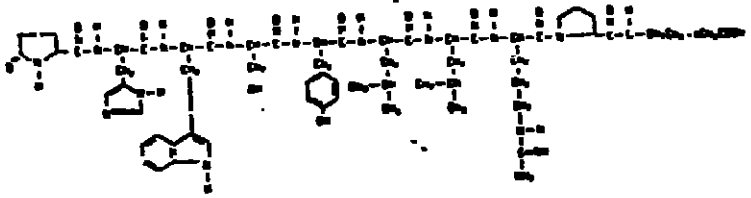
Rx: 3626/
80-8000-R2—Rev. April, 1985

LUPRON™

leuprolide acetate injection

DESCRIPTION

LUPRON (leuprolide acetate) is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The chemical name is 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



LUPRON is a sterile, aqueous solution intended for subcutaneous injection. It is available in a 2.8 ml multiple-dose vial containing 5 mg/ml of leuprolide acetate, sodium chloride for tonicity adjustment, 9 mg/ml of benzyl alcohol as a preservative and water for injection. The pH may have been adjusted with sodium hydroxide, and/or acetic acid.

CLINICAL PHARMACOLOGY

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy. Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs.

In humans, subcutaneous administration of single daily doses of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrogen and estradiol in pre-menopausal females). However, continuous daily administration of leuprolide acetate results in decreased levels of LH and FSH in all patients. In males, testosterone is reduced to castrate levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These decreases occur within two to four weeks after initiation of treatment, and castrate levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to three years.

Leuprolide acetate is not active when given orally. Bioavailability by subcutaneous administration is comparable to that by intravenous administration. Leuprolide acetate has a plasma half-life of approximately three hours. The metabolism, distribution and excretion of leuprolide acetate in man have not been determined.

INDICATIONS AND USAGE

LUPRON (leuprolide acetate) is indicated in the palliative treatment of advanced prostatic cancer. It offers an alternative treatment of prostatic cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient. In a controlled study comparing LUPRON 1 mg/day given subcutaneously to DES (diethylstilbestrol), 3 mg/day, the survival rate for the two groups was comparable after two years treatment. The objective response to treatment was also similar for the two groups.

CONTRAINDICATIONS

There are no known contraindications to the use of LUPRON.

WARNING

Isolated cases of worsening of signs and symptoms during the first few weeks of treatment have been reported. There is a report with another LH-RH analog where such worsening may have contributed to a rapid fatal outcome in two cases.

PRECAUTIONS

Patients with a metastatic vertebral lesion and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see "ADVERSE REACTIONS" section).

Patients with known allergies to benzyl alcohol, an ingredient of the drug's vehicle, may present symptoms of hypersensitivity, usually local, in the form of erythema and induration at the injection site.

Information for Patients: See information for Patients which appears after the "HOW SUPPLIED" section.

Laboratory Tests: Response to leuprolide acetate should be monitored by measuring serum levels of testosterone and acid phosphatase. In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. Castrate levels were reached within two to four weeks and were maintained were maintained for as long as drug administration continued. Transient increases in acid phosphatase levels occurred sometimes early in treatment. However, by the fourth week, the elevated levels usually decreased to values at or near baseline.

Drug Interactions: None have been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies were conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). In mice no pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 30 mg/day without demonstrable pituitary abnormalities.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

Clinical and pharmacologic studies with analogs similar to leuprolide acetate have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 30 weeks. However, no clinical studies have been conducted with leuprolide acetate to assess the reversibility of fertility suppression.

ADVERSE REACTIONS

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. This transient increase was occasionally associated with a temporary worsening of signs and symptoms, usually manifested by an increase in bone pain (see "WARNINGS" section). In a few cases a temporary worsening of existing hematuria and urinary tract obstruction occurred during the first week. Temporary weakness and paresthesia of the lower limbs have been reported in a few cases.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction which, if aggravated, may lead to neurological problems or increase the obstruction.

In a comparative trial of LUPRON (leuprolide acetate) versus DES, the following adverse reactions were reported in 3% or more of the patients:

	LUPRON (N = 98)	DES (N = 101)
	Number of Reports	
Cardiovascular		
Congestive Heart Failure	1	3
Edema (peripheral)	8	25
Thrombophlebitis/ Phlebitis/ Pulmonary Emboli	3	7
Central Nervous System		
Anxiety	0	3
Dizziness	6	4
Pain	5	3
Headache	5	2
Paresthesia	3	0
Endocrine		
Gynecomastia/ Breast Tenderness	3	40
Hot Flushes	51	11
Impotence	3	11
Gastrointestinal		
Anorexia	2	3
Constipation	3	1
Nausea/Vomiting	5	26
Musculoskeletal		
Bone Pain	3	1
Muscle Spasms	0	3

The following additional adverse reactions were reported in less than 3% of the patients in this study: *Cardiovascular* — tachycardia, arrhythmias, myocardial infarction; *Gastrointestinal* — gastrointestinal bleeding; *Hemic/Lymphatic* — decreased hematocrit and hemoglobin; *Integumentary* — erythema and ecchymosis at the injection site, rash, hair loss, itching; *Miscellaneous* — asthenia, increased BUN and creatinine, fatigue, fever, facial swelling; *Musculoskeletal* — myalgia; *Nervous System* — blurred vision, vertigo, insomnia, memory disorder, convulsions, numbness; *Respiratory* — difficulty breathing, pleural rub, worsening of pulmonary fibrosis; *Urogenital* — hematuria, decreased urine stream (probably due to the physiologic/pharmacological action of the drug).

OVERDOSAGE

In rats subcutaneous administration of 200 to 400 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart of this phenomenon. In early clinical trials with leuprolide acetate doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

Label: ONG
NDA No: 19-010 Rec'd. 4-30-85
H.B. 7
5-21-85

(N) 3626)
00-0000 R2 -- Rev April, 1985

LUPRON™

leuprolide acetate injection

HBN

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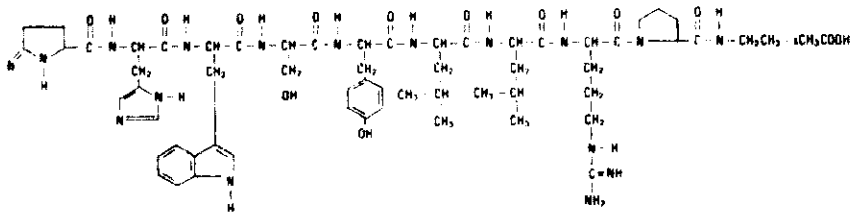

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Information for Patients: See Information for Patients which appears after the "HOW SUPPLIED" section.

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Clinical and pharmacologic studies with analogs similar to leuprolide acetate have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 20 weeks. However, no clinical studies have been conducted with leuprolide acetate to assess the reversibility of fertility suppression.

ADVERSE REACTIONS

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	LUPRON (N = 98)	DES (N = 101)
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Dizziness	6	4
Pain	5	3
Headache	5	2
Paresthesia	3	0
Endocrine		
Gynecomastia/ Breast Tenderness	3	49
Hot Flashes	51	31
Impotence	2	11
Gastrointestinal		
Anorexia	2	3
Constipation	3	1
Nausea/Vomiting	5	16
Musculoskeletal		
Bone Pain	3	1
Muscle Spasms	0	3

The following additional adverse reactions were reported in less than 3% of the patients in this study: *Cardiovascular* — cardiac arrhythmias, myocardial infarction; *Gastrointestinal* — gastrointestinal bleeding; *Hemic/Lymphatic* — decreased hematocrit and hemoglobin; *Integumentary* — erythema and ecchymosis at the injection site, rash, hair loss, itching; *Miscellaneous* — asthenia, increased BUN and creatinine, fatigue, fever, facial swelling; *Musculoskeletal* — myalgia; *Nervous System* — blurred vision, lethargy, insomnia, memory disorder, sour taste, numbness; *Respiratory* — difficulty breathing, pleural rub, worsening of pulmonary fibrosis; *Urogenital* — hematuria, decrease in testes size (probably due to the physiological/pharmacological action of the drug).

OVERDOSAGE

In rats subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart of this phenomenon. In early clinical trials with leuprolide acetate doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

DOSAGE AND ADMINISTRATION

The recommended dose is 1 mg (0.2 ml) administered as a single daily subcutaneous injection. As with other drugs administered chronically by subcutaneous injection, the injection site should be varied periodically.

NOTE: As with all parenteral products, inspect container's solution for discoloration and particulate matter before each use.

HOW SUPPLIED

LUPRON (leuprolide acetate) is a sterile solution supplied in a 2.8 ml multiple-dose vial, NDC 0300-3626-28. Refrigerate until dispensed. Patient may store unrefrigerated below 86°F. Avoid freezing. Protect from light – store vial in carton until use.

Each 0.2 ml contains 1 mg of leuprolide acetate, sodium chloride for tonicity adjustment, 1.8 mg of benzyl alcohol as preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

Revised: April, 1985.

U.S. Patent Nos. 4,005,063 and 4,005,194.

INFORMATION FOR PATIENTS

NOTE: Be sure to consult your physician with any questions you may have or for information about LUPRON (leuprolide acetate) and its use.

WHAT IS CANCER?

Cancer is a disease characterized by uncontrolled growth and spread of abnormal body cells. Normally, the cells that make up all parts of the body reproduce themselves in an orderly manner so that growth occurs, worn out tissues are replaced and injuries repaired. Occasionally, certain cells grow into a mass of tissue called a tumor. Some tumors are benign; others are malignant, or cancerous.

Benign tumors may interfere with body function and may require surgical treatment but they do not invade neighboring tissue and seldom threaten life. However, malignant tumors invade and destroy normal tissue. By a process called metastasis, cells break away from a malignant tumor and spread through the blood and lymphatic systems to other parts of the body where they form new tumors. Sometimes cancer grows and spreads rapidly; sometimes the process takes years.

One very common place for cancer to develop in men is the prostate gland.

WHAT IS THE PROSTATE?

The prostate is a male sex gland about the size of a chestnut. It lies just below the urinary bladder and surrounds the first inch of the urethra, the canal that carries urine from the bladder during urination. The secretion of the prostate provides part of the fluid for ejaculation.

TREATMENT OF PROSTATIC CANCER

Your doctor has a choice of treatments for prostatic cancer including surgery, radiation and drugs. The best choice for a particular patient usually depends on whether the cancer was found early or in an advanced stage.

The growth and function of the normal prostate gland is dependent upon the male hormone testosterone. If you have a prostatic tumor, its growth is usually stimulated by testosterone as well. For this reason, decreasing the body's supply of testosterone often controls tumor growth and relieves pain and difficulty in urinating.

The primary source of testosterone is the testes; therefore, one way to reduce production of testosterone is to remove the testes by surgery.

Another way is for men to take a female hormone, estrogen. This also causes the body to stop making testosterone. Estrogens have potential side effects such as swelling of the breasts, fluid retention, blood clotting problems, and decrease in libido and impotence.

Another choice is LUPRON which will also decrease testosterone production. LUPRON has potential side effects, such as hot flashes and decrease in libido and impotence. It may also initially aggravate signs and symptoms of your disease by temporary stimulation of the tumor during the first one to two weeks of treatment.

WHAT IS LUPRON?

LUPRON (leuprolide acetate) is chemically similar to gonadotropin releasing hormone (GnRH or LH-RH), a hormone which occurs naturally in your body.

Normally, your body releases small amounts of LH-RH, and this leads to events which stimulate the production of testosterone.

However, when you inject LUPRON (leuprolide acetate), the normal events that lead to testosterone production are interrupted and testosterone is no longer produced by the testes.

LUPRON must be injected because, like insulin which is injected by diabetics, LUPRON is inactive when taken by mouth.

If you were to discontinue the drug for any reason, your body would begin making testosterone again.

DIRECTIONS FOR USING LUPRON (leuprolide acetate)

1. Wash hands thoroughly with soap and water.
2. If using a new bottle for the first time, flip off the plastic cover to expose the gray rubber stopper. Wipe metal ring and rubber stopper with an alcohol wipe each time you use LUPRON. Check the liquid in the container. If it is not clear or has particles in it, DO NOT USE IT. Exchange it at your pharmacy for another container.
3. Remove outer wrapping from one syringe. Pull plunger back until the tip of the plunger is at the .2 mark.
4. Take cover off needle and push the cover into the appropriate hole in the Daily Dose Reminder area. Push the needle through the center of the rubber stopper on the LUPRON bottle.
5. Push the plunger all the way in to inject air into the bottle.
6. Keep the needle in the bottle and turn the bottle upside down. Check to make sure the tip of the needle is in the liquid. Slowly pull back on the plunger, until the syringe fills to the .2 mark.
7. Toward the end of a two-week period, the amount of LUPRON left in the bottle will be small. Take special care to hold the bottle straight and to keep the needle tip in liquid while pulling back on the plunger.
8. Keeping the needle in the bottle and the bottle upside down, check for air bubbles in the syringe. If you see any, push the plunger *slowly* in to push the air bubble back into the bottle. Keep the tip of the needle in the liquid and pull the plunger back again to fill to the .2 mark.
9. Do this again if necessary to eliminate air bubbles. Remove needle from bottle and lay syringe down on the syringe rest. DO NOT TOUCH THE NEEDLE OR ALLOW THE NEEDLE TO TOUCH ANY SURFACE.
10. To protect your skin, inject each daily dose at a different body spot.
11. Choose an injection spot. Cleanse the injection spot with another alcohol wipe.
12. Hold the syringe in one hand. Hold the skin taut, or pull up a little flesh with the other hand, as you were instructed.
13. Hold the syringe alongside the skin and slide the needle quickly just under the skin as far as it will go. Inject the drug by pushing in the plunger as far as it will go.
14. Hold an alcohol wipe down on your skin where the needle is inserted and withdraw the needle at the same angle it was inserted.
15. Use the disposable syringe only once and dispose of it properly as you were instructed. A waste area is provided in the LUPRON Patient Administration Kit. Needles thrown into a garbage bag could accidentally stick someone. NEVER LEAVE SYRINGES, NEEDLES OR DRUGS WHERE CHILDREN CAN REACH THEM.

SOME SPECIAL ADVICE

- You may experience hot flashes when using LUPRON (leuprolide acetate). During the first few weeks of treatment you may experience increased bone pain, increased difficulty in urinating, and less commonly but most importantly, you may experience the onset or aggravation of nerve symptoms. In any of these events, discuss the symptoms with your doctor.
- You may experience some irritation at the injection site, such as burning, itching or swelling. These reactions are usually mild and go away. If they do not, tell your doctor.
- Do not stop taking your injections because you feel better. You need an injection every day to make sure LUPRON keeps working for you.
- Use only the syringes provided in the kit, as other types may dispense an incorrect dose. If for any reason you cannot use one of the syringes, contact your doctor or pharmacist for advice.
- When the drug level gets low, take special care to hold the bottle straight up and down and to keep the needle tip in liquid while pulling back on the plunger.
- Do not try to get every last drop out of the bottle. This will increase the possibility of drawing air into the syringe and getting an incomplete dose. Some extra drug has been provided so that you can withdraw the recommended number of doses.
- Tell your pharmacist when you will need your next LUPRON kit so it will be at the pharmacy when you need it.
- This drug may be stored at room temperature (not above 86°F). Do not store near a radiator or other very warm place.
- Do not leave your drug or hypodermic syringes where anyone can pick them up.
- Keep this and all other medications out of reach of children.

Manufactured for TAP Pharmaceuticals
North Chicago, IL 60064, U.S.A.
by Abbott Laboratories
North Chicago, IL 60064

MOR

NDA 19-010
LUPRON
Leuprolide Acetate
TAP Pharmacetuticals/Abbott Labs.

Medical Officer's Review of ORIGINAL NEW DRUG APPLICATION Amendment No. 4, dated December 4, 1984, received DEcember 24, in this office, January 2, 1985.

Date of this Review: January 3, 1985

This Amendment consists of:

A. Clinical Safety Update,

B. Final Printed Labeling, including package insert, vial label and vial carton.

C. Initial Advertising and Promotional Material, and

D. Drug Experience Reports (1639s).

A. Clinical Safety Update:

Updating the Adverse REactions, which originally comprised from the study onset to 1/1/83, to 10/1/84, although changing the absolute numbers (making them, of course, larger) does not significantly change the differences between the Lurpon and DES groups. The sponsor's proposal not to change these figures for the present label are acceptable.

B. Final Printed Labeling

Conforms in every way with all matters specified and discussed here on September and October 18, and should be approved.

C. Initial Advertising and Promotional Material

The claims conform with the approved label.

D. Drug Experience Reports (1639s)

These have been reviewed with individual reports and will be tabulated at a later date to save time.

C.A. Schaffenburg, M.D.
1/3/85

JUL 6 1984

Medical Officer Consultation on NDA

NDA: 19-010

Applicant: Abbott Laboratories
TAP Pharmaceuticals

Date Consultation Request Received: June 21, 1984

Date Completed: July 2, 1984

Name of Drug: Leuprolide (L)

Category: Anticancer

Indication: "Palliative treatment of advanced prostate cancer.

General:

A. Objective tumor response in prostate cancer is a much softer efficacy parameter than with other tumor types. This is because most of the metastases are in bone which is a difficult site to assess for objective tumor response.

B. Time to treatment failure is also a rather soft efficacy parameter because of "A" above and particularly as measured in this NDA. In study M 81-017 patients are assessed at 12 week intervals, but chest X-ray and digital rectal exam were performed only if previously positive. Study terminations for A R's are treated by applicant as equivalent to disease progression. This biases the outcome in favor of L. In study M 80-036 patients in the DES group were examined every 6 months and the L group every 3 months, increasing the risk of finding earlier treatment failure in the latter group. Again chest X-ray and digital rectal exams were done only if previously positive.

C. The most reliable efficacy parameter is survival from start of treatment. One would anticipate a median survival of between two and three years in this group of patients.

Controlled Clinical Studies:

A. M 81-017 Randomized DES(N-101) versus L (N-98) in Stage D2 prostatic cancer with no prior chemotherapy or hormonal therapy.

1. The L group appears sicker regarding time from diagnosis of Stage D2 (62 days versus 133 days) and pre-entry acid phosphatase (22 versus 34).

2. Objective Tumor Response

DES has better CR + PR (46% versus 38%) and Cr + PR + stable is ~~equal~~ (85% versus 86%). ~~No statistical~~ analysis is submitted.

3. Time to Treatment Failure

Median follow-up for this parameter is approximately 30-40 weeks. Estimated median time to failure is between 40-50 weeks. There is no significant difference between the two treatment arms, but no statistical analysis is presented to show the power of the study to demonstrate a significant difference between the two treatment arms. In the opinion of the reviewing statistician, Dr. Leung, the data is not sufficiently mature to permit such analysis.

4. Survival from Start of Treatment

Median follow-up for this parameter is approximatley 80 weeks. Curves are still declining and median survival is expected between 2-3 years based on other studies. There is no significant statistical difference between the two treatment groups, but no statistical analysis is performed to show the power of the study to detect a difference between the two treatment groups. In the opinion of the reviewing statistician, Dr. Leung, the data is not sufficiently mature to permit such analysis. Since the time from diagnosis of Stage D2 to start of treatment was 62 days for the L group and 133 days for the DES group, it would be appropriate to correct for this by performing analysis of survival from date of diagnosis of Stage D2 disease.

5. Bone Pain and Analgesic Use

DES had better relief of bone pain during the study ($p = .031$) and also less analgesic use ($p = .126$).

B. M 80-036 Historical Control

DES or Orchiectomy (N-83) versus L (N-47) in Stage D2 prostate cancer with no prior chemotherapy or hormonal therapy.

1. Objective Tumor Response

L had better CR + PR (40% versus 22%, no statistical analysis), but the DES or Orchiectomy group had better CR + PR + STABLE (84% versus 72%, $p = 0.11$).

2. Time to Treatment Failure in Responders (CR + PR + STABLE)

This data was not updated for the historical control group in applicant's April 1984 submission. In applicant's original submission median follow-up appears to be approximately 30 weeks for the DES group and only 25% had failed. Thus no definitive analysis can be done because the data is not sufficiently mature. One wonders why applicant has not combined DES and orchiectomy patients as it did for the other efficacy parameters. One also wonders why only responders are being evaluated.

3. Survival From Start of Treatment

This data was not updated for the historical control group in applicant's April 1984 submission. In applicant's original submission the median follow-up for the DES or Orchiectomy group patients is approximately 40-50 weeks and L patients approximately 70 weeks. Median survival has not been reached. Curves are still declining and median survival is expected between 2 and 3 years based on other studies. There is no significant statistical difference between the two treatment groups, but no statistical analysis is performed to show the power of the study to demonstrate a difference between the two treatment groups Dr. Leung, the reviewing statistician believes the data is not sufficiently mature to permit such analysis.

C. Safety

In study M 81-017 DES (N-101) versus L (N-98) DES has 15 serious cardiovascular events versus 6 for L (vol. 4.1, page 80). Reviewer has not included peripheral edema as this is not comparable in magnitude to the other cardiovascular events. Note there was history of prior thrombophlebitis in 25% of DES patients versus 15% of L patients.

L causes a temporary increase in testosterone levels during the first two weeks of therapy associated with a temporary flare up of tumor related symptoms in approximately 10% of patients. In study M 80-036 9% of Leuprolide patients had transient increased bone pain, 4% transient worsening of performance status and 4% worsening of urinary obstruction.

Discussion:

NDA 19-010
LUPRON
Leuprolide Acetate
TAP/Abbott

Medical Officer's Review of Final Printed Label dated 1/3/85.

Date of this Review: April 1st 1985.

As fully discussed with the Oncology Advisory Committee at the meeting held on March 29, 1985, the printed LABEL conforms in every way with the specifications discussed before with the Metabolism & Endocrinology Division, with the following possible modifications:

1. INDICATIONS AND USAGE

After the last sentence, add " Present findings indicate that DES may present advantages for the treatment of pain due to bone metastases."

2. ADVERSE REACTIONS

The facts bare the statement as is because serum testosterone was only elevated in the first four days, going back to baseline values at the end of eight days and below (to 25% of baseline) by the end of the second week. By the fourth week serum testosterone levels were at castrate levels. Clinical signs of worsening bore out the above inasmuch as they occurred, for the most part, in the first week.

In my opinion, this Section requires no change.

The last paragraph, last sentence of this section already states that the decrease in testes size, observed in less than 3% of patients, is (probably) due to the physiological/pharmacological action of the drug. Data from innumerable studies in males, aimed at contraception, have shown this to be the case and the word "probably" may be omitted.

BIOAVAILABILITY REQUIREMENTS

I don't know what the deficiencies are in this area, but it would seem to me that evidence of a full castration effect should be enough to prove the drug's bioavailability.

RECOMMENDATIONS

The label should be approved as is with the addition only of the sentence above under INDICATIONS AND USAGE.

C.A. Schaffenburg, M.D.
4/1/85

NDA 19-010
LUPRON (Leuprolide Acetate) Injection
ABBOTT's LHRH Analogue

Medical Officer's Note concerning LABEL copy resulting from Nov, 1st, 1984 meeting and received Nov. 2, in this office, Nov. 5.

Date of this note: November 5, 1984

The submitted copy conforms with all agreed upon changes. Note the following:

1. When approval letter issues, sponsor must be notified that Page 4 of label must drop "Pediatric Use" statement as not applicable at present.

2. Adverse Reactions listed on Page 5 must be updated, as agreed.

C. A. Schaffenburg MD
C.A. Schaffenburg, M.D.
11/05/84

cc: NDA Orig
HFN-810
HFN-810/JGueriguian
HFN-810/CSchaffenburg/rde/11.5.84

MS
10/06/85

NOV 7 1984

NDA 19-010
Leuprolide Acetate

Abbott Laboratories
TAP Pharmaceuticals

Medical Officer's Summary of Submitted Data with NDA dated December 20, 1983, received in my Office January 4, 1984.

Date Review Began: January 9, 1984
Date Review Completed: March 1st, 1984

I. BACKGROUND

The IND which led to the present submission was originally with the Oncology Division, HFN-150, and transferred to us about two years ago. Following the periodic meetings with the sponsor, led to a general agreement concerning the parameters deemed necessary to assess safety and efficacy in order to obtain approval of an NDA.

At the time of our first meeting with the sponsor some of the study protocols had been concluded, namely studies in pre- and post-menopausal breast cancer patients, and although in light of our present knowledge of the mechanism of action of this and similar LHRH analogues, beneficial effects were not expected to be seen in post-menopausal women, it was agreed that data pertaining to such cases would be accepted merely to substantiate safety of the drug. The case applies too when prostatic cancer patients having had an orchiectomy before initiation of leuprolide therapy were selected for study.

The present review summary takes into account the breast cancer and post-orchiectomy data only as far as they may support safety of the drug.

This review concludes with a recommendation for the speedy approval of this submission.

II. COMPOSITION OF THIS NDA

This NDA consists of nineteen (19) volumes containing result of the clinical data supporting safety and efficacy of the drug for the treatment of cancer of the prostate. A summary of the pertinent clinical literature, list of participating investigators, proposed label, report of adverse drug experiences, form part of the 19 volumes. In addition there are three (3) volumes of microfiche Case Report Forms equivalent to what would be Volumes 20 to 137.

Results of all preclinical studies supporting this NDA were submitted on April 15, 1983, in seven (7) volumes.

APR 12 1984

III CLINICAL STUDIES IN PROSTATIC CANCER

A. Controlled Studies (Protocols M80-036 and M81-017

1. General Considerations

Largely due to ethical and practical considerations mostly only patients with Stage D2 prostatic cancer were chosen for study. These considerations had to do with the fact that it was felt unjustified to expose patients with earlier stages to an as yet unknown therapy, and also that, unfortunately, prostatic cancer is often not diagnosed till it has reached the metastatic stage.

It is now well established that LHRH agonistic analogues such as leuprolide, when given in large doses and for prolonged periods of time operate a "medical gonadectomy" in both sexes by suppressing the pituitary/gonadal axis. This suppression is obtained after an initial period of pituitary/gonadal stimulation of varied duration owing to the intrinsic agonistic effects of these drugs, effects which last until a "paradoxical" suppressive effect takes place. This initial period, usually not lasting more than four weeks and often less constitutes a present disadvantage which can only be overcome by additional methods which are not part of this NDA.

The above reasons make it clear why it could not be expected that the drug work in post-menopausal breast cancer patients or, for that matter, in post-orchiectomy patients. The sponsor has become aware of this and has used data in the breast cancer patients to support safety only.

Efficacy data have to do with two aspects of drug action,
a) evidence of pituitary/gonadal suppression as demonstrated by hormonal analyses, and
b) evidence of the effects of this suppression on tumor status.

2. Design of Studies

There were two controlled studies, both multicenter, most of them conducted by investigators in the U.S.A., although patients studied in Canada , Mexico, Greece, Japan and England, were included inasmuch as studies followed the same protocols.

Study M80-036

This was considered a Phase II, open, multicenter study to evaluate the safety, efficacy and endocrine effects of leuprolide in advanced prostatic cancer patients. One of its objectives was a dose titration. Patients were required to have a histologically diagnosed prostatic cancer unamenable to therapy by conventional methods.

Patients were required to have a performance status of 0 to 3, as defined below, and to meet a number of requirements which would permit an objective evaluation of disease progress. Patients who had had previous chemotherapy, major surgery (including prostatectomy), adrenalectomy or hypophysectomy, were excluded from study, but initially sixty (60) patients who had undergone an orchiectomy or received previous hormone therapy were included. After this all patients were required to be previously untreated.

The drug was administered daily by subcutaneous injection. Patients or members of their families were instructed to administer the injections at home. They were initially randomized to receive either 1 or 10 mg daily and evaluated at periodic intervals for efficacy. Patients evaluated as having no response (see Efficacy evaluations below), or experiencing progress of the disease on the tenth (10) or sixteen (16) week of therapy, received 20 mg/day. If disease progression continued they were dropped from the study.

The study was open and non-comparative. However, a retrospective control was obtained from the National Prostatic Cancer Project (NPCP), consisting of a group of DES/orchiectomy patients forming part of one arm of NPCP Prot. 1300.

Study M81-017

This was designed as a Phase III comparative study in which patients were randomized to leuprolide 1 mg/day or DES 1 mg t.i.d., 3mg/day/day)

Patients were also Stage D2 as for the previous study but they were required not to have had previous therapy, including orchiectomy or hormonal therapy. There was a conditional cross-over between the two groups, determined by side effects which were intolerable to the patient or signs of progressive disease.

Other enrolment requirements, such as performance status, lack of severe renal or hepatic disease, remained as for previous study.

B. Criteria for Efficacy Evaluation

These criteria included an assessment of androgen suppression by periodic hormonal determinations, and an assessment of disease progression (or lack thereof), which included periodic evaluations of subjective or objective changes according to a set of criteria established by the NPCP.

a) Hormonal determinations for Study M80-036 included FSH, LH, PRL, Testosterone (T), dihydrotestosterone (DHT) and cortisol. In some of the non-orchiectomized patients , androstenedione, 3-alphaandrostenediol, P and 17-OH P, and E2, were done in addition.

b) Objective Response Criteria

These have been established by the NPCP. They are based on changes in the bone scan, serum acid phosphatase and other areas of tumor involvement. They fall into four basic categories:

Complete Response (CR), which includes evidence of disappearance of tumor masses and other evidence of disease (osteoblastic, osteolytic lesions, evidence of liver involvement and general deterioration of patient status, such as weight loss).

Partial Response (PR), including a partial change in the above parameters.

Objectively Stable (NC), which comprises evidence that there has been no significant progress in any of the above parameters.

Progression (P), which would include all evidence that the disease has progressed, with the possible exception of an increase in acid phosphatase alone.

c) Subjective Response

This includes measurement of performance status and evaluation of pain according to a graded scale.

Performance status is assessed according to an Eastern Cooperative Oncology Group modification of the Karnofsky scale, which grades patient status on a scale from 0 (fully active) to 4, which is completely disabled and confined to bed or chair, with stages in between.

Bone pain was evaluated by patients in Study M80-036 as None, Mild (intermittent, controlled by analgesics); Moderate (requires regular use of analgesics/narcotics); and Severe- requiring regular use of narcotics.

The same was evaluated for patients in protocol M81-017 according to a combination of severity parameters as before, frequency (less or more than 50% of the time) and use of analgesics and /or narcotics as well as frequency of same

C. Criteria for the Evaluation of Safety

These included all accepted clinical and laboratory criteria followed at periodic intervals and compared to the baseline status of all of these parameters.

Because of the adenomatous changes found in the anterior pituitary of rats at very high leuprolide doses in the toxicity studies, patients were required to have periodic x-rays of the sella turcica.

Investigators were asked to report all adverse effects and to make an assessment as to whether they considered them to be possibly or probably drug related.

IV RESULTS

a) Study M80-036

A total of 118 patients were enrolled in this study. Thirty-one (31) had had a previous orchiectomy, 28 had been treated with DES or other hormones, and 59 had not been previously treated. Most (111) had Stage D2 disease, and seven (7) Stage C or D1. Eighteen (18) were considered non-evaluable for efficacy.

There were 83 patients in the DES arm of the NPCP 1300 study with previously untreated stage D2 disease which were considered evaluable, and 71 of them were in the study long enough to permit evaluation of objective response. They were compared to the previously untreated group of the present protocol. Pre-study characteristics were comparable in both groups with the exception that there were 21% of previously untreated patients in Protocol M80-036 with a performance status of 2 or worse as compared to 10% of patients in NPCP 1300.

b) Study M81-017

There were 199 patients, 98 of whom were randomized to leuprolide and 101 to DES. Five in the former group and six in the latter were considered non- evaluable for efficacy. Two additional patients were excluded from the analysis of objective response because the institution where they were studied lacked bone scan facilities. They were included in the analysis of subjective response. Thus, there were 92 leuprolide patients and 94 DES patients in the analysis of objective response. All patients were included in the analysis of safety data.

There were no statisticallly significant differences in pre-study characteristics between the two groups, with the exception of time from the date of diagnosis to date of treatment, which was longer for the DES patients.

V. EFFICACY

1. Endocrine Response

Because of the agonistic effects of leuprolide there was an initial rise in serum T and DHT, with the exception, of course, of the orchiectomized patients. Values in the untreated patients in both protocols, however, had returned to baseline by the eighth (8) day, were below baseline by week two (2) and had reached castrate levels by week four (4) (Table).

Testosterone (ng/dl)
Normal Range = 350-1030 ng/dl
Mean levels +- S.E.

Time in Study	Study M80-036	Study M81-017
Prestudy	360.1 +- 30.38	408.1 +- 23.44
Day 4	668.8 +- 75.32	*
Day 8	339.1 +- 52.60	435.5 +- 32.48
Week 2	125.4 +- 29.50	102.3 +- 11.75
Week 4	21.6 +- 3.16	20.4 +- 1.42

* Not required.

The mean testosterone and DHT levels for patients in both protocol studies appear in figures 1 to 4

2. Objective Response (Assessment of Tumor Status)

In order to ensure the impartial evaluation of data the sponsor held in house meetings with consultants and investigators to discuss cases in which classification of response was doubtful. When interpretation was difficult the rating was downgraded.

Since the control group (DES) for patients in M86-036 protocol were provided from the NPCP data of Protocol 1300, to make them comparable to the protocol study, only patients in both groups who had been on treatment long enough were evaluated for efficacy.

In Study M81-017 both groups, leuprolide and DES were studied simultaneously and therefore criteria for evaluation were the same for both. Patients who failed treatment shortly after enrollment either crossed over to the alternative treatment or dropped out of the study. The rate at which this occurred was different for the two treatment groups with more early failures for the DES group. Since the first objective response evaluation was scheduled for week 12, the analysis of response at this time would have artificially biased, increasing the favorable response rate for the DES patients. For this reason an analysis of objective response to the first treatment based only on patients who reached the week 12 evaluation does not adequately reflect the clinical response to treatment. Therefore the objective response analysis in this study consisted of a "No progression" category, which included the patients whose objective response was complete (CR), partial response (PR), or no change (NC), and a "Treatment Failure" category. This latter category included the patients with objective progression and those for whom an objective response evaluation was not possible because of early drug discontinuation resulting from severe adverse reactions, clinical progression, or death.

(The above premises, which are clinically valid, may not be so from a strictly statistical point of view, and this will form part of the final evaluation and recommendations concerning this NDA),

Study M80-036

Results are expressed in terms of patients showing no progression, which includes those with CR + PR + NC. The total percentage in this category for patients who had had previous treatment was 48%. For patients who had had an orchiectomy, this total was 23%.

The objective response in previously untreated patients appears in the following table:

	Objective Response				
	No Progression				
Study Treatment	CR	PR	NC	P	Patients
Leuprolide	1 (2%)	18 (38%)	15 (32%)	13 (28%)	47
DES/Orch.	1 (1%)	8 (11%)	51 (72%)	11 (15%)	71

The combined rates (CR + PR + NC) for the previously untreated stage D2 patients in the two groups, leuprolide and DES are, respectively, 72% and 84%, figures which are not statistically significant. By these criteria, therefore, the efficacy of these two forms of therapy is comparable.

Study M81-017

By the criteria stated above, 79 of the 92 evaluable patients on leuprolide (86%) and 80 of the 94 evaluable patients on DES (85%) had a favorable objective response (No Progression), therefore showing no difference between the two forms of therapy. These figures appear in the table below.

Initial Treatment	Objective Favorable Response to Treatment (No Progression)			Treatment Failures		
	CR	PR	NC	Obj. Prog.	Other*	Total
Leuprolide	1 (1%)	34 (37%)	44 (48%)	10 (11%)	3 (3%)	92
DES	2 (2%)	41 (44%)	37 (39%)	2 (2%)	12 (13%)	94

* Patients in this category were not on their initial treatment long enough for a Week 12 objective response evaluation.

Three of the evaluable patients on leuprolide and 12 on DES who discontinued their initial treatment before Week 12 were considered treatment failures for various reasons. Two on leuprolide because of adverse reactions or pain. Seven on DES because of adverse reactions, four died, and one had clinical evidence of progression

3. Duration of Response and Survival

i. Duration of Response

The duration of response was defined as the time from study entry, counted from the first dose, to the first evaluation of Progression for patients whose best objective response was CR, PR, or NC, with a cut-off date of 1/1/83.

The survival type functions were estimated using the Kaplan-Meier method and comparison between such functions were carried out using the Gehan-Breslow or the Mantel-Cox procedures.

Figures 5 and 6 represent the duration of response for patients in protocol M80-036 (previously untreated) and M81-017, respectively. Duration of response (in weeks) is plotted on the horizontal axis and the estimated percentage of patients favorably responding to treatment (CR, PR, NC) is plotted on the vertical axis. Since many of the patients were still responding at the cut-off time their actual response is only partially known. The estimated percentages are not generally equal to the percentages of such patients among all responders.

The curves for leuprolide and the NPCP group are not significantly different. The majority of responders at the time of data collection were still responding. An estimate of the median duration of response for the leuprolide groups is 93 weeks. The median for the NPCP group could not yet be estimated. The 75th percentile of the duration of response distributions are estimated to be 51 weeks and 35 weeks for the leuprolide and NPCP groups, respectively. That is, it is estimated that 75% of the patients responding favorably to treatment with leuprolide will have shown no evidence of progression for at least 51 weeks, while 75% of responders to treatment with DES or orchiectomy will have shown no evidence of progression for at least 35 weeks

Similar data for study M81-017 appear in Figure 6. Only evaluable patients with no progression who reached the Week 12 evaluation are included in this analysis. There were 79 such patients in the leuprolide group and 80 patients in the DES group. The Kaplan-Meier estimates of the distributions are shown in this figure. The two distributions are not significantly different.

The duration of response data were only partially known in some cases and these data were therefore censored. The degree of censorhip was 86% for patients on leuprolide and 93% for patients on DES

Study M81-017. Because of the conditional crossover design there was a large number of DES evaluable patients who did not reach the Week 12 evaluation due to adverse effects or other reasons. The "Time to treatment failure" therefore may more appropriately represent the duration of response for both treatment groups. Treatment failure was defined as follows: disease progression, termination of treatment due to adverse reaction, or death. Time to treatment failure was censored by the cutoff date for data analysis, patients who dropped out, or patients who crossed over for reasons other than adverse reactions or progression.

Figure 7 represents the Kaplan-Meier estimated distribution curves of the time to treatment failure for all evaluable patients, 93 for leuprolide and 95 for DES. There was no significant difference. ($p = 0.578$ using the Gehan-Breslow, and $p = 0.606$ using the Mantel-Cox test).

The Kaplan-Meier estimates of the distributions of duration of first treatment for DES and leuprolide are shown in figure 8. Since 77% of the patients randomized to leuprolide and 71% of the DES patients were still receiving their initial therapy, the validity of these estimates is questionable.

ii. Survival

Survival time data are incomplete as of the cutoff date for all studies and although the sponsor has made estimates of expected survival for all groups by methods used for handling censored data, these estimates, which seem to show no difference between treatment groups cannot be presently taken into consideration

4. Subjective Response

Difficult as it is to quantitate subjective responses they are most important in assessing how it is that the patient himself views the effects of therapy on his disease. Such consideration should be most times as important, if not more so, than mere estimates or data on survbival time by itself.

The most important parameters to assess subjective response are bone pain and performance status, as compared to baseline.

i. Study M80-036

Bone pain and performance status responses are summarized in Tables 5 and 6 for all evaluable Stage D2 patients and according to best response. Of the 94 evaluable patients 14 reported no bone pain throughout the study. Of the remaining 80, one experienced worsening of pain and 55 (69%) reported improvement during treatment. Among the previously untreated patients there was a difference of 28% in the rate of improvement of bone pain, favoring responders over non-responders, with a p value of 0.08. The orchiectomized or previously hormone treatment patients showed no difference between responders and non-responders.

Nine of the 94 patients had a normal performance status throughout the study. Seven of the remaining 85 (8%) reported deterioration and 44 (52%) reported improvement. Among the preciously untreated patients responders had a significntly greater rate of improvement in performance status than non-responders ($p = 0.001$). Previously treated patients showed no difference.

ii. Study M81-017

No statistically significant differences between tne DES and leuprolide treated patients were noted on the following variables: performance status, urinary signs and symptoms, and bone pain. Both groups showed a significant reduction in bone pain and analgesic use, and although DES patients showed a greater reduction in bone pain this was not accompanied by a decrease in analgesic use. Table 7 represents these data

5. Changes in Acid Phosphatase

Acid phosphatase decreased from prestudy levels in 86% of previously untreated patients, in 69% of the hormone-treated patients and in 57% of orchiectomized patients in Study M80-036. They increased in 12%, 27%, and 40% in those three groups respectively. There was no change in the remaining patients.

In Study M81-017, prostatic acid phosphatase or acid phosphatase values decreased at Week 12 in 70% and 85% of the patients initially on leuprolide or DES respectively. Ten percent of the patients treated with leuprolide and 5% of the patients receiving DES showed an increase in acid phosphatase at Week 12

6. Testosterone

Study M80-036

By day 8 and Week 2 only 48% and 7% of patients, respectively, had elevated testosterone levels, after which they remained at castrate levels for the rest of the study in all patients patients throughout the end of the study. Five of 55 previously untreated patients had a transient increase in bone pain at day 8, probably related to initial agonistic effect of leuprolide, and 2 of 55 worsening of performance status, probably for the same reason. both of which effects were no longer present at week 2. The same appeared to occur with signs and symptoms of urinary obstruction in two patients

ii. Study M81-017

Changes from baseline in testosterone, acid phosphatase, bone pain severity, and performance status compared for the DES and leuprolide groups at various periods of time are shown in Tables 8 through 11. Briefly summarized these changes are as follows:

Testosterone: Bearing in mind interassay variability, 34% of the patients on leuprolide had increased values over baseline at one week while only 2% of the DES patients showed such an increase. By the end of the second week however, levels of T were below baseline for all patients in both groups.

Acid Phosphatase: At Week 1, 25% of the patients on leuprolide and 20% of the DES group had an increase of 25% or more. By Week 4, 19% and 4% of leuprolide and DES patients, respectively, had elevated values, difference which is statistically significant. This difference, however, disappears by Week 12.

There were no apparent significant differences in Bone Pain and Performance Status between the two groups after Week 2.

7. Patients Who Crossed Over to the Alternate Treatment (M81-017).

As of data collection time 28 patients had crossed over to the alternate treatment. Thirteen patients crossed over from leuprolide to DES and 15 patients crossed over from DES to leuprolide. The reasons for these crossovers are summarized below:

Study M81-017, Reason for Crossover

Initial Treatment	Disease Progression	Adverse Reaction	Other	Unknown	Total
Leuprolide	10 (77%)	1 (8%)	1 (8%)	1 (8%)	13
DES	4 (27%)	10 (67%)	1 (7%)	0	15
Total	14 (50%)	11 (39%)	2 (7%)	1 (4%)	28

From this table it will become evident that most patients crossing over from leuprolide to DES did so because of disease progression while those crossing over from DES to leuprolide did so because of adverse reactions.

VI SAFETY

1. Laboratory Tests and Physical Findings

From the beginning of the study the patients were suffering from signs and changes characteristic of their age and of Stage 2 prostatic cancer. There were therefore many abnormal laboratory findings to begin with. There were no clinically significant changes during the study which the investigators could asttribute to the treatment with the exception of those listed below.

Study M80-036

Two patients had hypercreatinemia as a sign of obstructive uropathy which subsided after a week or two of treatment with leuprolide.

In Study M81-017 there were abnormal laboratory values considered to be drug related (leuprolide) by the investigator in two patients (222 and 311). One patient, evaluated NC had elevated alkaline phosphatase values at baseline which continued to increase during therapy. (It is not clear to this reviewer why an analogue such as leuprolide would affect this enzyme other than by failing to stop progress of the disease). The other patient, who had had a low hematocrit and hemoglobin level prestudy continued to show such low values and developed besides a temporary rise in BUN and creatinine, considered possibly drug related by the investigator. (The association to drug seems to me doubful again, other than by the factor mentioned before)

Adverse Effects

Since this may possibly be the most important advantage of this proposed treatment of cancer of the prostate, as discussed under the general discussion and recommendations, it is worth it to dwell on this subject in some detail.

In Study M80-036, 69/118 patients experienced adverse effects. The most frequently reported as hot flashes/sweating (41%). Such symptoms were higher (61%) in the previously untreated group as compared to 32% in the hormone treated and 10% in the orchiectomized patients.

Other frequently reported adverse effects were local reactions at the injection site (11%), and impotence, decrease libido and decrease in testicular size (all due to the mode of action of the drug which effects a "medical orchiectomy").

In Study M81-017, 79/101 patients initially on DES (78%) experienced one or more adverse reactions during their initial treatment. These 79 patients reported a total of 164 adverse reactions. Seventy-two of the 98 patients initially assigned to leuprolide (73%), experienced one or more adverse reactions during treatment. These 72 patients reported a total of 129 ARs. Reactions in both groups break down as follows:

Leuprolide, 98 patients, 52% hot flashes/sweating while only 11% of patients on DES reported such symptoms. On the other hand, gynecomastia and breast tenderness were observed in 49% of DES patients and only 3% of leuprolide patients. These are the most frequently reported adverse effects.

	Number Reported on Leuprolide (N=98)	Number Reported on DES (N=101)
Gynecomastia/breast tenderness	3	49
Hot flashes	51	11
Impotence*	2	11
Nausea/vomiting	5	16

+Many of the patients on both leuprolide and DES were impotent before starting treatment

Cardiovascular Adverse Reactions

Many of the patients had cardiovascular diseases before starting therapy.

In Study M80-036, CV-related effects were noted in four patients who were in the study longer than ten weeks: one patient died of acute MI; one experienced high BP and two experienced palpitations. The first of these patients entered with a history of cardiovascular disease. Additionally, four of the patients who discontinued treatment prematurely (before Week 10) did so for the following CV related reasons: progressive pre-existent cardiovascular disease and an acute subendocardial MI; pre-existent recurrent transient ischemic attacks; a cerebrovascular accident; and death from "pulmonary embolism, heart failure and possibly an acute MI." Edema was reported in the study in 15 patients, 11 of whom had a previous history of either edema (8 patients) or cardiovascular disease (3 patients). None of these cardiovascular related effects were reported by the investigators to be drug related.

In the comparative Study M81-017, the total of documented ARs (in both "Adverse Effects" and "Adverse Events" Case Reports) were as follows:

	Leuprolide N=98			DES N=101		
Reaction	Adverse Effects	Adverse Events	Total No. of Reactions	Adverse Effects	Adverse Events	Total No. of Reactions
Peripheral Edema	2	6	8	16	7	23
Thrombo/phlebitis	1	0	1	6	0	6
Congestive heart fail.	1	0	1	2	1	3
Myocardial inf.	1	1	2	0	1	1
Cardiac Arrhythm.	1	1	2	1	0	1
Pulm. emboli	0	0	0	1	0	1
Angina	0	0	0	1	0	1
CV cause of death	0	0	0	0	2	2
TOTAL			14			38

Differences in the incidence of peripheral edema and thrombophlebitis between leuprolide and DES patients had p values of 0.006 and 0.12, respectively. All of the patients in both groups who had an MI had a history of cardiovascular disease before starting therapy. One patient on DES developed pulmonary emboli.

As stated previously, both Study M80-036 and M81-017, showed the prevalent leuprolide related effects to be: hot flashes (100/216 patients), impotence /decreased libido (22/216), local skin reaction at site of injection (19/216), decrease in testes size and atrophic genitalia (16/216), and a skin rash in seven (7/216)

Leuprolide is therefore associated with a higher incidence of hot flashes and sweating, which are signs and symptoms of the "castration effect" of the drug, while DES treatment showed a higher incidence of thromboembolic phenomena, edema, nausea/vomiting, and gynecomastia/breast tenderness, all due to estrogenic effects.

VII. OTHER STUDIES

As indicated initially, there were other studiers, some of which have been compiled merely as a back up for safety.

a) Patient included in a Compassionate Protocol M82-037 were too few by the time of the cutoff date and are not considered here. They were all Stage D2 patients .

b) Study M83-018 . In an effort to prevent the initial stimulation due to the agonistic action of leuprolide, DES was given to the patients by two different methods: in one, DES, 3 mg/day, was given alone for a week before starting leuprolide, after which both drugs were given together for an additional week; the second method started with both drugs given together for a total of two weeks. After this fortnight therapy by both approaches leuprolide continued being administered as the sole therapy. Neither approach proved capable of suppressing the initial rise in testosterone. although the number of patients was small and the methods might deserve further exploration in order to determine whether initial exacerbation of symptoms may be prevented.

c) Breast Cancer Studies

Six Phase I STudies were performed in 48 patients to determine tolerance of the drug. The most frequently reported adverse reaction was a local reaction at the site of injection. There were some slight elevations of SGOT, SGPT, and alkaline phosphatase, considered by the investigators not to be clinically significant.

Phase II Studies in pre- and post-menopausal breast cancer patients in a total of 100 such patients, although showing a possibly significant improvement (44% partial response, 20% objectively stable) were not pursued further. A "medical castration" effect was seen as shown by the "down-regulation" of gonadotropins with parallel decreases in estrogen and progesterone. Side effects consisted of local reactions at the injection site (31%), nausea and vomiting (16%), and hot flashes (14%).

VIII. OVERALL CONCLUSIONS AND RECOMMENDATIONS

A. EFFICACY

In order to put the following conclusions and recommendations in perspective there are two facts which must be kept in mind: firstly, that when this project was transferred to HFN-130, frequent, periodic meetings with the sponsor were held, at which times presentations of available data were done, whereby it became evident that leuprolide therapy was an effective method of producing a "medical orchiectomy"; and, secondly, that when this became evident, the sponsors were encouraged by our Division to make an early application for drug approval. From these two facts it emerges that some of the data presented with this NDA are necessary imccomplete since in many cases a majority of patients were still in therapy by the cutoff date of 1/1/83. This is an inevitable consequence of having an early application and it was understood by both the sponsors and our Division.

From the above it will become evident that some factors, perhaps critical for a definitive evaluation of this form of treatment for prostatic cancer, cannot at present be totally assessed in a manner which two or three years down the road might appear somewhat different. I don't believe, however, that such eventual differences will change some fundamental facts, and neither do I believe that awaiting such final evaluation in order to approve this new therapy would serve any useful purposes while depriving a good number of prostatic cancer patients of a therapy which I find advantageous, an opinion which I have found shared by a number of investigators with greater expertise than mine in this area.

And now lets see what blanks we may still find in this application as it now stands. Since most patients in Protocol M81-017 were still undergoing treatment by the cutoff date (and this is perhaps the most important study, being a parallel comparative study between the presently accepted therapy with DES and the study drug), conclusions regarding duration of remission or favorable response cannot be arrived at with confidence. Neither can we place any credence, again defendable with confidence, in any projections, by whatever statistical methods, of possible survival time by either DES or leuprolide treated patients. I am therefore disregarding these projections. Survival time, however, important as it is in the long run may become less so from a sound clinical point of view when one considers in addition the effect of either drug on the <u>quality of life</u>. And this latter factor, still impossible to assess in its entirety at present, may nevertheless emerge if only as a scumble from the side effects picture examined later under <u>Safety</u>.

Another drawback of the studies, recognized by the sponsors, is that the time from diagnosis to treatment was less for the leuprolide patients than for the DES group. Important as this factor may be it does not seem to have played a significant effect on the final results as presently evaluated. At any rate, patients in both groups suffered from what is, for all practical purposes, the final stage of a serious disease

From the point of view of efficacy alone, therefore, all we may safety conclude at present from the data presented, and bearing in mind the above caveats, is that leuprolide therapy of Stage D2 cancer of the prostate patients appears to be as effective as the presently accepted therapy by either surgical castration, or DES, or both

B. SAFETY

Following C. Huggins' basic studies in the forties on the effect of castration on prostatic structure and function, both castration and DES have remained the basic approach to the treatment of cancer of this gland. Both treatments, some times used together, are considered efficacious as a palliative approach. As a potent estrogenic substance, however, DES achieves a "medical castration-like" effect (lowering gonadotropins and testosterone secretion) at the expense of a number of serious side effects, particularly of a cardiovascular nature. Thus, thromboembolic phenomena, both deep vein and coronary, are known to be complications of DES therapy. Other side effects of DES which, while less serious are nevertheless contributing to a less acceptable quality of life in patients already burdened by old age and poor cardiovascular systems, are gynecomastia, sometimes painful, and nausea and vomiting. And it is here that a favorable picture emerges when therapy with leuprolide is compared with that of DES, where all of the above complications of DES therapy were shown not to be present or else attributable to leuprolide in this patient population already at risk. This becomes evident when one compares the reasons for switching therapy recorded for patients given that option under protocol M81-017, which was due to disease progression in patients with leuprolide going to try DES and to adverse effects in the DES patients switched to leuprolide.

C. FINAL REQUIREMENTS AND RECOMMENDATIONS

Given all the above considerations it seems clear to me that the following conclusions and recommendations are justified:

1. That leuprolide presents an acceptable and probably advantageous alternative to the present methods of treating cancer of the prostate, to wit, DES and/or surgical castration,

2. That it has significant advantages over surgical castration in that the psychologically traumatic effect of removal of the testes is allayed, particularly when, as is the practice, prosthetic replacement is done.

3. That it also presents significant advantages over DES therapy from the point of view of avoiding the drug induced serious side effects, such as the thromboembolic phenomena, and lack of other systemic, though less serious side effects, such as gynecomastia and nausea/vomiting which further compromise the already poor quality of life of prostatic cancer patients.

4. That while a final assessment of the definitive role of leuprolide therapy in cancer of the prostate may not yet be confidently established from the point of view of survival time, it nevertheless offers significant advantages to permit this treatment to occupy a place next to other presently accepted forms of therapy.

Future studies will have to assess, not only the eventual effect of leuprolide therapy on survival time and quality of life, but also to look for possible means of avoiding the initial agonistic, stimulatory effects of the drug, present for two to four weeks, which are, if nothing else, painful or disagreeable to the patient. To this effect, too, early approval and use of the drug in current urological practice, will serve not only the above purposes but also permit use of the drug in the earliear stages of the disease, thus allowing for a better understanding of its final role in treatment of this condition

Thus this FINAL RECOMMENDATION may be made:

That the present NDA for leuprolide treatment of cancer of the prostate be speedily approved with the modifications I hereby propose for the LABEL as attached, and,

That the sponsor be requested to submit, in one or two years' time, the additional data on survival and patient quality of life, as compared to DES therapy.

PROPOSED LABEL CHANGES

TRADEMARK (To be Determined)

DESCRIPTION
TRADEMARK (leuprolide acetate ijection) is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone, as measured by a number of clinical and pharmacologic tests. Because of this greater potency, when given in high doses and for prolonged periods of time, it exerts a "paradoxical" inhibition of suppression of the pituitary/gonadal axis in both sexes. The chemical name is 5-oxo....etc., acetate with the following structural formula:

Insert formula.

TRADEMARK is a sterile, aqueous solution intended for subcutaneous injection. Leuprolide is not active when given orally. It is available in multiple dose vials containing 5 mg/ml of leuprolide acetate, sodium chloride for tonicity adjustment, 9 mg/ml of benzyl alcohol as a preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

CLINICAL PHARMACOLOGY
Delete this first paragraph at bottom of Page 2. Otherwise this whole section remains as is.

INDICATIONS AND USAGE

TRADEMARK (leuprolide acetate) is indicated in the palliative treatment of advanced prostatic cancer. Leuprolide offers an important alternative to treatment with estrogens such as DES in view of these drugs known adverse effects on thromboembolic and other cardiovascular phenomena in a population already at high risk because of age and existing malignancy. Patients with Stage D2 prostatic cancer have shown marked objective and subjective improvement after treatment with leuprolide. In a controlled clinical study comparing TRADEMARK, 1 mg/day given subcutaneously, to DES, 3 mg/day, 86% of the patients on leuprolide and 85% of the patients on DES had a favorable objective response to treatment. Reports of treatment of Stage D2 prostatic cancer patients for a period of up to two years to date have not shown an association of this form of therapy with the cardiovascular side effects known to occur with drugs such as DES.

CONTRAINDICATIONS

There are no known contraindications to the use of leuprolide.

PRECAUTIONS

General: As is, and add, at the end of this paragraph, after (See ADVERSE REACTIONS section): Patients known to have an allergy to benzyl alcohol, which is an ingredient of the drug's vehicles, may present symptoms of hypersensitivity, usually local, in the form of erythema and induration.

Information for Patients: As is

Laboratory Tests: Third line down: delete "non-orchiectomized, otherwise as is.

Carcinogenesis, Mutagenesis, Impairment of Fertility: As is, with the exception of last paragraph under this section, which must be substituted for the following:
Clinical and pharmacologic studies with similar analogues have shown a full reversibility of fertility suppression when the drug is discontinued after after continuous administration for periods of up to 20 weeks.

Pediatric Use: Delete

ADVERSE REACTIONS

As is.

OVERDOSAGE

In rats, subcutaneous administration of 250 to 500 times the recommended human dose results in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart to this phenomenon. In early clinical trials with leuprolide doses as high as 20 mg/day for up to two years caused no adverse effects differing from the recommended 1 mg/day dosage.

DOSAGE AND ADMINISTRATION
As is.

HOW SUPPLIED
As is.

INFORMATION FOR PATIENTS

WHAT IS CANCER?
As is

WHAT IS THE PROSTATE?
As is.

TREATMENT OF PROSTATIC CANCER

As is with the exception of the last line of the fourth paragraph down, where "progressive hardening of the arteries" must be substituted by "blood clotting problems".

WHAT IS TRADEMARK?

As is, with the exception of the second paragraph, which should read:

"Normally, your body releases small amounts of GnRH, and this sets in motion events which stimulate the production of testosterone as well as scimulate the production of sperm. However, when you inject TRADEMARK daily, the normal events that lead to testosterone and sperm production are interrupted and testosterone is no longer produced in the testes. TRADEMARK must be injected because, like insulin, it is inactive by mouth

(The underlined sentences, to be inserted, need not be underlined in the final copy).

DIRECTIONS FOR USING TRADEMARK

As is.

SOME SPECIAL ADVICE

As is.

C. A. Schaffenburg, M.D.

C.A. Schaffenburg, M.D.
This Complete Review and Document finished on March 28, 1984.

cc:
HFN-130
HFN-220
HFN-130/CASchaffenburg/3/28/84
Wang No. 3803C

I recommend approval, but for alternate, palliative treatment. Also, I would like to read the statistician's review & recommendations. Finally, the firm should send us a formal protocol for a Phase IV study of survival and/or quality of life. The protocol, approved by us, would be appended to the approval letter and made ~~contingent~~ conditional part of that approval.

PHARM

NDA 19-010

Review #1

TAP Pharmaceuticals
Abbott Park
North Chicago, Ill

March 1, 1984

Submission: December 18, 1983

Review and Evaluation of Pharmacology and Toxicology Data

Drug: Leuprolide acetate (Abbott-43818; D-Leu^6, des-Gly-NH$_2^{10}$, Pro-ethylamide^9)-GnRH, an agonist of LHRH.

Related: ---

Indication: Prostatic carcinoma

Dosage: 1 mg/day sc (20 ug/kg)

A considerable number of pharmacology studies were performed which revealed that leuprolide acts as a LHRH agonist and has the expected paradoxical effect of both stimulation and inhibition of pituitary gonadotropin release. Studies with leuprolide as an anti-tumor agent are reviewed in detail.

Anti-tumor animal studies with leuprolide

Use of Abbott-43813 as treatment of prostatic carcinoma in the androgen-dependent Noble Rat.

Final progress report August 1, 1980.

Animals: Six groups of 25 rats/group.
- T_1 control (no treatment)
- T_2 castrate
- T_3 A-43813 20 ug BID
- T_4 A-43813 20 ug BID plus testosterone (T)
- T_5 A-43813 100 ug BID
- T_6 A-43813 100 ug BID plus T

Animals received 1 mm^3 transplants sc. When tumors reached about 32 mm^3, treatments were initiated and continued for 12 weeks. Testosterone was administered in 2 cm silastic implants.

Organ weights: Groups T_3 and T_5 exhibited a dose-dependant weight suppression of the testes, prostate and seminal vesicles. Administration of T reversed the weight suppression of the prostate and sv but not the testes.

Gonadotropin levels: Serum prolactin levels were elevated in groups T_3 and T_5 and this elevation was potentiated by T administration. Serum LH levels were elevated at 3 wks in the treated groups but levels fell below basal at 6 wks. Only the HD group showed continued LH suppression. T administration prevented the initial LH increase and potentiated the suppression at 6 and 12 wks.

Testosterone levels: T was increased by treatment at 3 wks and suppressed at 6 and 12 wks.

Acid phosphatase: Treated groups had lowered AP values at 3, 6 and 12 wks. T administration produced variable results.

Tumor growth: At 12 wks, tumor volume was less in the HD group than in the untreated control but remained larger than the castrate control group. T treatment did not increase tumor volume. Due to variability in tumor volume at the beginning of the study, tumor growth kinetics were used as the method of analysis. With this method the tumor growth rate in the HD was the same as in the castrate controls. T administration did not alter the drug effect.

Histology: Sections of various tissues showed no consistant qualitative differences between treatment groups. The testes were not examined.

Interim report on the effects of leuprolide on the R3327-G rat prostatic adenocarcinoma.

Animals: Copenhagen x Fisher F_1 hybrid rats. 15 males/group

1 control (untreated)
2 orchiectomized
3 A-43818 1 ug/kg/day sc
4 A-43818 50 ug/kg/day sc
5 A-43818 1000 ug/kg/day sc

Animals were implanted with 2×10^7 R3327-G rat prostatic adenocarcinoma cells sc. Treatments commenced 14 days after implantation and continued for 20 days.

Treatment with leuprolide produced a dose-related decrease in serum T and testes weight. At the HD, there was a significant reduction in tumor growth rate when compared to untreated controls but the growth rate reduction was less than in the castrate group. No significant decrease in tumor weight was observed in the leuprolide treated groups. Survival was enhanced by leuprolide at the HD over untreated controls.

Toxicology

Acute SC Toxicity Study of Abbott-43818 in Mice and Rats. Study No. 75-313.

The LD_{50} in male and female mice and rats is greater than 100 mg/kg sc.

Three-Month Toxicity of Abbott-43818 in Rats. Study No. 75-473.

Subcutaneous administration of 1, 2 or 4 mg/kg Leuprolide to rats resulted in reduced food consumption and growth in males and increased growth in treated females. In treated females, water consumption was increased with an increase in urine output and a decrease in osmolality and specific gravity. Significantly increased adrenal weight was observed in all treatment groups. Atrophic changes and decreased weight were observed in both male and female reproductive organs. Two additional 3-month toxicity studies in rodents were performed using doses of 10, 30, 100 and 300 mg/kg (rats, study no. T78-092) and 20, 60, 200 and 600 mg/kg (mice, study no. T77-509). In rats, these high doses produced marked skin necrosis at the site of injection and hyperplasia and hypertrophy in the pituitary. In mice, Leuprolide administration produced necrosis at the injection site, increased serum cholesterol in the 20, 60 and 200 mg/kg groups and hypertrophic cells in the pituitaries of female mice treated with 200 mg/kg. Castration cells were frequently seen in the low dose groups. The maximum tolerated dose was calculated to be 60 mg/kg.

Effect of Two or Seven Days of SC Administration of Abbott-43818 on the Testes of Rats. Study No. 76-129.

Rats were treated with 1 mg/kg/day Leuprolide for 2 or 7 days and sacrificed immediately following treatment or after a recovery period of seven days. Testes were examined grossly and histologically.

The testes from treated and recovery rats weighed less than controls except for those rats treated for 2 days without a recovery period. The testes showed various degrees of testicular degeneration which were detectable within 2 days. The severity of the lesions were greater in testes of rats sacrificed 7 days after cessation of treatment indicating that the effects continued after drug withdrawal.

Two-Year Combined Chronic Toxicity and Carcinogenicity Study of Abbott-43818 Administered SC to Rats. Study No. TA78-537, October 1, 1981.

Six-month interim report.

Sprague-Dawley rats were administered 0.6, 1.5 and 4.0 mg/kg/day Leuprolide acetate. Drug effects included necrosis at the injection site, decreased bw gain in MD and HD males and generally greater bw gain in treated females. RBC count, hematocrit and hemoglobin levels were higher in treated females than in controls as was urine protein levels. Mean alkaline phosphatase values for the two high dose group females was elevated over control values and SGOT and SGPT were higher in HD females than controls. Serum glucose and cholesterol were significantly higher in treated than untreated females. In males, serum Na was lower in the treated groups and significant differences in SGOT and bilirubin levels occurred between groups with no apparent treatment or dose relationship.

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Organ weight changes in males included increased adrenal weights and decreased weight of liver, kidney and primary and secondary sex organs. In females, treated rats exhibited greater body and adrenal weight, decreased relative heart, relative kidney, brain, pituitary and reproductive organ weights. Microscopic observations included the expected atrophic effects on the reproductive organs. The testes had evidence of interstitial fibrosis and calcification of the seminiferous tubules. There was a general increase in the amount of fat (decreased cellularity) in the bone marrow of the spinal column of treated males and females.

Twelve-month interim report.

Although significant differences between treated and control groups occurred in a variety of clinical chemistry and hematology parameters, these differences were scattered and not dose-related and probably not treatment-related. Mean hematocrit, hemoglobin and RBC count were higher in treated females than in controls. Treated females also exhibited lower urea nitrogen, total serum protein and albumin. Increased serum alkaline phosphatase and cholesterol occurred in females of the high dose only. Bone marrow hypocellularity was present in treated animals. Organ weights were as expected with decreases in the reproductive organs. Pituitary weight was increased in males and decreased in females with the first appearance of adenomas.

24-Month Final Report.

Scab/edema formation and alopecia at the injection site was common in the treated groups. In general, treated males gained less and treated females gained more weight than controls during the course of the study although at the end of the study (day 720) HD females weighed less than controls.

Mear hematocrit, hemoglobin and RBC counts were increased over control values for all treated females. In MD and HD males, white blood counts were lower than controls and in 6 of these animals, there was bone marrow hypocellularity. No other drug-related changes were observed.

Testicular seminiferous tubule degeneration, necrosis and mineralization was prevalent with an incidence approaching 100% in each treatment group although the control group had an incidence near 50%.

Bone-marrow hypocellularity was present only in treated animals (68% LD, 72% MD and 58% HD females and 4% LD, 16% MD and 26% HD males) which seemed to be due to an increase in fat without qualitative deterioration of the cellular marrow. This effect is drug related and was explained by the sponsors as being a physiologic response to the hormonal activity of Leuprolide. The significance of this finding is not readily apparent in light of the elevated hematocrit, erythrocyte and hemoglobin values seen in treated females.

Organs with significant numbers of tumors are tabulated below.

	Dose (mg/kg/day)			
	0	0.6	1.5	4.0
Pancreas				
Islet-cell adenoma				
females	1/99	10/50	6/50	4/50
males	8/100	8/50	2/50	2/50
Testes				
interstitial-cell adenoma	3/100	7/50	6/50	2/50
Pituitary adenoma				
females	30/100	29/50	41/50	42/50
males	22/99	35/50	38/49	46/50

Three-Month Dose Ranging Toxicity Study of Abbott-43818 Administered SC to Mice. Study No. T77-509.

Groups of 10 male and 10 female ICR mice were injected daily with 20, 60, 200 and 600 mg/kg Leuprolide. A significant treatment-related increase in serum cholesterol was noted in the MD and HD males and LD and HD females. No other dose or treatment-related changes were seen in any of the hematology and clinical chemistry parameters. Absolute and relative kidney weights were lower in treated male mice than in controls. Hypertrophic cells were observed in the pituitary of the HD females and castration cells were frequently seen in the LD and MD mice. Other than atrophy of the accessory sex glands and necrosis at the injection site, no other treatment-related histological changes were noted.

Two-Year Carcinogenicity Study of Abbott-43818 Administered SC to Mice. Study No. TD78-538, October 31, 1981.

Mice of the ICR strain were injected sc with 0.6, 6 and 60 mg/kg/day Leuprolide acetate. No significant dose-related toxicological effects were noted in the treated mice other than the expected treatment related atrophic changes in the reproductive organs.

	Dose (mg/kg/day)			
	0	0.6	6	60
Hepatocellular carcinoma				
females	1/101	5/51	0/51	2/52
males	11/103	9/49	6/51	4/52

There was no treatment-related change in pituitary adenomas or islet-cell adenomas in the mouse.

Three-Month Toxicity Study of Abbott-43818 Administered Subcutaneously in Sexually Mature Female Monkeys. Study No. 75-474.

Sexually mature Rhesus monkeys were treated with 1, 2 or 4 mg/kg/day. No significant drug-related changes in body-weight gain, ophthalmology, hematology, blood chemistry or urinalysis were noted. A 2-3 fold decrease in uterus and vagina weight was noted with an atrophic histology. No histologic differences were observed between the mammary glands, adrenals and pituitaries of treated and control monkeys.

Three-Month Toxicity Study of Abbott-43818 Administered SC in Sexually Mature Male Monkeys. Study No. 75-557.

Rhesus monkeys were treated with 1, 2 or 4 mg/kg/day Leuprolide. Treatment related changes included increased urine output in the HD with decreased specific gravity, osmolality and pH. There was a significant decrease in the weights of the testes, seminal vesicles and prostate. Histologically, the testes of treated monkeys were atrophic with collapsed tubules, thickened tunica albuginea and an increase in connective tissue between the tubules.

Twelve-Month Toxicity Study of Abbott-43818 Administered SC to Cynomolgus Monkeys. Study No. TC78-667.

Monkeys were administered 0, 0.6, 4 and 10 mg/kg/day Leuprolide acetate (6 males and 6 females per group). Treated males but not females gained less weight than controls. No changes in ophthalmology or urinalysis were noted. Scattered statistically significant differences between treated and control groups occurred in several hematological and clinical chemistry parameters with no apparent relationship to treatment except for a possible dose-related increase in serum alkaline phosphatase during the final days of the study.

Leuprolide administration resulted in decreased weight of primary and secondary sex organs for both males and females. There was also a decrease in the absolute mean heart weight in treated groups when compared to control. Relative heart weights, however, were not consistantly decreased. A significant dose-related increase in pituitary weight was seen for males but not for females.

Histological changes were confined to the reproductive organs. There were no meaningful microscopic differences between the pituitaries of the control and treated groups. No mention was made of bone marrow hypocellularity.

Teratology Studies

Teratology studies were done in accordance with Segment II guidelines. The studies in rabbits (study no. TE78-389) and rats (study no. T77-584A) showed leuprolide to be embryolethal in the range of 0.1 to 1 ug/kg/day in rabbits and at 10 ug/kg/day in rats. Surviving fetuses exhibited no drug-related visceral or skeletal abnormalities.

Mutagenicity studies involved use of the Ames test (Litton Bionetics, Inc.) 0.1-1000 ug leuprolide/plate with or without rat liver f9 mixture. Also, an in vivo cytogenetics test of rat bone marrow chromosomes (1,2 and 4 mg/kg, study no. T77-272A) and a dominant lethal test in the mouse (1, 2 and 4 mg/kg, study no. T77-515D) were performed. None of the three studies revealed any evidence of mutagenicity by leuprolide.

Evaluation

Leuprolide acetate has the expected pharmacological profile of an LHRH agonist. After an initial stimulation, Leuprolide treatment results in a decrease in serum gonadotropin levels and circulating steroid levels. It seems to be effective in the treatment of androgen-dependent prostatic cancer although perhaps not as effective as orchiectomy. The toxicological profile of Leuprolide is also what is to be expected from a LHRH agonist. Leuprolide treatment results in decreased weight and general atrophy of the reproductive organs. Testicular mineralization occurs in rats but not monkeys and its significance is uncertain. A significant decrease in testicular size does occur in all species treated with the agonist. There are other, inconsistant, effects of Leuprolide in the various toxicology studies but potentially the most serious effect of Leuprolide, in my view, is its effect on spinal column bone marrow. This increased fat deposition and subsequent hypocellularity was explained as a physiological response to the drug. The sponsor states that there was no alteration in the type or number of hematopoietic cells in the peripheral circulation. The bone marrow that was present was normal in appearance and there was no change in the erythroid and myeloid cell ratios. Nevertheless, this effect did not occur in untreated animals but was apparent in 68% of the females and 4% of the males at the lowest dose administered (30X HTD). Bone marrow hypocellularity was not reported in the toxicity studies on Buserelin or Nafarelin where lower doses were used. The only other consistant adverse effect of Leuprolide was the increased erythrocyte, hematocrit and Hb values in female rats. The sponsor stated that the values were well within the range of biological and analytical variability with no morphologic evidence of increased erythropoiesis.

Leuprolide administration produced a dose-related increase in pituitary adenomas in rats. There was approximately a two-fold increase in pituitary adenomas in both males and females at the low dose (600 ug/kg) with no no-effect dose demonstrated. The sponsor's explanation is that Leuprolide acts as a constant stimulator of gonadotroph function resulting in hyperplasia and ultimately, production of tumors. However, in the method and dose employed, Leuprolide does not stimulate but actually inhibits pituitary gonadotropin synthesis and secretion. Nevertheless, the possibility exists that Leuprolide at the same time may be acting as a stimulator of other cell functions which could result in pituitary adenomas. There is no obvious reason to suggest that the same process could not occur in humans. However, the development of pituitary tumors is a relatively common response to an altered endocrine enviornment in rats. Leuprolide administration did not produce pituitary tumors in mice and there was no microscopic change in the pituitaries of Cynomologus monkeys treated with Leuprolide for 12 months.

Since this is the first LHRH agonist to be tested for carcinogenicity, we do not know if pituitary tumor production is specific for Leuprolide or is common to all agonists. Other tumors which were significantly increased by Leuprolide treatment included pancreatic islet-cell adenoma and testicular interstitial-cell adenoma. These were not dose-related and neither of these tumors were seen in agonist treated mice or monkeys. Overall, Leuprolide treated rats had fewer tumors than did the controls.

In general the toxicity studies done in monkeys revealed that Leuprolide, at doses of up to 500X MID was remarkably non-toxic. Except for the expected effects on the reproductive organs, there was no consistant toxic effect of Leuprolide on any parameter in either male or female Rhesus or Cynomolgus monkeys.

H Jordan

Alexander Jordan

cc
Original NDA 19-010
HFN 220
HFN 130
HFN 130 Pharmacology
HFN 130 AJordan
3137C

V. Berliner 2/27/8

TABLE I

SUMMARY OF ACUTE TOXICITY STUDIES PERFORMED WITH ABBOTT-43018

Reference Number Investigator Study No. Where Performed (Report Date)	Species (Strain)	Route	Dosage (mg/kg) M	F	No. of Animals M	F	Mortalities M	F	LD_{50} (mg/kg) M	F	Observations
Reference #1 Abbott Labs. (Nov. 1975)	Mouse (ICR)	PC	100	100	10	10	0	0	>100	>100	Signs included decrease activity, dyspnea and excessive stretching both sexes of both species.
	Rat -- (Long-Evans)	PC	100	100	10	10	0	0	>100	>100	

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TABLE 2

SUMMARY OF MUTAGENICITY STUDIES PERFORMED WITH ABBOTT-43818

Reference Number Investigator(s) Study No. Where Performed (Report Date)	Type of Study	Test-Organism	Dosages	Conclusions
Reference #2	Ames test	Salmonella typhimurium strains TA-1535, TA-1537, TA-1538, TA-98, TA-100	0.1, 1.0, 10, 100, 500, 1000 mcg/plate	No mutagenic activity with or without rat liver S9 mixture.
Reference #3	In vivo cytogenetics	Rat (Sprague-Dawley, 5 M/group)	1, 2, 4 mg/kg (subcutaneous)	No mutagenic effect on bone marrow chromosomes.
Reference #4	Dominant lethal	Mouse (CD-1, 10 M/group)	1, 2, 4 mg/kg (subcutaneous)	No mutagenic effect demonstrated.

Assessment
ABBOTT-43818 appears to be devoid of mutagenic potential as assessed by three mutagenicity screens of widely varying endpoint.

TABLE 3

SUMMARY OF TERATOLOGY STUDIES PERFORMED WITH ABBOTT-43818

Reference Number Investigator(s) Study No. Where Performed (Report Date)	Treatment Duration	Species (Strain, Sex, Etc.)	Route	Dosages (mcg/kg/day)	Conclusions
Reference #5	Gestation days 6-15	Rat (SD, 20 F/group)	SC	1, 3, 10	Four-fold increase in resorptions at 10 mcg/kg/day. Survivors showed no increase in abnormal development. "No-effect" level was 3 mcg/kg/day.
Reference #6	Gestation days 6-18	Rabbit (New Zealand white, 15 F/group)	SC	0.1, 0.3, 1.0	Embryolethal at all tested dosages; survivors exhibited no drug-related abnormalities.

Assessment

Dosages in the teratology studies were limited by the embryolethal effects of this potent analog of the naturally occurring gonadotropin releasing hormone. These were not the first studies to demonstrate post-coital contraceptive effects of greater than physiologic levels of GnRH [see Proc. Soc. Exptl. Biol. Med. 152: 29-32 (1976); Endocrine Res. Comm. 3: 359-376 (1976)]. Therefore, although even low levels of ABBOTT-43818 are likely to prove embryolethal, animal studies indicate that survivors are able to develop normally.

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TABLE 4

SUMMARY OF SUBCHRONIC AND CHRONIC TOXICITY STUDIES OF ABBOTT-43818

Reference Number Investigator(s) Study No. (Report Date)	Treatment Duration	Species (Strain, Sex, etc.)	Route	Dosages (mg/kg/day)	Conclusions
Reference #7	Once daily for 3 months	Rat (Sprague-Dawley, M&F, 10/sex/group)	SC	T_0 - 0 T_1 - 1 T_2 - 2 T_3 - 4	"No-toxic-effect" dosage was 4 mg/kg/day.
Reference #8	Once daily for 2 days or 7 days (5 rats/group necropsied at the end of treatment period and 5 rats/group necropsied after a 7-day recovery period)	Rat (Sprague-Dawley M, 75 controls and 10 treated/group)	SC	T_0 - 0 T_1^a - 1 T_1^b - 1	Two days of drug treatment were sufficient to produce testicular atrophy.

Comments/Findings

- The drug was dissolved in normal saline. Controls received normal saline only. Dosage volume for all groups was 1 ml/kg/day. Lot #34-731-AL of ABBOTT-43818 was used.
- One T_3 female died on day 92. The death was not considered to be drug-related.
- Food consumption and growth were slightly lower in treated males than in control males. Growth and occasionally food consumption were slightly increased in treated females.
- Increased urine volume was observed in treated females.
- Treated females stopped cycling during the first week of treatment and remained in metestrus throughout the treatment period.
- Testes of treated males were observed to be smaller than testes of control males on day 15 and remained smaller throughout the treatment period.

Urinalysis:

- Decreased urine osmolality and specific gravity were noted in treated females.

Hematology:

- No drug-related differences in hematology values were observed.

Clinical Chemistry:

- No drug-related differences in clinical chemistry values were observed.

Anatomic Pathology:

- Organ Weights. Differences at necropsy included increased adrenal weights in all treated groups; decreased testis, prostate and seminal vesicle weights in all treated male groups; and decreased ovary, uterus and vagina weights in all treated female groups.
- Gross and Microscopic Pathology. Atrophic changes were observed in the ovaries, uterus, vagina, mammary glands, prostate, seminal vesicles and testes of treated animals. Testicular atrophy was also observed in the control males. However, the degree of testicular change was less severe in controls than in treated males.
- All dosages of ABBOTT-43818 produced marked effects on the reproductive organs consistent with the endocrine nature of the drug.

[a]Animals treated for 2 days.

[b]Animals treated for 7 days.

TABLE 4 (CONT.)

SUMMARY OF SUBCHRONIC AND CHRONIC TOXICITY STUDIES OF ABBOTT-43018

Reference Number Investigator(s) Study No. (Report Date)	Treatment Duration	Species (Strain, Sex, etc.)	Route	Dosages (mg/kg/day)	Conclusions
Comments/Findings - The drug was dissolved in normal saline. Five controls were not treated, ten received normal saline for 2 days and ten received normal saline for 7 days. The dosage volume for all groups was 1 ml/kg/day. Lot #34-751-AL of ABBOTT-43018 was used. - The testes from treated and recovery rats weighed less and were grossly smaller than those of control animals except in treated rats necropsied immediately after two days of treatment. - The testes of treated animals showed various degrees of testicular atrophy that were detectable histologically after two days of treatment. It was apparent that the atrophy was more severe and extensive in animals necropsied seven days following the last day of treatment.					
Reference #9	Once daily for 3 months	Rhesus Monkeys (sexually mature F, 3/group)	SC	T_0 - 0 T_1 - 1 T_2 - 2 T_3 - 4	"No-toxic-effect" dosage was 4 mg/kg/day.
Comments/Findings - The drug was dissolved in normal saline. Controls received normal saline only. Dosage volume for all groups was 1 ml/kg/day. Lots #37-784-AL and #39-820-AL were used. - There were no mortalities. - No biologically significant differences in body weight or food consumption were observed. - Treated females did not complete a menstrual cycle during the last two months of treatment. Clinical Pathology: - No drug-related changes were observed in urinalysis, hematology or clinical chemistry values. Anatomic Pathology: - Organ Weights. Decreases in weights of uterus and vagina were observed for all treated groups. - Gross and Microscopic Pathology. Atrophic changes in the uterus and vagina and cessation of follicular development in the ovaries was seen in all treated groups. - All dosages of ABBOTT-43018 produced marked effects on the reproductive organs consistent with the endocrine-like activity of the drug.					
Reference #10	Once daily for 3 months	Rhesus Monkeys (sexually mature M, 3/group)	SC	T_0 - 0 T_1 - 1 T_2 - 2 T_3 - 4	"No-toxic-effect" dosage was 4 mg/kg/day.
Comments/Findings - The drug was dissolved in normal saline. Controls received normal saline only. Dosage volume for all groups was 1 ml/kg/day. Lots #32-731-AL and #39-820-AL were used. - There were no mortalities. - No drug-related changes in body weight or food consumption were observed. - A decrease in the size of the testes of three of nine treated monkeys was observed.					

01

TABLE 4 (CONT.)

SUMMARY OF SUBCHRONIC AND CHRONIC TOXICITY STUDIES OF ABBOTT-43818

Reference Number Investigator(s) Study No. (Report Date)	Treatment Duration	Species (Strain, Sex, etc.)	Route	Dosages (mg/kg/day)	Conclusions
Comments/Findings (Cont.) Urinalysis: - Increased urine volume was observed for T_3 monkeys on day 90. - Decreased specific gravity, osmolality and pH were observed for all T_3 monkeys on day 90. Hematology and Clinical Chemistry: - No drug-related changes were observed. Anatomic Pathology: - Organ Weights. Drug-related decreases were observed in the weights of testes, prostate and seminal vesicles of treated monkeys. - Gross and Microscopic Pathology. Atrophic changes were observed in testes, prostate and seminal vesicles of treated animals. Similar changes wa also seen in one control monkey. - All dosages of ABBOTT-43818 produced marked effects on the reproductive organs consistent with the endocrine nature of the drug.					
Reference #11	Once daily for 12 days	Rat (Sprague-Dawley NSF, 12/sex/group)	SC	T_0 - 0, days 0-11 T_1 - 20, days 0-2 - 75, days 2-5 - 280, days 6-8 - 1060, days 9-11	"Toxic-effect" dose was 1060 mg/kg/day Irritation at inje site at 280 mg/kg
Comments/Findings - The drug was dissolved in normal saline. Controls received normal saline only. Lot #64-911-AL was used. - Several deaths occurred at 1060 mg/kg/day. - Body weight and food consumption were depressed at 1060 mg/kg/day. - Significant local irritation of the injection sites was noted at 280 and 1060 mg/kg/day.					
Reference #12	Once daily for) months	Rat (Sprague-Dawley, NSF, 10/sex/group)	SC	T_0 - 0 T_1 - 10 T_2 - 30 T_3 - 100 T_4 - 300	Maximum-tolerated dosag not established because pituitary hyperplasia a all dosages.
Comments/Findings - The drug was dissolved in normal saline. Controls received normal saline only. Dosage volume for all groups was) ml/kg/day. Lot #58-238-AL of ABBOTT-43818 was used. - One T_4 female rat died on day 23. The remainder of the T_4 rats and the T_3 rats were terminated on days 28 and 47, respectively, because of marked skin necrosis at the injection sites. - Retardation of body weight gain and decreased food consumption were observed in the T_4 and T_3 groups (both sexes). - Numerous signs of degeneration were observed in the tissues surrounding the injection sites of T_2, T_3 and T_4 groups.					

TABLE 4 (CONT.)

SUMMARY OF SUBCHRONIC AND CHRONIC TOXICITY STUDIES OF ABBOTT-43818

Reference Number Investigator(s) Study No. (Report Date)	Treatment Duration	Species (Strain, Sex, etc.)	Route	Dosages (mg/kg/day)	Conclusions

Comments/Findings (Cont.)

Clinical Pathology:

- No drug-related changes were observed in urinalysis, hematology or clinical chemistry values.

Anatomic Pathology:

- Organ Weights. Statistically significant decreases in mean relative brain weight of T_2 males and mean absolute and relative adrenal weights of T_1 females were observed. Statistically significant decreases were observed in mean absolute heart weights of T_1 and T_2 males, mean absolute and rel kidney and liver weights of T_1 and T_2 males and mean relative liver weights of T_2 females. Organ weight changes were not related to discernible morphologic lesions.
- Gross and Microscopic Pathology. Pituitary hyperplasia occurred in 3/20 T_1 and 17/20 T_2 rats. Pituitary hypertrophic cells were seen in 16/20 T_1 and 19/20 T_2 rats. Atrophic changes were seen in the sex organs of treated animals of both sexes. Changes to sex organs were an expected result pharmacologic effect of the drug. Marked skin lesions at the injection sites were observed in T_2, T_3 and T_4 animals of both sexes. Skin lesions lesser severity were seen in T_1 and control rats of both sexes.

Reference #13	Once daily for 6 months	Rat (Sprague-Dawley MRF, 10/sex/group, plus 6 animals which died or were killed during the first 6 months of treatment)	SC	T_0 - 0 T_1 - 0.6 T_2 - 1.5 T_3 - 4.0	See final report, reference #17.

Comments/Findings

- The drug was dissolved in normal saline. Controls received normal saline only. Dosage volume for all groups was 1 ml/kg/day. Lot 093-766-AL of ABBOTT-43818 was used.
- Three T_0 males, one T_0 female, one T_1 male and one T_2 female died or were killed in a moribund condition during the 6-month period. The deaths were not treatment-related.
- The 6-month body weight gains were less for the T_2 and T_3 males and greater for all drug-treated female groups. Food consumption was increased for all drug-treated female groups.

Urinalysis:

- No drug-related differences in urinalysis parameters were observed.

Hematology:

- No drug-related differences in hematology parameters were observed.

Clinical Chemistry:

- Serum alkaline phosphatase levels were elevated in T_2 and T_3 females. This change was interpreted as an exaggerated pharmacologic effect.

Anatomic Pathology:

- Organ Weights. Mean weights of ovaries, testes and male accessory sex organs for all treated groups were significantly less than for their respe control group.
- Gross and Microscopic Pathology. Drug-related atrophic changes were observed in ovary, uterus, vagina, testis, epididymis, prostate, seminal ves and male mammary gland. Interstitial fibrosis was observed in the testes of the T_1 group and tubular calcification occurred in T_1, T_2 and T_3 males. Chronic cellulitis was observed at the injection sites of T_0, T_1, T_2 and T_3 rats. The severity of the cellulitis increased with increasi dosages. Ulcerative dermatitis occurred among male and female T_3 animals. Increased fat deposition was observed in the vertebral bone marrow of T_1, T_2 and T_3 males and females with the females most affected. This apparent drug- and dose-related increase in fat in the bone marrow was inter as a physiologic response to the hormonal activity of ABBOTT-43818.

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TABLE 4 (CONT.)

SUMMARY OF SUBCHRONIC AND CHRONIC TOXICITY STUDIES OF ABBOTT-43818

Reference Number Investigator(s) Study No. (Report Date)	Treatment Duration	Species (Strain, Sex, etc.)	Route	Dosages (mg/kg/day)	Conclusions
Reference #14					
	Once daily for 12 months	Rat (Sprague-Dawley MRF, 10/sex/group, plus 27 animals which died or were killed in the second 6-mo period)	SC	T_0 - 0 T_1 - 0.6 T_2 - 1.5 T_3 - 4.0	See final report, reference #17.

Comments/Findings

- The drug was dissolved in normal saline. Controls received normal saline only. Dosage volume for all groups was 1 ml/kg/day. Lot #93-766-A1 of ABBOTT-43818 was used.
- Five T_0 males, three T_1 males, three T_2 males, three T_3 males, three T_0 females, three T_1 females, three T_2 females and four T_3 females died or were killed in a moribund condition during months 6-12 of drug treatment.
- Body weights and weight gain of T_3 males were significantly lower than T_0 males. Females of T_1, T_2 and T_3 groups had significantly higher body weights than their control group. No consistent differences in food consumption were seen.
- No significant differences in water consumption were observed.

Urinalysis:

- T_3 females showed significantly higher urine output than the T_0 females.
- There were no toxicologically significant differences in urinalysis parameters.

Hematology:

- There were no toxicologically significant differences in hematology parameters.

Clinical Chemistry:

- Treatment-related increases in serum alkaline phosphatase and cholesterol were observed in T_3 females. Both of these changes were interpreted as exaggerated pharmacologic effects.

Anatomic Pathology:

- Organ Weights. Drug-related decreases in mean absolute and relative weights for ovary, uterus, testis and male accessory sex organs in T_1, T_2 and T_3 animals were observed when compared to controls. All drug-treated male groups had higher relative pituitary weights than the control group
- Gross and Microscopic Pathology. Drug-related adenomatous, hypertrophic and hyperplastic changes with cellular atypia were seen in the anterior lobe of the pituitary gland of T_1, T_2 and T_3 males and females. The pituitary adenomas were restricted to T_2 and T_3 males. Atrophic changes were seen in ovary, uterus, vagina, testis, accessory sex organs and mammary gland of all drug-treated groups. Mild drug- and dose-related chron cellulitis was observed at the injection sites of T_1, T_2 and T_3 animals. Focal ulcerative dermatitis occurred among T_2 and T_3 animals. Increase fat deposition was observed in the vertebral bone marrow of all drug-treated groups. This apparent drug- and dose-related increase in fat in the marrow was interpreted as a physiologic response to the hormonal activity of ABBOTT-43818.

TABLE 4 (CONT.)

SUMMARY OF SUBCHRONIC AND CHRONIC TOXICITY STUDIES OF ABBOTT-43818

Reference Number Investigator(s) Study No. (Report Date)	Treatment Duration	Species (Strain, Sex, etc.)	Route	Dosages (mg/kg/day)	Conclusions
Reference #15					
	All findings included in final report. See reference #17 below.				
Reference #16					
	All findings included in final report. See reference #17 below.				
Reference #17	Once daily for 2 years	Rat (Sprague-Dawley, M & F, 120/sex/group for T_0 and 70/sex/group for T_1-T_3).	SC	T_0 0 T_1 0.6 T_2 1.5 T_3 4.0	Administration of ABBOTT-43818 was associated with increased incidences of pituitary adenoma and testicular necrosis and/or degeneration. These effects were ascribed to the hormonal activity of the drug.

Comments/Findings

- The drug was dissolved in normal saline. Controls received normal saline only. Lot #93-766-AL of ABBOTT-43818 was used.
- Rate of survival was similar for all treated groups and their respective control groups.
- The percentage of animals which developed palpable masses was higher for control groups compared to drug treated groups.
- Body weight and weight gains of treated males were less than controls and were decreased in a dosage-related manner. Body weights at the end of study and body weight gain were significantly depressed for the T_3 females compared to the controls.
- Water consumption was less for all treated female groups compared to the control group.
- Urine output was lower for T_3 males and T_1, T_2 and T_3 females when compared to their respective controls.

Clinical Pathology:

- No toxicologically meaningful changes in urinalysis, hematology or clinical chemistry parameters were observed.

Anatomic Pathology:

- Organ Weights. Mean absolute weights of testis, ovary and uterus were significantly lower than respective control mean values for all treatment groups. Mean absolute and relative pituitary weights were significantly greater than control mean values for T_2 and T_3 males and T_3 females.
- Gross and Microscopic Pathology. A drug-related statistically significant positive trend for pituitary adenomas was apparent for both males and females. The increased incidence of pituitary adenomas was not unexpected in view of the known effects of hormonally active agents in rats. Additional effects noted, secondary to the pharmacologic activity of ABBOTT-43818, were atrophic changes in both male and female reproductive organs and testicular degeneration/necrosis in all treated male groups. Apparent bone marrow hypocellularity, resulting from a pharmacologic increase in fat content was observed in all drug-treated groups. Injection site lesions, characterized by superficial dermatitis and infiltration of the subcutis by mixed inflammatory cells, occurred more frequently in treated rats than controls. Ulceration at the injection site was observed infrequently and only in T_2 and T_3 animals.

TABLE 4 (CONT.)

SUMMARY OF SUBCHRONIC AND CHRONIC TOXICITY STUDIES OF ABBOTT-43818

Reference Number Investigator(s) Study No. (Report Date)	Treatment Duration	Species (Strain, Sex, etc.)	Route	Dosages (mg/kg/day)	Conclusions
Reference #18	Once daily for 15 days	Mouse (ICR M&F, 12/sex/group)	SC	T_0 - 0, days 0-14 T_1 - 4, days 0-2 20, days 3-5 100, days 6-8 500, days 9-11 2500, days 12-14	"Toxic-effect" dosage was 2,500 mg/kg/day with irritation at injection site at 500 mg/kg/day.
Comments/Findings - The drug was dissolved in normal saline. Controls received normal saline only. Lot #64-911-AL of ABBOTT-43818 was used. - One male died at 2500 mg/kg/day dosage level. - Significant local irritation at the injection sites was noted at 500 and 2500 mg/kg/day.					
Reference #19	Once daily for 3 months	Mouse (ICR M&F, 10/sex/group)	SC	T_0 - 0 T_1 - 20 T_2 - 60 T_3 - 200 T_4 - 600	Maximum-tolerated dose was 60 mg/kg/day.
Comments/Findings - The drug was dissolved in normal saline. Controls received normal saline only. Dosage volume for all groups was 5 ml/kg/day. Lot #18-230-AL of ABBOTT-43818 was used. - Five T_4 male mice died between days 9 and 28. Treatment of all T_4 animals was discontinued on day 28 because of necrosis at the injection sites and survivors were killed and necropsied on day 29. - No drug-related effect on body weight or food consumption were seen. Clinical Pathology: - No biologically significant treatment-related changes were observed in hematology and clinical chemistry parameters. Anatomic Pathology: - Organ Weights. No treatment-related changes of biological significance were seen. - Gross and Microscopic Pathology. Hypertrophic cells were observed in the pituitaries of all T_3 female mice. Atrophic changes were present in the sex organs of all treated male and female groups. These atrophic changes were ascribed to the pharmacologic effects of ABBOTT-43818. Marked skin lesions at injection sites were observed in T_3 and T_4 mice.					
Reference #20	Once daily for 2 years	Mouse (ICR, M&F, approximately 100/sex/group for T_0 and 50 sex/group for T_1-T_3).	SC	T_0 - 0 T_1 - 0.6 T_2 - 6.0 T_3 - 60.0	ABBOTT-43818 was not considered to be carc in this study.

TABLE 4 (CONT.)

SUMMARY OF SUBCHRONIC AND CHRONIC TOXICITY STUDIES OF ABBOTT-43818

Reference Number Investigator(s) Study No. (Report Date)	Treatment Duration	Species (Strain, Sex, etc.)	Route	Dosages (mg/kg/day)	Conclusions
Comments/Findings - The drug was dissolved in normal saline. Controls received normal saline only. Lot #91-752-AL of ABBOTT-43818 was used. - Rates of survival were similar for all treated groups and their respective control groups. - The percentage of animals that developed palpable masses was similar for all groups of each sex. - T_3 male and female groups had greater incidence of signs of irritation at the injection sites. - Body weight gain over the two-year period was less for the T_1, T_2 and T_3 males than the respective control groups. - Gross and Microscopic Pathology. Evidence of atrophic changes was observed in primary and accessory sex organs of all drug-treated groups. No statistically significant positive trends in tumor incidence with dosage were found.					
Reference #21					
	Once daily for 21 days	Cynomolgus Monkey (M, 2/group)	SC	T_0 - 0, days 0-20 T_1 - 4, days 0-6 increased to 50, days 7-20 T_2 - 10, days 0-20 T_3 - 25, days 0-20	No signs of toxicity were noted. Irritation at injection sites was present at 25 mg/kg/day after 21 days of treatment
Comments/Findings - The drug was dissolved in normal saline. Controls received normal saline only. The dosage volume for all groups was 1 ml/kg/day. Lot #68-984-AL of ABBOTT-43818 was used. - Signs of local irritation at the injection site were observed in the T_3 group.					
Reference #22					
	Once daily for 1 year	Cynomolgus Monkey, (sexually mature, M&F, 6/sex/group)	SC	T_0 - 0 T_1 - 0.6 T_2 - 4.0 T_3 -10.0	"No-toxic-effect" dosage was 10 mg/kg/day.
Comments/Findings - The drug was dissolved in normal saline. Controls received normal saline only. The dosage volume for all groups was 1 ml/kg/day. Lots #91-799-AL, #91-752-AL and #92-766-AL of ABBOTT-43818 were employed. - One T_3 male died on day 109. Its death was not drug-related. - No biologically significant differences in body weight and food consumption were observed. - All drug-treated females ceased menstruation after day 19. Clinical Pathology: - No drug-related differences of toxicologic significance were observed in urinalysis, hematology or clinical chemistry parameters. Anatomic Pathology: - Organ Weights. Marked weight reductions were found in the primary and accessory sex glands of both sexes in all drug-treated groups. A drug- and dosage-related increase in male pituitary weights was found. All of the above weight differences were ascribed to the pharmacologic activity of the drug. - Gross and Microscopic Pathology. Atrophic changes were observed in the primary and accessory sex glands of both sexes of all drug-treated groups. These changes were ascribed to the pharmacologic activity of the drug.					

CHEM

A. 1. NDA/IND # 19-010

Applicant/~~Sponsor~~: TAP Pharmaceuticals Date Completed: 4-2-85

Address: Abbott Park
North Chicago, IL 60064

2. Product Name(s): LUPRON (leuprolide acetate)

3. Dosage Form(s) and Route(s) of Administration: Injection, 5mg/ml
S.C.; Rx

4. Pharmacological Category and/or Principal Indication:
Antineoplastic.

5. Structural Formula and Chemical Name(s):
See Chem. Rev. #1 dated 9-19-83

B. 1. Initial Submission 7-8-83 (Manufacturing controls)

2. Amendments: 12-19-84 submits FPL and clinical safety update.

C. Remarks: Approval package was sent to HFN-210 on 1-8-85 and later returned to HFN-210 for presentation to Executive Advisory Committee. Chem. Rev. #5 dated 2-8-85 concludes that methods validation is regarded as acceptable, but some revisions and corrections of the methods are recommended.

D. Recommendation and Justification

FPL is acceptable from the chemist's standpoint. Recommend approval of the application. Letter regarding methods validation will be issued. See Chem. Rev. #5.

4/4/85

H. B. Nelson

Chemist's Review # 1

Review and Evaluation of Manufacturing Controls Data

A. 1. NDA/IND # 19-010

CLASS: 1A

Date Completed: 9-19-83

Applicant/Sponsor:
TAP Pharmaceuticals

Address: Abbott Park
North Chicago, IL 60064

2. Product Name(s): Leuprolide acetate

Codes: Abbott-43818
TAP-144

Proposed Trade Name: Onconil

3. Dosage Form(s) and Route(s) of Administration: Multiple dose

Injection, 5 mg/ml; S.C.; 2 ml and 5 ml vials.

4. Pharmacological Category and/or Principal Indication:

Antineoplastic - LHRH analog (prostatic carcinoma)

5. Structural Formula and Chemical Name(s):

H-5-oxoPro-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NEt. CH_3COOH.x H_2O

B. 1. Initial Submission of manufacturing controls section is dated 7-8-83 and was rec'd for review on 7-15-83.

2. Amendments:

3. Supporting IND, NDA, DMF and Letters of Authorization: Letter from dated 6-28-83 allowing reference to their DMF Letter from Labs dated 4-6-83 allowing reference to

C. Remarks: Investigations with this drug have been carried out over the past seven years under IND They will be the manufacturer of the drug and all communications will be with Abbott. The applicant is responsible for marketing of the drug.

The new drug substance (NDS) has been produced by The synthetic information provided in the IND and in this application is for process. However, they will no longer supply the NDS in the future. Abbott is in the process of developing a synthetic process of ther own. Initially marketed drug will still be manufacturered from material until the application can be supplemented to provided for synthe of the NDS by Abbott (Telecon of 8-25-83 with Mr. Dean Sundberg of Abbott).

D. Conclusions and/or Recommendations

Manufacturing controls information is deficient. Labeling not yet submitted.

cc: Orig. IND
HF 30
HFN-102/Kumkumian
HFN-130/HBNunn/9/19/83/skw/10/3/83
R/D init. by DJKertesz/9/27/83
Wang No. 2341C

OCT 7 1983

Helmut B. Nunn
10-5-83

Division Name: MED P/HFN-130
Chemist's Review #2

Review and Evaluation of Manufacturing Controls Data

A. 1. NDA 19-010 CLASS: 1A

Applicant: TAP Pharmaceuticals Date Completed: 3-7-84
Address: Abbott Park
North Chicago, Illinois 60064

2. Product Name(s): Leuprolide acetate

3. Dosage Form(s) and Route(s) of Administration: Injection, 5 mg/ml; S.C.; 2 ml and 5 ml multiple dose vials with 1.6 ml and 4 ml fill volumes respectively.

4. Pharmacological Category and/or Principal Indication: Antineoplastic (prostatic cancer).

5. Structural Formula and Chemical Name(s): See Chem. Rev. #1 dated September 19, 1983.

B. 1. Initial Submission of manufacturing controls section is dated July 8, 1983.

2. Amendments: December 22, 1983 provides add'l mfg. controls information; December 20, 1983 submits the clinical section and labeling.

3. Supporting IND, NDA, DMF and Letters of Authorization: Letter from dated September 8, 1983 allowing reference to their DMF

C. Remarks:

Chem. Rev. #1 dated September 19, 1983 found mfg. controls information deficient. Our letter of October 27, 1983 detailed the deficiencies. Labeling was not available.

D. Conclusions and/or Recommendation:

Manufacturing controls information remains deficient. Labeling needs revision.

H. B. Nunn 3/20/84
H. B. Nunn, Chemist

cc:
Orig. NDA
HFN-130
HFN-130/HBNunn/3/7/84/sw/3/20/84
R/D init. by: DJKertesz/3/9/84/3/13/84
Wang No. 3902C

MAR 23 1984

Division Name: DMEDP HFN-810
Chemist's Review #3

Reviewed
CMS
8/14/

Review and Evaluation of Manufacturing Controls Data

A. 1. ~~IND~~ NDA 19-010

Applicant: TAP Pharmaceuticals
Address: Abbott Park
North Chicago, IL 60064

Date Completed: 8-7-84

2. Product Name: Leuprolide acetate

3. Dosage Form and Route of Administration: Injection, 5 mg/ml, s.c.; 2 ml and 5 ml vials

4. Pharmacological Category and/or Principal Indication: Antineoplastic

5. Structural Formula and Chemical Name: See Chem. Rev. #1 dated 9-19-83

B. 1. Initial Submission of manufacturing controls section is dated 7-8-83

2. Amendments: 3-7-84 submits clinical portion of the SBA. 5-4-84 provides additional manufacturing controls information. 5-30-84 consists of the validation package.

C. Remarks: Chem. Rev. #2 dated 3-7-84 found manufacturing controls information still deficient and labeling needed revision. The 5-4-84 amendment is in response to our deficiency letter of 4-6-84.

D. Conclusions and/or Recommendations: Manufacturing controls are now approvabe pending satisfactory completion of methods validation. Revised draft labeling is forthcoming.

H.B. Nunn 8/13/84
H.B. Nunn, Chemist

cc:
IND Orig.
HFN-810
HFN-810/HBNunn/8/7/84/DB/8/13/84
R/D init. by: DJKertesz/5/8/84
Wang No. 6382C

AUG 13 1984

Division Name: MEDP, HFN-810
Chemist's Review #4

Review and Evaluation of Manufacturing Controls Data

A. 1. NDA #19-010 Date Completed: November 13, 1984

Sponsor: TAP Pharmaceuticals
Abbott Park
North Chicago, Illinois 60064

2. Product Name: LUPRON (Leuprolide Acetate)

3. Dosage Form and Route of Administration: Injection, 5 mg/ml, s.c.

4. Pharmacological Category and/or Principal Indication: Antineoplastic

5. Structural Formula and Chemical Name: See Chem. Rev. #1 dated September 19, 1983.

B. 1. Initial Submission: July 8, 1984 (Manufacturing controls)

2. Amendments: November 1, 1984 submits a revised draft insert. November 8, 1984 provides the Summary Basis of Approval (SBA).

C. Remarks: Chem. Rev. #3 dated August 7, 1984 found manufacturing controls approvable pending satisfactory completion of methods validation. Revised labeling was pending.

The draft insert in the November 1, 1984 amendment is satisfactory from the chemist's standpoint. This insert contains the text agreed upon in the November 1, 1984 meeting with the applicant.

The SBA in the November 8, 1984 amendment is acceptable.

D. Conclusions and/or Recommendations: Manufacturing controls remain approvable pending satisfactory completion of methods validation by DDC, HFN-180. Draft labeling is now satisfactory.

H. B. Nunn

H. B. Nunn, Chemist

cc:
Orig. NDA
HFN-810
HFN-810/HBNunn/11/13/84/sw/11/15/84
R/D init. by: DJKertesz/11/13/84
Wang No. 7513C

NOV 26 1984

Division Name: MEDP, HFN-810
Chemist's Review #5

Review and Evaluation of Manufacturing Controls Data

A. 1. IND 19,010 Date Completed: February 8, 1985

Sponsor: TAP Pharmaceuticals
Address: Abbott Park
North Chicago, Illinois 60064

2. Product Name(s): LUPRON (leuprolide acetate)

3. Dosage Form(s) and Route(s) of Administration: Injection, 5 mg/ml; S.C.; Rx

4. Pharmacological Category and/or Principal Indication: Antineoplastic.

5. Structural Formula and Chemical Name(s): See Chemist Review #1 dated September 19, 1983.

B. 1. Initial Submission: July 8, 1983 (Manufacturing controls)

C. Remarks: Chemist Review #4 dated November 13, 1984 found manufacturing controls to remain approvable pending satisfactory completion of methods validation by DDC. Draft labeling was satisfactory. Approval letter was sent to HFN-800 on January 8, 1985.

The attached Review Notes pertain only to methods validation.

D. Conclusions and/or Recommendations:

Methods validation has now been completed and is regarded as acceptable. However, some revisions and corrections of the proposed methods are recommend. See attached "Draft of Chemist's Letter to Applicant."

H. B. Nunn

H. B. Nunn, Chemist

cc:
Orig. IND
HFN-810
HFN-810/HBNunn/2/8/85/sw/3/15/85
R/D init. by: DJKertesz/2/11/85
Wang No. 0987D

E. Review Notes:

Samples and Results: Memo from Drug Standard Research Branch (Dr. Sheinin), HFN-180 dated January 25, 1985 concludes that several questions must be addressed by the applicant before the proposed methods will be suitable for regulatory and control purposes. However, both laboratories (DDC and CHI-DO) obtained satisfactory results which are summarized below. Results from CHI-DO were received on August 21, 1984 from HFO-620 without comments. See Draft of Chemist's Part of Letter to Applicant for recommended revisions of the proposed methods.

Summary of Methods Validation Results

NDS Lot 56-225-AL

Procedure	Limits	DDC	Abbott	CHI-DO

Dosage Form Lot 56-138-AR

Identification-HPLC
Assay (%)-HPLC
Benzyl alcohol (%)-HPLC

Division Name: MEDP, HFN-810
Chemist's Review #6

Review and Evaluation of Manufacturing Controls Data

A. 1. NDA 19-010 Date Completed: April 3, 1985

Applicant: TAP Pharmaceuticals
Address: Abbott Park
North Chicago, Illinois 60064

2. Product Name(s): LUPRON (leuprolide acetate)

3. Dosage Form(s) and Route(s) of Administration: Injection, 5 mg/ml; S.C.; Rx.

4. Pharmacological Category and/or Principal Indication: Antineoplastic.

5. Structural Formula and Chemical Name(s): See Chemist Review #1 dated September 19, 1983

B. 1. Initial Submission: July 8, 1983 (Manufacturing controls)

2. Amendments: December 19, 1984 submits FPL and clinical safety update.

C. Remarks: Approval package was sent to HFN-800 on January 8, 1985 and later returned to HFN-810 for presentation to Oncology Advisory Committee.

Chemist Review #5 dated February 8, 1985 concludes that methods validation is regarded as acceptable but some revisions and correction of the methods are recommended.

D. Conclusions and/or Recommendations:

FPL is acceptable from the chemist's standpoint. Recommend approval of the application. Letter regarding methods validation still to be issued. See Chemist Review #5.

H. B. Nunn

H. B. Nunn, Chemist

cc:
Orig. NDA
HFN-810
HFN-810/HBNunn/4/3/85/sw/4/10/85
R/D init. by: DJKertesz/4/4/85
Wang No. 1257D

BIO

FOI

Leuprolide Acetate
(Lurpon, Subcutaneous Injection)
NDA 19-010
Reviewer: Anita Shah
Wang #[redacted]
1-0

Abbott Laboratories
Abbott Park
Illnois 60664
Submission Dated:
August 5, 1986

JUN 3 1987

Review of Responses to Deficiencies in a NDA

Background:

The bio-study of this NDA 19-010 was reviewed on Dec 11, 1984 and the firm was asked to resolve the various deficiencies in the study. It was agreed that the firm could do so in the post marketing period. This submission contains the responses to the various deficiencies stated for the bio-study.

Deficiencies and responses by the firm are provided in attachment 1.

Comment to Deficiency 1:

The response to the deficiency No. 1 is acceptable. Since there is no information on the possible metabolites of leuprolide, the firm has checked the cross-reactivities in rat serum of various synthetic analogs of leuprolide and some fragment of leuprolide (which could be possible metabolites). However since the 0-hour plasma sample appeared to contain no detectable levels of drug it rules out the possibility of endogenous interferences in the assay. The firm has also validated the sensitivity of the assay to 100 ug/ml.

Comment to Deficiency 2:

The firm has submitted the individual AUC_{0-24} values determined from the observed plasma data. THe power to detect a 20% difference of the mean AUC's is about 83% at α=0.05. The study therefore has sufficient power.

Comment to recommendation (1):

The firm has identified the composition of the marketed dosage form. In a telephone conversation with Dean Sundberg (Regulatory Affairs) on 4/7/87, it was learned that the formulation used in the bio-study was the same as that used in the clinical studies.

Comment to recommendation (2):

The firm has submitted the labelling information. Response to comment #2 is acceptable.

Comment to recommendation (3):

Response to comment #3 is acceptable.

Comment to recommendation (4):

There is no informtion on the metabolism of this drug. The firm's protein binding data is not very reliable because of a high degree of the drug binding to the filtration membrane, however they estimate less than 80% binding to human plasma.

Conclusion:

The responses to the deficiencies and recommendations that were raised in a review dated December 11, 1984 are acceptable. Therefore, the bio-study that was originally filed on December 20, 1983 is now found to be acceptable. The responses submitted on 8/5/85 to NDA 19-010, which address the deficiencies and recommendations that were raised in a Division of Biopharmaceutics review dated 12/11/84, are acceptable.

Anita Shah 5/29/87
Anita Shah, Ph.D.
Pharmacokinetics Evaluation Branch

RD Initialed by John P. Hunt 5/21/87
FT Initialed by C.T. Viswanthan, Ph.D. CTV 5/13/87

cc: NDA 19-010 Orig., HFN-810, HFN-226(A. Shah), HFN-344(Turner), Drug, Chron and FOI files

AS:lyt [redacted] 5-27-87

Leuprolide

DRUG

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics
Office of Drug Standards

DATE : November 27, 1984 DEC 11 1984

TO : Dr. Sobel
Director, Division of Endocrine/Metabolic Drugs
HFN-130

FROM : Jerome P. Skelly, Ph. D.
Acting Director, Division of Biopharmaceutics
HFN-220

SUBJECT: Deferral of in vivo Bioavailability/Bioequivalence requirements;
1 mg s[redacted]; NDA 19-010
Abbott Laboratories; December 20, 1983

BACKGROUND:
Leuprolide is a synthetic nonapeptide analog of the naturally occurring gonadotropin releasing hormone (GnRH). Leuprolide acts as a gonadotropin inhibitor and is chemically unrelated to the steroids. Its structure is designated by the following notation:

$$(\text{D-Leu } 6,\ \text{des-Gly-NH}_2^{10},\ \text{proethylamide}^{9}) - \text{GnRH}$$

Following chronic administration of leuprolide in laboratory animals there is an inhibition of gonadotropin release, with the consequence that ovarian or testicular function is supressed.
The findings that leuprolide caused regression of chemically induced mammary tumors, and reduced hormonal levels in male and female rats, led to the investigation of its therapeutic use in human breast and prostatic cancer patients.
About 300 breast and prostatic cancer patients have been enrolled in ongoing Phase II and III studies with leuprolide. The doses range from 1 to 10 mg injection SC once a day, for as long as the patients continue to have clinical benefit from the treatment.

DISCUSSION:
Only one Bio-Study (M83-019) was submitted in support of this NDA. It was performed by Keith G. Tolman, M.D. at the Drug Research Center, University of Utah Medical Center, Salt Lake City, Utah. The objectives of the study were to compare the bioavailibility of 1 mg of Leuprolide (Lot #49-644AR) after SC and IV injection and to characterize the pharmacokinetic profile of Leuprolide. This was a single dose, randomized two period crossoyer study using six healthy male subjects with a one week washout period. Leuprolide plasma concentrations were determined by a radioimmunoassay (RIA) based on a method published in Endocrinol. Japan 1980: 27 (5) 593-605 by IYAMAZAKI and HOKADA. This study was found unacceptable mainly because the RIA assay employed was not fully validated.

CONCLUSION:
Deferral of the bioavailability requirements is recommended under CFR 320.22(5)(e) because leuprolide is animportant oncologic drug. The issues stated in the bio-review should be addressed in Phase IV studies.

Jerome P. Skelly

Jerome P. Skelly, Ph. D.
Acting Director,
Division of Biopharmaceutics

Prepared by Lesley R. Frank, Ph.D.
Initialed by M.K.Yau, Ph.D.
Initialed by Mei-Ying Huang, Ph.D.

cc: NDA 19-010 orig., HFN-220 (Skelly, ~~Malinowski,~~ Shulman), HFN-225 (Frank), HFN-130 (Sobel), Chron, Drug, Review, and Division Files.

LRF:kek:dea:[redacted]:11-28-84

Leuprolide
SC injection 1 mg
NDA 19-010
Reviewer: Lesley R. Frank, Ph.D.
Wang # [redacted]

Abbott Laboratories
Abbott Park
North Chicago, IL 60064
Subission Date:
December 20, 1983

DEC 1 1 1984

Bioavailability/Bioequivalence Study

Background:

Leuprolide is a synthetic nonapeptide analog of the naturally occurring gonadotropin releasing hormone (GnRH). Leuprolide acts as a gonadotropin inhibitor and is chemically unrelated to the steroids. It's structure is designated by the following notation:

(D-Leu 6, des-Gly-NH_2^{10}, proethylamide^9) - GnRH

Following chronic administration of leuprolide in laboratory animals there is an inhibition of gonadotropin release, with the consequence that ovarian or testicular function is supressed.
The findings that leuprolide caused regression of chemically induced mammary tumors, and reduced hormonal levels in male and female rats, led to the investigation of its therapeutic use in human breast and prostatic concer patients.
About 300 breast and prostatic cancer patients have been enrolled in ongoing Phase II and III studies with leuprolide. The doses range from 1 to 10 mg injection SC once a day, for as long as the patients continue to have clinical benefit from the treatment.

Study M83-019

Investigator: Keith G. Tolman, M.D.
Site: Drug Research Center
University of Utah Medical Center
Salt Lake City, Utah

Drug: Leuprolide Acetate (Lot 49-644 AR)
1 mg/subject

Objectives:
To compare the bioavailability of 1 mg of Leuprolide after SC and IV injection and to characterize the pharmacokinetic profile of leuprolide.

Design:
Six healthy male subjects were selected from volunteers available to the Drug Research Center in Salt Lake City. Their ages ranged from 23-31 years; their weights ranged from 150-214 pounds. The subjects were judged to be in good health based on medical histories, physical examination, laboratory tests; chest X-rays and ECG's

This was a single dose randomized, two period crossover study. The regimens (IV or SC) were administered according to subject number, so that one-half of the subjects received each regimen in the first period of the study. The regimen was reversed among the subjects one week later during the second period, such that each subject received each regimen upon completion of the study. A one week washout period was observed. Pre-dose fasting fron all food and drink (exept water) commenced 11:30 pm, eight hours before dosing.

Standard meals were served 2, 5 and 10 1/2 hours post dosing.

Five ml of blood were drawn at the following times: 0, 5, 10, 15, 20, 30, and 45 minutes, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours post dosing.

Subjects were instructed not to use any other medications during the study. Subjects taking chronic medication or with pre-study hormonal levels outside the normal range by ±10% were excluded.

Analytical Procedures:

A radio immunoassay (RIA) for the determination of Leuprolide in plasma was used. The procedure was based on a method published in Endrocrnol. Japan 1980: 27(5)593-605 by IYAMAZAKI and HOKADA. Antibody was raised in rabbits by conventional methods and was provided to Abbott Laboratories by Takeda Pharmaceutical Co. Osaka, Japan. Radioiodinated leuprolide was used as tracer. The antisera showed a tendency to cross react with LH-RH analogues, though the degree of the cross-reactivity differed among individual sera. The antibody was previously shown to be highly specific against various natural hormones and against some synthetic analogs of leuprolide. For analysis, 200 ml of plasma or serum was mixed with diluted antiserum (200 ml) and tracer (100 ml ca. 10,000-20,000 cpm) solutions. The mixture was incubated at 5°C for at least 24 hours, and the antibody-bound radioactivity method using either Immunobead Second Antibody reagent or Double Antibody Precipitating Suspension. A set of standard leuprolide solutions was assayed along with the unknown samples to derive a daily calibration curve.

Standard deviations within replicates were ±10%.

Statistical and Pharmacokinetic Analysis:
Analysis of variance was performed on serum concentrations for the sampling times, and on the AUC serum-time curves for each route of administration. The effects included in the ANOVA model were route, period and subject.
The SC and IV plasma data were fit to a 2 COM open model using NONLIN, a nonlinear least square regression computer program.

Results

Appended to this review are tables B-1 and B-2, representing the plasma leuprolide values and the ANOVA calculations respectively.

Individual $AUC_{0-\infty}$ ranged from 94 to 189 ng hr/ml and 81 to 163 ng hr/ml for the IV and SC dose, respectively. The mean $AUC_{0-\infty}$ was 126 ± 33 ng hr/ml after IV administration and 119 ± 35 ng hr/ml after SC administration. There was no significant difference in $AUC_{0-\infty}$ between the two treatment routes by ANOVA. A 19% difference could be detected with an $\alpha = 0.05$ and a power of 80%.

The IV data was fit to a bolus injection 2-COM open model, with a β = 2.9 hours.

The SC data was also fit to a 2-COM open model with elimination from the central compartment and 1st order absorption from the injection site, with β = 3.6 hours.

The difference between the two mean beta half-lives was statistically significant.

A summary of NONLIN fits of leuprolide concentration data and pharmacokinetic parameters can be found in table 3, appended herein.

No adverse reactions were reported.

Comments:

1. Regarding specificity of the RIA assay, the sponsor references the YAMAZAI & OKADA article, which uses antisera that was tested and validated in rats, not in humans. Cross-reactivity to endogenous substances and leuprolide analogs was present. There also existed lot-to-lot variability with respect to the antisera which lead to the variable recoveries cited in this article (104-127%). The sponsor states that the synthetic analogs of leuprolide with which the sera crossreacts, have not been established to be the metabolites of leuprolide. What the metabolites of leuprolide are, in humans, has not been established in this submission, so lack of cross-reactivity of the antisera in the human has not been established.

The limits of sensitivity tested by this assay appears to be [redacted] pg - [redacted] pg per tube, However validation data was only presented for [redacted] pg/ml [redacted] pg/ml (± SD), thus putting the lower limit of this assay at [redacted] ng/ml. Furthermore, it is stated that as reliable quantitation at 5 pg cannot always be obtained the sponsor suggets a lower limit of [redacted] pg/ml, corresponding to [redacted] pg/tube.

2. Based on the $AUC_{0-\infty}$ values which were estimated by NONLIN, the bioavailability of leuprolide after SC and IV administration were comparable and showed no statistically significant difference with respect to $AUC_{0-\infty}$. A 19% difference could be detected with α = 0.05 and a power of 80%.

3. As expected, the maximum plasma concentrations obtained after the IV and SC administrations were significantly different. They were 121.3 ± 41.3 ng/ml (observed immediately after IV dosing) and 32.8 ± 11.6 ng/ml (observed at 0.5 hour after SC dosing). The medical reviewer should be aware of this difference when the clinical saftey and efficacy data are evaluated.

Deficiencies

1. The RIA assay should be validated for cross-reactivity in the human, as it was in the female Sprague-Dawley rat. Additionally, the sensitivity of the assay should be validated down to 100 pg/ml.

2. Individual $AUC_{0-24\ hr}$ values as determined from the observed plasma data (not computer fit data) are not reported. This result should be submitted along with the study power to detect 20% difference of the mean $AUC_{0-24\ hr}$ at α of 0.05 level.

Recommendations:

The bioequivalency study No. M83-019 found in volume 12 (December 20, 1983) and conducted by Keith G. Tolman M.D. at Salt Lake City, Utah, has been found to be unnacceptable by the Division of Biopharmaceutics due to the reason stated in Deficiencies 1 and 2. In order to meet the Biopharmaceutics requirements, the sponsor should resolve Deficiencies 1 and 2 and address the following issues:

1. Identify the injection vehical of the proposed marketing product.

2. Submit the labeling information.

3. Address the dose proportionality of Leuprolide. This is needed because patients have been given doses ranged from 1 to 10 mg SC injection once a day in the ongoing Phase II and Phase III studies.

4. Provide information regarding to the drug metabolism (especially about active metabolite(s) if exsistant, and route of elimination) and protein binding of Leuprolide in humans.

Normally, the above issues must be resolved by the sponsor before the drug will be recommended for approval. However, after a discussion with Dr. Sobel who requests that the biopharmaceutics deficiencies of leuprolide be addressed in a post-marketing period, the Division has agreed, for good course, to let the sponsor to resolve the biopharmaceutics deficiencies in a Phase IV period. This deferral is granted on the basis of CFR 320.22e because Leuprolide is classified as a 1A drug and it represent a significant contribution to the area of Oncology.

Lesley R. Frank

Lesley R. Frank, Ph.D.
Pharmacokinetics Evaluation Branch I

RD Initialed by M.Yau, Ph.D.
FT Initialed by M.Y.Huang, Ph.D. MYH 12/4/84

cc: NDA 19-010 orig., HFN-130 (2), HFN-225 (Frank), Chron, Division, Drug, and Review Files

LRF/dea/kek/[redacted] (11/14/84)

Table B 1
Plasma Leuprolide Levels
(Clinical Protocol M83-P191

Subject	Concentration in Ng Per ML: Hours After Dosing: 0	0.0833	0.167	0.25	0.333	0.5	0.75	1	1.5	2	2.5	3	4	5	6	8	12	24	Area Under 0-Infin Curve (Hr Ng/ML)
Intravenous Dosing																			
-11																			
-12																			
-13																			
-14																			
-15																			
-16																			
Mean	(121.3)	114.3	31.2	67.6	68.2	43.3	32.2	26.3	20.2	15.2	13.4	11.3	8.1	6.4	4.9	2.4	1.1	0.2	125.8
S.D.	(41.3)	26.8	34.9	17.6	18.1	14.2	8.2	8.3	5.4	2.7	3.0	3.6	2.1	2.3	1.9	0.6	0.3	0.1	32.9
S.E.M.	(16.8)	10.6	15.6	7.2	7.4	5.8	3.3	3.4	2.2	1.1	1.2	1.2	0.9	0.9	0.8	0.7	0.1	0.0	13.4
Subcutaneous Dosing																			
-11																			
-12																			
-13																			
-14																			
-15																			
-16																			
Mean	0.0	8.5	16.0	26.7	29.7	32.0	32.5	28.9	24.0	18.7	18.6	14.2	9.6	6.0	5.0	3.1	1.2	0.2	110.6
S.D.	0.0	5.5	9.0	10.2	10.2	11.6	13.2	12.3	7.0	5.0	4.6	5.4	2.4	2.3	2.1	0.9	0.3	0.1	34.7
S.E.M.	0.0	2.2	3.6	4.2	4.2	4.7	5.4	5.0	3.2	2.0	1.9	2.2	1.0	0.9	0.9	0.4	0.1	0.0	14.2

NOTE: Asterisks indicate aberrant values that were not used in any calculations. See text.
Parenthesis indicate values estimated by extrapolation of NONLIN-generated best-fit curves.

Table B-2

STUDY M83-019: LEUPROLIDE (Abbott-43818) BIOAVAILABILITY STUDY: Subcutaneous vs Intravenous

RESULTS OF ANALYSIS OF VARIANCE

DEPENDENT VARIABLE: HR_12

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PR > F	R-SQUARE	C.V.
MODEL	7	0.82333333	0.11761905	7.43	0.0356	0.928571	11.1021
ERROR	4	0.06333333	0.01583333		STD DEV		HR_12 MEAN
CORRECTED TOTAL	11	0.88666667			0.12583057		1.13333333

SOURCE	DF	TYPE I SS	F VALUE	PR > F	DF	TYPE IV SS	F VALUE	PR > F
SN	5	[illegible]6667	9.18	0.0259	5	0.72666667	9.18	0.0259
PER	1	[illegible]3333	0.84	0.4107	1	0.01333333	0.84	0.4107
TRT	1	0.08333333	5.26	0.0835	1	0.08333333	5.26	0.0835

DEPENDENT VARIABLE: HR_24

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PR > F	R-SQUARE	C.V.
MODEL	7	0.08000000	0.01142857	6.86	0.0409	0.923077	17.4964
ERROR	4	0.00666667	0.0016667		STD DEV		HR_24 MEAN
CORRECTED TOTAL	11	0.08666667			0.04082483		0.23333333

SOURCE	DF	TYPE I SS	F VALUE	PR > F	DF	TYPE IV SS	F VALUE	PR > F
SN	5	0.07666667	9.20	0.0258	5	0.07666667	9.20	0.0258
PER	1	0.00333333	2.00	0.2302	1	0.00333333	2.00	0.2302
TRT	1	0.00000000	0.00	1.0000	1	0.00000000	0.00	1.0000

DEPENDENT VARIABLE: AUC

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PR > F	R-SQUARE	C.V.
MODEL	7	11050.34583333	1578.62083333	11.48	0.0163	0.952604	9.5947
ERROR	4	549.80333333	137.45083333		STD DEV		AUC MEAN
CORRECTED TOTAL	11	11600.14916667			11.72394279		122.19166667

SOURCE	DF	TYPE I SS	F VALUE	PR > F	DF	TYPE IV SS	F VALUE	PR > F
SN	5	8896.04416667	12.94	0.0140	5	8896.04416667	12.94	0.0140
PER	1	1999.50083333	14.55	0.0189	1	1999.50083333	14.55	0.0189
TRT	1	154.80083333	1.13	0.3484	1	154.80083333	1.13	0.3484

Table 3

Summary of NONLIN Fits of Plasma Leuprolide Concentration Data

(Clinical Protocol M83-019)

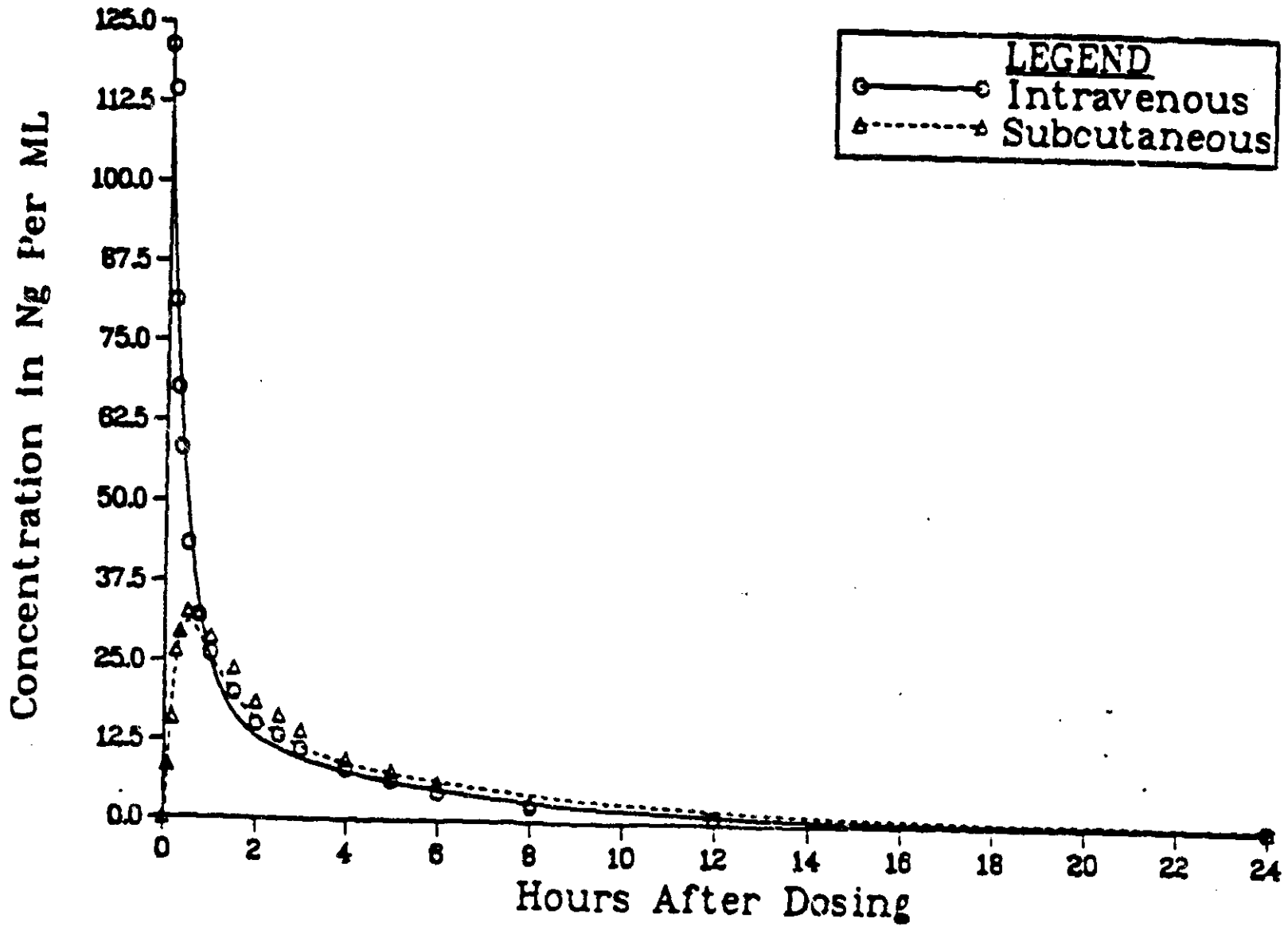
Subject	K_{Abs} (Hr^{-1})	K_{21} (Hr^{-1})	K_{12} (Hr^{-1})	K_{Net} (Hr^{-1})	V_1 (L)	Beta (Hr^{-1})	Half-Life (Hrs)	0-Inf AUC (Hr Ng/ML)	C_{Max} (Ng/ML)	T_{Peak} (Hr)
Intravenous Dosing										
11										
12										
13										
14										
15										
16										
Mean		0.679	1.292	0.956	9.2	0.243	2.9*	125.8		
S.D.		0.107	0.375	0.209	3.6	0.042		32.9		
Subcutaneous Dosing										
11										
12										
13										
14										
15										
16										
Mean	4.16	0.426	0.213	0.374	25.1	0.192	3.6*	118.6	32.3	0.6
S.D.	0.99	0.224	0.212	0.063	9.7	0.064		34.7	11.1	0.1

*Note: Calculated from corresponding mean value of beta.

Figure 1

Mean Plasma Leuprolide Levels With NONLIN-Generated Best-Fit Curves

(Clinical Protocol M83-019)



STAT

185 15406

Statistical Review and Evaluation

NDA #: 19-510/Drug Class:1A Date: APR 13 1984

Applicant: Tap Pharmaceuticals (thru Abbott Laboratories)

Name of Drug: Leuprolide Acetate (Injectable)

Documents Reviewed: Volumes 4.1, 4.6, 4.8 and 4.9 of NDA 19-510 dated 2/2/84 (Submission dated 12/14/83) by Center of Drugs and Biologics.

I. Background and Summary

The sponsor submitted two multicenter clinical trials in support of the safety and efficacy of leuprolide acetate in the palliative treatment of advanced prostatic cancer in previously untreated patients.

Study M81-017 is an ongoing multicenter open trial with DES as the concurrent control. Study M80-036 is also an on-going multicenter open trial without concurrent control; the control arm from an on-going study (#1300) organized by the National Prostatic Cancer Project group (NPCP) is used as a retrospective control for the purpose of comparison. Data cutoff date at time of analysis for both studies was 1/1/83 at which time over 80% of the patients were still responding.

Based on my review of these two studies which are discussed in detail in Sections II and III, I conclude that the relative efficacy between leuprolide and DES/orchiectomy cannot be determined at this time due to the heavily censored data and recommend that the sponsor should provide an updated analysis which will include data for an additional 15 months. The safety profile of leuprolide thus far appeared to be favorable in comparison to DES.

I have discussed my comments with the clinical reviewer, Dr. Schaffenburg (HFN-130), and he is in agreement with the above conclusions.

II. Study M81-017

A. Study Description

This is an on-going, randomized, multicenter, conditional crossover, open study. Patients who had stage D2 adenocarcinoma of the prostate and had no previous hormonal or chemotherapy treatment were randomized to receive either leuprolide, 1 mg/day, or diethylstilbestrol (DES), 3 mg/day. Patients who showed either definite evidence of progression or intolerable side effects were to be crossed over to the other treatment.

Two hundred and two (202) male patients were enrolled in the study by 21 investigators. This submission includes summaries of data (except survival) current as of the cutoff date of 1/1/83. Survival data are current as of 6/10/83.

Patients were to report to the investigator on Day 8 and at the end of Weeks 2, 4, 8 and 12. Thereafter, patients were to report every 6 weeks. At the end of Week 12, and every 12 weeks thereafter, the investigator was to assess the objective response to treatment.

Objective response was defined according to the National Prostatic Cancer Project (NPCP) group's criteria. The categories are Complete Response (CR), Partial Response (PR), Objectively Stable (NC) and Progression (P). Other efficacy variables include Time to Progression, Duration of Treatment, Survival, Performance Status, Subjective Response (Improved, Same or Worsened), Bone Pain and Urinary Signs and Symptoms. Safety was monitored by laboratory values and the reporting of any adverse event that might be drug related on a special adverse effect form.

B. Result of the Study

The following table is a breakdown on patients according to whether they were evaluable or not as classified by the sponsor.

	Leuprolide	DES
Randomized	101	101
Not Evaluable	8	6
Eval. but w/o wk. 12 data	3	12
No objective response data	1	1
Eval. with wk. 12 data	89	82

Twenty-one and 28 patients in the Leuprolide group and the DES group, respectively terminated their first treatment (either dropped out or crossed over).

However, the reasons for termination were significantly different between treatment groups. More patients in the leuprolide group than in the DES group (16 vs. 6) terminated the first treatment because of progression. The opposite was true because of adverse reactions (2 vs. 14). Patients whose initial treatment was leuprolide terminated their treatment significantly ($p < .002$) later than patients treated initially with DES (mean 216 days vs. 124 days). Patients randomized to DES appeared to be sicker than patients randomized to leuprolide.

For patients who were in the study long enough to have at least a Week 12 evaluation, the best objective response of DES patients was significantly better than that of the leuprolide patients.

	Best Objective Response				
	CR	PR	NC	P	Total
leuprolide	1	34	44	10	89
DES	2	41	37	2	82

Time to first progression, time to treatment failure and survival were not significantly different between the two treatment groups as of the cutoff date (1/1/83) of data collection. However, since more than 80% of the patients were still responding, no conclusion could be drawn at the time of data analysis. Duration of treatment was longer for the leuprolide group than for the DES group. However, the high level of censoring makes definitive conclusion difficult.

Subjective response over the duration of the study was classified as 'Improved' (at least one 'Improved' and no 'Worsened'), 'Worsened' (at least one 'Worsened' and no 'Improved') and 'Same' (all 'Same' or mixtures of 'Improved' and 'Worsened'). An integrated score (weighted average of the subjective response over time) was also used. There was no statistically significant difference between the two treatments in either analysis. The variable Performance Status was similarly analyzed and there was no significant difference between treatments either. The variable Bone Pain was categorized according to a combination of severity and frequency of pain. An integrated score (average over time) was also used. A similar scheme was used for the variable Analgesic Use. A comparison of the integrated Bone Pain and integrated Analgesic Use variable showed that patients on DES experienced a greater reduction in their bone pain ($p=.03$) and analgesic use ($p=.13$) than did leuprolide patients. Urinary signs and symptoms were not significantly different between leuprolide and DES patients.

Because leuprolide's mechanism of action is to stimulate the pituitary gland, an initial stimulation in testosterone levels was observed as expected. Thus patients in the leuprolide group actually felt worse in the initial 2 to 4 weeks before they felt better.

Adverse Reactions

The following table provides the number of patients who experienced certain frequently occurring adverse reactions. The number in parentheses is the number of patients with adverse reactions during the initial treatment period only.

	leuprolide	DES	p-value
Hot flash	57 (51)	12 (11)	.0001
Gynecomastia	4 (3)	30 (29)	.0001
Breast tenderness	-	20	-
Impotence	4	11	-
Cardiovascular	9 (6)	29 (27)	.0001
Nausea & Vomiting	6 (5)	18 (16)	.02

The main adverse reactions were hot flash in the leuprolide group and gynecomastia in the DES group. Frequencies of other adverse reactions were lower for leuprolide patients than for DES patients. All patients had abnormal laboratory values in hematology, clinical chemistry and urinalysis data reported over the course of the study. There were significant between group differences in 5 of 10 hematology parameters (hematocrit, WBC, neutrophils, lymphocytes and basophils) and 9 of 15 clinical chemistry parameters (calcium, phosphorus, cholesterol, BUN, total protein, albumin, total bilirubin, LDH and acid phosphatase) at Week 12.

C. Reviewer's Comments

It would appear that the objective variables, time to progression and survival should be considered as primary efficacy variables. However, the relative efficacy between leuprolide and DES could not be determined at the time of analysis because the study is still on-going and over 80% of the patients were still responding as of 1/1/83. A statistical non-significance based on the limited data available is meaningless. An updated analysis would certainly shed more light on the issue of relative efficacy between leuprolide and DES.

Another difficulty in the interpretation of the data is that the baseline prognosis between the two treatments does not appear to be comparable. For example, time from the date of D2 diagnosis to date of treatment was longer for the DES patients than for leuprolide patients (mean 142 days vs. 64 days).

The proportion of patients with history of thromboembolic disease was higher in the DES group than in the leuprolide group (25% vs. 15%). Perhaps these imbalances explain the substantially larger number of DES dropouts before the Week 12 evaluation (DES 12 vs. leuprolide 3). These early dropouts in the DES group were sicker at entry than those of the leuprolide group. For example, these DES patients had a higher average level of prostatic acid phosphatase and higher tumor burden.

If one ignores these early dropouts and confines the analysis to only patients with at least a Week 12 evaluation, then the best objective response of the DES group was significantly better than that of the leuprolide group. However, if one includes the early dropouts as treatment failures (treated the same as progression) in the analysis, the two groups were essentially similar. Taking into consideration that the DES group was sicker at entry, this would still seem to indicate a slight edge for the DES group. However, as commented earlier, it is too early to decide whether there is any significant difference between the two treatments at this stage.

The possibility of investigators' bias could not be excluded. According to the sponsor, there were indications that the investigators were less reluctant to take a patient off treatment with DES than leuprolide once treatment failed to curb the progression of the disease or when adverse reactions developed. If this was the case, the variable duration of treatment would not be useful as an indication of treatment success.

The variables subjective Response, Performance Status, Bone Pain, etc. are measures of quality of life. These are important measurements also, according to the clinical reviewer, Dr. Schaffenburg, HFN-130. However, except for Bone Pain which appeared to favor the DES treatment, there were essentially no differences between the two treatments. It should be commented that Subjective Response did not always agree with the Objective Response in this study. In about 10% of the patients the Subjective Response rating was in the opposite direction from the Objective Response. In all such cases except one in each treatment group the Subjective Response was 'Improved' while the Objective Response was 'Worsened'.

Because the study is on-going and was in fact at an early stage when data were collected and analyzed, the duration of the treatment among patients varied widely. The sponsor made an effort to summarize the outcomes of the many efficacy variables over different lengths of treatment periods by using integrated scores and categorizaiton of combination variables. Although the approach appeared to be reasonable given the nature of the data, the validity of these schemes is questionable. However, the analysis at a fixed time point, e.g., at Week 12 as is provided by the sponsor is valid.

In conclusion, the data presented as of 1/1/83 should be considered as an interim analysis which does not provide conclusive evidence as to the efficacy of leuprolide in comparison with DES. No conclusion could be drawn based on the variables Time to Progression and Survival since over 80% of the patients were still responding. Based on patients with evaluable Week 12 data, DES appeared to be superior in the variables, Best Objective Response and Bone Pain. More patients in the leuprolide group crossed over or dropped out because of progression of the disease and more patients in the DES group did so because of adverse reactions. However, whether patients who dropped out or crossed over due to adverse reactions in the DES group should be considered as treatment failures is questionable because there was an imbalance in the willingness of the investigators to switch patients to other treatments as pointed out by the sponsor. Leuprolide appeared to be less toxic than DES.

III. Study M80-036

A. Study Description

This was a Phase II, multicenter open study in which all patients received leuprolide. The initial design of the study called for entry of 60 patients stage C, D1, or D2 of whom at least 30 were previously treated. Preliminary analysis showed a poor response rate among previously treated patients and on June 30, 1981 an amendment to the protocol increased the sample size to 120 and required that all patients entered from that date be previously untreated and Stage D2.

The control arm of a study by the National Prostatic Cancer Project group (NPCP) (consisting of patients who received treatment with DES or orchiectomy) was used as a retrospective control to compare with Study M80-036. The

Objective Response criteria are the same for both studies and the two studies were open for patient accession within a month of each other. For the leuprolide study, the first assessment of response was to be done at Week 10 then at Week 16 and once every other month thereafter. For the NPCP study, the assessment frequency was once every 3 months.

The efficacy variables are Objective Response, Duration of Response (for responders only), Duration of Treatment, Bone Pain and Performance Status.

B. Result of the Studies

Both the M80-036 and the NPCP studies were still on-going as of the data cutoff dates of 1/1/83 for the M80-036 Study and 3/3/83 for the NPCP Study.

One hundred eighteen (118) patients were enrolled in the leuprolide study of which 100 patients were evaluable. The following table provides the number of evaluable patients by previous treatment and Stage D2.

	Prior Treatment			
	None	DES	ORCH	Total
Stage D2	47	21	26	94
Other	6	0	0	6
Total	53	21	26	100

All 93 patients in the control arm of the NPCP Study were previously untreated stage D2. Five patients were considered non-evaluable and 17 other patients were recent entries without efficacy data. This left 71 patients for the purpose of comparison.

Since there were only 6 patients of stage D1, or C, the analysis is limited to Stage D2 patients only. The following table provides the number of D2 patients in Study M80-036 classified by their best objective response and prior treatment.

Prior Treatment	CR	PR	NC	P	Total
None	1 (2%)	18 (38%)	15 (32%)	13 (28%)	47
Orchiectomy	0	0	6 (23%)	20 (77%)	26
Hormonal	0	1 (5%)	9 (43%)	11 (52%)	21
Total	1 (1%)	19 (20%)	30 (32%)	44 (47%)	94

Leuprolide appeared to be ineffective for previously treated patients who had a significantly longer time from diagnosis to study entry when compared to untreated patients. The following table compares the best response in previously untreated patients between Study M80-036 and the control arm of the NPCP study.

Study/Treatment	CR	PR	NC	P	Total
M80-036/Leup.	1 (2%)	18 (38%)	15 (32%)	13 (28%)	47
NPCP/DES	0	7 (15%)	34 (74%)	5 (11%)	46
NPCP/ORCH	1 (4%)	1 (4%)	17 (68%)	6 (24%)	25
NPCP (All)	1 (1%)	8 (11%)	51 (72%)	11 (15%)	71

The rate of progression in leuprolide patients (28%) was significantly higher (p=.04) than that of the NPCP DES control patients (11%). The rates of 'Objective Improvement' (CR + PR) of leuprolide and DES (or DES/orch) were significantly different in favor of leuprolide.

For patients whose best response was either CR, PR or NC, the 'Duration of Response' (time from study entry to first progression) was compared between leuprolide patients and the NPCP/DES (or DES + Orch) patients. Although the leuprolide curve dominated the NPCP curve at this time, no conclusion could be drawn since the majority of the patients were still responding as of 1/1/83. Similarly, no conclusion could be drawn from the survival data; more than 80% of the patients were still alive.

Subjective Response and quality of life were not compared with the NPCP study. For the M80-036 study, the sponsor stated that bone pain and performance status improved more in the responders than in the non-responders. Furthermore, it was claimed that patients showed improvement in their quality of life during treatment regardless of their objective response.

In the leuprolide study, patients were initially randomized to either 1 mg/day or 10 mg/day. The 10 mg/day dosage was dropped subsequently after an interim analysis which showed that there was no dose response relationship.

The early phenomena of leuprolide treatment were similar to those of the Study M81-017. The following table provides the numbers of patients who experienced some of the more frequent adverse reactions in the leuprolide study. No comparison was made between this and the NPCP study.

Endocrine System

Hot flash/Sweating	65
Impotence	8
Libido Decrease	8

Integumentary System

Local reaction at inj. site	13

Digestive System

Nausea/Vomiting	16

Cardiovascular System	
Edema	15
Nervous System	
Dizziness	8
Memory disorders	5
Numbness	5
Respiratory System	
Shortness of Breath	10
Urogenital System	
Dysuria	7
Miscellaneous	
Chills/Fever	11
Weakness	26
Other Pain	12

The sponsor concluded that leuprolide is as efficacious as DES or orchiectomy for the treatment of prostatic carcinoma in previously untreated Stage D2 patients.

C. Reviewer's Comments

As the sponsor pointed out, Study M80-036 was not designed as a comparative study. The use of a retrospective control group from the NPCP Study is an effort by the sponsor to show that leuprolide is comparable in efficacy to DES/orchiectomy in previously untreated patients. However, it is well-known that comparisons with a historical control group are less reliable than are comparisons with a concurrent control group. In the present case the type of patients in the control arm of the NPCP study appeared to be comparable to the leuprolide patients and the objective response criteria were the same. The major difficulty in the comparison would seem to lie in the possible difference in the investigator's assessments between the two studies. Based on the criteria for the different objective responses, the categories of Complete Response (CR) and Progression appear to be clear cut. However, the classifications of Partial Response (PR) and No Change (NC) are less clear. Thus, a comparison between the two treatments based on distinctions including PR and NC would not be very meaningful because different investigators were involved in the two studies. However, a distinction based on Progression or No Progression in the comparison of the treatments would seem more reasonable. Subjective response should not be used in the comparison (and was not by the sponsor).

The variable Duration of Response should be interpreted with caution since it involves only responders. The longer duration of response in the leuprolide group should not be interpreted as evidence of superiority when the percentage of responders was smaller than in the NPCP control arm (72% vs. 85%). A more reasonable approach is to use the variable Time to Progression and include both responders and non-responders. However, the sponsor has not done this. Another useful efficacy variable is survival. Like Study M81-017, this study (M80-036) and the NPCP study are still on-going and the majority of patients were still responding as of the date of data cutoff (1/1/83). The sponsor's conclusion that leuprolide is as efficacious as DES/orchiectomy based on the limited data is pre-mature even if no statistical significance between them could be demonstrated at this point. The heavily censored data preclude definitive conclusions. The statistical testings of subjective response in the comparison between responders and non-responders in the leuprolide patients are not meaningful since these groups were determined by the outcome of the treatment rather than groups with pre-determined characteristics.

IV. Conclusions to be Conveyed to the Sponsor

The conclusion that leuprolide was as efficacious as DES/orchiectomy in the treatment of prostatic cancer in previously untreated patients is pre-mature at this time based on the limited data from studies M80-036 and M81-017. The majority of patients were still responding as of 1/1/83 when the data collection was cut off for analysis. The heavily censored data preclude definitive conclusion on their relative efficacy. The sponsor should do an updated analysis including the 15 months that have elapsed since then. The updated analysis should pay more attention to the variables Time to Progression and Survival. In the analysis of Time to Progression, both responders and non-responders should be accounted for (for example, the time to progression for a non-responder would be zero).

In Study M81-017, some prognostic variables (time from date of D2 diagnosis to date of treatment and history of thromboembolic disease) were not comparable between DES and leuprolide patients. This should be taken into account in future analysis. For example, the Cox regression with covariate adjustments may be appropriate.

In the reporting of adverse reactions, the use of the life table method should be considered.

Hoi M. Leung, Ph.D.
Mathematical Statistician

cc: Orig., NDA 19-032
HFN-130
HFN-130/Dr. Schaffenburg
HFN-224/Dr. Lisook
HFN-713/Dr. Dubey
HFN-713/Dr. Leung
Chron.
File: DRU 1.3.2 NDA
HMLeung/njs/4/11/84/0095n

Concur: Dr. Pledger 4/13/84

Dr. Dubey 4/13/84

Statistical Review and Evaluation

Date: JUN 28 1984

NDA #: 19-010/Drug Class: 1A

Applicant: Tap Pharmaceuticals (thru Abbott Laboratories)

Name of Drug: Leuprolide Acetate (Injectable)

Documents Reviewed: One un-numbered desk copy of NDA 19-010 dated 4/23/84.

The contents of this review have been discussed with the clinical reviewer, Dr. Schaffenburg, HFN-810 and he is in agreement with my conclusions.

I. Background

This is an addendum to my previous review dated 4/13/84 in which I stated that the relative efficacy between leuprolide and DES could not be determined due to the heavily censored data and recommended that the sponsor should provide an updated analysis which would include data for an additional 15 months.

This submission is an updated analysis which includes data as of January 1, 1984, 12 months additional data.

II. Reviewer's Comments on the Updated Analysis

In the updated analysis, the variables time to death, time to treatment failure and time to objective progression (responders) were analyzed by the Kaplan-Meier estimate. The between treatment group comparison was done by the Gehan-Breslow test and the Mantel-Cox test. These are acceptable standard techniques in survival analysis. We will examine the results of the updated analysis in the following.

A. Study MBI-017

There were 93 and 95 evaluable patients, respectively, in the leuprolide and DES group compared to 89 and 82 patients, respectively, in the original submission since a few more patients had reached the 12 week cutoff point for evaluability.

1. Time to Death

The original data on time to death had a data cutoff date of 6/10/83. Thus, the updated analysis here represents data for only an additional period of slightly less than 6 months. The percentage of censoring was 69% and 72% for the leuprolide and DES group, respectively. Due to the high degree of censoring, the median survival time for either group is still not estimable. The two survival curves (See Appendix) are not statistically significantly different and they cross at week 75. The estimated 12 month survival rate was 86% for leuprolide and 78% for DES and the 18 month survival rates were 74% for leuprolide and 76% for DES. Survival rates beyond 18 months are not estimable at this time because only a few patients had reached that time point. Interpretation of survival rates is complicated by the fact that patients who crossed over to the alternate treatment are counted in the

initial treatment group. The number of deaths occurring in patients who crossed over is not given.

Note that the apparent slight advantage of leuprolide over DES in the first year could be attributable to the fact that there were more seriously ill patients in the DES group than in the leuprolide group at the beginning. Taking this into consideration, it appears that the survival experiences up to 18 months between leuprolide and DES treated patients were very similar.

2. Time to Treatment Failure

Time to treatment failure is defined as the number of weeks from the first dose to the time of either disease progression, termination of treatment due to adverse reaction or death. As of January 1, 1984, the percent censored was 42 and 53 percent, respectively, for the leuprolide and DES group. The two curves (See Appendix) are practically indistinguishable. They crossed each other at least 10 times. The trend of the treatment failure pattern in the original submission appears to be continuing here. The estimated median time to treatment failure was 49 weeks for leuprolide and 48 weeks for DES. The failure rates at 1 year were 53% and 58%, respectively, for leuprolide and DES. Unless there is a dramatic departure from the current trend, it is unlikely that a statistically significant difference will occur when the study is completed.

3. Time to First Progression

This variable is defined for those patients whose best objective response on the initial study drug was "No Progression". It is the number of weeks from the first dose to the first time progressive disease was reported on the initial study drug following an objective response of "No Progression". This variable may be censored by continuing treatment without progression as of January 1, 1984, dropouts, deaths, lost to follow-up or crossover to the other treatment for reasons other than progression. Thus, it can be seen that the percent of censoring in this variable could be high even when the study is completed. As of January 1, 1984, the percent of censoring was 53% and 79% for the leuprolide and DES group, respectively. It appears that there is a higher percentage of censoring in the DES group than in the leuprolide group. A plausible explanation is that investigators were more willing to switch patients from the DES group to the leuprolide group than vice versa. Also, there were more dropouts in the DES group due to adverse reactions than in the leuprolide group. These patients were considered to be censored in this analysis. Because of the many constraints that defined this subgroup, this variable is of limited value compared to the variables survival and time to treatment failure. Taking the data at face value there was no statistically significant difference between the two treatments though the DES curve slightly dominated (better in response) the leuprolide curve.

Safety

Two patients (#243 and #321) developed venous thrombosis while on leuprolide. According to the investigator, patient #243 had no previous history of venous thrombosis and patient #321 had a possible history of venous thrombosis before starting leuprolide. For detailed information, see Form 1639 in the submission.

B. Study M80-036

Recall that this was a "leuprolide only" study in three types of patients: previously untreated, orchiectomized and previously treated with hormone. It was concluded in my previous review (4/13/84) that leuprolide appeared to be less effective in the latter two subgroups of patients than in the previously untreated patients. A retrospective DES control group from a concurrent study (NPCP-1300) was used for the purpose of comparison between leuprolide and DES in previously untreated patients. I stated in my previous review that no conclusion could be drawn from the survival data since over 80% of the patients were still alive then. Unfortunately, for reasons unknown to this reviewer, the updated analysis only provides survival, and time to progression for the 3 subgroups in Study M80-036, the comparative analysis for the control arm of the NPCP study is absent. No new conclusion could be drawn from the information provided.

III. Conclusions to be Conveyed to the Sponsor

For Study M80-017, the updated analysis showed that the previous trends from the original submission in the variables survival, time to treatment failure and time to progression appear to be unchanged. There were no statistically significant differences between leuprolide and DES in these analyses. However, many of the estimates are unreliable because there are still large proportions of censored data. A final analysis including all efficacy and safety data should be provided when the study is completed. For Study M80-036, the comparative analysis for the control arm of the NPCP-1300 study should have been provided but was not. A final comparative analysis should be provided when the study is completed.

Hoi M. Leung

Hoi M. Leung, Ph.D.
Mathematical Statistician

cc: ✓Orig. NDA 19-010
HFN-810
HFN-810/Dr. Schaffenburg
HFN-810/Dr. Sobel
HFN-224/Dr. Lisook
HFN-713/Dr. Dubey
HFN-713/Dr. Leung
Chron.
File: DRU 1.3.2 NDA
HMLeung/njs/plt/06/25/84/34594/0130n

Concur: Dr. Pledger 6/25/84

Dr. Dubey 6/26/84

FIGURE 1
STUDY M81-017: TIME TO DEATH
(ALL EVALUABLE PATIENTS)

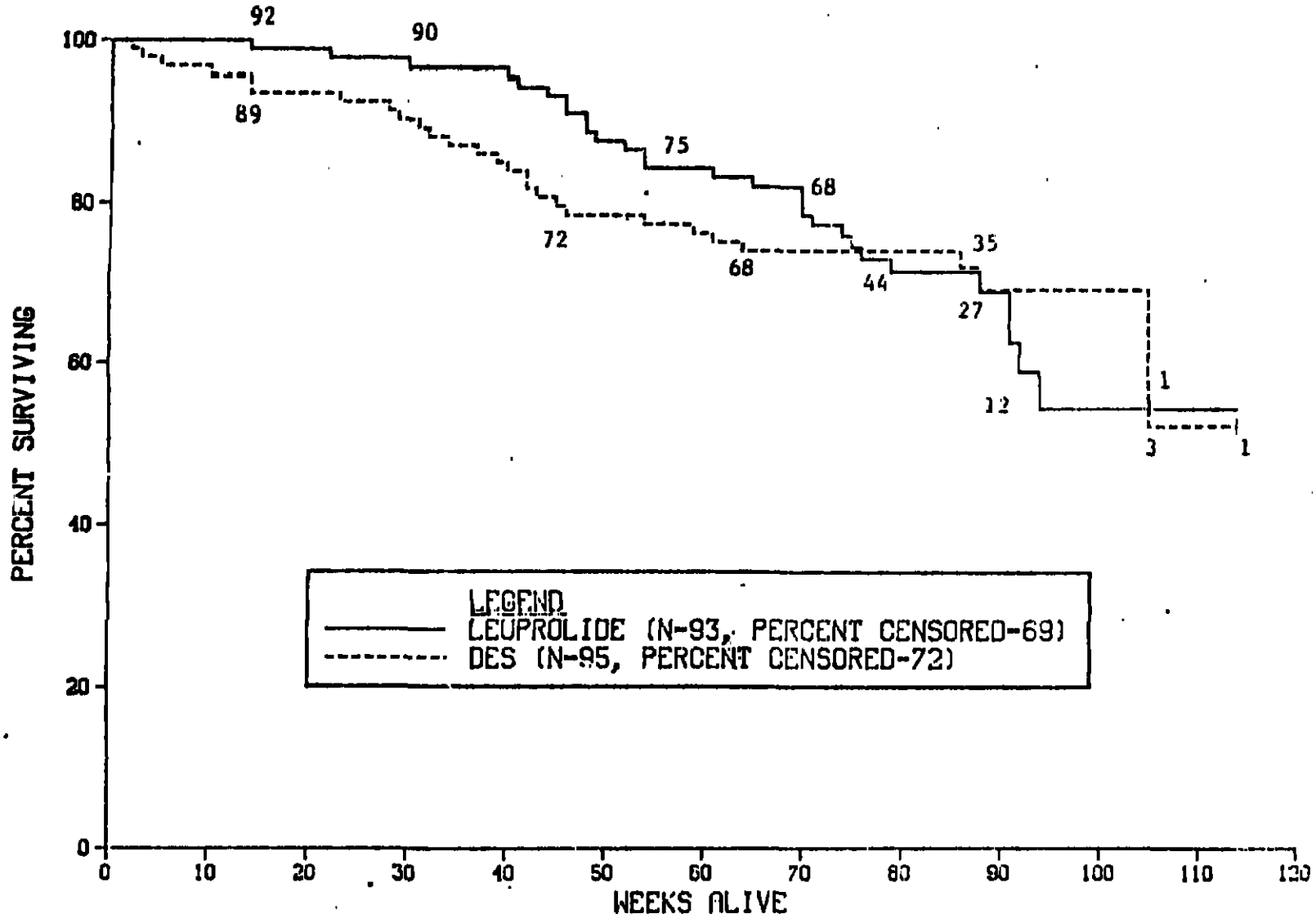


FIGURE 2
STUDY M81-017: TIME TO FIRST TREATMENT FAILURE
(ALL EVALUABLE PATIENTS)

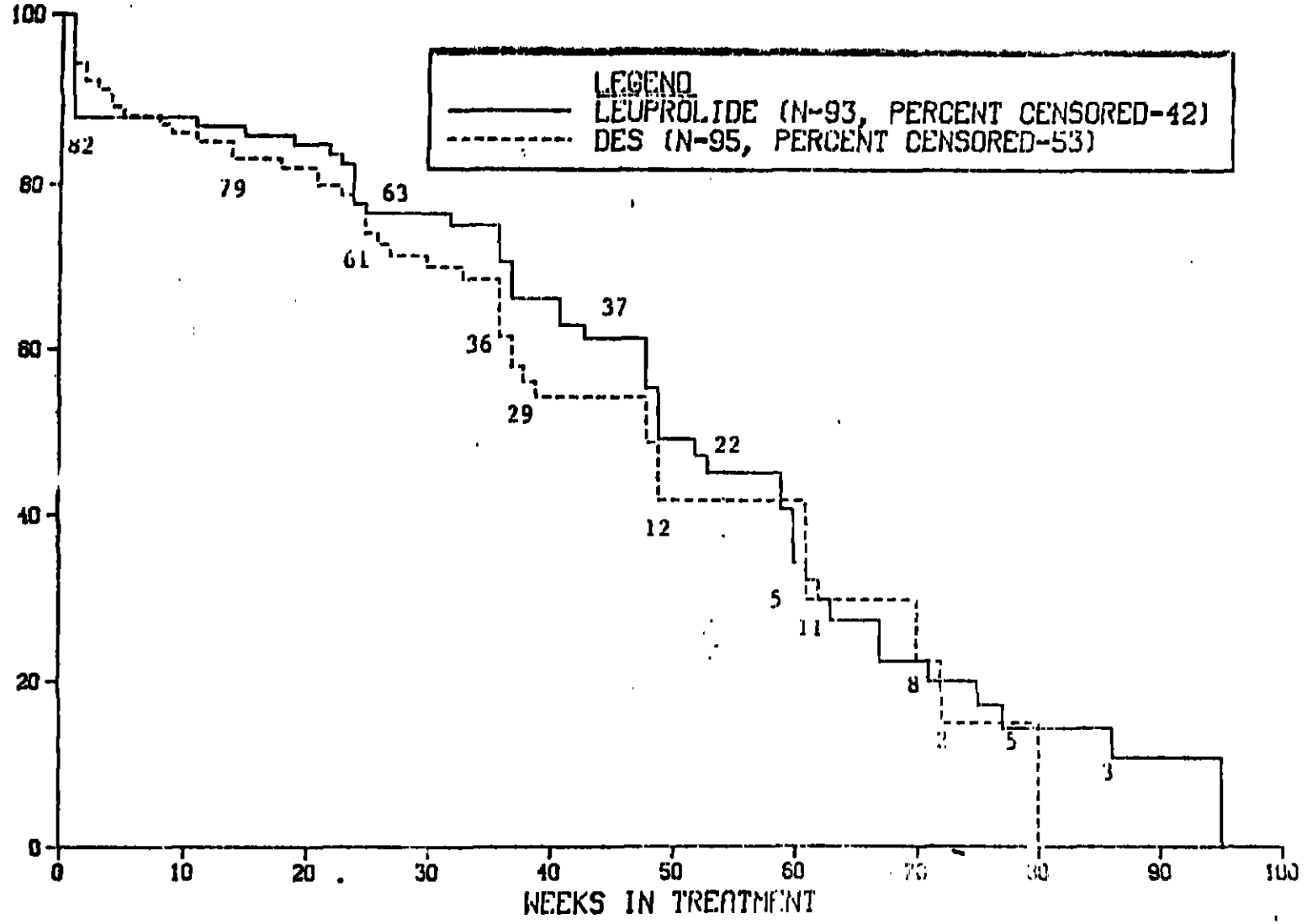
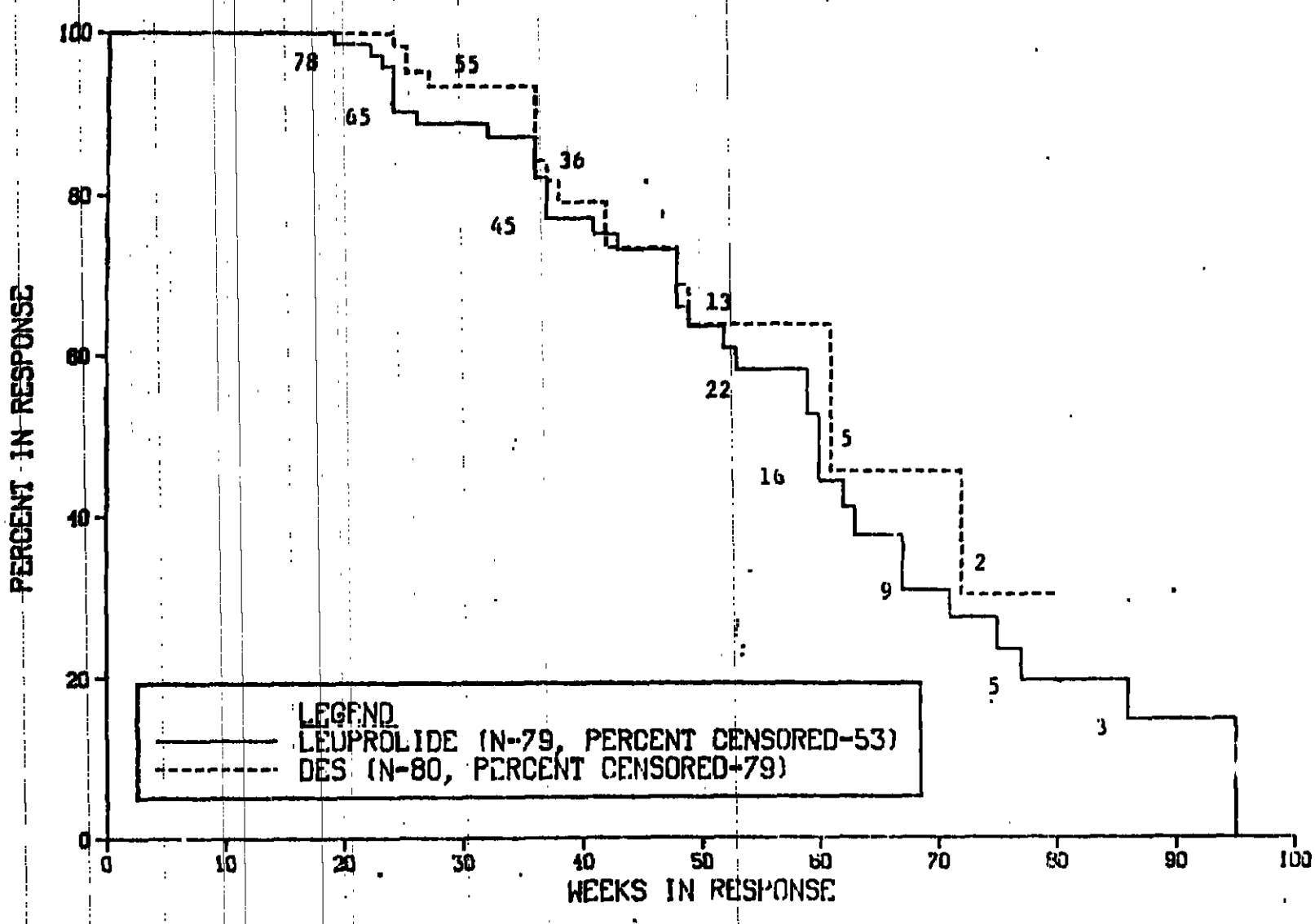


FIGURE 3
STUDY M81-017: TIME TO FIRST OBJECTIVE PROGRESSION
(RESPONDERS AMONG EVALUABLE PATIENTS)



Statistical Review and Evaluation

Date: [illegible]

NDA #: 19-010/Drug Class: 1A

Applicant: Tap Pharmaceuticals (thru Abbott Laboratories)

Name of Drug: Leuprolide Acetate (Injectable)

Documents Reviewed: One un-numbered desk copy of NDA 19-010 dated 9/20/34.

The contents of this review have been discussed with the clinical reviewer, Dr. Schaffenburg, HFN-810 and he is in agreement with my conclusions.

I. Background

This submission contains updated information as of 8/1/84 on survival time, time to treatment failure, quality of life, adverse reactions and causes of death for Study M81-017 and survival information for Study M80-036. In addition, survival data are presented for the NPCP-1300 study updated as of 8/10/84. The readers are referred to the previous two statistical reviews dated 4/13/84 and 6/28/84 for other comments on these studies.

II. Reviewer's Comments on the Updated Analysis

In this second updated analysis, the duration of response was compared between responders among previously untreated evaluable stage D2 prostatic cancer patients in the M80-036 leuprolide study and those in the control arm of the NPCP-1300 study. Figure 1 in the Appendix shows the two response curves. The two curves cross a few times before 40 weeks but the control group of the NPCP-1300 study appears to dominate the leuprolide group in the M80-036 study after week 40. Twenty-two (65%) of the 34 responders among the leuprolide patients relapsed compared to 34 (43%) of the 80 responders in the NPCP-1300 study. The sponsor claimed that the two curves were not statistically significantly different (p=.45) using the generalized Wilcoxon rank test. However, it should be pointed out that the validity of this test is based on an assumption that the patterns of censoring between the two groups are similar. In the present situation, the proportions of censoring between the two groups do not appear to be similar (35% in M80-036 vs. 57% in NPCP-1300). The median duration of response was estimated at 80 weeks (standard error 17 weeks) for the M80-036 group and at 116 weeks (standard error 27 weeks) for the NPCP-1300 group.

There was no update on the duration of response for the M81-017 study in this submission. However, as pointed out in my last review (6/28/84), this variable in the M81-017 study would be difficult to interpret because of the conditional crossover nature of the study. The censoring would be high for this variable even when the study is completed. Instead, the differences in

number of crossovers and dropouts for the two treatment groups were given. However, there are also problems in the interpretation which is discussed in the following.

1. Crossover

Thirty-six patients in the leuprolide group crossed over to DES compared to 28 DES patients who crossed over to leuprolide. Thirty-three of the 36 patients in the leuprolide group crossed over to DES because of disease progression compared to half of the 28 patients in the DES group who crossed over for the same reason. Most of the other half of the crossovers in the DES group did so because of adverse reactions. Conditional on the patients who crossed over, the DES patients tended ($p < .10$) to crossover earlier than the leuprolide patients (Fig. 2 in Appendix). The willingness of the investigators to switch DES patients to leuprolide in the early stage of the treatment apparenty influenced this result.

Because the proportion of crossovers in the leuprolide group was somewhat higher, a more informative analysis of the crossover pattern than was provided here would be the use of time to crossover as an endpoint for all patients (noncrossover or those not yet crossed over being treated as censored observation).

2. Dropouts

The proportions of patients dropping out between the two treatment groups were comparable (28/94 for leuprolide vs. 30/99 for DES). However, the time to dropout was significantly sooner for the DES patients than for the leuprolide patients (Fig. 3 in Appendix). For example, 15 DES patients dropped out within 6 months compared to only one leuprolide patient who did so. The following table provides information on the number of patients and the reasons for dropout.

Reason	Leuprolide	DES
Progression	16	5
Adverse Reaction	1	6
Death	6	10
Other Causes	5	9
All Causes	28	30

3. Time to Treatment Failure

Time to treatment failure was defined as time from initial treatment to either death, termination of initial treatment due to progressive disease or termination of initial treatment due to intolerable side effects. Sixty-two of 94 patients (66%) failed in the leuprolide group compared to 54 of 99 patients (55%) in the DES group. The two failure curves (Fig. 4 in Appendix) crossed several times before week 62 after which they diverged. There was no

statistically significant difference between the two curves. Note that death, progressive disease and intolerable side effects were considered to be equivalent in this evaluation. The first two events were objective whereas the event of intolerable side effects was considered to be subjective. Whether the pooling of such events is meaningful or not is questionable in view of the willingness by investigators to switch DES patients to leuprolide because of side effects.

Survival

Study M80-036

The survival pattern of the leuprolide patients was compared with that of the DES/ORCH arm of the NPCP-1300 study. Twenty-nine of 47 (62%) leuprolide patients died in the M80-036 study compared to 30 of 96 DES/ORCH patients (31%) who died in the NPCP-1300 study (Fig. 5 in Appendix). The median time of survival was estimated as 121 weeks for leuprolide patients and 154 weeks for the DES/ORCH patients. The sponsor claimed that the difference was not statistically significant by the generalized Wilcoxon rank test.

As commented earlier, the validity of the generalized Wilcoxon rank test and many other tests in survival analysis depends on the assumption of similar censoring patterns between the two treatment groups. The much higher censoring in the DES/ORCH group casts doubt on the validity of the generalized Wilcoxon rank test in the present situation. The sponsor explained that the percentage of "genuinely" censored data in the DES/ORCH patients is much lower because 20 of the 66 patients with incomplete survival data are actually lost to follow-up and their survival information will not change in future updates. This reviewer feels that it is unfortunate that such a large number of patients were lost to follow-up. However, this does not legitimize the validity of the comparison in the survival analysis. If one assumes that all the censored patients were still alive and grossly compare the proportion of deaths in the two groups, then the difference in mortality between the two groups (62% in leuprolide vs. 31% in DES/ORCH) would be highly significant by a chi-square test (p=.0005). In reality, this difference would probably be over estimated since many of the patients lost to follow-up more than 12 months ago could have been dead at the time of evaluation. The sponsor also provided a comparison based on Time from Diagnosis to Death (Fig. 7 in Appendix). Seven patients in the M80-036 study and 12 patients in the NPCP-1300 study were excluded because these patients were diagnosed over two years prior to study entry. The survival curve from the national survey (N=4325) was given as a reference. The difference between the two survival curves (M80-035 and NPCP-1300) using time from diagnosis to death was smaller than that using time from study entry to death. However, the previous comment on the unknown effect of unequal censoring also applies here. The lower survivorship in the national survey cannot be used as a valid comparison for the current studies because this survey was done on a voluntary basis on patients over a period of 5 to 10 years ago. There is a time factor, and possible selection bias could not be excluded.

It is difficult to arrive at a conclusion in these comparisons because of uncertainties created by the large number of patients lost to follow-up in the NPCP-1300 study. Unfortunately, this is the only study in this NDA which compared the survival between leuprolide and a control group, albeit, a historical control, that was not confounded by the conditional crossover as was done in the M81-017 study.

Study M81-017

Recall that this is a conditional crossover study. Thus one is not comparing the survival of patients treated with leuprolide with that of patients treated with DES, but rather the survival of patients treated with leuprolide as first treatment followed by DES (or any other treatment if they dropped out) to that of patients treated with DES as primary therapy followed by leuprolide or another treatment. Forty-two of 94 patients (45%) in the initial leuprolide treatment group had died compared to 40 of 99 patients (40%) in the initial DES group who had done so. The two survival curves (Fig. 6 in Appendix) were not statistically significantly different. Note that it is difficult to separate the contribution in mortality of each treatment because of the crossover nature of the study. Among the 42 deaths in the initial leuprolide group, 23 had switched to DES whereas 14 of the 40 deaths in the initial DES group had switched to leuprolide. The following table provides information for the duration of each treatment in patients who crossed over to the alternate treatment before their deaths.

Duration (weeks)

	Leuprolide				DES			
	Mean	(S.E.)	Median	(Range)	Mean	(S.E.)	Median	(Range)
Initial Leuprolide (n = 23)	42	(22)	41	(5, 95)	12	(10)	11	(1, 42)
Initial DES (n = 14)	27	(23)	21	(4, 80)	41	(32)	36	(2, 89)

At the date of data cutoff (8/1/84), more than half of the patients were still alive and the median time of survival for each group could not be estimated at this time. If the current trend continues, no significant difference in survival between the two groups would be expected. Similarly, there was no significant difference between the two groups when time from histologic diagnosis to death was examined (Fig. 8 in Appendix).

Quality of Life (Study M81-017)

Quality of life was measured by Performance Status and Bone Pain. Comparison treatment groups were made for the first 12 weeks and as an overall measurement for the first treatment.

1. Performance Status

There was no statistically significant difference between leuprolide and DES in either the first 12 weeks or overall first treatment rating. Numerically, leuprolide was better than DES in the category of "improved" (leuprolide 41% vs. DES 31%) for the first 12 weeks but was worse than DES in the overall first treatment in the category of "worsened" (leuprolide 28% vs. DES 18%).

2. Bone Pain

There was no statistically significant difference between leuprolide and DES in either Integrated Bone Pain or Analgesic Use for the first 12 weeks. However, DES was significantly (p=.04) better in the Integrated Bone Pain score in the overall first treatment. The sponsor explained that this was probably because patients randomized to leuprolide remained longer on their initial treatment than patients randomized to DES. The merit of this argument is not understandable.

Adverse Reactions (Study M81-017)

The type and trend in adverse reactions remained unchanged in this update (as of 1/1/84). There were significantly more patients with cardiovascular events and gynecomastia in the DES group than in the leuprolide group and there were significantly more patients with hot flashes in the leuprolide group than in the DES group.

Conclusions to be Conveyed to the Sponsor

Study M80-036

For both the duration of response (responders only) and survival, the censoring between M80-036 and the NPCP-1300 studies were different, i.e., the censoring in the NPCP-1300 study was much higher than that of Study M80-036. The validity of the generalized Wilcoxon rank test is based on an assumption of similar censoring patterns in the two comparison groups, and it is not clear the extent to which such an imbalance in censorships would affect the result of the analysis. It is unfortunate that 20 patients in the NPCP-1300 study were lost to follow-up. However, knowing that the dropouts in follow-up could not be recovered for the necessary information does not reduce the censoring in the NPCP-1300 study.

Study M81-017

The apparent early crossovers or dropouts in the DES group could be due to adverse reactions and/or physicians' willingness to let DES patients crossover or drop out sooner than necessary compared to patients in the leuprolide group. This practice could also affect the conclusion with respect to the

variable Time to Treatment Failure where the subjective evaluation of termination of treatment due to intolerable side effects was considered to be equivalent to the relatively objective evaluations of progressive disease and death.

There was no statistically significant difference in survival between patients treated with leuprolide initially and those treated with DES initially though there was insufficient information to evaluate the median survival time at this point. Because of the conditional crossover nature of the study, it is not possible to separate the contribution of each treatment to survival.

Hoi M. Leung, Ph.D.
Mathematical Statistician

cc: Orig. NDA 19-010
HFN-810
HFN-810/Dr. Schaffenburg
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HFN-344/Dr. Lisook
HFN-713/Dr. Dubey
HFN-713/Dr. Leung
Chron.
File: DRU 1.3.2 NDA
HMLeung/PLT/10/05/84/34594/#0984r

Concur: for Dr. Pledger

Dr. Dubey 10/10/84

Appendix

FIGURE 1

STUDIES M80-036 AND NPCP-1300: DURATION OF OBJECTIVE RESPONSE
(RESPONDERS AMONG PREVIOUSLY UNTREATED EVALUABLE STAGE D2 PATIENTS)

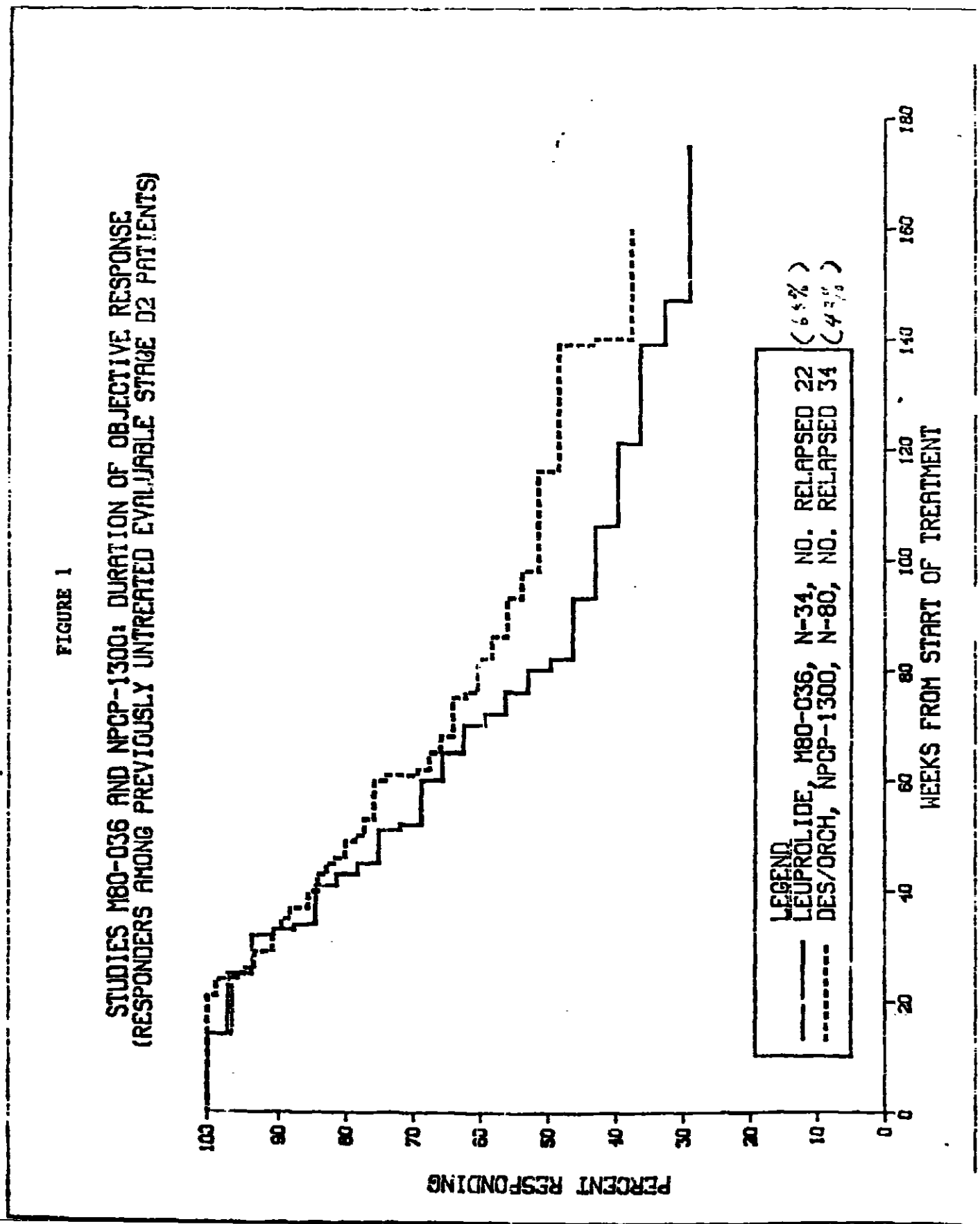


FIGURE 2
STUDY M81-017: TIME FROM START OF TREATMENT TO CROSSOVER
(EVALUABLE PATIENTS WHO CROSSED OVER)

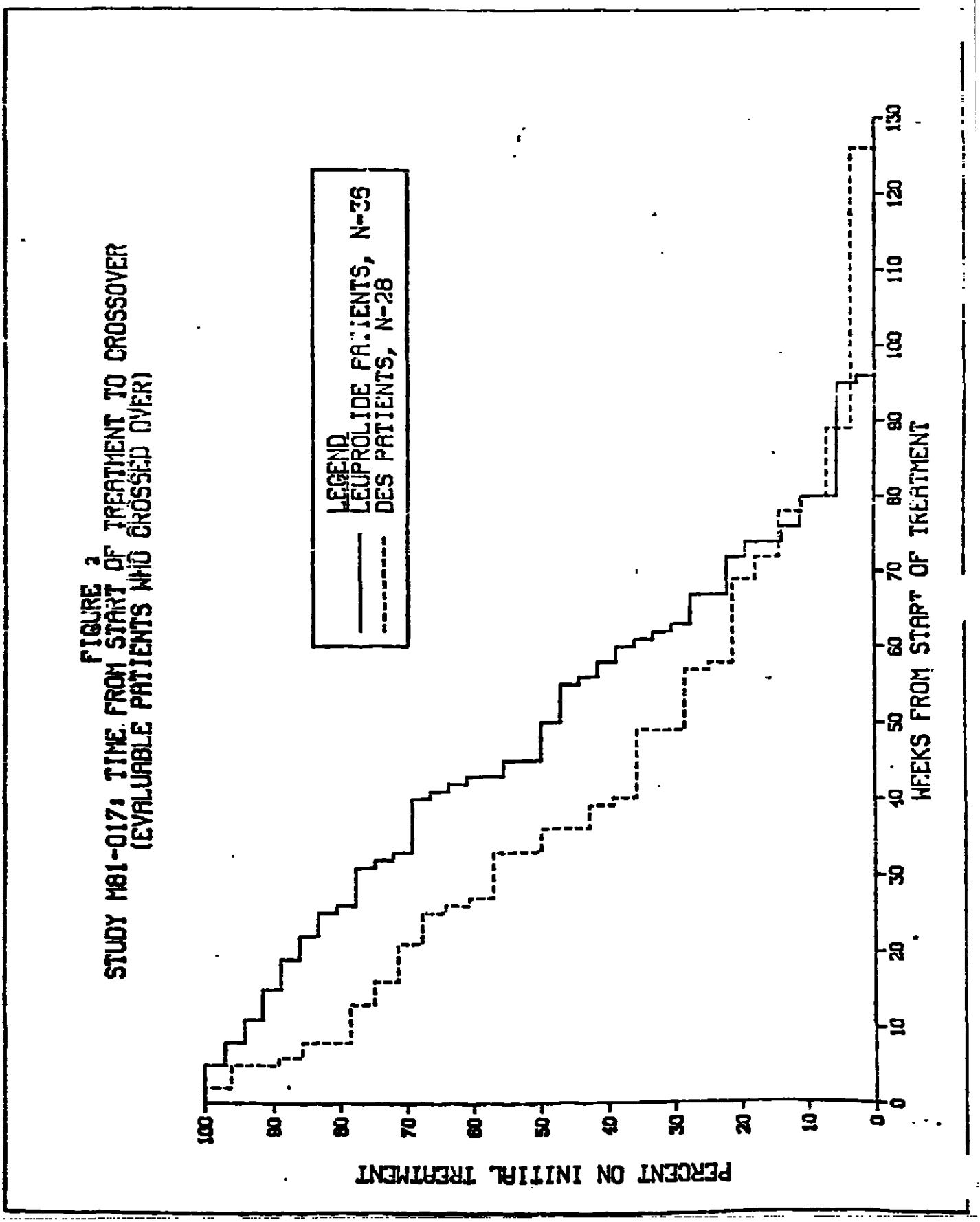


FIGURE 3
STUDY M81-017: TIME FROM START OF TREATMENT TO DROPPING OUT
(EVALUABLE PATIENTS WHO DROPPED OUT)

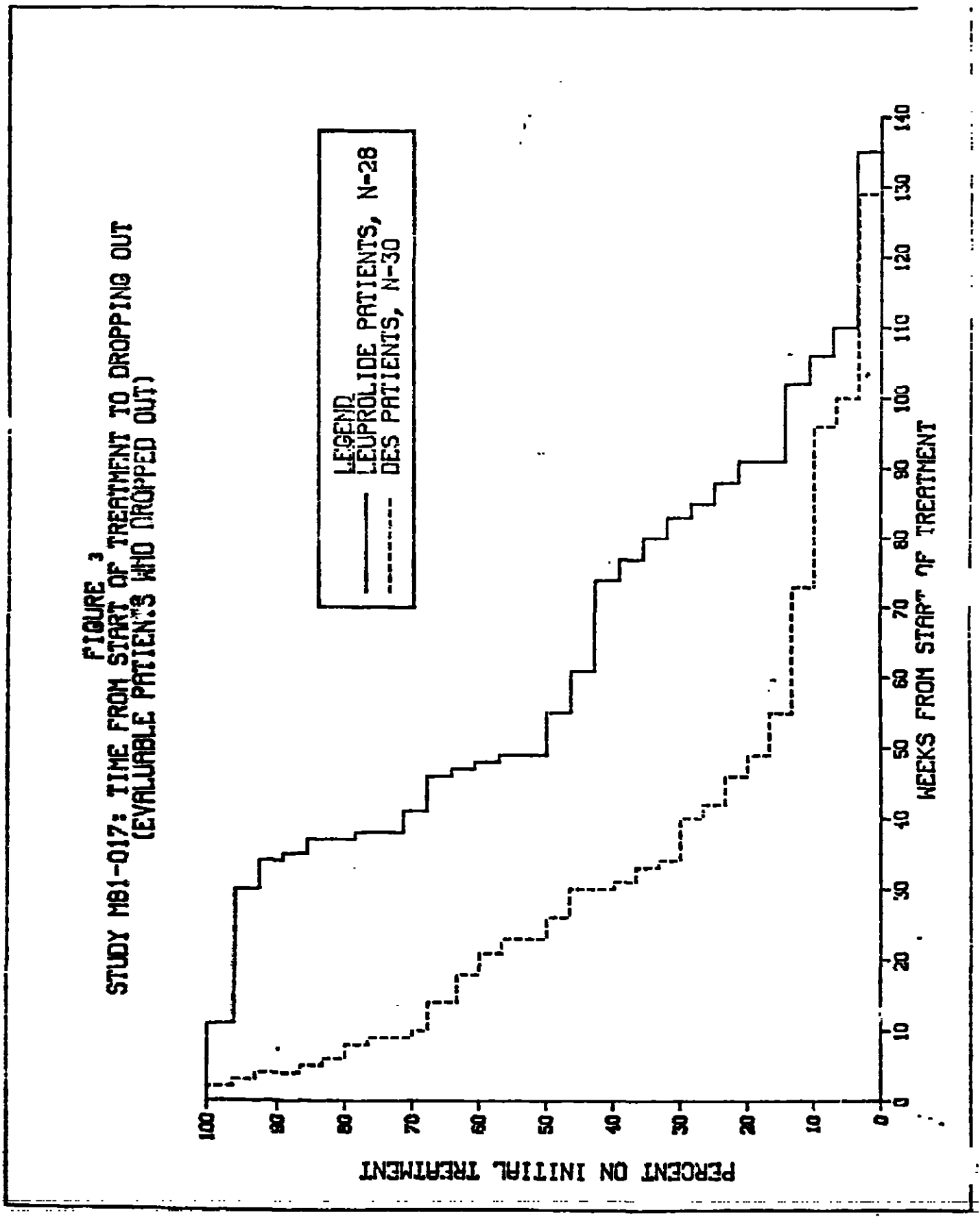


FIGURE 4
STUDY M81-017: TIME TO TREATMENT FAILURE (Death, Progressive Disease, Intolerable side effects)
(EVALUABLE STAGE D2 PATIENTS)

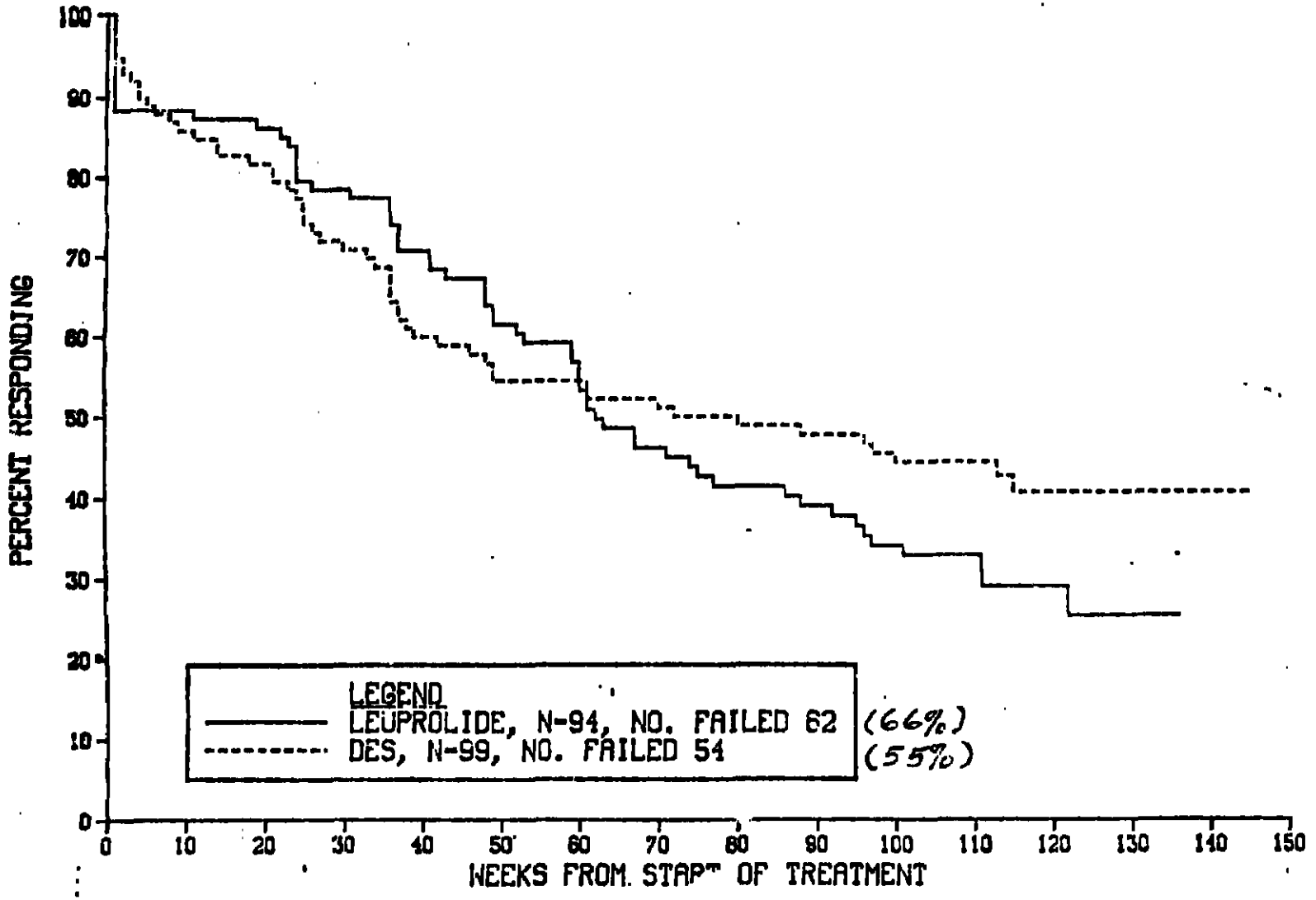


FIGURE 5

STUDIES M80-036 AND NPCP-1300: TIME FROM STUDY ENTRY TO DEATH
(EVALUABLE PREVIOUSLY UNTREATED STAGE D2 PATIENTS)

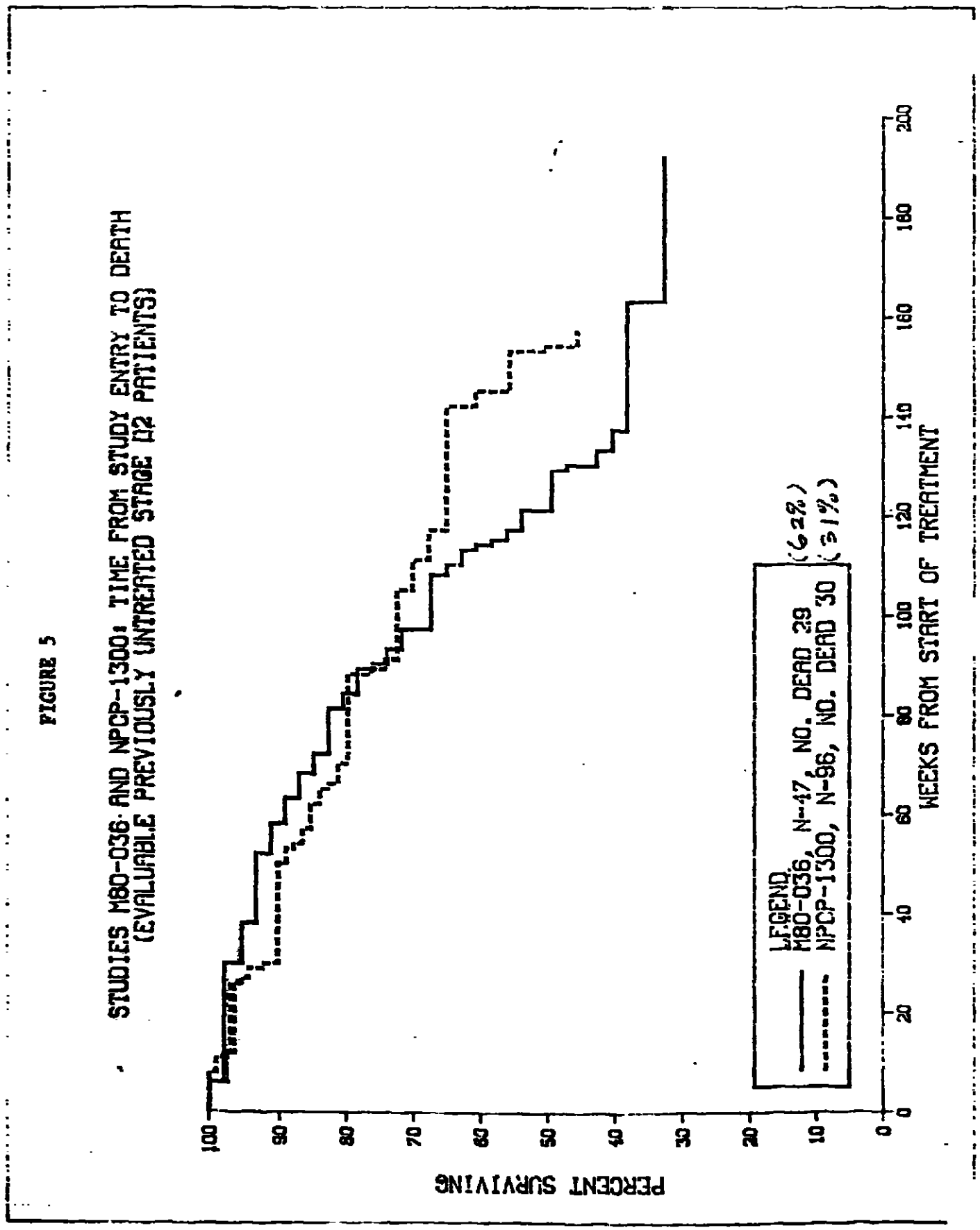


FIGURE 6

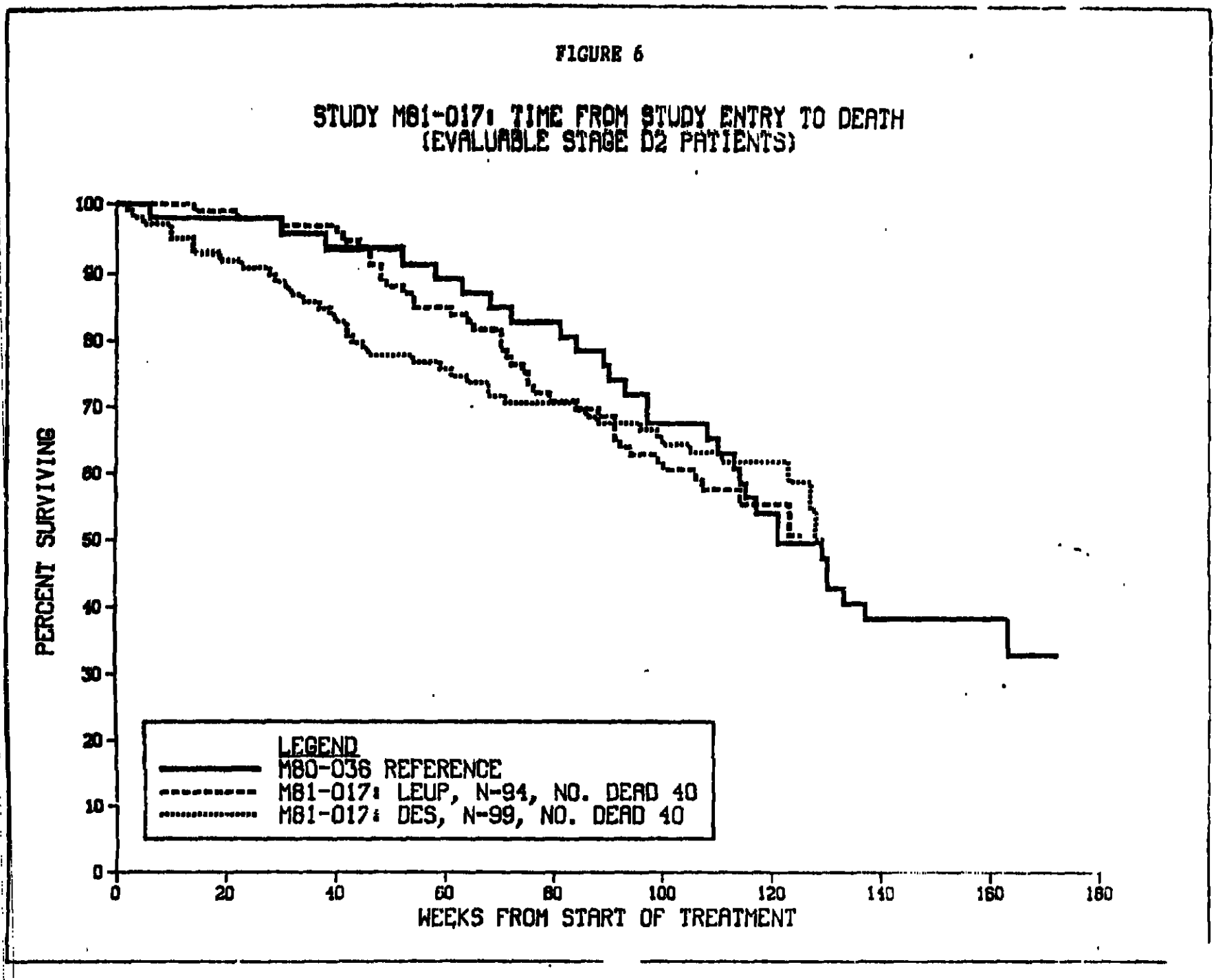

STUDY M81-017: TIME FROM STUDY ENTRY TO DEATH
(EVALUABLE STAGE D2 PATIENTS)
PERCENT SURVIVING
100
90
80
70
60
50
40
30
20
10
0
0
20
40
60
80
100
120
140
160
180
WEEKS FROM START OF TREATMENT
LEGEND
M80-036 REFERENCE
M81-017: LEUP, N-94, NO. DEAD 40
M81-017: DES, N-99, NO. DEAD 40

FIGURE 7

STUDIES M80-036 AND NPCP-1300: TIME FROM DIAGNOSIS TO DEATH
(EVALUABLE PREVIOUSLY UNTREATED PATIENTS)

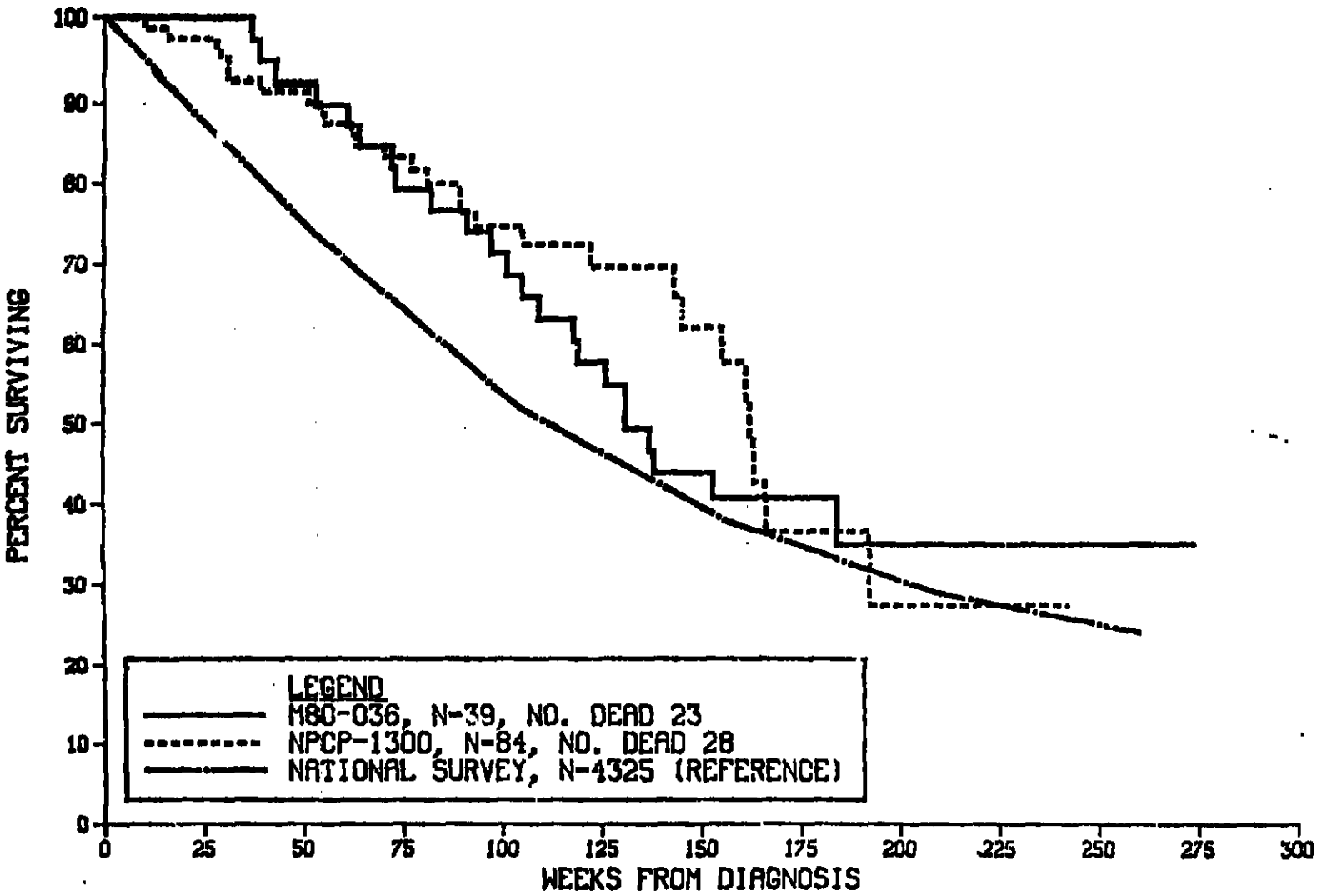
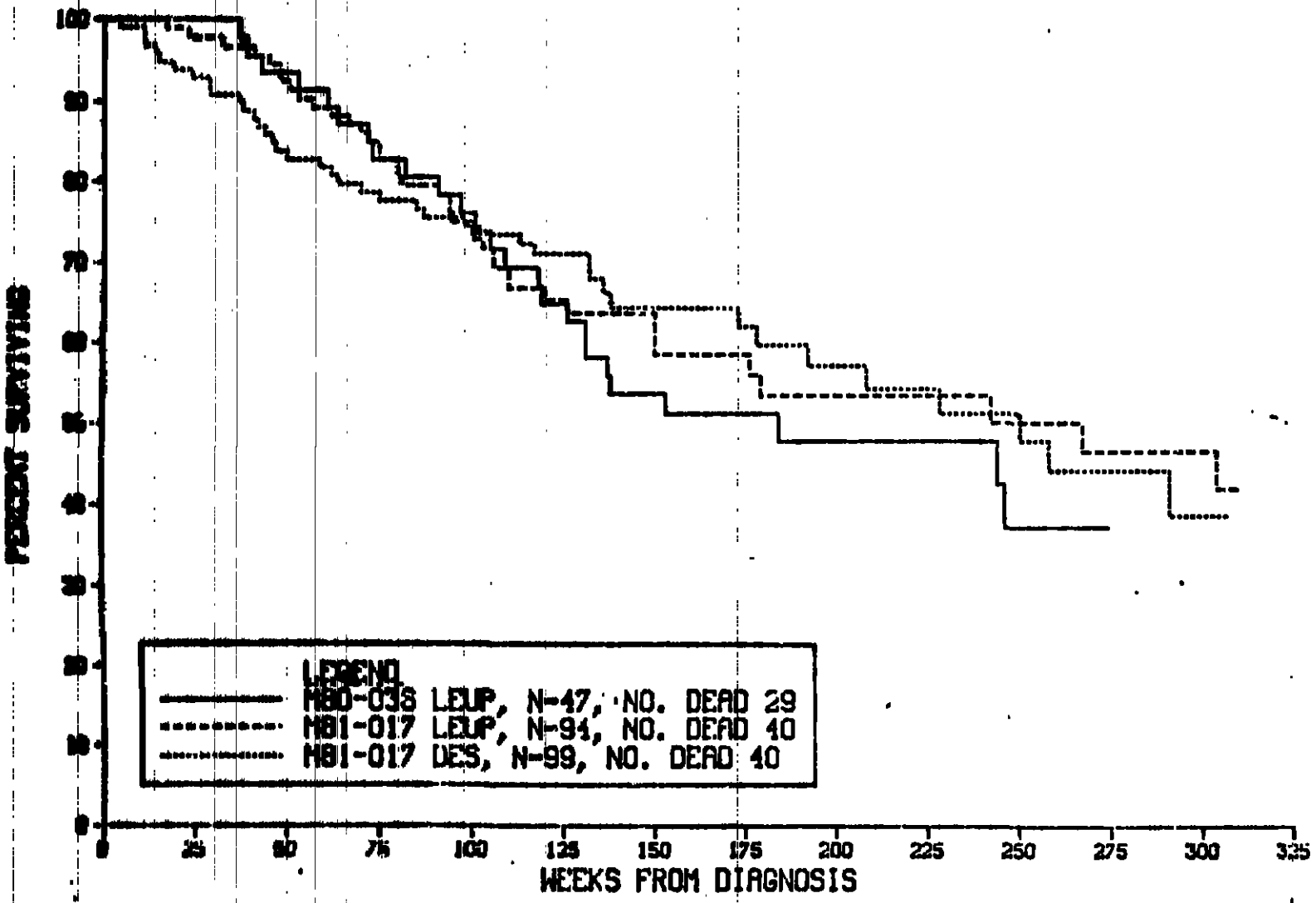


FIGURE 8

STUDIES M81-017 AND M80-036: TIME FROM HISTOLOGIC DIAGNOSIS TO DEATH
(EVALUABLE STAGE D2 PATIENTS)



Statistical Review and Evaluation

Date: FEB 12 ..

NDA #: 19-010/Drug Class: 1A

Applicant: Tap Pharmaceuticals (thru Abbott Laboratories)

Name of Drug: Leuprolide Acetate (Injectable)

Documents Reviewed: Volume 8.1 (Amendment No. 5) of NDA 19-010 dated 2/1/85

I. Background

This submission contains updated survival information through 1/31/85 for the conditional crossover study M81-017. For detailed information on this and other relevant studies (M80-036, NPCP-1300), please refer to my previous statistical reviews (10/11/84, 6/28/84 and 4/13/84).

II. Sponsor's Updated Survival Information on Study M81-017

As of January 31, 1985, 45 of the 94 patients in the Leuprolide/DES group had died. The median survival time from study entry is estimated to be 146 weeks (S.E. 10 weeks). For the DES/Leuprolide group, 47 of 99 patients had died. The 50.54th percentile of the survival time is estimated to be 136 weeks (S.E. 10 weeks). It would take one more death to reach the median survival time for this group. The sponsor estimated that the median survival time would be around 140 weeks when it is reached. The two curves are not statistically significantly different (p=0.71 by the generalized Wilcoxon rank test and p=0.99 by the log rank test).

The median survival time from histologic diagnosis was estimated as 242 weeks (S.E. 50-100 weeks) for the Leuprolide/DES group and 250 weeks (S.E. 20-50 weeks) for the DES/Leuprolide group. The two sets of survival curves are provided in the Appendix.

III. Reviewer's Comments

The two survival curves from Study M81-017 are similar. They crossed each other several times between weeks 50 and 70 and again between weeks 135 and 145. There is no statistically significant difference in these two curves and probably will not be when all the patient's are followed to death unless a drastic departure from the current trend takes place. Asymptotic 95% confidence limits on the median survival time could be constructed by using the formula: Estimated median survival $\pm$ 1.96 S.E. Based on this estimation, a 95% confidence interval for the median survival from study entry of the Leuprolide/DES group would be (126, 166) weeks and the corresponding interval for the DES/Leuprolide group would be (120, 160) weeks.

One concern is in the interpretation of the survival information of this study. Since this is a conditional crossover study, many patients in either treatment group received both Leuprolide and DES at different time points. It is conceivable that the survival patterns of the two groups would be similar regardless of alternate treatments. Information on the duration of each regimen of the two groups is provided only for those patients who crossed over and died subsequently (see 10/11/84 review). It would be difficult to conclude that the median survival of the crossover regimen would be no worse than DES based on this study alone. The best one could do is to use the survival information of the NPCP-1300 study as a comparison. This study was used by the sponsor as the historical control group for Study M80-036. The median survival time for the NPCP-1300 (DES/ORCH) study was estimated as 154 weeks (S.E. 12 weeks). Thus, it would seem that median survival from the crossover regimen (Leuprolide/DES) is in line with that of the NPCP-1300 study (146 vs. 154 weeks). It should be noted that this is a very crude comparison. The problems of using historical controls are well-known. However, this appears to be the best one could do from the available data. Note also that the median survival time of the Leuprolide patients (M80-036) was estimated as 121 weeks (S.E. 12 weeks). This was considerably smaller than the 154 weeks (S.E. 12 weeks) from the NPCP-1300 study. The difference was not statistically significant because of the small sample size of Study M80-036 (N=47).

IV. Summary Conclusions

Based on the updated information on Study M81-017, approximate 95% confidence limits for the median survival time from study entry are estimated to be 146 + 20 weeks for the Leuprolide/DES regimen and 140 + 20 weeks for the DES/Leuprolide regimen. This appears to be in line with the median survival time of the DES/ORCH patients in the NPCP-1300 study (95% confidence limits: 154 + 24 weeks). This comparison does not take into consideration the possible problems of using a historical control group.

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HFN-150/Dr. Johnson
HFN-224/Dr. Lisook
HFN-713/Dr. Dubey
HFN-713/Dr. Leung
Chron. File: DRU 1.3.2 NDA
Dr. Leung//x34594/rp/2/12/85/#1157r

Concur: Dr. Plevyak 2/12/85

Dr. Dubey 2/12/85

FIGURE 10
STUDY M81-017: TIME FROM STUDY ENTRY TO DEATH
(EVALUABLE STAGE D2 PATIENTS)

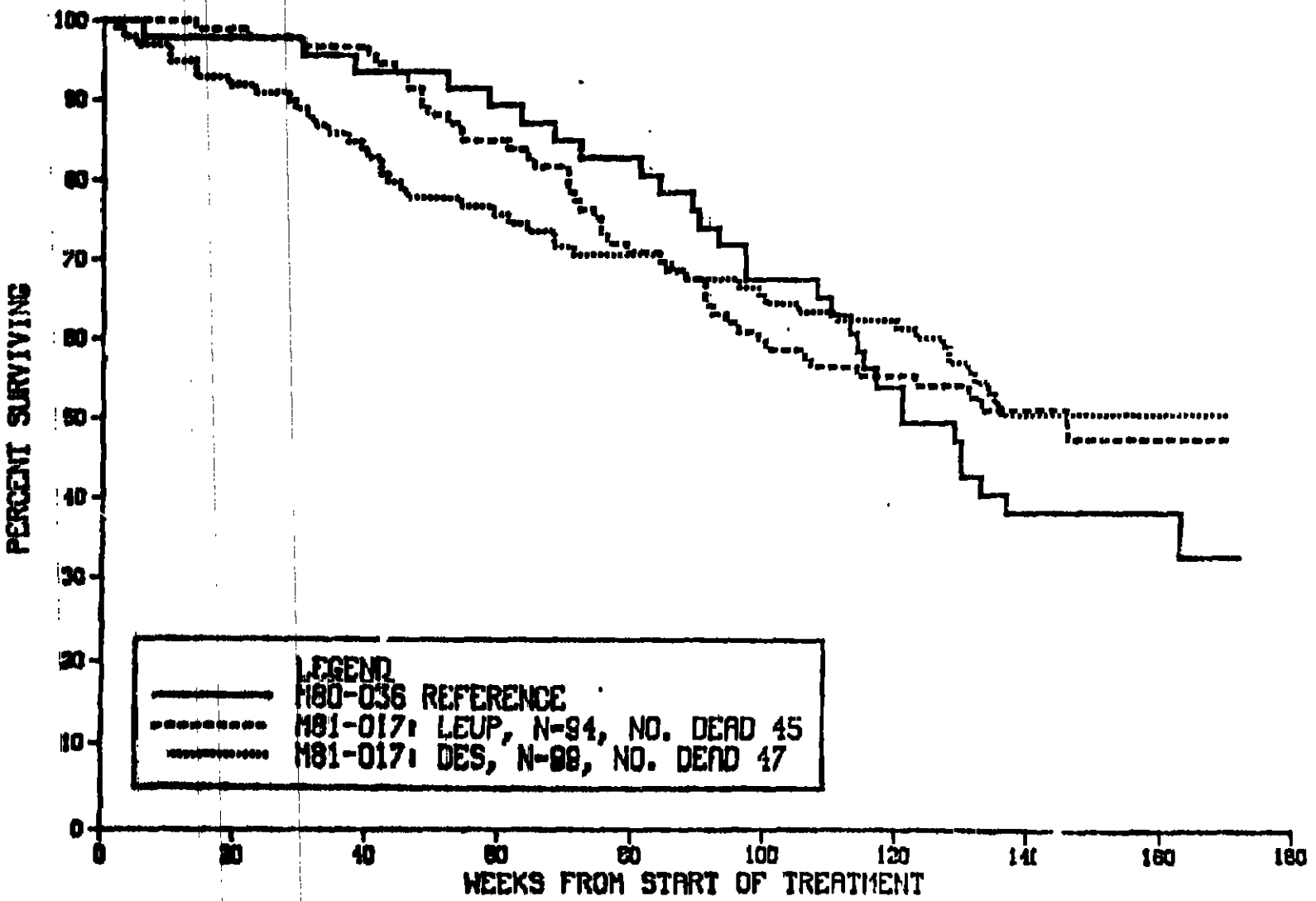
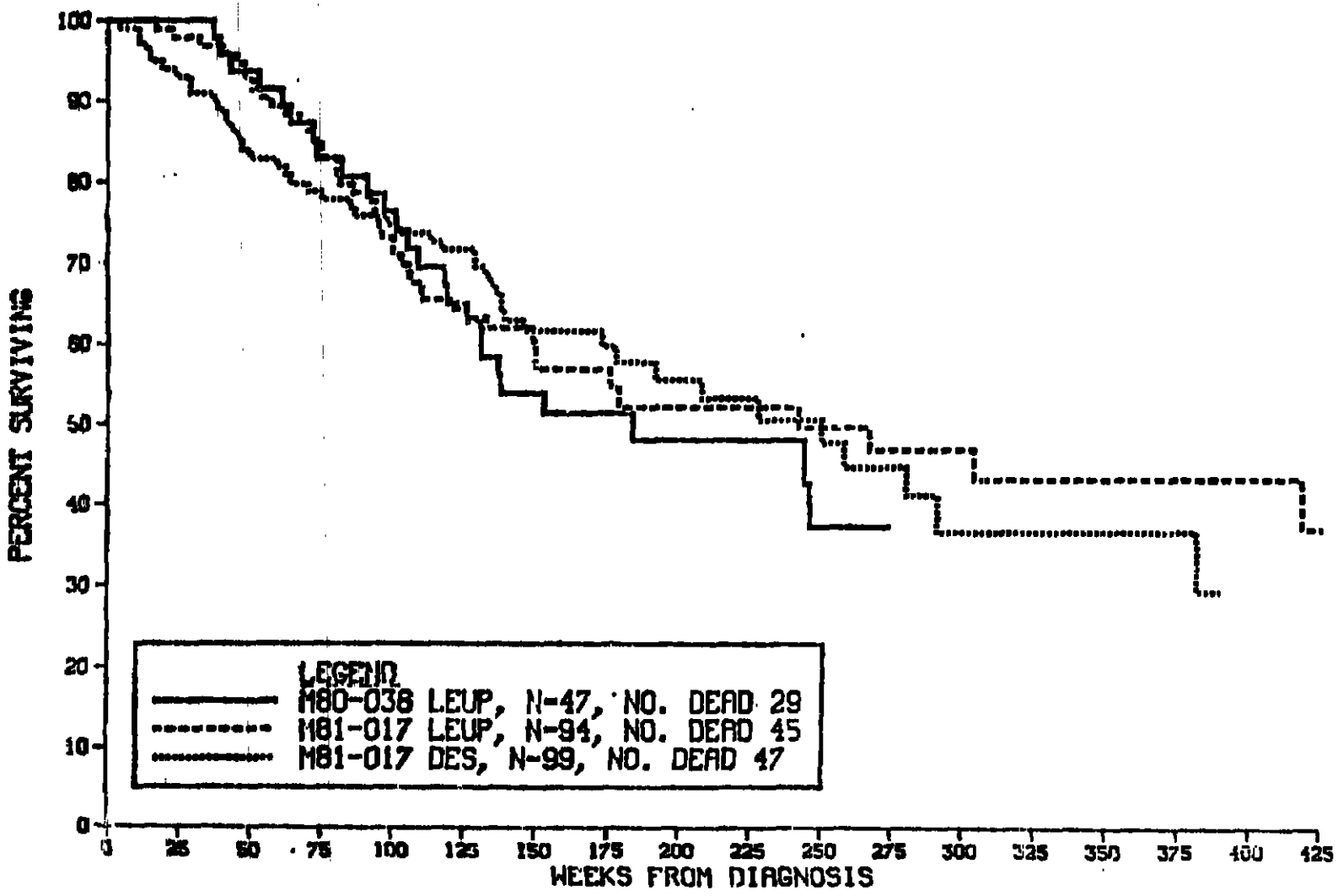


FIGURE 12
STUDIES M81-017 AND M80-036: TIME FROM HISTOLOGIC DIAGNOSIS TO DEATH
(EVALUABLE STAGE D2 PATIENTS)



NDA 19010

List of Investigators

Appendix A (Continued)

Study	Investigator(s)	Study Description
M81-017	Mostafa M. Elhilali, M.D. John Trachtenberg, M.D. Royal Victoria Hospital Montreal, P.Q., Canada H3A 1A1	Phase III Prostatic Cancer Study
	Marc Garnick, M.D. Dana Farber Cancer Institute 44 Binney Street Boston, MA 02115	
	Andrew G. Glass, M.D. Kaiser Permanente 3414 N. Montana Avenue Portland, OR 97227	
	John H. Glick, M.D. Hospital of the University of Pennsylvania 3400 Spruce Street Phildaelphia, PA 19104	
	L. Michael Glode, M.D. John Wettlaufer, M.D. University of Colorado Medical Center 4200 East Ninth Avenue Denver, CO 80262	
	Anthony F. Greco, M.D. Vanderbilt University Hospital 21st Avenue South Nashville, TN 37232	
	Patrick D. Guinan, M.D. Cook County Hospital 1825 W. Harrison St. Chicago, IL 60612	
	Harold Harvey, M.D. Allan Lipton, M.D. The M.S. Hershey Medical Center Pennsylvania State University 500 University Drive Hershey, PA 17033	

Appendix A

List of All Clinical Investigators for Leuprolide Acetate

Study	Investigator(s)	Study Description
M80-036	Pierre R. Band, M.D. Gilles Beland, M.D Institut de Cancer de Montreal Centre Hospitalier Notre-Dame Montreal, Quebec Canada	Phase II Prostatic Cancer Study
	Mario A. Eisenberger, M.D. Norman L. Block, M.D. University of Miami Hospitals and Clinics Miami, FL	
	Robert P. Gibbons, M.D. Roy J. Correa, Jr., M.D. The Mason Clinic Seattle, WA 98111	
	Andrew G. Glass, M.D. Kaiser Permanente Portland, OR	
	L. Michael Glode, M.D. John Wettlaufer, M.D. University of Colorado Denver, CO	
	Anthony F. Greco, M.D. Vanderbilt University Hospital Nashville, TN	
	David Heber, M.D., Ph.D. Jacob Rajfer, M.D. Harbor - UCLA Medical Center Torrance, CA	
	James N. Hueser, M.D. Boone Clinic Columbia, MO	
	Hyman B. Muss, M.D. Martin I Resnick, M.D. Bowman Gray School of Medicine Winston-Salem, NC	

Appendix A (Continued)

Study	Investigator(s)	Study Description
M20-036	Richard J. Santen, M.D. Harold A. Harvey, M.D. Allan Lipton, M.D. The M.S. Hershey Medical Center Hershey, PA	Phase II Prostatic Cancer Study
	Harvey G. Schneir, M.D. UCLA VA Hospital Sepulveda, CA	
	Joseph A. Smith, M.D. University of Utah Medical Center Salt Lake City, UT	
	Gerald H. Sokol, M.D. Tampa General Hospital Tampa, FL	
	Barry S. Stein, M.D. Temple University Hospital Phildaelphia, PA	
M81-017	Gilles Beland, M.D. Pierre R. Band, M.D. Centre Hospitalier Notre-Dame 1560 est. Sherbrooke Montreal, Quebec H21 4MI Canada	Phase III Prostatic Cancer Study
	Norman L. Block, M.D. Mario A. Eisenberger, M.D. University of Miami Hospitals and Clinics 1475 N.W. 12th Avenue Miami, FL 33136	
	Roy J. Correa, Jr., M.D. Robert P. Gibbons, M.D. The Mason Clinic 1100 Ninth Ave. Seattle, WA 98111	
	Jaime de la Garza, M.D. Instituto Nacional de Cancerologia San Buenaventura S/N Mexico City, Mexico (Tlalpan, D.F.)	

Appendix A (Continued)

Study	Investigator(s)	Study Description
M81-017	David Heber, M.D., Ph.D. Jacob Rajfer, M.D. Harbor, UCLA 1000 West Carson Street Torrance, CA 90509 John Hoskins, M.D. 1200 Euclid Avenue Sioux Falls, SD 57105 Martin I. Resnick, M.D. Case Western Reserve University School of Medicine and University Hospitals 2065 Adelbert Road Cleveland, OH 44106 Harvey Schneir, M.D. VA Hospital 16111 Plummer Street Sepulveda, CA 91343 Roohollah Sharifi, M.D. Thomas E. Lad, M.D. University of Illinois 840 South Wood St. Chicago, IL 60612 Joseph A. Smith, M.D. University of Utah Medical Center 50 North Medical Drive Salt Lake City, UT 84132 Gerald Sokol, M.D. Tampa General Hospital Davis Island Tampa, FL 33606 Mark F. Soloway, M.D. University of Tennessee 956 Court Road Memphis, TN 38103	Phase III Prostatic Cancer Study

Appendix A (Continued)

Study	Investigator(s)	Study Description
M81-017	Barry S. Stein, M.D. Temple University Hospital 3401 Broad Street Philadelphia, PA 19140	Phase III Prostatic Cancer Study
M82-037	Philip E. Ashburn, M.D. Wake Internal Medicine Consultants 2800 Blue Ridge Boulevard Raleigh, NC 27607	Compassionate Study
	Alpheus T. Appenheimer, M.D. Warmolts Family Medical Center 305 N. Fourth St. Oregon, IL 61016	
	Joseph A. Smith, M.D. University of Utah Medical Center 50 N. Medical Drive Salt Lake City, UT 84132	
M83-018	Joseph A. Smith, M.D. University of Utah Medical Center 50 N. Medical Drive Salt Lake City, UT 84132	DES Lead-in Study
	Barry S. Stein, M.D. Temple University Hospital Philadelphia, PA	
	John Trachtenberg, M.D. Toronto General Hospital Department of Urology Toronto Ontario, Canada M5T ILG	
M83-019	Keith Tolman, M.D. Abbott Research Center University of Utah Medical Center 50 N. Medical Drive Salt Lake City, UT 84132	Bioavailability Study
M76-008	Thomas E. Davis, M.D., and David P. Rose, M.D., Ph.D. University of Wisconsin Madison, WI	Phase I Breast Cancer Study

Appendix A (Continued)

Study	Investigator(s)	Study Description
M77-005	Alcide Chapdalaine, M.D. Maisonneuve-Rosemont Hospital Montreal, Canada	Phase I, Female Volunteers
M77-010	D. R. London, M.D. Queen Elizabeth Hospital Birmingham, England	Phase I, Female Volunteers
M77-028	Alcide Chapdalaine, M.D. Maisonneuve-Rosemont Hospital Montreal, Canada	Phase I, Female Volunteers
M77-037	George Tolis, M.D. Panteleimon Clinic Athens, Greece	Phase I Breast Cancer Study
M78-003/M78-022	L. Michael Glode, M.D. William Robinson, M.D. University of Colorado Medical Center, B-171 4200 East Ninth Avenue Denver, CO 80262 Mark A. Hardy, M.D. George C. Escher, M.D. Columbia Presbyterian Hospital 630 West 168th Street New York, NY 10032 Harold Harvey, M.D. Allan Lipton, M.D. Milton S. Hershey Medical Center Pennsylvania State University 500 University Drive Hershey, PA 17033 Richard L. Landau, M.D. University of Chicago 950 East 59th Street Chicago, IL 60637 Albert Segaloff, M.D. Alton Ochsner Medical Foundation 1520 Jefferson Highway New Orleans, LA 70121	Phase II Breast Cancer Study

Appendix A (Continued)

Study	Investigator(s)	Study Description
M79-007/M79-021	Pierre Band, M.D. Institut du Cancer de Montreal Montreal, Quebec, Canada Jaime de la Garza, M.D. National Institute of Cancerology Mexico City, Mexico Rodolfo Diaz-Perches, M.D. General Hospital Mexico City, Mexico Andrew Glass, M.D. Kaiser-Permanente Clinic Portland, OR L. Michael Glode, M.D. University of Colorado Medical Center Denver, CO Harold Harvey, M.D. Milton S. Hershey Medical Center Hershey, PA Harvey Lerner, M.D. Pennsylvania Hospital Philadelphia, PA David Plotkin, M.D. Memorial Cancer Research Foundation Culver City, CA Albert Segaloff, M.D. Alton Ochsner Medical Foundation New Orleans, LA George Tolis, M.D. Royal Victoria Hospital Montreal, Quebec, Canada Yvonne Van Loon, M.D. Silver Bow Hospital Butte, MT Charles Vogel, M.D. University of Miami Miami, FL	Phase II Breast Cancer Study

Appendix A (Continued)

Study	Investigator(s)	Study Description
M80-004	Pierre R. Band, M.D. Institut du Cancer de Montreal Centre Hospitalier Notre-Dame Montreal, Quebec, Canada Robert W. Frelick, M.D. Wilmington Medical Center Wilmington, DE Andrew G. Glass, M.D. Kaiser Permanente Hospital Portland, OR L. Michael Glode, M.D. University of Colorado Denver, CO Anthony F. Greco, M.D. Medical Center North Vanderbilt University Hospital Nashville, TN Harold A. Harvey, M.D. Allan Lipton, M.D. The M.S. Hershey Medical Center Hershey, PA James N. Hueser, M.D. Boone Clinic Columbia, MO Loren J. Humphrey, M.D. Shawnee Mission Medical Center Shawnee Mission, KS Harvey J. Lerner, M.D. Pennsylvania Hospital Philadelphia, PA Hyman B. Muss, M.D. Bowman Gray School of Medicine Winston-Salem, NC David Plotkin, M.D. Brotman Medical Center Culver City, CA	Phase II Breast Cancer Study

Appendix A (Continued)

Study	Investigator(s)	Study Description
M80-004	Gerald Sokol, M.D. Tampa General Hospital Tampa, FL Charles L. Vogel, M.D. Comprehensive Cancer Center Miami, FL	Phase II Breast Cancer Study
Japanese (Takeda) Breast Cancer Study	Tetsuo Taguchi Department of Surgery Institute for Microbial Disease Osaka University Osaka, Japan Hisanori Kawaji Central Research Division Takeda Chemical Industries, Ltd.	Phase I Breast Cancer Study

MISC

Organs with significant numbers of tumors are tabulated below.

	Dose (mg/kg/day)			
	0	0.6	1.5	4.0
Pancreas				
Islet-cell adenoma				
females	1/99	10/50	6/50	4/50
males	8/100	8/50	2/50	2/50
Testes				
interstitial-cell adenoma	3/100	7/50	6/50	2/50
Pituitary adenoma				
females	30/100	29/50	41/50	42/50
males	22/99	35/50	38/49	46/50

Three-Month Dose Ranging Toxicity Study of Abbott-43818 Administered SC to Mice. Study No. T77-509.

Groups of 10 male and 10 female ICR mice were injected daily with 20, 60, 200 and 600 mg/kg Leuprolide. A significant treatment-related increase in serum cholesterol was noted in the MD and HD males and LD and HD females. No other dose or treatment-related changes were seen in any of the hematology and clinical chemistry parameters. Absolute and relative kidney weights were lower in treated male mice than in controls. Hypertrophic cells were observed in the pituitary of the HD females and castration cells were frequently seen in the LD and MD mice. Other than atrophy of the accessory sex glands and necrosis at the injection site, no other treatment-related histological changes were noted.

Two-Year Carcinogenicity Study of Abbott-43818 Administered SC to Mice. Study No. TD78-538, October 31, 1981.

Mice of the ICR strain were injected sc with 0.6, 6 and 60 mg/kg/day Leuprolide acetate. No significant dose-related toxicological effects were noted in the treated mice other than the expected treatment related atrophic changes in the reproductive organs.

	Dose (mg/kg/day)			
	0	0.6	6	60
Hepatocellular carcinoma				
females	1/101	5/51	0/51	2/52
males	11/103	9/49	6/51	4/52

There was no treatment-related change [illegible]ituitary adenomas or islet-cell adenomas in the mouse.

TABLE 4 (CONT.)

SUMMARY OF SUBCHRONIC AND CHRONIC TOXICITY STUDIES OF ABBOTT-43818

Reference Number Investigator(s) Study No. (Report Date)	Treatment Duration	Species (Strain, Sex, etc.)	Route	Dosages (mg/kg/day)	Conclusions
Comments/Findings (Cont.) Urinalysis: - Increased urine volume was observed for T_3 monkeys on day 90. - Decreased specific gravity, osmolality and pH were observed for all T_3 monkeys on day 90. Hematology and Clinical Chemistry: - No drug-related changes were observed. Anatomic Pathology: - Organ Weights. Drug-related decreases were observed in the weights of testes, prostate and seminal vesicles of treated monkeys. - Gross and Microscopic Pathology. Atrophic changes were observed in testes, prostate and seminal vesicles of treated animals. Similar changes we also seen in one control monkey. - All dosages of ABBOTT-43818 produced marked effects on the reproductive organs consistent with the endocrine nature of the drug.					
Reference #11					
	Once daily for 12 days	Rat (Sprague-Dawley M&F, 12/sex/group)	SC	T_0 - 0, days 0-11 T_1 - 20, days 0-2 - 75, days 2-5 - 280, days 6-8 - 1060, days 9-11	"Toxic-effect" dose was 1060 mg/kg/day irritation at injection site at 280 mg/kg/
Comments/Findings - The drug was dissolved in normal saline. Controls received normal saline only. Lot #64-911-AL was used. - Several deaths occurred at 1060 mg/kg/day. - Body weight and food consumption were depressed at 1060 mg/kg/day. - Significant local irritation of the injection sites was noted at 280 and 1060 mg/kg/day.					
Reference #12					
	Once daily for 3 months	Rat (Sprague-Dawley, M&F, 10/sex/group)	SC	T_0 - 0 T_1 - 10 T_2 - 30 T_3 - 100 T_4 - 300	Maximum-tolerated dosage not established because pituitary hyperplasia a all dosages.
Comments/Findings - The drug was dissolved in normal saline. Controls received normal saline only. Dosage volume for all groups was 3 ml/kg/day. Lot #38-250-AL of ABBOTT-43818 was used. - One T_4 female rat died on day 25. The remainder of the T_4 rats and the T_3 rats were terminated on days 28 and 47, respectively, because of marked skin necrosis at the injection sites. - Retardation of body weight gain and decreased food consumption were observed in the T_4 and T_3 groups (both sexes). - Numerous signs of degeneration were observed in the tissues surrounding the injection sites of T_2, T_3 and T_4 groups.					

2. Efficacy: Symptomatic Improvement:

The following tables summarize the symptomatic improvement seen in patients who were enrolled in the two studies.

M86-031

% (#) Improvement in Criteria during Lupron Treatment
Final Evaluation (Table 8)

	Lupron	Placebo	p
Dysmenorrhea	96% (26/27)	38% (8/21)	<0.001
Pelvic Pain	85% (22/26)	43% (9/21)	<0.001
Dyspareunia	47% (7/15)	30% (3/10)	0.150
Pelvic Tenderness	73% (19/26)	33% (7/21)	<0.001

It is interesting to note the placebo effect. About 30-40' of patients in the study noted improvement of their symptoms. In the final analysis, 63% of lupron treated patients and 50% of placebo treated patients showed improvement in pelvic induration and the difference was not statistically significant (p value of 0.23) (not shown in the above table).

When compared to baseline, dysmenorrhea and pelvic pain continued to improve in the lupron treated patients although the effect had plateaued by the second month (Please see Figure 1 and Table 1a attached to the end of the review). Pelvic tenderness and induration significantly improved in the lupron treated patients when compared to baseline scores but placebo patients showed no further improvement with treatment. Placebo patients showed no improvement, while dyspareunia showed no improvement in either group.

c. Conclusions

(1) Scientific

1. Efficacy: AFS scoring system

In spite of some variation between the studies of the two GNRH analogues which have been submitted for NDA approval, it is reassuring to know that both studies came up with a similar change in endometriosis score. It is apparent that the analogues do decrease AFS scoring at the end of treatment, and there is about a 35-50% decrease in the scoring of the disease. We do not have data on adhesions and various anatomical differences in the lupron study as we do in the nafarelin study.

Similar to the nafarelin study, about 50-60% of patients (50% in nafarelin study and 62% in the present study) showed improvement with treatment of analogues.

In addition, it is clear from this study and the nafarelin study that the patients who probably benefit the most from analogue treatment are the patients with mild and moderate diseases as categorized by AFS scoring. Patients who have severe disease are not as likely to respond and patients with mild disease do not appear to show any further improvement. Unlike the present study, the nafarelin study did show much improvement in patients with mild or Stage I disease.

It is also important to note that like the nafarelin study, complete remission occurred in only a very few patients (10/211). Thus, this form of treatment quiets the disease, but does not eradicate it. It is clear from relapse rates, that the disease is quiescent with the treatment, but does recur.

Laboratory changes were much the same as have been seen in other studies. Lupron treated patients showed a slight rise while danazol patients showed a significant rise in hemoglobin. SGPT rose in one lupron and many danazol patients and SGOT rose in several lupron and many more danazol patients. Alk Phos rose in lupron treated patients. BUN increased in the lupron patients as noted in the previous study. HDL cholesterol decreased in the danazol patients. Adverse events were similar to that noted in previous studies.

Pharmacokinetics Studies: Peak levels of lupron were found 30 mins after dosing, but there appeared to be a great deal of variability with the intranasal dosing. For this reason, the sponsor decided to not pursue studies with intranasal dosing.

far.

In a subsequent submission, a few of the patients who were retested showed resolution of bone loss. However, the retesting was performed at various intervals and again may reflect this particular group of patients rather than provide general reassurance.

Laboratory Evaluations (Tables 28 and 29):

Table 28 lists the changes in lab values by individual values and by crosstabulation. A few lupron treated patients showed changes in lipids, altering from normal to high. A few patients also showed a rise in LDH phosphorus. A few patients showed a rise in hemoglobin from low to normal. SGOT, hemoglobin, hematocrit and LDL rose in a quite few patients. Table 29 lists a summary of changes in lab values by treatment groups. The lab tests which showed significant changes either from baseline or between groups are mentioned below:

Hemoglobin and Hematocrit: Both factors rose in both groups, although the rise in the danazol treated groups was significantly greater. However, the rise in hematocrit/hemoglobin was all within the normal range. The mechanism of action of the two drugs is probably different, since lupron caused the rise by stopping menstrual bleeding while danazol, in addition, has an androgenic effect on the bone marrow.

Blood counts: Platelet count rose with danazol and white blood cell count fell with lupron. Slight leukopenia has been noted with other analogues.

Uric acid: Uric acid rose with lupron. This was also noted in the nafarelin NDA. However, the clinical significance is not clear.

BUN/Creatinine: BUN rose with lupron and fell with danazol. Creatinine rose with both lupron and danazol. The changes were slight and may not have clinical significance.

Protein: Total protein rose with both drugs while albumin rose with lupron. Since lupron is not broken down by the P450 system in the liver, it is not likely that it induces protein synthesis.

Liver tests: SGOT, Alk Phos, and LDH rose with both drugs/ The rise in SGOT was more significant for danazol and the rise in Alk Phos more significant for lupron. The former is the well-known effect of danazol on the liver and the latter reflects bone turnover due to the hypoestrogenic state.

Lipids: Total cholesterol, and LDL rose while HDL fell significantly with danazol. Triglycerides, LDL and HDL rose with lupron. The rise in LDL was not as high as with danazol. The HDL/LDL ratio was adversely affected by danazol, but not by lupron.

Table 20 provides individual hormone data (estradiol - ng/dl; and progesterone- ng/dl) evaluated at baseline, 3rd and 6th months for lupron and danazol treated patients. Table 21 and 22 summarize the data. Lupron does suppress hormones more profoundly than danazol, lupron patients showing statistically significant suppression of estradiol from baseline for within group and when compared to danazol at the 3 and 6 month evaluation. The progesterone levels show significance when compared to danazol only at the 6 month analysis. Both lupron and danazol suppress estradiol and progesterone when compared to baseline for both analysis.

Analgesic Score (Table 23):

The mean and median amount of analgesics used by patients in both groups appear to be similar, although no statistical information is available. The standard deviation of the lupron group appears to be slightly higher, although again no statistical information is provided.

Changes in vital signs (Table 25):

Most of the vital signs did not vary significantly between the treatment groups, although the lupron patients had a slight end of treatment diastolic blood pressure. Although both groups gained weight, the danazol patients gained more weight and showed significance from baseline and from lupron patients.

Bone Mineral Density Changes (Table 26 and 27):

Table 26 lists all the individual values for each test. Table 27 gives the mean percent changes in the bone content using various techniques. The numbers of patients in some groups are extremely small (Please see attached table taken from the NDA). The tests where the largest numbers of patients were entered were for spine-dual photon, hip-femoral neck and spine CT scan (there were only 8/9 patients in this study). Statistically significant decreases were noted in spine-dual photon, hip-femoral neck, calcaneus-single photon and spine CT scan. It is to be expected that these techniques would show the greatest changes, since they measure estrogen sensitive bone changes. %age change from baseline was -4.3% for dual photon and -7.0% for CT scan. These numbers vary somewhat from the data in the M86-031 study and also from the nafarelin study. In the 031 study, CT scan showed a -11.8% decrease in bone mineral density. In the nafarelin NDA, the loss by dual photon at the end of the treatment period was 3.6%. (Nafarelin NDA which had higher numbers of patients showed a total vertebral loss of bone of 4.3% and 5.8% by dual photon. Trabecular bone loss by CT scan was 8.7%). In the TAP submission (Lupron for), the dual photon loss was and by CT scan, the loss was The variability between all these studies are troublesome. The summary section of this review contains a table of all the information available in the three NDA's submitted so

the change appears to have occurred by the first month. (Please see Figure 2 and Table 1b attached to the end of the review).

Patient evaluation of pain (Tables 16, 17 and 18):

The three tables contain a summary of analysis of patient evaluation forms. Each table consists of monthly summaries of the three symptoms evaluated in this study.

Dysmenorrhea: Data for individual months is interesting, since very few lupron patients complained of dysmenorrhea after the first month, while the danazol patients took a little longer to reach amenorrhea, if they did at all. Hence, the change from baseline was most significant for the lupron patients within the first month. The few patients who did not show improvement from dysmenorrhea showed very little change after the second month, the danazol patients, on the other hand, continued to show improvement every month, with significant improvement from baseline right until the last month, when only a few patients continued to complain of dysmenorrhea. Throughout the study, the differences between lupron and danazol were not statistically significant. In the final analysis, both showed significant change from baseline.

Pelvic Pain: In this category, both groups of patients noted improvement from baseline which was statistically significant ($p < 0.05$) for all lupron and danazol treated groups at every monthly analysis and in the final analysis. It is interesting to note that in both groups, the improvement in this symptom had stabilized by the second month, with not much further improvement in the rating after that analysis.

Dyspareunia: This rating is interesting, since it is the one rating which was significantly greater with danazol treatment, most likely due to the fact that danazol does not result in vaginal dryness and decreased libido due to the hypoestrogenism caused by lupron. It is also interesting that the decrease in pain which may account for part of the relief of dyspareunia is not great enough to eliminate the discomfort due to the hypoestrogenism. In fact, at each month, danazol treated patients showed greater improvement in this symptom than lupron patients for the same month. Danazol patients show rapid improvement from baseline during the first month, but lupron patients do not show improvement from baseline until the third month. The same difference in effect was carried through to the final analysis.

Evaluation of menstrual cycles in the two groups (Table 1):

Lupron seems to be superior to danazol in suppression of menses in a greater number of patients, and also acts more rapidly.

Evaluation of Hormone Data (Tables 20, 21 and 17):

treatment period (or within 2 weeks of completion of the study).

2. Prior to start of treatment, patients will receive an endometriosis history, other medical, menstrual and fertility history.

3. Baseline E2 and P levels pre study and q 12 weeks during the study.

4. Clinical evaluation will be done every 4 weeks, but pelvic exam will be done pre-study and every 12 weeks.

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

6. Baseline blood tests, including hemoglobin, cholesterol, etc. All lab tests will be repeated at 24 weeks. Pregnancy test will be performed within one week prior to entry into the study.

7. Clinical baseline evaluation of bleeding patterns and extent of bleeding, as measured by date of first day of last two menstrual cycles and/or irregular vaginal bleeding, and average cycle length every 4 weeks. Duration and amount of uterine bleeding will also be recorded.

8. Clinical evaluation of signs and symptoms will be recorded. They are: pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness and induration. The patient will asses the existence and severity of the three symptoms. Frequency of analgesic use will be recorded to determine score. Coital frequency will also be recorded. The physician will assess the two signs and grade them according to severity. All assessments will be mild, moderate or severe. Symptoms and signs will be rated during each clinical visit 4 weeks apart. While pain measurements will be used, they will not be used as primary efficacy parameter.

9. Radiological evaluation of bone mineral content will be assessed prior to start of therapy and at 24 weeks (or within 2 weeks of completion of the study). Several methods were used to measure bone density, including dual photon or CT scan of the spine to assess trabecular bone will be performed. Single photon of the wrist and hip/femoral neck studies were also be done.

(6) Safety considerations

(a) Clinical studies:

Adverse reactions will be monitored and severity duly noted and recorded, including its relationship to study drug.

(b) Laboratory studies:

i. Routine: Cholesterol and other routine lab tests

placebo group showed improvement from baseline during the first and second months, during times when lupron patients showed no statistical difference from baseline.

Evaluation of menstrual cycles in the two groups:

Most of the lupron treated patients had become amenorrheic during the second month, with only two patients (428 and 429) continuing to menstruate after the second month. Most of the placebo treated patients did not loose their menstrual periods.

Evaluation of Hormone Data (Tables 15, 16 and 17):

Table 15 provides individual hormone data (estradiol - g/dl; and progesterone- ng/dl). Table 16 is a summary of both levels. Both tables show adequate suppression of both hormones with upron but not with placebo, as is to be expected. Table 17 documents changes with each month. In this table, it is clear that estradiol and progesterone levels suppress early in treatment and remain suppressed throughout the treatment period, to levels of less than 30 pg/ml for estradiol.

Analgesic Score (Table 18):

The amount of analgesics used by patients in the upron treated group was considerably less than with the placebo treated group. No significance value is attached to the data.

Changes in vital signs (Table 19):

None of the vital signs varied significantly between the treatment groups, although the placebo patients had a lower starting blood pressure.

Bone Mineral Density Changes (Table 20 and 21):

Table 20 lists all the individual values for each test. Table 21 gives the mean percent changes in the bone content using various techniques. The numbers of patients in each group is extremely small. For instance, there was only one placebo patient in the dual photon group, and only 2 in spinal CT scan. By the latter procedure, there was a -11.8% decrease in bone mineral density, but we have no post-treatment recovery values. Such information was available with the nafarelin NDA. The loss by dual photon at the end of the treatment period was -3.6%. (Nafarelin NDA which had higher numbers of patients showed a total vertebral loss of bone of -4.3% and -5.8% by dual photon. Trabecular bone loss by CT scan was -8.7%). It is not clear whether the CT measurement in the NDA is total or trabecular bone measurement. I suspect that it is total vertebral bone measurement. In any case, the loss in this study is greater than in the nafarelin study. In the TAP submission 19943 (Lupron for), the dual photon loss was and by CT

(a) Patient Population

Demography

i. Number 30 in each of two arms.
ii Age Pre-menopausal women at least 18 years of age.
iii Sex Female

(b) Clinical characteristics for inclusion

The following criteria were used for including patients in the study:

1. Patients should have pain which is classified by the Biberoglu and Behrman classification as being more than mild. Those patients who have mild pain will not be included. Patients should have moderate or severe symptoms in at least one of these categories: pelvic pain (outside of menses), dyspareunia or pelvic tenderness.

2. The patient will have endometriosis established by laparoscopy and possibly, color photography. Laparoscopy must be performed within three months prior to the study.

3. Patients may be included if they have undergone only partial removal of the genital tract or had previous surgery for endometriosis.

4. The patient must have normal menses for at least two cycles prior to entry. If she had previous therapy, laparoscopy must be performed after discontinuation of previous therapy.

5. Pregnancy test must be performed within one week prior to entry must be negative. The patient must use a barrier contraceptive during the study. Patients must not desire pregnancy.

(c) Exclusion criteria: The following patients will be excluded:

1. Those with mild pain or induration only.
2. Previous therapy within three months prior to study.
3. Positive pregnancy test or nursing mothers.
4. Previous exposure to lupron.
5. Diagnosis of osteoporosis or a bone density > 2 SD of age matched controls.

(5) Procedure

(a) Specific formulations used in the study, including the control drug: 3.75 mg of lupron depot to be given IM once every 4 weeks. The placebo contains no active drug. The drug is placed

for only 6 months. No data exist for residual bone loss found in women treated for longer than 6 months or for repeat treatments.

2. Treatment of pain of endometriosis is probably the only valid use of the analogues, since the clinical significance of decrease in endometrial implants are not known at this time.

3. The analogues are not indicated for infertility associated with endometriosis, since there are no data to show that treatment with analogues in any way alters fertility outcomes.

OTHER TREATMENTS:

Other medical treatments have been studied. In fact, gestrinone, gossypol, clomiphene, tamoxifen, and prostaglandin synthetase inhibitors have all been used in some studies. Gestrinone is presently being used in Europe. All these treatments suffer from the same problems outlined above, namely, all are temporary measures for the treatment of endometriosis.

for a number of years. Overall, all analogues work similarly, to suppress symptoms and signs of endometriosis, but as with other treatments, represent a temporary relief of disease process rather than a cure. The side-effect profile of the analogues vary from danazol, being those associated with hypogonadism. Of primary concern is bone loss due to hypoestrogenism and possible adverse effects on lipids if hypoestrogenism is continued for long periods of time. The time frame over which such changes would become of major concern to the well-being of the patient is not really known at this time. The following table provides the success rates noted by different studies to date. Studies on lupron are reviewed in the body of the NDA review. The following table is simply an overview.

TABLE 6 (taken from refs. # 8) [8]

Table II - Regression of endometriosis in patients who underwent follow-up laparoscopy

Author	Year	Patients (no.)	Classification	Percentage decrease of implant score	Percentage decrease of total score
Lemay	1884	9	AFS	81%	54%
Schriock	1985	7	AFS	87%	35%
Lemay	1986	15	R-AFS	75%	45%
Yee	1986	5	R-AFS	79%	—
Cirkel	1986	40	AFS	86%	—
Fraussen	1986	23	AFS	54%	30%
Jelley	1986	23	AFS	—	67%
Corson	1986	100	AFS	—	45%* 46%**
Tummon	1987	16	?	—	28%* 38%**
Pepping	1987	10	?	—	52%
Steingold	1987	15	AFS	61%*** 59%****	49%* 37%**

* 400 mg im/day
** 400 mg x 2 im/day
*** Proximal examination
**** Mid/distal examination

Recently, the relative benefit/risk ratio of the two regimens was discussed in a public forum by the agency. The advisory committee recommended approval of an GNRH analogue for endometriosis. Testimony presented during the meeting brought out these facts:

1. There is residual bone loss in women treated with GnRH analogues for 6 months. The amount of loss is similar to the loss encountered in amenorrheic runners. In spite of this loss, there is no evidence at the present time indicating that the long term fracture threshold may be adversely affected if women are treated

SURGICAL THERAPY:

Surgical therapy is usually reserved as an adjunct to infertility and for reconstructive surgery in advanced stages of endometriosis. The use of danazol or GnRH analogues in preparation for surgery has been suggested, since both agents may shrink the size of implants. However, surgical treatment is limited since it is difficult to repeat surgery. In addition, removal of some implants by surgery does not correct basic pathophysiology of the disease and recurrence is inevitable. Recurrence rates following reconstructive surgery are given below (refs. #7.)

TABLE 4

[illegible] RECURRENCE OF ENDOMETRIOSIS FOLLOWING RECONSTRUCTIVE SURGERY

AUTHOR	PATIENTS	RECURRENCES		OBSERVATION PERIOD

GNRH ANALOGUES:

GnRH, a hypothalamic releasing hormone, is released in a pulsatile fashion and stimulates LH release, which is also secreted in a pulsatile fashion. When given continuously, the hormone down regulates receptors in the pituitary which results in suppression of LH and FSH, after an initial stimulatory phase, resulting in hypoestrogenic, anovulatory, hypogonadism. Long-acting GnRH analogues are synthetic analogues of GnRH, with various substitutions of the native decapeptide, rendering them more stable. Since endometriosis is a disease which manifests itself during the reproductive years of a woman's life, the objective of the treatment modality is to suppress ovulation and the menstrual cycle, thereby suppressing the growth of endometrial foci.

The analogues have been studied for treatment of endometriosis

PROGESTOGENS ONLY:

Hypoestrogenic, hyperprogestogenic status causes decidual transformation of the ectopic lesions. However, breakthrough bleeding is common and there can be prolonged periods prior to resumption of menses once the treatment is stopped (7). Treatment success does not differ from combined therapy and poor cycle control and early recurrence are common (please see table below, derived from refs. #7).

TABLE 3

A. RECURRENCE OF ENDOMETRIOSIS FOLLOWING GESTAGEN-THERAPY

AUTHOR	TYPE OF GESTAGEN	DOSE	DURATION	PATIENTS n	OBSERVATION PERIOD	RECURRENCES n	%
[illegible]	[illegible]	10–30	6–12	18	—	3	16
[illegible] 1971	[illegible]	30	6	18	6 months – 10 years	4	22
[illegible] et al. 1970	[illegible]	5	-	44	—	15	(34
[illegible] et al. 1981	[illegible]	5	6	67	[illegible]	8	12
[illegible] 1986	[illegible] / [illegible]	10–30	6–10	11	10 d ([illegible])	3	27

hepatic failure, hepatic adenomas hepatic peliosis and cholestatic hepatitis have been reported to the FDA, with periods of use ranging from 3 weeks to 7 years. Many patients discontinue treatment because of androgenic side-effects. Although danazol has been shown to be effective in suppressing endometrial implants and pain relief, recurrence does occur, about 15-20% within the first year following treatment and another 5% for each following year of observation (7). Recurrence rates in several studies are noted in the table below, derived from refs. # 7.

TABLE 2

In addition, recent studies have shown that medical, and possibly, surgical treatment of endometriosis, may not result in any long term improvement in fertility.[5,6]

Medical treatment for endometriosis has been based on creating a hypogonadal or pseudopregnancy state. Various hormonal treatments and their mechanism of action are mentioned below:

TABLE 1 (taken from refs.# 7) [7]

ENDOCRINE EFFECTS OF HORMONAL REGIMENS FOR THE TREATMENT OF ENDOMETRIOSIS

	LH*	FSH*	E_2*	P*	A*	COMMENTS
PSEUDOPREGNANCY REGIMENS	↓↓	↓↓	↓↓	↑↑	NC	DECIDUALISATION OF ENDOMETRIUM
PROGESTIN-ONLY REGIMENS	↓	↓	↓	↑↑	NC	SYNTHETIC C-19 PROGESTINS HAVE ANDROGENIC EFFECTS
DANAZOL	NC	NC	↓	↓	(↓)	DIRECT INHIBITION OF OVARIAN STEROIDOGENESIS; PROMINENT ANDROGENIC SIDE EFFECTS
GESTRINONE	↓	↓	↓	↓	↓	DIRECT ANTIPROGESTATIONAL AND ANDROGENIC EFFECTS ON THE ENDOMETRIUM

*↓ = decrease, ↑ = increase, NC = no change

A brief discussion of the various treatment modalities available presently follows.

DANAZOL:

Danazol is one of two drugs approved in the U.S. for the treatment of endometriosis. Danazol is an isooxazole derivative of ethisterone, and has some androgenicity via its main metabolite, ethisterone. Because of its androgenic properties, Danazol can cause marked weight gain, hirsutism, voice changes, and other side-effects, including, on occasion, severe depression. Danazol acts by a variety of ways, not all of which have been characterized well. Pulsatile gonadotropin secretion is often suppressed, progesterone action at the endometrium is suppressed, SHBG and CBG levels are suppressed, and estradiol levels are lowered, although not to postmenopausal levels. In addition, lipids are adversely affected, with a rise in LDL and lowering of HDL. A few adverse reaction have been reported with many years of use of danazol, although labeling does not recommend prolonged use. Fulminant

4. Pharmacodynamics and Pharmacokinetics: Please see Biopharmaceutics review.

5. Clinical Background:

Background:

Endometriosis is a complex and chronic condition which affects women during their reproductive years. The condition may really be two different diseases, as Dr. Wilson notes in his review in the book "Endometriosis" (1). The severe disease manifest by pelvic adhesions and distortion of reproductive organs may really be a surgical disease, while the mild form of the disease may be more amenable to medical therapy.

Endometriosis affects approximately 1 in 15 women, although the epidemiological data is not well defined.[1] Epidemiological definition of this disease is poor because symptoms of the disease, namely, dysmenorrhea, pelvic pain, dyspareunia and infertility can be associated with many other gynecologic conditions, and unless, in each case, laparoscopy or other anatomical definition of endometrial implants can be made, the clinician and the patient cannot be sure of the diagnosis.

Another major problem is lack of satisfactory classification of the disease, which can predict desired clinical outcomes, for instance, fertility, symptom relief, etc.[2,3] It is not unusual for asymptomatic patients to be found to have endometriosis during laparoscopy. Patients with severe symptoms may not necessarily be those with widespread disease. Location of endometrial implants may contribute to symptoms as much as extension of disease. The Revised American Fertility Society Scoring system attempted to classify this disease in terms of location of implants or adhesions, but such laparoscopic classification may not necessarily provide an understanding of the pathophysiology of symptoms in this disease and may not necessarily correlate with desired outcomes, namely fertility or pain control.

There are at present no treatments available which could eradicate endometriosis. All treatments available only assist in relieving symptoms. In fact, medical treatments presently used, namely, Danazol, oral contraceptives and other hormonal treatments are all associated with only partial success or with enough side-effects to make them only temporary treatments for endometriosis. This could be due to the fact that endometriosis becomes quiescent during treatments, but does not regress completely. Recent studies have shown that improvement of implants seen on laparoscopy may not correlate with regression of the activity of the implants. In one study, histological examination revealed that secretory and glandular elements remain within the implants that have improved visually, regardless of the type of treatment.[4]

MINUTES OF THE 18th ONCOLOGIC DRUGS ADVISORY COMMITTEE
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration

MARCH 28-29, 1985

Held at Parklawn Building, Conference Rooms D, E, F, and G
5600 Fishers Lane
Rockville, Maryland 20857

Members Present

Martin D. Abeloff, M.D., Chairman
Evan M. Hersh, M.D.
Richard B. McHugh, Ph.D.
John S. Holcenberg, M.D.
Charlotte D. Jacobs, M.D.
Elaine M. Smith, M.D.
Rodger J. Winn, M.D.
Charles G. Moertel, M.D.
George P. Canellos, M.D.

Absent

Susan A. Pitman, M.D.

Executive Secretary

David F. Hersey, Ph.D.

Consultants

Jean D. de Kernion, M.D.
Michael Thorner, M.D.

FDA Staff/Participants

John F. Palmer, M.D.
Solomon Sobel, M.D.
John R. Johnson, M.D.
Gregory P. Burke, M.D.
Donald N. Buell, M.D.
Robert Justice, M.D.
A. T. Gregoire, Ph.D.
Richard Stein, Ph.D.
H. Leung, Ph.D.
James M. Bilstad, M.D.

These summary minutes for the March 28-29, 1985 meeting of the Oncologic Drugs Advisory Committee were approved on May 27, 1985.

"I certify that I attended the March 28-29, 1985 meeting of the Oncologic Drugs Advisory Committee and that these minutes accurately reflect what transpired."

David F. Hersey

David F. Hersey, Ph.D.
Executive Secretary

Martin D Abeloff

Martin D. Abeloff, M.D.
Chairman

LIST OF INDUSTRIAL REPRESENTATIVES MAKING
PRESENTATIONS OR AVAILABLE TO RESPOND
TO COMMITTEE QUESTIONS

Lederle Laboratories

Kenneth Cartwright, M.D.
Lawrence Posner, M.D.
Gary Dukart, M.D.
Judith Goldberg, Sc.D.
Edward McKeon, M.D.
John Noble Ph.D.

Consultants

Joseph Allegra, M.D.
John M. Bennett, M.D.
C. Kent Osborne, M.D.

Farmitalia Carlo Erba/
Adria Laboratories

F. Nicolis, M.D.
C. Young, M.D.
J. Armand, M.D.
F. Torti, M.D.
F. Muggia, M.D.
A. Casazza, M.D.
J. Page, M.D.

Abbott Laboratories

Dean Sundberg
Frank Steinberg, M.D.
L. Michael Glode, M.D.
Joseph A. Smith, M.D.
Marc Garnick, M.D.

MINUTES OF ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

MARCH 28-29, 1985

The nineteenth meeting of the Oncologic Drugs Advisory Committee was opened by the Executive Secretary with the introduction of four new members including a new chairman of the committee. A brief presentation was made on the importance and role of advisory committees to the Food and Drug Administration (FDA).

The Chairman, Dr. Abeloff, then began the scientific and technical part of the meeting introducing Dr. Johnson, FDA, who outlined the agency's requirements for approval of new cancer drugs.

The committee next undertook a review of a new drug application NDA 19-297 Novantrone (mitoxantrone), sponsored by Lederle Laboratories. The chair noted that questions posed by FDA to the committee and certain questions posed by a committee member were sent to Lederle before the meeting. Presentation was then made by an FDA medical officer, Dr. Burke, whose presentation focused on the 5 controlled pivotal studies identified as such by the sponsor. Three of 5 studies involved mitoxantrone as a single agent compared to doxorubicin as second line therapy of breast cancer. The fourth study was a non-randomized historical retrospective comparison of mitoxantrone one as a single agent versus doxorubicin as front line therapy in advanced breast cancer while the 5th study was a randomized prospective design where mitoxatrone was substituted for doxorubicin comparing CMF with CAF, as front line therapy for advanced breast cancer. A detailed presentation with slides was made for all of these studies.

In the first study reviewed, FDA's main concern was whether or not there was adequate statistical power to discern relevant clinical differences. There was no analysis of overall survival. There was also some question of the appropriateness of the positive control. Major concerns in the 2nd study were again the question of whether there is adequate power to discern relevant clinical differences with regard to both response rates and quality of life. There was a lack of overall survival data and also the subjective and objective responses should have been analyzed separately. A similiar review was made of the other pivotal studies. Noteworthy also was the issue of cardiotoxicity which is perhaps the most important issue for the drug in terms of its relative cardiotoxicity vis-a-vis the standard agent, doxorubicin. The clinical data contains only small numbers of patients treated at total doses greater than 100 mg/m^2, so any estimation of cummulative incidence of cardiotoxicity has to take into consideration the size of the denominator. In summarizing, the FDA concerns are best described by the questions posed to the committee (copy attached) and reiterated by Dr. Burke.

In response to a question posed by the committee, Dr. Burke noted that most of the individual studies showed a trend toward favoring doxorubicin in terms of response rates and time to treatment failures, but in the pooled date the trends did not quite become statistically significant. A number of other questions were raised by the committee, some of which were deferred for the Lederle presentation on mitoxantrone.

Dr. Cartwright began the presentation for Lederle noting that they would concentrate on the data in the NDA though noting that the studies were not stopped at the time of submission of data to FDA and at the end of their presentation they would show data on the additional patients. Among Dr. Cartwright's comments, he noted that of the 4450 patients, a third came from American sponsored trials, and that in a data base of this size they had an opportunity to look at the incidence of some of the serious side effects, notably congestive heart failure. He noted there were 60 cases of congestive failure, 57 of which had predisposing risk factors. Patient selection, study parameters, and monitoring were discussed.

Dr. Posner's (Lederle) presentation was directed primarily at survival and safety data, and included a review of the pivotal studies using their analysis based on all randomized patients with regard to response rate, time to treatment failure, and survival. In summing up the studies and presentation, Dr. Posner concluded by saying the data showed that Novantrone (mitoxantrone) and doxorubicin have comparable efficacy as measured by response rate, time to treatment failure, quality of life, and survival based on pretreatment drug, and performance status. The adverse experience profile of mitoxantrone is superior to that of doxorubicin with specific reference to the comparative incidence of mucositis and stomatitis, nausea, vomiting and alopecia. It is also less cardiotoxic when compared by the incidence rates of clinical congestive heart failure with increasing cumulative dose or by serial changes in left ventricular ejection fraction.

There followed a brief presentation of Lederle's new data and a series of questions by the committee. It was made clear by the Chair that this new data would not be used by the committee in its final discussion and deliberation regarding approvability or non-approvability of the drug.

The committee began its formal discussion of the NDA with a series of questions to the company including those specifically raised by Dr. Moertel and sent to the company prior to the meeting, following which general committee discussion began. A number of committee members raised their concerns about the studies and the data. Included here was the feeling that these were premature studies compared to what the applicant originally intended. Based on the data available it seemed a strong possibility that mitoxantrone would prove inferior in terms of objective response rates, initial progression of disease, and duration of response, had the studies gone on to full maturity (completion). Questions on the size of the studies and clearer evidence of lesser cardiotoxicity were also felt to be of major concern. The numbers of patients in the cross-resistance part of the studies were also felt to be small. After extensive further discussion, and a review of the FDA questions relating to this drug and the committee's consensus response, the committee voted to recommend that the drug mitoxantrone not be approved, noting that the committee in general felt hopeful about the drug and that more data might be forthcoming to confirm that hopefulness.

The committee next considered NDA 50-595 epirubicin sponsored by Farmitalia Carlo Erba/Adria. As with the previous drug, presentations were made by an FDA staff member which was then followed by a number of company

representatives, headed by Professor Nicolis, prior to discussion by the committee. This NDA contained 5 pivotal controlled studies. Among the concerns of the studies highlighted by FDA were power considerations in terms of the size of the studies and their ability for comparing overall survival between groups of patients. In a number of the studies the applicant did not consider early failures in the denominator for evaluability.

It was noted that only slightly over half of the studies had case report forms which were reviewable. Reasons for non-reviewability included non-translated foreign language and illegibility. The committee noted that printed material submitted to it by the company was in some cases different from that provided by FDA, and that FDA had not reviewed the updated data recently submitted by the applicant.

A number of company representatives then made presentations to the committee with slides to illustrate their points. Questions by committee members were addressed to each presentor following his presentation. A key point raised by the committee concerned the assumption that epirubicin was less cardiotoxic than doxorubicin since, had they used a comparable myelotoxic dose of both drugs the results might have shown the same effect. The main issue is how the cardiotoxic dose relates to the therapeutic dose. In point of fact, the small number of cases makes it difficult to prove there is less cardiotoxicity. A brief but detailed review was presented by the applicant on cardiotoxicity, including biopsy studies, to substantiate lesser cardiotoxicity in the epirubicin-treated patients. The question relating to the reliability of the MUGA scan and whether it is physiologically predictive was also discussed in some detail.

The Committee discussion following the applicant's presentation raised several points. In terms of efficacy, the sample size in all of the studies appears to be too small. There was only one study in which the design was truly adequate. The power of the studies was also felt to be inadequate. Survival data was limited by the numbers involved and in some cases was not dealt with at all. Following the committee discussion, the committee voted unanimously not to recommend approval of the NDA at this time. The committee then suggested that new studies and/or reopening or extending certain of the previous studies would be useful.

The committee next considered NDA 19-010 leuprolide sponsored by TAP/Abbott Laboratories. This NDA was referred to this committee by the Division of Metabolic and Endocrine Drug Products (DMEDP), FDA, which reviewed it. The initial presentation was made by Dr. Sobel, Director of that division. Dr. Sobel noted that a representative of the Endocrinologic and Metabolic Drugs Advisory Committee was attending the meeting and that the NDA was brought to the Oncologic Drugs Advisory Committee rather than their own committee because of the preponderance of oncologic considerations. It was pointed out that DMEDP recommends approval of the drug for the treatment of metastatic prostate carcinoma, with restrictions to situations where surgical castration or DES treatment were unacceptable.

Specifically mentioned in the FDA presentation was the fact that leuprolide achieves an effective medical castration for long periods of time and appears to be complete. Complete suppression of testosterone levels occurred out to 44 months. Some concern was expressed over the first few weeks of use because of a stimulating effect ("flare") on the pituitary albeit the effect wears off after several weeks. Several patients that had impending ureteral obstructions or vertebral bone collapse did show ureteral obstruction and increasing bone pain which disappeared after one or two weeks. Response of bone pain (secondary to metastatic disease) was considered an important factor, and although numbers were small, DES appeared to be superior to leuprolide in regard to bone pain, although bone pain improvement did occur with leuprolide. Two studies were submitted to demonstrate survival data, and the Division concluded there was sufficient data to establish that there was no significant difference in survival with either DES or leuprolide.

Based on their review DMEDP recommended approval of the drug but not as first line treatment noting that where one has concerns about cardiovascular effects and/or thromboembolism associated with the use of DES, one should consider leuprolide. A number of questions were raised by the committee for Dr. Sobel's response including the power of the studies with respect to demonstrating survivorship.

Presentations were then made by a number of individuals representing the applicant. The company noted that no new information was being presented other than more detailed slides. Data was presented from the clinical trials to illustrate the ability of leuprolide to suppress testosterone. A review of the controlled trials in patients with prostatic cancer treated with leuprolide was subsequently made with their conclusion that leuprolide does produce sustained suppression of serum testosterone, that it is a very safe drug devoid of many of the side effects of oral estrogens, and that with proper patient selection the initial so-called flare phenomenon does not present a clinical problem in a substantial majority of patients. Results of a randomized study using leuprolide and oral estrogens was presented showing comparable response rates using the NPCP criteria with estrogen-treated patients. Median survival estimates were 146 weeks for leuprolide versus 136 weeks for the estrogen group.

There followed a series of specific questions by the committee to the company representatives after which the committee heard from the two consultants brought in for a discussion of this NDA. It was made clear during this question and answer period that although the Oncology Division did not review the individual case report forms in this NDA, they did have an opportunity to review the Medical Officer's report and their concerns, as expressed in a consultant review, were sent to the committee members as a part of the FDA package on leuprolide.

A number of comments were then made by the two consultants Drs. Thorner and de Kernion. Dr. Thorner stated his agreement with the points made by Dr. Sobel and noted that the data clearly show a delay of one month for medical castration to occur and that there is a transient increase in testosterone citing that the committee needed to decide whether this had any significance

or not. He proposed a change in the labeling under clinical pharmacology to revise the 2-4 week period shown to 4 weeks. Dr. de Kernion agreed with earlier statements to the effect that orchiectomy is still the best primary treatment. He indicated he was not entirely convinced that survival is equivalent between leuprolide and DES on the basis of the data but felt the data strongly suggests that they are. He also felt that cardiovascular side effects were less severe with leuprolide based on the data presented but was still not sure about pain control. He pointed out that the acute phase of elevated testosterone would become an issue of major concern when drug was released to the medical community. While uneasy about some aspects of the drug, he felt that it could be an alternative only in patients who do not or cannot accept orchiectomy and/or in patients with cardiovascular disease who could not tolerate DES.

The committee then began its discussion prior to making its recommendations with the discussion centering mostly around the pain issue, cardiovascular side effects, interval to progression, survival and certain aspects of the statistical analysis.

With regard to the labeling it was suggested that the charts in the labeling use the more updated data with cardiovascular side effects. Dr. Thorner's earlier change regarding time of testing testosterone levels was reiterated.

The committee voted overwhelmingly in favor of recommending approval of the drug. The committee took an additional vote in agreement with the proposed labeling that "leuprolide is an alternative treatment to DES or surgical castration" rather than using the more stringent wording suggested by Dr. Sobel. This vote was unanimous. The committee also voted unanimously that the labeling as proposed, with recommended changes, was adequate.

The committee then took up the subject of Lymphoma Clinical Trials with specific reference to those aspects germane to new drug evaluation and approval. Dr. Justice (FDA) presented background information on the subject. In essence, the presentation noted that recent regimens for poor prognosis NHL appear to achieve superior complete remission and survival by including more drugs in the therapeutic regimens. These better results are probably achieved at the expense of increased toxicity. There have been no controlled randomized studies to demonstrate that one of the newer regimens is superior to the others or to CHOP.

A series of questions on the topic were sent to the committee members prior to the meeting. These were then addressed by the committee in the discussion which followed the presentation. Among the remarks made, it was pointed out that in all of the trials that histology, while fine, isn't enough and that other prognostic factors should also be looked at. CHOP, like it or not, is the standard multi-drug regimen used in this country by practioners in the treatment of diffuse large cell lymphomas. Further discussion ensued on the watch and wait issue as well as the type of patients selected for trials. The committee then proceeded to respond to the specific questions raised by FDA (see attachment). On the subject of Questions 1 and 2, should new drug studies be stratified by histological subtypes or be limited to one subtype,

the committee consensus seemed to be that they should be stratified but not limited and that new drug approvals should specify the subtype. Regarding Question 3, the committee seemed to feel one needs to describe study population and selection factors carefully. On Question 4, there was no disagreement to accepting a control of chlorambucil, possibly approving a new drug with same survival but less toxicity and better quality of life. Considerable discussion then evolved around multi-drug therapy and ascertaining the benefit of adding another drug to a regimen without having demonstrated the individual contribution of each agent. The committee pretty much agreed that with regard to efficacy they were looking at survival which would take a long time. Question 6, Chair said yes with no disagreement by committee. Questions 7 and 8 were discussed briefly.

At this point the committee took up the agenda item relating to labeling for safe handling of cancer drugs. Dr. Buell of FDA made the initial presentation. Handouts relating to the subject were previously provided to the committee and, essentially, FDA was asking the committee whether there should be something in the labeling of approved drugs that pertains to their safe handling, and should containers bearing such drugs bear a hazardous warning label. The presentation included a number of slides identifying cytotoxic agents, aerosol dissemination and use of hoods to control it, methods of handling drugs, etc. During the committee discussion it became apparent that a number of committee members felt the need for more real evidence regarding the tangible dangers associated with handling such drugs. There was no question that there was legitimate concern but most members felt that with a number of organizations currently addressing the issues, it would be premature for the committee to make specific recommendations. A suggestion was made that the most one might say on the package insert for these drugs is that they are possibly hazardous and care should be taken in their use and disposal, although the committee generally agreed that they would not suggest that the package inserts contain anything other than what is presently in them at this time. Committee members were asked to send any suggestions for studies on this topic to Dr. Hoth of NCI who indicated earlier that they were considering supporting work in this area. The meeting was adjourned.

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TENTATIVE AGENDA
ONCOLOGIC DRUGS ADVISORY COMMITTEE
Nineteenth Meeting
28-29 March, 1985

Thursday, 28 March 1985
Conference Room D and E - Parklawn Building
Friday, 29 March 1985
Conference Room G and H - Parklawn Building
5600 Fishers Lane, Rockville, Maryland 20857
ALL SESSIONS OPEN

THURSDAY, 28 MARCH
A.M. SESSION

8:30 - 8:45 Welcome, Announcements, and Introduction of New Members - Dr. Hersey, FDA

8:45 - 9:15 FDA Requirements for Approval of New Cancer Drugs - Dr. Johnson, FDA

9:15 - 12:15 Discussion of NDA 19-297 Novantrone (Mitoxantrone)- Lederle Laboratories
Initial Presentation - Dr. Burke, FDA
Presentation by Lederle Laboratories-
Introductory Remarks - Dr. Cartwright
Main Presentation - Dr. Posner
OPEN COMMITTEE DISCUSSION

12:15 - 1:15 LUNCH

P.M. SESSION

1:15 - 4:15 Discussion of NDA 50-595 Epirubicin - Farmitalia Carlo Erba/Adria Laboratories
Initial Presentation, Dr. Burke, FDA
Presentation by Prof. Nicolis, M.D., Farmitalia Carlo Erba/Adria Laboratories
OPEN COMMITTEE DISCUSSION

4:15 - 4:30 Status Report of Action Taken by FDA on Previous Committee Recommendations - Dr. Hersey, FDA

FRIDAY, 29 MARCH
A.M. SESSION

8:30 - 8:40 Announcements - Dr. Hersey, FDA

8:40 - 11:40 Discussion of NDA 19-010 Leuprolide (Lupron)
TAP/Abbott Laboratories
Initial Presentation - Dr. Sobel, FDA
Presentation by TAP/Abbott Laboratories
In Order of Presentation
Introduction - Mr. Sundberg
Overview - Dr. Steinberg
Endocrine Background and Responses - Dr. Glode
Study M 80 - 036 - Dr. Smith
Study M 81 - 017 - Dr. Garnick

Concluding Statement - Dr. Steinberg
Presentation by Consultants -
Dr. Lipsett, Dr. Thorner, Dr. de Kernion
OPEN COMMITTEE DISCUSSION

11:40 - 12:40 LUNCH

P.M. SESSION

12:40 - 1:55 Lymphoma Clinical Trials - Opening Remarks -
Dr. Justice, FDA
Appropriate Standard for Comparison with Test Regimens in Good Prognosis Non-Hodgkins Lymphoma
What is the Contribution of Adriamycin (Doxorubicin) to the CHOP Regimen in Non-Hodgkins Lymphoma?
OPEN COMMITTEE DISCUSSION

1:55 - 3:45 Discussion on Labeling for Safe Handling of Cancer Drugs -
Initial Remarks - Dr. Buell, FDA
OPEN COMMITTEE DISCUSSION

3:45 - 4:45 Open Public Hearing

CONSOLIDATED

FDA Questions for ODAC Regarding Novantrone NDA 19-297
and Epirubicin NDA 50-595

A. For each Study:

1. Is the study design adequate? Has the control treatment previously been shown to benefit the study population regarding survival or quality of life? If a combination drug study, has the contribution of Adriamycin to the control treatment been demonstrated?

2. Does the study have the power to detect any significant clinical differences that may exist between test and control treatments?

3. Does the study provide adequate comparison of test and control treatments regarding overall survival? Quality of life? If there is a crossover design, is adequate assessment of overall survival precluded?

4. Is there adequate data on comparison of cardiotoxicity of test and control regimens? What is the appropriate maximum total dose of the test drug and what is the risk of cardiotoxicity at this dose? How should cardiotoxicity be monitored and at what frequency?

B. Is the NDA approvable at this time? If not, what additional data is needed and can it be obtained from present studies, extensions of present studies or are additional studies needed?

FDA Questions for ODAC Regarding Leuprolide NDA 19-010
TAP/Abbott Laboratories

It is the recommendation of the Division of Metabolism and Encocrinologic Drug Products that therapy for metastatic prostatic carcinoma with leuprolide be approved but that it be restricted to use in situations where DES or surgical castration are not acceptable.

(1) Does the Oncologic Drugs Advisory Committee agree with this recommendation?

(2) Does the labeling provide the physician with adequate information for the correct use of leuprolide in the treatment of prostatic carcinoma?

Questions for FDA ODAC

NON-HODGKIN'S LYMPHOMAS

Pathology

1. Should new drug studies be stratified by histologic subtype or be limited to one histologic subtype?

2. Should new drug approval specify histologic subtype?

Low Grade Lymphomas

3. Should new drugs be tested in all patients or only those with progressing disease (symptomatic)?

4. What should the control regimen be? Has efficacy been shown for the control, i.e., must the test drug be equal to or better than the control?

5 What efficacy parameters should be required?

Diffuse Large Cell and High-Grade Lymphomas

6. Has the contribution of doxorubicin to the CHOP regimen been convincingly demonstrated?

7. When a new drug is substituted for a similar drug should the new drug combination be required to be superior to the original combination before granting approval?

8 When a new drug is added to a "standard" regimen, should the new drug treatment be required to be superior to standard treatment before granting approval?

Questions for FDA ODAC

Safe Handling of Anticancer Drugs

1. Should the package insert contain instructions for safe handling? If so, what material should be included?

2. Should drug containers bear a hazardous warning label to better insure proper handling and disposal procedures?