CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-088

MEDICAL REVIEW(S)

FEB 28 2000

NDA 21-088

MEDICAL OFFICER'S MEMO

FROM: Norman S. Marks, MD
Medical Officer

TO: Susan Allen, MD
Acting Division Director, HFD-580

THROUGH: Dan Shames, MD
Urology Team Leader, HFD-580

DATE: February 28, 2000

RE: Resolution of all outstanding labeling and clinical issues related to the clinical review of NDA 21-088, Viadur™

The purpose of this memorandum is to inform the Acting Division Director that all relevant clinical issues regarding Viadur™ (NDA 21 088) have been resolved. The final package insert, physician instruction manual, and patient package insert are considered acceptable from a clinical perspective.

In the opinion of this reviewer, there are no outstanding clinical issues.

/S/ LD 2/28/00

Concur /S/
TL 2/29/00

NDA 21 088
Stamp date received – 30 April 1999
Review completed – 15 February 2000

FEB 17 2000

MEDICAL OFFICER REVIEW OF NEW DRUG APPLICATION

Drug substance – leuprolide acetate
Drug product – DUROS™ Leuprolide implant
Trade name – Viadur™
Indication – palliative treatment of advanced prostate cancer
Dose and route – 120 microgram/day administered by continuous subcutaneous infusion over a twelve month period
Sponsor – Alza Corporation
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210

Table of Contents

1.0 Summary

VIADUR™ leuprolide implant is a sterile, single-use device designed to deliver a continuous, steady-state dose of leuprolide acetate subcutaneously over a twelve month duration of therapy. The device is implanted under local anesthesia in the subcutaneous space in the upper inner arm and is intended to be removed under local anesthesia after twelve months. The product is indicated for the palliative treatment of men with advanced prostate cancer.

The safety of this product was evaluated in 131 patients with histologically-confirmed adenocarcinoma of the prostate. Patients received either two implants [n=24] or one implant [n=107] for up to 104 weeks. Patients who reached the end of the 52 week treatment period had the implant removed and replaced with another single device. Safety endpoints included adverse events, vital signs, laboratory tests, concomitant medications, and an evaluation of the implant-removal-reimplant procedures and wearability unique to this device. Review of the safety database identified no safety concerns that would prevent approval of this product.

The efficacy of this product was evaluated in the 107 patients who received a single implant at baseline and a single implant at the removal-reimplantation at 52 weeks. The basis for assessment of efficacy was the rate of success of the device in achieving medical castration [serum testosterone < 50 ng/dL] by week 4 and maintaining castrate levels during the 12 months of use. In addition, the product was evaluated during the eight weeks [weeks 52 through 60] after removal-reimplantation for the incidence of flare of testosterone. Review of the efficacy data submitted showed that the VIADUR™ device demonstrated efficacy at rates similar to the performance of other depot leuprolide products currently approved and marketed for similar indications.

From a clinical perspective, this product is safe and effective and a recommendation for approval has been made.

2.0 Background

2.1 Regulatory history – This drug product was developed under [redacted]. A pre-IND meeting was held with the FDA, HFD-510 on October 5, 1995 and the IND was filed [redacted]. An end-of-phase II meeting was held with the Division of Reproductive and Urological Drug Products [DRUDP] on August 7, 1997 and a pre-NDA meeting with DRUDP on May 27, 1998. The NDA was received on April 30, 1999 and is being examined as a standard 10 month review. A full waiver request for pediatric labeling was submitted on April 30, 1999. A four month safety update was submitted as an amendment to this NDA on October 14, 1999.

The current submission contains 108 volumes. The volumes reviewed for this clinical review include volumes 1.1-1.3, 1.59, and 1.67-1.106.

2.2 Clinical background - The use of orchiectomy as a means of castration for treatment of advanced prostate cancer has been an accepted and standard treatment of adenocarcinoma of the prostate since the seminal work of Charles Huggins in the 1940's and 1950's. The procedure was felt to offer palliation for those patients who were demonstrating either local or systemic effects of their prostate cancer—local obstruction at the bladder outlet or of the ureters or systemic complaints of aesthenia, weight loss, or bone pain. No studies have shown that castration will cure this cancer or prolong survival.

Until 20 years ago, the use of estrogenic compounds, generally oral estrogen as diethlystilbestrol [DES], was often offered as an alternative to surgical castration. The dose of estrogen used varied widely in clinical practice, from intravenous doses of 500 mg of stilphostrol to the use of 1 to 100 mg of oral estrogen as DES. The most commonly prescribed dosage of DES had been a 5 mg single daily dose. The Veterans Administration Cooperative Urological Group [VACURG] studies of the 1960's reported an increased incidence of cardiac, thrombophlebotic, and thromboembolic adverse events [AEs] in patients treated with DES 5mg for this indication. Patients also reported gynecomastia and GI adverse reactions on DES 5 mg. The second study of the VACURG series demonstrated that 1 mg of DES was as effective as the 5 mg dose and did not produce the AEs noted at 5 mg. Nevertheless, DES 3 mg became the "accepted dose" when another study reported that the 3 mg dose reliably produced castrate levels of testosterone. A trial of 1 mg DES versus 3 mg was never done to determine whether the lower dose could match placebo, orchietomy, or DES 3 mg in efficacy and safety.

The lack of appeal to many patients of surgical castration and the adverse effects of estrogen therapy lead investigators to pursue alternative methods of reversible medical castration.

The production of testosterone by the Leydig cells of the testes is regulated by the release of LH by the anterior pituitary gland. Blocking the release of LH will decrease production of testosterone. The decapeptide hormone GnRH, produced in the hypothalamus, controls LH release. The development of synthetic analogues of GnRH with a greater affinity for receptors in the pituitary has allowed their use as *competitive agonists*, blocking the release of LH, and decreasing testosterone production to castrate levels.

In December 1983, the synthetic gonadotropin-releasing hormone [GnRH], leuprolide acetate, was submitted as NDA 19 010 [TAP Pharmaceuticals]. The primary clinical trial, study M81-017, was offered to support the registration of this first synthetic GnRH agonist for the palliative treatment of advanced prostate cancer.

The study compared leuprolide acetate, 1 mg as a daily subcutaneous dose against DES, 1-mg tid oral dose.

- The population studied was men with symptomatic stage D2 adenocarcinoma of the prostate with measurable metastatic disease.
- The evaluable population included 92 patients [initial leuprolide treatment] and 94 patients [initial DES treatment].
- The study design was a conditional crossover design. Patients were switched from one treatment arm to the alternative treatment for either progression or intolerable side effects. No blinding of investigators or subjects was done.
- The primary efficacy endpoint was the rate of objective favorable response by National Prostate Cancer Project [NPCP] criteria. Treatment failure was defined as either objective progression of metastatic disease or intolerable side effects.

- Efficacy results
  - Objective favorable response (either complete response [CR], partial response [PR] or no change [NC] by NPCP criteria) for the leuprolide group was recorded for 79 of 92 patients and for 80 of 94 DES patients.
  - Ten of 92 patients in the leuprolide group and 2 of 94 patients in the DES group had evidence of objective progression by NPCP criteria.
  - Three of 92 patients in the leuprolide group and 12 of 94 patients in the DES group were categorized as failures for "other" reasons, usually intolerable side effects.

Leuprolide acetate [Lupron™ 1 mg; TAP Pharmaceuticals] was approved 9 April 1985 for the palliative treatment of advanced prostatic cancer.

- The opinion of the oncology advisory committee and the division director was that this therapy was "second-line" treatment in men in whom surgical castration or estrogens were not indicated or not acceptable to the patient.

The first depot dose of Lupron was approved [NDA 19 732] in January 1989 as a 7.5 mg dose administered every 28 days. In study M85-097 the testosterone suppression rate achieved at week 4 for this formulation was reported as 91%.

The three month depot Lupron, 22.5 mg and four month depot, 30 mg were approved December 1995 [NDA 20517] and May 1997 [NDA 20517, S-002]. The testosterone suppression rate at week 4 in these three registration studies were reported as 92%, 97%, and 94%. No confidence intervals were reported.

- Lupron depot, 1-month, 3-month, and 4-month formulations, are labeled as indicated in the palliative treatment of advanced prostatic cancer as an alternative treatment of prostatic cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient.

2.3 Scientific Rationale for DUROS™ Leuprolide Implant

The administration of leuprolide, as a subcutaneous daily dose or as a depot dosage by release from polymer microspheres, has been accepted as the preferred method of achieving castration in patients in whom castration is indicated for palliative treatment of prostate cancer. The depot dose is administered as a deep intramuscular injection at 30, 90, or 120-day intervals. The depot formulation cannot be retrieved, once administered. In the post-marketing experience with leuprolide depot, studies in the peer-reviewed literature have reported that delay in dose administration beyond the recommended interval has resulted in loss of suppression of testosterone. Repeat administration of the depot dose has occasionally been reported to produce clinical flare symptoms associated with a transient flare in serum testosterone during the first days after repeat dosing.

The Duros™ leuprolide implant is designed to deliver a continuous therapeutic dose of medication subcutaneously for twelve months. The sponsor believes that the implant will result in increased compliance, less chance for an "acute-on-chronic" testosterone flare, and also offer the opportunity for early removal of the device if indicated for adverse effects or disease progression.

2.4 Pre-Clinical Studies with DUROS™ Leuprolide Implant

Animal toxicity studies were performed in rats, swine, and dogs.

- In study BIO-95-B025-4904 the local toxicity of several prototype implant systems were assessed by insertion in the dorsal subcutaneous space in male rats. Leuprolide was evaluated in formulations with propylene glycol, water, or DMSO for up to 32 weeks. After removal, the tissue was scored for irritation using a standard scoring scale for encapsulation, fluid accumulation, and vascularity. Local histological examination was performed. The sponsor reports that there were no "unexpected" toxicities, no treatment-related mortalities or clinical changes compared with control animals. The titanium reservoirs caused "mild irritation macroscopically and microscopically at all excision times".

- In study BIO-95-B026-4904, two types of prototype reservoirs [titanium versus high density polyethylene] were implanted in Hanford miniature swine to assess ease of implantation and removal, wound site healing, tendency of the implant to migrate, and gross assessment of biocompatibility by standard scoring after four and twelve weeks. These assessments were performed immediately after removal at weeks four or twelve or after a 3-week recovery period at weeks 7 and 15. The study suggested that implantation, localizing and retrieval of implants was possible, that migration of implants was minimal, and that wound healing was satisfactory. No infections or implant expulsions were noted over the 12-week treatment period.

- In study BIO-95-B046-4904, sexually mature male beagle dogs were studied for up to 14 months. The initial implant was localized and removed at twelve months and a second implant placed and monitored for two more months. DUROS™ Leuprolide Implants were placed in the dorsal subcutaneous space. Sham-operated animals and dogs receiving injections of one-month depot leuprolide served as controls. No treatment-related gross or microscopic necropsy findings were noted except those effects on the male genital system expected as a pharmacological effect of the GnRH agonist.

2.5 Clinical Study with DUROS™ Leuprolide Implant

Based on these animal studies, the to-be-marketed device was studied for tolerability of implant placement, removal and wearability in healthy male volunteers. In study C-95-063, six healthy male volunteers, between the ages of 30 and 54, were

implanted with a placebo implant, containing no interior components or drug. The subjects were assessed over the eight week treatment period, the implants removed and subjects followed for four weeks after removal. Investigators rated the implant placement as "very easy" and subjects tolerated the procedure without difficulty. During the wearing period, investigators identified no significant evidence of swelling, inflammation or infection. Diary records noted little discomfort reported by subjects. Removal was rated by investigators as "very" or "somewhat" easy in five subjects; in one subject the removal was "somewhat difficult". The implant was noted to be encapsulated in all subjects; no fluid accumulation was identified. Following removal, the wound healing was found to be satisfactory by investigators. Subjects rated pain/sensation as "none" at weeks 1, 2, and 4 post-removal.

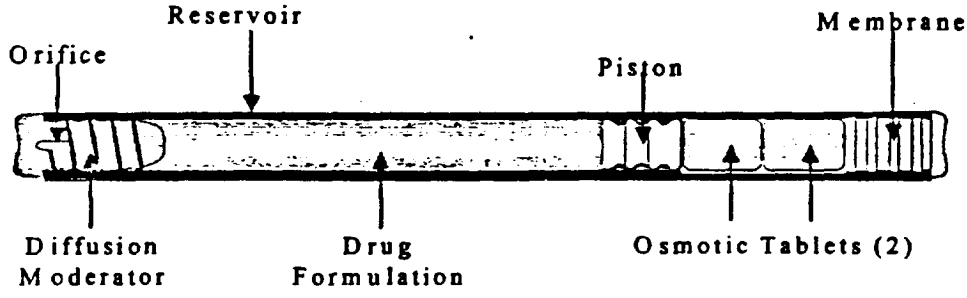
2.6 Description of the DUROS™ Leuprolide Implant

The to-be-marketed device is a sterile, non-pyrogenic, non-biodegradable, single-use device, designed to deliver a continuous, steady-state dose of leuprolide acetate subcutaneously over a twelve month duration of therapy. The device is implanted under local anesthesia in the subcutaneous space in the upper inner arm, to rest in the groove between the biceps and triceps muscles. The device in intended to be removed under local anesthesia after twelve months. A second device may be placed in the same tract to continue therapy as clinically appropriate.

The device has been developed from a technology similar to that used in veterinary medical research and treatment for over 15 years. The original product, the sponsor's ALZET™ osmotic pump has been used for investigational purposes in laboratory animals. Over the past decade, the sponsor's VITS [Veterinary Implantable Therapeutic Systems] has been used to deliver continuous doses of bioactive proteins in field animals. This experience forms the basis for the development of DUROS™.

The implant consists of a 4x45 mm titanium cylinder capped on one end by a polyurethane rate-controlling membrane and on the other by a polyethylene diffusion moderator. Within this reservoir is an elastomeric piston separating the drug formulation, leuprolide acetate dissolved in dimethyl sulfoxide [DMSO], from the osmotic engine. The engine is composed of two tablets containing sodium chloride, sodium carboxymethylcellulose, povidone, magnesium stearate, and sterile water for injection.

DUROS® Leuprolide Implant System



After implantation in the subcutaneous space, water is drawn into the reservoir through the rate-controlling membrane in response to the osmotic gradient between the osmotic tablets and the fluid in the subcutaneous space. The water causes the osmotic engine to expand, exerting pressure on the piston. Movement of the piston delivers the leuprolide acetate through the diffusion moderator and into the subcutaneous space. The drug delivery rate is dependent on the characteristics of the osmotic engine and the rate-controlling membrane.

3.0 Summary of NDA Clinical Section –

3.1 Overview and efficacy endpoints

The clinical section of the NDA includes two phase III, open-label, historical control studies. Both studies are composed of a 52-week treatment phase for efficacy data and a 52-week safety extension to allow for 104 weeks of safety data. Both studies define the primary efficacy endpoint as the achievement of testosterone suppression by 6 weeks and the maintenance of suppression over the 52 weeks of primary implantation. The study design allows for assessment of any "acute-on-chronic" biochemical flare of testosterone or LH after the removal and reimplantation at one year. The design provides for monitoring for continued suppression of testosterone over the eight weeks following reimplantation.

3.2 Safety endpoints

Standard safety endpoints include adverse events, vital signs, concomitant medications, and laboratory test results. Safety endpoints specific to the evaluation of the titanium osmotic pump device include assessment of insertion and removal

procedures, implant site reactions, patient "wearing" tolerability, and anti-leuprolide antibody formation.

3.3 Dose-Ranging study

The first study, C-96-011, is characterized by the sponsor as a dose-ranging study, comparing the efficacy of one implant [group 1, n=27 patients] to two implants [group 2, n=24 patients] over a sixty week treatment duration, that included a 52 week initial implant of one or two implants, the removal of the implant[s] and replacement by a single implant in both groups. Reimplanted patients were then followed with frequent testosterone and LH levels for an additional eight weeks. The safety extension phase continued through 104 weeks of therapy with the second implant removed at that time. A subset of the 42 patients who completed the 104 week trial received a third implant and are being followed for further safety information.

With the submission of the four month safety update on 14 October 1999, all study patients had been followed to either withdrawal or week 104. This efficacy and safety data is available for evaluation and review.

3.4 Confirmatory Efficacy/Safety study

The second registration study, C-97-010, is characterized as an confirmatory efficacy and safety study, with eighty patients receiving a single implant for 52 weeks, the implant removed/replaced with a single implant and the patients followed for eight more weeks to the 60 week efficacy endpoint. At the time of the four-month safety update, data from all eighty patients enrolled was available through 60 weeks for assessment of safety, with efficacy data available for the 70 patients who completed 60 weeks of treatment. Seventy patients, implanted with a second device had not completed the safety extension phase. The safety data for those 70 patients was not included in this review. The last patients in this study were scheduled to have their implants removed in December 1999.

4.0 Study C-96-011-06 - *Feasibility, Functionality and Dose Ranging Study of DUROS™ Leuprolide Implantable Therapeutic System in Patients with Advanced Prostate Cancer*

4.1 Study Overview

This study was conducted at nine sites in the United States. The principal Investigator was Jackson Fowler, Jr. M.D., .S. The first patient enrolled on 21 March 1997. The last patient completed month 14 on 20 August 1998 and month 24 on 29 June 1999. The study design was an open label, historical-controlled study. The efficacy data was derived

from the performance of the implant over the first 52 week treatment period and the first eight weeks following reimplantation. The safety data was provided for the entire 52 week treatment phase and the 52 week safety extension phase.

4.2 The primary objectives of the study were to:

- Evaluate the pharmacodynamic effects of DUROS™ leuprolide implant on the serum testosterone levels in patients with prostate cancer
- Evaluate the safety, tolerability, and acceptability of the implant over the duration of treatment and during implantation and removal procedures
- Evaluate the pharmacokinetic performance of the two dose levels
- Select the lowest effective dose for use in the confirmatory trial

4.3 Study population – Fifty-one male patients with histologically-confirmed adenocarcinoma of the prostate were enrolled in an open label, historical control study. Patients were allowed to have any stage of prostate cancer, but were required to have a life expectancy of > 1 year, a performance status of 0 to 2 by Eastern Cooperative Oncology Group [ECOG] criteria, and a serum testosterone of > 150 ng/dL.

4.3.1 Stratification - Patients enrolled were stratified into three categories:

- Those defined as having *advanced cancer* with a PSA of > 6.0 ng/mL and clinical or radiological evidence consistent with stage D1/D2 disease by bone scan or CT scan of the lower abdomen
- Those defined as having evidence of *failure to cure after radical prostatectomy* for stage A2, B. or C disease, with a PSA of > 0.4 ng/mL
- Those defied as having evidence of *failure to cure after external beam radiation therapy* for stage A2, B, or C disease, with a serum PSA > 6.0 ng/mL or a 50% increase from a nadir PSA value of
- > 2.0 ng/mL.

4.4 Study Design

4.4.1 Dose and duration of treatment

Two treatment doses were administered. Twenty-seven patients received one implant and twenty-four received two implants. At removal and reimplantation after the 12-month treatment interval, all patients in both groups received one implant.

4.4.2 Primary Efficacy Endpoint

The primary efficacy endpoint was the testosterone suppression success rate. This was defined as a percentage of those patients who:

- Completed > 48 weeks of treatment, achieved testosterone suppression [serum testosterone < 50 ng/dL] by week 6, and did not experience testosterone escape [serum testosterone > 50 ng/dL on two consecutive determinations] from the time of suppression through the end of treatment **[numerator]**
- Completed >48 weeks of treatment or discontinued because of testosterone escape **[denominator]**

4.4.3 Secondary efficacy variables included serum testosterone, serum LH, leuprolide, PSA, and leuprolide antibodies.

4.4.4 Safety variables included patient assessment of sensation associated with the implant presence on a daily basis and patient assessment of the implant and removal procedure. Evaluation of the implant/removal procedure by the investigator was also performed to assess local wound reactions, infection, healing, and migration.

4.5 Conduct of the study

- Visit One [screening] – Patients received a general medical and prostate cancer history, physical examination, complete blood count, serum chemistries, and urinalysis.

- Visit Two [implantation] – On the day of the surgical implantation, patients were randomly assigned to receive either one implant or two. Vital signs and laboratory work [serum testosterone, LH, PSA, leuprolide, and leuprolide antibodies] were obtained.

- Follow-up Visits [days 3 and 7 after implant and weeks 2, 3, 4, 6, 8, then every 4 weeks through week 52] – Patients were followed with vital signs, laboratory work and assessment of adverse events and other safety measures.

- End-of-Treatment visit [removal/reimplantation-week 52] – The device [or devices] was removed and a single implant replaced in both group 1 and group 2 patients. Vital signs, laboratory work and safety assessments were performed.

- Follow-up Visits/Safety extension phase [days 3 and 7 after re-implant, weeks 54, 55, 56, 58, 60, then every 4 weeks through week 104] - Patients were followed with vital signs, laboratory work and assessment of adverse events and other safety measures.

4.6 Statistical analysis plan

At enrollment, patients were randomized equally between the two treatment groups and stratified by the three specified strata for disease status/previous treatment. For

analysis of the primary efficacy endpoint, the data were pooled across the centers and disease strata within the two treatment groups.

The two treatment groups were compared for baseline demographic and clinical characteristics using a two-sample t test for numerical data or Fisher's Exact test for categorical data.

Point estimates with two-sided 95% confidence intervals were constructed for the efficacy variable of interest. The sponsor investigated the impact of use of anti-androgens at any time during treatment on the efficacy outcome variables. The pharmacokinetic endpoints were reported using descriptive statistics. Safety outcome variables were reported with summary statistics.

4.7 Reviewer comments on study C-96-011 design issues

- *The population enrolled in this study is similar to those in earlier trials of leuprolide for treatment of adenocarcinoma of the prostate. The enrollment criteria included men with confirmed adenocarcinoma of the prostate, with serum testosterone levels > 150 ng/dL, and with an ECOG performance status of 2 or greater.*

  However, in addition to patients with advanced, stage D2 prostate cancer [with PSA > 6.0 and clinical or radiological evidence of disease], this population included patients with earlier stage disease. These men had elevation of PSA after treatment with surgery or radiation therapy for clinically localized disease. The increase in PSA after local treatment is thought to be evidence of recurrent disease, either locally recurrent or distant metastases. If no measurable disease can be identified by imaging studies, these men are considered to have D0 disease, [i.e.early advanced disease, no longer localized]..

  Since it is well-accepted current urological practice to offer these men GnRH agonist therapy, the policy of the Division has been to allow for enrollment of these patients. In discussions between the sponsor and the Division during pre-NDA drug development of DUROS™, the inclusion of this earlier stage patient population was agreed upon.

- *Although the study protocol specified a six week time point as the definition of success in achieving medical castration with DUROS™, the ability of this drug to reliably decrease serum testosterone levels to < 50 ng/dL at 4 weeks will be one measure of efficacy in the assessment of this product.*

  Currently available leuprolide products have reported success rates of 91 to 97 % in studies submitted to support their approval.

- *Although the study protocol specified two consecutive serum testosterone levels > 50 ng/dL as the definition of escape from maintenance, the ability of this drug to*

maintain castrate levels of testosterone without any levels > 50 ng.dL will be one measure of efficacy in the assessment of this product.

Currently available leuprolide products have reported only rare occurrences of escape, generally < 2% of patients, and occurring most often just before repeat dosing or as an "acute-on-chronic" effect during the first few days after repeat dosing.

- *Although not identified as a primary efficacy endpoint in the study protocol, one measure of efficacy in the assessment of this product will be its ability to continue to suppress serum testosterone levels during the first several weeks after repeat dosing at the time of removal/reimplantation.*

5.0 Study C-97-010-03 - *Safety and Efficacy Study of DUROS™ ~~Leuprolide~~ Implantable Therapeutic System in Patients with Prostate Cancer*

5.1 Study Overview

This study was conducted at 19 centers in the United States. The principal investigator was Jackson Fowler, Jr. M.D., S. The first patient enrolled on 10 October 1997 and the last patient was scheduled to have his implant removed at the end of the safety extension phase, December 1998.

5.2 The primary objectives of the study were to:

- Confirm the efficacy and safety of one implant of DUROS™ leuprolide implant in patients with prostate cancer
- Evaluate both general and disease-specific measures of health-related quality of life [HRQOL]

5.3 Study population - Eighty patients were enrolled in this open-label, historical control, multi-center trial. Patients had histologically-confirmed adenocarcinoma of the prostate and either:

- no previous therapy for cancer and a PSA of > 6.0 ng/mL but without a requirement for clinical evidence of metastatic disease
- previous definitive therapy with radical prostatectomy for clinically localized disease with biochemical evidence of treatment failure [i.e. serum PSA > 0.4 ng/mL]
- previous definitive therapy with external beam radiation therapy for clinically localized disease with biochemical evidence of treatment failure [i.e. serum PSA > 6.0 ng/mL or 50% increase from nadir value above 2.0 ng/mL

5.4 Study Design

5.4.1 Dose and duration of treatment

All eighty patients enrolled received a single DUROS™ leuprolide implant. The implant is designed to delivery leuprolide at a nominal rate of 120 micrograms/day over the twelve-month treatment duration. At twelve months, the device was removed and replaced with a second device for a second twelve-month interval.

5.4.2 The primary efficacy endpoint, as in the previous study, was the serum testosterone suppression success rate.

5.4.3 Secondary variables included serum LH and leuprolide concentrations, serum PSA, and HRQOL measures.

- A pharmacokinetic evaluation was performed on a subset of 21 patients. Sampling of serum testosterone, LH, and leuprolide levels was performed at more frequent intervals in the first week after implantation [4 hours, 1, 2, and 5 days after implantation in addition to the regular sampling at days 3, 4, and 7].

5.4.4 Safety variables were identical to those in the dose-finding study. Adverse events, laboratory test values, physical exam findings, vital signs, and concomitant medications were documented at all visits.

5.5 Conduct of the study

- Visit One [screening] – Patients received a general medical and prostate cancer history, physical examination, HRQOL assessment, complete blood count, serum chemistries, and urinalysis.

- Visit Two [implantation] – On the day of the surgical implantation, vital signs and laboratory work [serum testosterone, LH, PSA, leuprolide, and leuprolide antibodies] and HRQOL assessments were obtained.

- Follow-up Visits [days 3 and 7 after implant and weeks 2, 3, 4, 6, 8, then every 4 weeks through week 52] – Patients were followed with vital signs, laboratory work and assessment of adverse events and other safety measures. A subset of the group returned for measurement of serum testosterone, LH, and leuprolide at 4 hours, days 1, 2, and 5 after implantation. Health-related quality of life assessments were obtained at weeks 12, 24, 36, and 52.

- End-of-Treatment visit [removal/reimplantation-week 52] – The device [or devices] was removed and a single implant replaced. Vital signs, laboratory work and safety assessments were performed.

- Follow-up Visits/Safety extension phase [days 3 and 7 after re-implant, weeks 54, 55, 56, 58, 60, then every 4 weeks through week 104] - Patients were followed with vital signs, laboratory work and assessment of adverse events and other safety measures.

5.6 Statistical Analysis Plan - The primary efficacy outcome was the testosterone suppression success rate. The sponsor also reported the intent-to-treat success rate, the overall treatment success rate, and the implant expulsion rate. The data was pooled across centers for analysis. The primary efficacy outcome rates were reported as point estimates with two-sided 95% confidence intervals constructed.

- A sub-population of patients was offered anti-androgens during the trial, if indicated for prevention of clinical flare or for symptomatic, metastatic disease. The efficacy outcomes of this group were summarized.
- HRQOL data were summarized.
- Pharmacokinetic data was summarized and reported descriptively.
- Safety data was reported as summary statistics.

5.7 Reviewer comments on study C-97-010 design issues

- *This study population differed from those in C-96-011 in allowing for untreated stage A2, B, and C patients, as long as they demonstrated a PSA of > 6.0 ng/mL. In the previous study, all treatment-naïve patients were required to have clinical or radiographic evidence of metastatic disease [i.e. stage D2].*

  Since the widespread availability and use of PSA as a screening test for prostate cancer, many patients are being identified with prostate cancer with high PSA levels but no measurable evidence of metastatic disease. It has become well-accepted urological practice in the United States to offer these patients hormone ablation therapy, particularly if they are not candidates for alternative primary therapies [surgery, radiation therapy].

  Because of this shift from later stage diagnosis to earlier stages at presentation, sponsors have found it increasingly difficult to enroll the numbers of stage D2 patients who remain the indicated population for the GnRH agonist. The Division has agreed that it is acceptable to include these earlier stage patients in the study population.

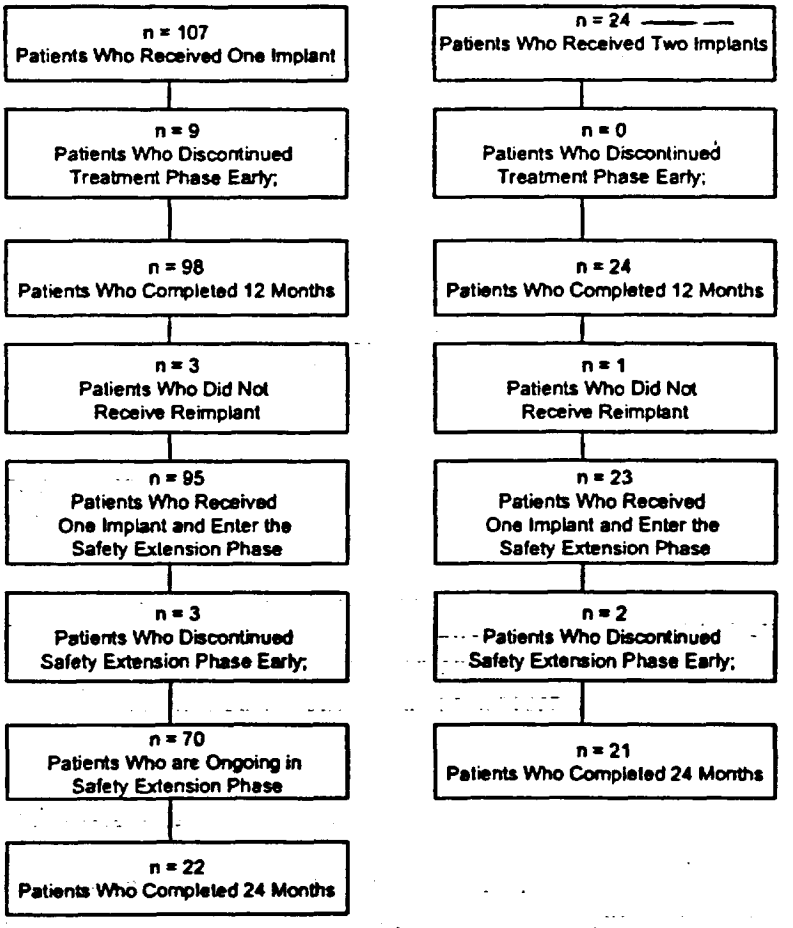
6.0 Disposition of Patients

6.1 Initial randomization and implantation [see figure A]

A total of **131 patients** were treated with DUROS® Leuprolide Implant in the two clinical studies.

DUROS™ Leuprolide Implant System: Summary of Safety Data, 4-month update

FIGURE A
Disposition of Treated Patients
Studies C-96-011 and C-97-010



Fifty-three patients were randomized in Study C-96-011. Two patients did not receive an implant [reasons: withdrew consent (patient # 206); non-compliance (patient # 400)]. Fifty-one patients were treated. Twenty-seven patients received a single implant for the 52-week treatment phase and a single implant at

removal/reimplantation. Twenty-four patients received two implants for the 52-week treatment phase and then a single implant at removal/reimplantation.

Eighty patients were treated in Study C-97-010. All patients received a single implant for the 52-week treatment phase and a single implant for the 52-week safety extension phase.

There were 107 patients who received a single implant (27 patients in Study C-96-011, and 80 patients in Study C-97-010).

6.2 Discontinuations and withdrawals during treatment phase

Of the 131 patients, nine patients discontinued during the 52 week treatment phase. Of these nine patients, 4 reported adverse events and 5 patients died.

6.2.1 Adverse events [4]

Of the four patients who discontinued, two patients had extrusion of the implant, one at day 65 and one on day 121. The other two adverse events were:

- Spinal cord compression due to progression of the adenocarcinoma of the prostate [patient 703, study C-97-010]
- Abdominal pain and ear disorder [patient 1002, study C-97-010]

Neither adverse event was considered by the sponsor as related to study medication.

6.2.2 Deaths [5]

Of the five deaths during the treatment phase, none were considered by the sponsor as related to study medication. These five patients included:

- Study C-96-011: a patient who died of aspiration pneumonia and congestive heart failure 114 days after initial implantation of one implant
- Study C-97-010: a patient who suffered a cardiac arrest secondary to ventricular fibrillation and coronary artery disease on day 67 post-insertion
- Study C-97-010: a patient with gastrointestinal bleeding and a ruptured abdominal aortic aneurysm 304 days after insertion
- Study C-97-010: a patient who died of pulmonary edema and a cardiac arrhythmia felt to be complications following an elective cervical laminectomy for spinal stenosis, 127 days post-insertion
- Study C-97-010: a patient who developed aspiration pneumonia after a cerebrovascular accident 297 days following insertion

One hundred twenty-two [122] patients completed the 52-week treatment phase.

6.3 Removal and reimplantation at week 52

Of the **122** patients who completed the Treatment Phase, four patients (3.1%) did not have implants reinserted for the Safety Extension Phase. One (0.8%) patient discontinued because of adverse events and three (2.3%) for personal reasons.

One hundred eighteen [118] patients were reimplanted and entered the 52-week safety extension phase.

6.4 Discontinuations during the safety extension phase

6.4.1 Discontinuations from Study C-96-011 [weeks 52-104]

Of the **118** patients who entered the safety extension phase, five (3.8%) patients from study C-96-011 died before week 104; all deaths were felt to be unrelated to study treatment by the sponsor.

Of the remaining **113** patients, 43 patients from study C-96-011 have completed week 104 and the full two years of safety data is included in this analysis. The remaining 70 patients had completed 60 weeks of treatment at the time of the four month safety update.

6.4.2 Discontinuations from Study C-97-010 [weeks 52-60]

No patient from this study had discontinued during weeks 52 to 60. All 70 patients who were reimplanted at 52 weeks are ongoing in the safety extension phase at the time of the 4-month safety update report of October 13 1999.

6.5 Disposition by individual study

6.5.1 Study C-96-011 [see figure B]

- **Twenty-seven** Group 1 patients were implanted. One patient died of aspiration pneumonia and congestive heart failure and the second patient discontinued because of partial extrusion of the implant. **Twenty-five** patients completed the Treatment phase and entered the Safety Extension phase. Three patients died during the Safety Extension Phase of disease progression [two patients] or multi-organ failure [one patient]. **Twenty-two** patients completed 24 months of therapy.

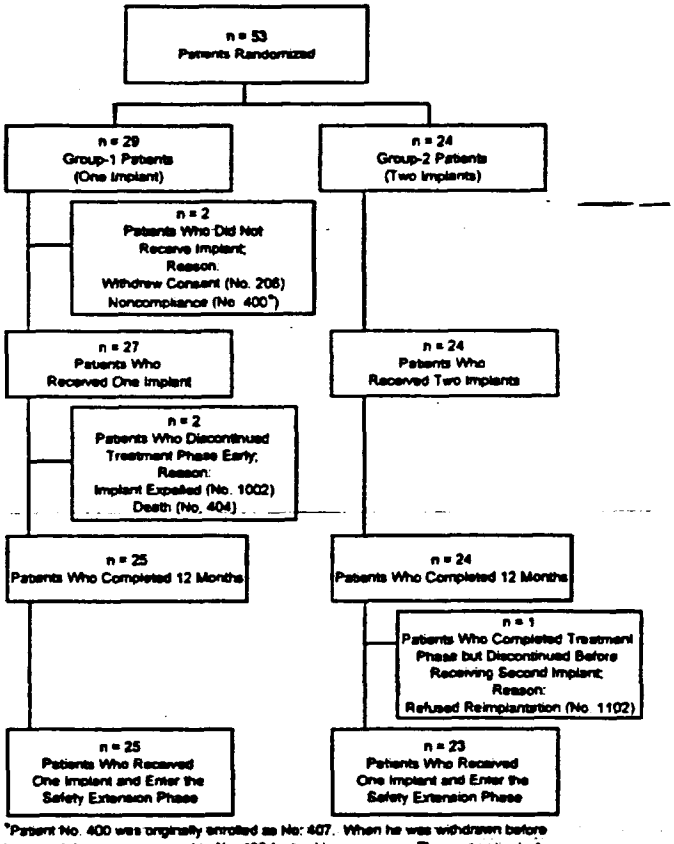
- **Twenty-four** Group 2 patients were implanted. One patient completed the 52-week treatment phase but refused to participate in the Safety Extension Phase for personal reasons. He was followed for an additional week to monitor healing of the implant removal site. **Twenty-three** patients entered the safety extension

phase. Two patients died during the Safety Extension Phase (gliobastoma; disease progression). **Twenty-one** patients completed 24 months of therapy.

- **Forty-three** patients completed 24 months of therapy.

Figure B

Patient Disposition: All C-96-011 Randomized and Treated Patients



*Patient No. 400 was originally enrolled as No: 407. When he was withdrawn before treatment, he was reassigned to No. 400 for tracking purposes. The next patient who enrolled was then assigned to No. 407.

Source:Appendix 13.2.2, Appendix 13.2.9

6.5.2 Study C-97-010 [see figure C]

Eighty patients were implanted. Four patients died of causes felt by the sponsor to be unrelated to study treatment. Three patients terminated because of:

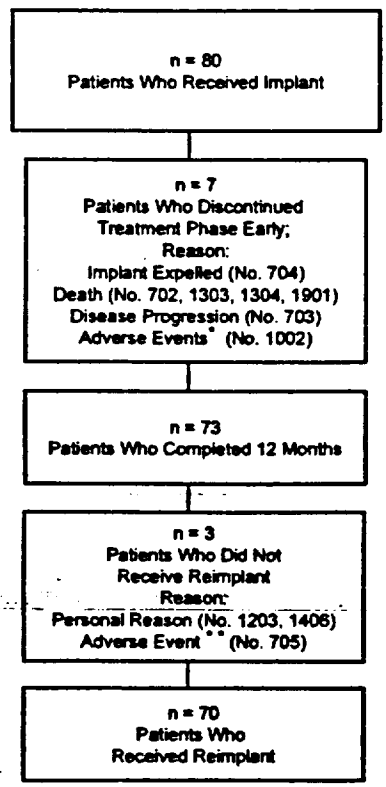
- disease progression
- extrusion of the implant
- abdominal pain with ear disorder.

Seventy-three patients completed the Treatment Phase

Three patients did not participate in the Safety Extension Phase and discontinued before reinsertion. One patient was terminated because of cognitive deficit, loss of memory, tremors, and abnormal gait and the investigator's concern about patient's ability to comply with study requirement. The other two patients refused to continue for personal reasons.

Seventy patients received a second implant. All 70 patients continued on study through the 14-month reporting period. No deaths or withdrawals were reported for this group at the four-month safety update of October 14, 1999.

Figure C
All C-97-010 Treated Patients



*Adverse Events Not Related to Study Drug (Abdominal Pain, Ear Disorder)
**Adverse Event Not Related to Study Drug (Cognitive Disorder)

Source: Appendix 13.2.2 Appendix 13.2.9

7.0 Assessment of Efficacy

7.1 Dose-Response Evaluation – Study C-96-011 was a dose-finding study, comparing two doses, a single implant [n=27] delivering a nominal dose of 120 micrograms/day and two implants [n=24] delivering a 240 microgram/day dose.

The sponsor reported that the demographic characteristics of these two groups did not differ statistically in age, race, height, weight, time since diagnosis, or distribution of disease stage/randomization strata. The clinical stage of the patients in the two treatment arms was:

Treatment arm	Group 1 –one implant [%]	Group 2 – two implants [%]
Stage A2	7.4	0
Stage B	22.2	29.2
Stage C	25.9	12.5
Stage D1	14.8	12.5
Stage D2	29.6	45.8

The two doses of DUROS™ Leuprolide Implant were compared for efficacy and safety in order to decide on a dose to reimplant at week 52 for the safety extension phase of study C-96-011 and to select the dose for the confirmatory C-97010 study.

An interim data analysis was performed when the first patient reached day 112. All patients in group 1 and group 2 were found to have serum testosterone levels of < 50 ng/dL at day 21 [n=25,24], 28 [n=23,24], 42 [n=20,21], 56 [n=19,20], 84 [n=11,14], and 112 [n=2,4].

The sponsor's specified primary efficacy endpoint, the 12-month testosterone suppression rate, was 100% in both groups. For the intent-to-treat population, the success rate was 96.3% in group 1 and 100% in group 2. One patient in group one experienced the expulsion of the implant at day 65 and was included as a treatment failure.

One implant was as effective as two implants in achieving suppression of serum testosterone to castrate levels by week 4 and maintaining suppression of those levels through week 52. No testosterone flare ["acute-on-chronic phenomenon"] was noted on removal/reimplant for either group 1 or group 2 patients.

Based on the findings in this dose-ranging study, the sponsor selected a single implant as the to-be-marketed formulation for confirmatory study in trial C-97-010.

7.2 Review of Pooled Efficacy Data from Studies C-96-011 and C-97-010

The data from patients who were implanted with one implant in either of the phase III trials was pooled to evaluate the DUROS™ system for efficacy. The group 1 patients [n=27] from study C-96-011 and eighty patients from study C-97-010 were included in this analysis. All patients who remained on treatment at week 52 received a single device at reimplant.

7.2.1 Demographics of study population

- Age – 11.2% between the ages of 50-64 and 88.8% were 65 or over
- Race – 75.7% Caucasian, 21.5% Black, 2.8% Hispanic
- Weight – mean, 86.7 ± 14.1 kg [range, 58-124 kg]
- Height – mean, 175.8 ± 6.9 cm [range, 145-189 cm]
- Prostate cancer stage
  - A2 – 3.7%
  - B1 – 20.6%
  - B2 – 13.1%
  - C – 35.5%
  - D1 - 12.1%
  - D2 - 15.0%

7.2.2 Disposition of study patients

Nine patients of the 107 who received a single implant discontinued the treatment phase early and were not reimplanted. Reason for discontinuation were:

- Death [5 patients]
- Implant expelled [2 patients]
- Disease progression [1 patient]
- Adverse events [1 patient]

Of the 98 patients eligible for reimplant, three declined to continue in the study [personal reasons, 2 patients; adverse event, 1 patient]. Ninety-five patients received a single implant at the 52-week reimplantation and were followed over the next eight weeks for evidence of continued efficacy and for assessment of any acute-on-chronic flare phenomenon.

7.2.3 Primary Efficacy Endpoint

The sponsor had designated the testosterone suppression success rate as the primary efficacy endpoint. This rate had been defined as those patients whose implants remained in place for twelve months and whose serum testosterone concentrations achieved castrate levels [< 50 ng/dL] within six weeks of implantation and then maintained a castrate level, without escape [two consecutive determinations > 50 ng/dL], for the duration of the twelve month treatment interval.

The denominator for this calculation was 98 patients. The nine patients [of 107] who discontinued before 52 weeks have been noted above.

One patient [# 605, study C-97-010] failed to achieve castrate levels of testosterone within six weeks. In this patient, castrate levels were reached at week 28 and remained suppressed, between 24 and 48 ng/dL, through week 52.

- The patient, Caucasian, weighed 66.7 kg, was 170.2 cm in height, and age 77 at enrollment. He was classified as having stage B2 prostate cancer. His baseline testosterone was 478ng/dL, increasing to 1007ng/dL at day 7, then decreasing to 134 ng/dL at week 3, and 78 ng/dL at week 4. His serum LH levels decreased below the normal male range by week 3. He demonstrated a PSA response to therapy with a baseline PSA of 87 ng/mL decreasing to 63 ng/mL at week 4, 23 ng/mL at week 16, and 15 ng/mL at the week 28 timepoint at which his serum testosterone was suppressed below the castrate level.

The sponsor reported the testosterone suppression success rate as 97/98, or 99% [95% CI: 94.4%, 99.9%]

7.2.4 Secondary analyses of primary endpoints

The sponsor reported a modified "intent-to-treat" success rate, an overall success rate, and an implant expulsion rate.

7.2.4.1 The *"intent-to-treat" success rate* was calculated as:

$$\frac{\text{104 patients who did not expel the implant or fail to suppress or maintain the serum testosterone at castrate levels [numerator]}}{\text{all 107 patients who received a single implant [denominator]}}$$

The three failures included:

- One patient who did not achieve a castrate level until week 28
- Two patients who extruded their implants during the treatment phase.
  - One implant was extruded at day 65, the second patient on day 121.

The "intent-to-treat" success rate was 97.2% [95% CI: 92.0%, 99.5%]

7.2.4.2 The over-all treatment success rate was calculated as:

$$\frac{\text{97 patients who did not expel the implant, fail to suppress/maintain at castrate levels and completed > 48 weeks of treatment [numerator]}}{\text{100 patients who completed > 48 weeks of treatment or discontinued because of testosterone escape or implant expulsion [denominator]}}$$

The three failures are listed above in section 7.2.4.1.

The overall treatment success rate was 97.0% [95% CI: 91.4%, 99.4%].

7.2.4.3 The expulsion rate was calculated as:

$$\frac{\text{2 patients who expelled their implants [numerator]}}{\text{100 patients who completed > 48 weeks of treatment or expelled their implants [denominator]}}$$

The expulsion rate was 2% [95% CI: 0.2%, 7.1%].

7.2.5 Secondary efficacy analyses were reported for:

- Serum testosterone concentration
- Serum leutinizing hormone [LH] concentrations
- Mean PSA concentrations
- Mean serum leuprolide concentrations
- Quality-of-life endpoints

7.2.5.1 Mean serum testosterone for all patients receiving one implant was 422.7 ±161.8 ng/dL at baseline, 690.8 ± 251.9 ng/dL at day 3, and 113.1 ± 91.6 ng/dL at week two. Serum testosterone decrease to below the 50 ng/dL level between weeks 2 and 4 in all but one patient. Serum testosterone remained suppressed below the 50 ng/dL level, once suppressed, in all study patients. Individual mean serum testosterone levels from weeks 6 through 52 ranged from 6.6 to 8.5 ng/dL.

7.2.5.1.1 More frequent sampling of serum testosterone during the first week was performed on 21 patients in study C-97-010.

- Mean serum testosterone at baseline was 443.1 ± 157.5 ng/dL, increased to 519.9 ± 189.8 ng/dL [four hours after implant] and 701.4 ± 222.8 ng/dL [day 3], then decreased to 440.0 ± 153.1 ng/dL [day 7] and 36.8 ± 23.5 ng/dL [week 3].

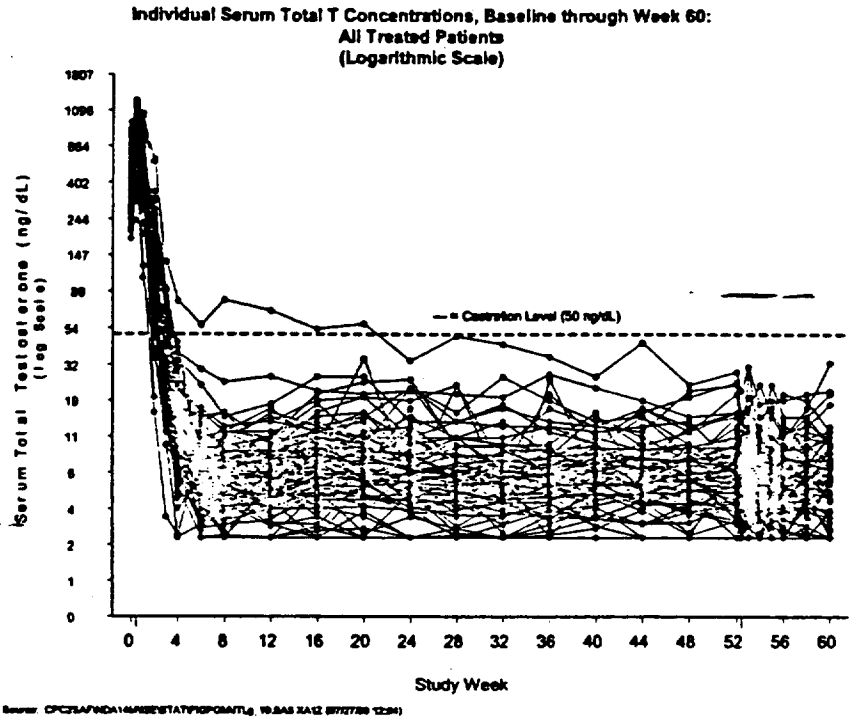
7.2.5.1.2 Acute-on-chronic testosterone flare [see figure D]

- The subset of patients receiving one implant in study C-96-011 were examined for "flare" of testosterone [acute-on-chronic phenomenon] during the eight weeks after the removal/reimplant procedure at 52 weeks. None of the 27 patients had an increase of testosterone over the 50 ng/dL castrate level, with suppression maintained in all patients through week 60.

- All 70 patients in study C-97-010 who received a reimplant at week 52 were followed from week 52 through week 60 for evidence of

testosterone flare. No patient demonstrated an increase in testosterone above castrate levels during this interval.

Figure D



Source: NDA 21 088, 4-month safety update, ISE, page 31, fig. E

7.2.5.2 Mean serum LH concentrations in the one-implant population demonstrated a similar increase from baseline levels by day 3 and then fell below baseline by day 7 and to below the normal limits of normal male range [< 1.5 mIU/mL] by week 3. Mean LH concentrations ranged between 0.009 and 0.29 mIU/mL from week 6 through 52.

In study C-97-010, two patients were noted to have transient increases in LH above the lower limit of normal male range during the 52-week treatment phase. The sponsor reports that in both patients the serum testosterone remained "suppressed".

7.2.5.2.1 Acute-on-chronic LH flare

- The subset of patients receiving one implant in study C-96-011 were examined for "flare" of LH [acute-on-chronic phenomenon] during the

two weeks after the removal/reimplant procedure at 52 weeks. None of the 27 patients had an increase LH over the 1.5 mIU/mL level [lower limit of normal range for males], with suppression maintained in all patients through week 60.

7.2.5.3 Mean serum leuprolide concentrations were reported through 60 weeks in study C-96-011 and also drawn during the first week after implantation in a special pharmacokinetic assessment in a subset of 21 patients from study C-97-010. The leuprolide concentration peaked at 16.9 ng/mL at four hours after implantation and decreased to 2.4 ng/mL at 24 hours. C_{avg} from day 3 through week 52 for patients in each study was 0.79 [study C-96-011] and 0.93 ng/mL [study C-97-010].

7.2.5.3.1 Inter-patient variability in leuprolide levels

- The sponsor reported that the inter-patient variability ~~for the~~ Cavg was "about 46%". Two journal articles [Mazzei et al, Drugs Exp Clin Res 15:373, 1989, Sennello et al, J Pharm Sci 75:158, 1986] are cited to compare this variability to the 30% variability reported for leuprolide when administered as a daily subcutaneous injection or in a depot microsphere formulation.

7.2.5.4 PSA concentrations were reported for all 107 patients in both studies who received one implant. Exploratory data analyses were performed in the total population and a subset of patients who had an elevated PSA at baseline and no prior treatment for prostate cancer. Changes from baseline [percentage of patients whose PSA decreased > 50 to < 90%, or > 90% decrease] were calculated at one, three, six, and twelve months after implantion for the entire population. In the subgroup analysis, the percentage of patients whose PSA values were normal [< 4.0 ng/mL] at one, three, six, and twelve months were reported.

7.2.5.5 Health-related Quality of Life

An exploratory analysis of ~~health-related~~ quality of life was performed using various sub-scales of the SF-36 instrument.

7.3 Reviewer comments on Integrated Summary of Efficacy

- *In spite of the sponsor's definition of success in achieving castration as a serum testosterone of < 50 ng/dL at six weeks, all but one patient achieved medical castration by week four. This time point is the interval from baseline by which other leuprolide formulations have been judged.*

- *In spite of the sponsor's definition of escape from maintaining of castration as two consecutive serum testosterone level > 50 ng/dL, no patient had a single*

determination above this level over the initial 52 week treatment interval, once medical castration was achieved.

- *No patient receiving a single implant and single reimplant at week 52 was found to have an increase in serum testosterone level above the 50ng/dL threshold when followed for an acute-on-chronic flare during weeks 52 to 60. Currently approved leuprolide drug products have demonstrated a low incidence of this testosterone flare phenomenon on repeat dosing. The performance of the DUROS™ implant is similar to those products and acceptable.*

- *In addition to the two expulsions reported in the 107 patients in the single implant group, one patient [of 24] in the two-implant arm of study C-96-011 experienced an expulsion. The sponsor claims that "incorrect placement of the implants" was a contributing factor. No substantial documentation is provided to support that claim, however.*

- *The sponsor's primary efficacy endpoint, testosterone suppression success rate, excluding those patients who do not complete the treatment interval and those who expel their implants, is acceptable as primary evidence of efficacy. While expulsion of the implant could be considered a failure, both the low incidence of expulsion and the ability to identify and correct this failure makes ability to achieve castration within four weeks and maintain suppression over the course of the implant the outcome of interest.*

- *The sponsor has used the results from the exploratory data analysis of PSA to make claims in their initial labeling proposal. PSA has not been demonstrated to be a surrogate marker for an important clinical outcome in the population of patients for which this sponsor is seeking an indication. The labeling for the 3-month and 4-month leuprolide microsphere formulations includes statements on changes in PSA levels for study populations and subgroups at various time points after depot dosing.*

8.0 Assessment of Safety

8.1 Safety database population

The safety database available for review at the time of the 4-month safety update of October 13, 1999 included all 131 patients enrolled and implanted in studies C-96-011 and C-97-010. The reporting period for extent of exposure is through week 104 for patients in study C-96-011 and through week 60 for patients in study C-97-010.

8.1.1 Demographics

8.1.1.1 Disease stage

The patient population included men with histologically confirmed adenocarcinoma of the prostate, and included patients with disease in clinical stages A2 through D2. 3.1% had stage A2 disease, 32.8% stage B, 31.3% stage C, 12.1% stage D1, and 20.6% stage D2.

8.1.1.2 Age

The mean age at enrollment was 73.3 years [range, 50-88 years].

8.1.1.3 Race

Seventy-three percent of patients were Caucasian, 23.7% were Black, and 3.0% were Hispanic.

8.1.1.4 Weight

Mean weight was 86.1 kg [range, 57-124 kg].

8.2 Drug exposure

Of the 131 patients enrolled, the mean treatment duration for total drug exposure [one or two implants] was 72.6 weeks [range: 8-113 weeks]. Eleven patients [8.4%] did not complete the 52-week treatment phase. 118 patients received a second implant and entered the safety extension phase.

8.3 Safety Endpoints

Safety endpoints in studies C-96-011 and C-97-010 included adverse events, clinical laboratory tests [including measurements of anti-leuprolide antibody formation], physical examinations, vital signs, and concomitant medication use.

8.3.1 Physician and patient assessments

Additional safety endpoints were physician and patient assessments of insertion and removal procedures, physician assessments of the insertion sites, and patient assessments of wearing sensations.

8.3.1.1 Physician assessments - After implant insertion, the investigator evaluated the ease of insertion, extent of bleeding, and adequacy of the trochar or implanter used during the procedure. At each visit, the investigator assessed the application site for erythema, edema, itching, pressure, pulling, pain, evidence of infection, bleeding, fluid

accumulation, and movement of the implant from its original position. Post-insertion application site evaluations were recorded in a separate case report form and were not merged with all adverse events. At implant removal, the investigator recorded the extent of bleeding and whether encapsulation or fluid accumulation occurred at the application site. The investigator also rated the ease of implant removal.

8.3.1.2 Patient assessments - After implant insertion, the patient assessed the adequacy of the anesthetic block and rated the severity of pressure, pulling, and pain. At each scheduled office visit, the patient assessed wearing sensations, including the extent to which he was aware of the implant, how comfortable or uncomfortable the implant was, and whether the implant affected normal daily activities (e.g. work, sleep, dressing, bathing, exercise, driving).

8.4 Deaths

8.4.1 Overview

Twelve deaths were reported: five during the Treatment Phase, five during the Safety Extension Phase, and two deaths in study C-97-010 occurring between the month 14 end of the safety extension phase and the August 15, 1999 data cut-off for the four-month safety report, dated October 13, 1999.

Of the five deaths during the treatment phase, none were considered by the sponsor as related to study medication. These five patients included:

- Study C-96-011: a patient who died of aspiration pneumonia and congestive heart failure 114 days after initial implantation of one implant
- Study C-97-010: a patient who suffered a cardiac arrest secondary to ventricular fibrillation and coronary artery disease on day 67 post-insertion
- Study C-97-010: a patient with gastrointestinal bleeding and a ruptured abdominal aortic aneurysm 304 days after insertion
- Study C-97-010: a patient who died of pulmonary edema and a cardiac arrhythmia felt to be complications following an elective cervical laminectomy for spinal stenosis, 127 days post-insertion
- Study C-97-010: a patient who developed aspiration pneumonia after a cerebrovascular accident 297 days following insertion

Five deaths occurred during the period including the Safety Extension Phase in Study C-96-011 through Month 24 and through Month 14 in Study C-97-010. All five deaths occurred in Study C-96-011; none were considered by the sponsor as related to study treatment.

- In Group 1, one patient (No. 301) died from multi-organ failure following postoperative hemorrhage secondary to cardiovascular surgery for unstable angina, myocardial infarction, and atrial fibrillation 497 days after the initial insertion. Two patients died from disease progression: one (No. 414) died 540 days after the initial insertion, and one (No. 605) died 537 days after initial insertion.
- In Group 2, two patients died: one (No. 202) from disease progression 687 days after initial insertion, and the other (No. 603) from glioblastoma 624 days after initial insertion.

The two deaths in study C-07-010 included a patient who died after a motor vehicle accident and a patient who died of metastatic bladder cancer.

8.4.2 Deaths in study C-96-011

- A 78-year-old man (No. 202, Group 2) was admitted to inpatient hospice care and died approximately 22 months following initial insertion with complaints of low back and leg pain, poor appetite, and confusion secondary to widespread bone metastases and disease progression.

- A 76-year-old man (No. 301, Group 1) was hospitalized for angina and myocardial infarction, and subsequently developed atrial fibrillation with rapid ventricular response approximately 16 months following initial insertion. He had a triple coronary artery bypass graft and aortic valve replacement and returned to the operating room for hemorrhage at the graft site. The bleeding resolved, but he developed acute hepatic failure and impaired kidney function, requiring dialysis. The patient developed sepsis and emboli in the extremities, and was maintained on a respirator. His condition of multi-organ failure continued to worsen, and the patient expired.

- A 74-year-old man (No. 404, Group 1) with a history of aortic stenosis, carotid stenosis, and cerebrovascular accident with right hemiparesis was hospitalized complaining of left shoulder pain (neuropathy) and lethargy approximately 4 months after initial insertion. He later became confused and was diagnosed with aspiration pneumonia. He developed CHF that was considered secondary to the pneumonia and died 9 days after admission. The causes of death were CHF and aspiration pneumonia.

- A 72-year-old man (No. 414, Group 1) was hospitalized for urinary tract infection (UTI) and hypercalcemia approximately 16 months after initial insertion. Urinalysis showed 78 to 80 WBCs and 4+ bacteria; calcium was 10.7 mg/dL. The patient received IV fluids and Pemedrinate to treat his hypercalcemia and

antibiotics for his UTI. His calcium level was 8.4 mg/dL after this treatment. A bone scan revealed progression of metastatic disease with new lesions in the skull, spine, ribs, and pelvis. The patient's bone pain was treated with morphine sulfate, and he was discharged 10 days after admission. His condition continued to deteriorate, and he died approximately 18 months after initial implant insertion.

- A 59-year-old man (No. 603, Group 2) died approximately 21 months after initial insertion as a result of a concurrent illness: glioblastoma multiforme. The patient had been diagnosed with temporal lobe neoplasm 6 months after initial insertion after experiencing profound behavior changes, including depression, aggression, and suicidal ideation. He had been hospitalized several times over the past year for seizures and palliative therapy.

- An 82-year-old man (No. 605, Group 1) was hospitalized with metastatic prostate cancer approximately 16 months after initial insertion. He was also treated for anxiety, thrush, and a sacral decubitus ulcer. His bone pain was treated with narcotics. The patient's condition improved, and he was discharged 5 days later. His condition continued to deteriorate over the next 2 months. He was admitted to hospice care and died approximately 18 months after initial insertion.

8.4.3 Deaths in Study C-97-010.

- An 85-year-old man (No. 702) with a history of coronary artery disease, cerebral emboli, chronic atrial fibrillation, angina, aortic stenosis, and episodes of bradycardia suffered a cardiac arrest approximately 2 months after initial insertion. Resuscitation was unsuccessful, and the patient died. The death certificate listed cardiac arrest secondary to ventricular fibrillation as a consequence of the patient's coronary artery disease. Approximately 2 weeks before death, the patient had been hospitalized for evaluation of recurrent syncopal episodes. He was discharged in stable condition with a diagnosis of syncope secondary to orthostasis and chronic atrial fibrillation.

- A 79-year-old man (No. 1303) was hospitalized approximately 10 months after initial insertion for gastrointestinal bleeding. He was diagnosed with ischemic colitis and a ruptured abdominal aortic aneurysm. He underwent surgical repair of the aneurysm and an aorta-duodenal fistula. The patient's condition deteriorated and he died.

- An 83-year-old man (No. 1304), with a history of severe coronary artery disease, aortic valvular disease, and aortic aneurysm, died unexpectedly after an elective cervical laminectomy for spinal stenosis approximately 4 months after initial insertion. His postoperative course was uneventful until the evening of the surgery, when he was found to be unresponsive; resuscitation efforts were unsuccessful. Pulmonary edema was found on autopsy, and other findings were suggestive of cardiac arrhythmia.

- A 77-year-old man (No. 1901) with a history of stroke was hospitalized with a massive stroke and seizures approximately 8 months after initial insertion and was discharged to a nursing home. Two weeks later, he was admitted with gastroenteritis and dehydration. The patient's sodium was 153 mmol/L, and his creatinine was 3.9 mg/dL. He was treated with IV fluids and antibiotics. At the time of discharge his sodium was 140 mmol/L and his creatinine was 2.9 mg/dL. Approximately one month later, the patient was admitted with aspiration pneumonia and sepsis. He was treated with antibiotics and IV fluids but his condition continued to deteriorate. The patient expired secondary to aspiration pneumonia approximately 10 months after initial insertion.

8.5 Serious Adverse Events

Forty patients reported at least one serious adverse event [SAE]. 21 SAEs were reported during the 24 months in Study C-96-011 and 19 SAEs during the 14 months of Study C-97-010.

All serious adverse events (SAEs) that occurred in the two studies were considered by the sponsor as unrelated to study treatment.

8.5.1 Disease progression

A number of patients were hospitalized with SAEs secondary to disease progression or other malignancies, recorded primarily as carcinoma (6 patients, 4.6%), disease progression (3 patients, 2.3%), neuropathy (4 patients, 3.1%), and paralysis (2 patients, 1.5%).

8.5.2 Cardio-vascular SAEs

Seventeen (13%) patients reported cardiovascular SAEs, including congestive heart failure, pulmonary embolism, angina, syncope, cerebrovascular accident, arrythymias, and myocardial infarction.

8.5.3 SAEs after 14 month reporting in study C-97-010

Adverse events occurring after Month 14 through August 15, 1999 for patients in Study C-97-010 were reported separately in the four-month safety update. Eight patients experienced serious adverse events, including two deaths, within that time frame. All were considered unrelated to study treatment by the sponsor. These include hospitalizations for new onset diabetes (No. 202), coronary artery disease and angina, hypotension (No. 903), motor vehicle accident, death (No. 905), extrahepatic cholestasis (No. 911), lung cancer (No. 1004), bladder cancer, anemia, renal failure (No. 1106), loss of balance, accidental injury (No. 1202), and bladder cancer and death (No. 2301).

8.5.4 Laboratory abnormalities were reported as SAEs in five patients. None were considered by the sponsor as related to study medication.

- Anemia was reported as an SAE in three patients. One patient had a hematocrit of 23.7% during a hospitalization for hemorrhage secondary to radiation cystitis, which resolved with control of the bleeding and transfusion (No. 413, in Study C-96 -011, Group 1). Another patient was treated for hypocalcemia, anemia, hypoalbuminemia, and leukopenia (all laboratory values unknown) during hospitalization for pneumonia (No. 610 in Study C-96 -011, Group 2). All laboratory abnormalities resolved by the time the patient was discharged 6 days later. In Study C-97-011, a patient experienced anemia (hemoglobin of 7 g/dL and hematocrit of 21%) caused by hemorrhagic cystitis, blood loss in stool, radiation therapy to the pelvis, and treatment with antifungal medication for Candida-positive blood and urine cultures. The patient refused any transfusions. Epogen was initiated (No. 2301). Anemia was ongoing at the time of the patient's death.

- A patient had an electrolyte abnormality (hyperosmolarity) during a hospitalization for gastroenteritis and dehydration (No. 1901, Study C-97-010). On admission, the patient's sodium was 153 mmol/L, and creatinine was 3.9 mg/dL. At the time of discharge, his sodium was 140 mmol/L and his creatinine was 2.9 mg/dL.

- There was one SAE of hyperkalemia (potassium was 7.7 mg/dL) secondary to treatment of CHF and coronary artery disease (Patient No. 602, Study C-96-011, Group 2). The hyperkalemia was treated with kayexalate and IV sodium bicarbonate and resolved 2 days later. The patient's subsequent serum potassium was 3.1 mg/dL.

- Hypercalcemia was reported in a patient with disease progression (Patient No.414 in Study C-96 -011, Group 1). The patient's calcium levels were 10.7 mg/dL on admission and 8.4 mg/dL following treatment with pamidronate.

8.6 All Adverse Events

One hundred twenty-seven of the 131 patients [96.9%] reported at least one AE. The most common AEs were vasodilation [88 patients, 67.2%] and application site reactions [73 patients, 55.7%]. Pain, of any description, was reported in by 60 patients [45.8%]. Adverse events associated with the physiological effects of medical castration included gynecomastia/breast enlargement [7 patients, 5.4%], breast pain, [4 patients, 3.1%], testis disorders [6 patients, 4.6%] , and impotence [3 patients, 2.3%].

8.6.1 Adverse Events Leading to Discontinuation of Study Medication

Of the 131 patients treated with DUROS® Leuprolide Implant, 4 (3.1%) discontinued study medication prematurely because of adverse events and 5 (3.8%) patients died during the Treatment Phase. None of the deaths or the adverse events were considered by the sponsor as related to study treatment. The

five deaths are described in detail in section 8.4. The four adverse events leading to study withdrawal included:

- Extrusion of implant [2 patients]
- Abdominal pain and ear disorder
- Spinal cord compression secondary to progression of metastatic adenocarcinoma of the prostate

Another patient withdrew from the study after completing the 52-week treatment phase but before enrolling in the safety extension phase. His adverse events were characterized as cognitive deficit, loss of memory, tremors, and abnormal gait.

8.6.2 Adverse Events associated with clinical disease flare

Six patients reported symptoms that may have been related to a clinical flare associated with the expected transient increase in serum testosterone in the first week after the initial implantation.

Three events were associated with pain.

- One patient had mild bone pain that started and resolved on the day after insertion.
- One patient reported back pain on the day of insertion. This patient later terminated from the study because of spinal cord compression secondary to disease progression.
- One patient developed bilateral posterior leg pain 2 days after insertion, which was treated with antiandrogens and resolved.

Three events were associated with voiding symptoms.

- One patient had urinary retention 4 days after insertion, which resolved the next day.
- Two patients had urinary frequency: one at 8 days after insertion, which resolved 10 days later, and the other at 7 days after insertion, which was ongoing at the end of the Treatment Phase.

8.6.3 Laboratory Test Results

Clinical laboratory evaluations (complete blood count with differential and platelets, blood chemistry, and urinalysis with microscopic examination) were performed at screening and at the end of Month 24 (for patients in Study C-96-011). The mean values for these results were displayed for patients in group 1 [one implant] and group 2 [two implants]. The sponsor claims that no clinically meaningful mean changes from baseline to end of study were noted.

8.6.3.1 Laboratory abnormalities reported as AEs

Laboratory abnormalities were also reported as non-serious adverse events.

- One patient experienced hyperglycemia (218 mg/dL) treated with glyburide.
- Six patients had hypercholesterolemia (values unknown) and were treated with lipid-reducing agents.
- Hyperlipidemia (values unknown) was reported in two patients, one of whom also had iron deficiency anemia.
- Five patients experienced mild anemia.

8.6.3.2 Anti-leuprolide Antibody Formation

In Study C-96-011, serum samples were evaluated for IgG and IgM antibodies to leuprolide, before insertion and during the 12-month treatment phase. The sponsor reports that no evidence of IgG antibodies were found in any of the 51 patients studied. Forty-four patients tested negative for IgM antibodies to leuprolide. The sponsor reports that, in the remaining seven patients, no rising titers were noted during the course of treatment with the implant.

8.7 Safety assessment of device implantation and tolerability

8.7.1 Application-Site Reactions [ASR]

Since one implant effectively suppressed testosterone to the castrate range and all patients received one implant at reinsertion, the primary application-site reaction analysis was done with patients who had a single implant (Group 1 of Study C-96-011, all patients in Study C-97-010, and all patients in the Safety Extension Phase of the studies).

A total of 71 (66.4%) of the 107 patients who received a single implant reported an ASR after initial insertion or reinsertion. Of the fifty patients who noted an ASR following initial insertion only, in 41 patients the reaction began and resolved within the first 2 weeks of insertion. Reactions persisted in 10 patients [20%]. Eleven [22.0%] patients developed ASRs (including expulsions, erythema, and itching) after the first 2 weeks following insertion. The most frequently reported ASRs were bruising and burning.

Four patients in Study C-96-011 had application-site infections/inflammations that were treated with oral antibiotics and resolved.

8.7.2 Implant extrusions

DUROS™ Implants were extruded through the incision site in three patients: two in Study C-96-011, and one in Study C-97-010. The sponsor claimed that "incorrect placement in physically active patients was a factor in two of the extrusions".

8.7.3 Physician assessment

The ease of insertion, length of incision, extent of bleeding, duration of the procedure, and adequacy of the trochar were evaluated by the investigator during initial implant, implant removal, and reinsertion in the 107 patients who received a single implant.

8.7.3.1 Primary implantation

Implant placement was rated as "very easy" or "somewhat easy" in 99.1% of patients. The mean duration of the initial implant was 4 minutes [range: 1 to 15 minutes].

8.7.3.2 Implant removal

At the twelve-month assessment, implant removal was rated as "somewhat difficult" in 13 of 107 patients with a single implant. The second implant removal procedure was evaluated in Study C-96-011 at the end of 24 months of treatment. All patients had received a single implant. Implant removal was rated as "somewhat difficult" in one patient in each group [n=43, total for both groups].

In two patients, fluoroscopy or x-ray was required for localization.

In study C-96-011, the bleeding was rated as "minimal" at the time of removal in 95% of patients. Encapsulation was described in 76% of patients in group 1 and 87.5% of patients in group 2.

Histopathological examination was performed on two patients in Study C-97-010 who died. The tissue surrounding the proximal and distal ends of the implant was evaluated. In one patient 20% of the sample from each end was fibrous tissue (collagen). There was no evidence of inflammation. There was scant polarizable foreign material in one of the two specimens from this patient, which the sponsor attributes to drug formulation extruded from the orifice of the implant. In the other patient a mild increase in collagen was noted in both the proximal and distal ends of the implant.

8.7.3.3 Reimplantation

The mean duration of the reinsertion procedure was 6.1 minutes [range: 1-28 minutes] in the 107 patients who received a single implant. Reimplantation was rated as "somewhat difficult" in three patients. In two patients, excess force was necessary to penetrate the dense fibrotic sheath that surrounded the previous device. In a third patient, the implanter handle broke during introduction of the implant.

8.7.3.4 Implant site assessment

In Study C-96-011, the investigators evaluated the application site at each visit (Day 3 through Week 60). Two weeks after initial implant insertion and 2 weeks after reinsertion, healing of the application site was rated "very good" in 96.3% of Group 1 patients and in 100% of Group 2 patients. In 7 patients in Group 1 and 10 patients in Group 2, the implant(s) moved from the original application site, usually migrating a few millimeters.

8.7.4 Patient assessments

After initial implant insertion (implantation) and reinsertion (reimplantation) in Study C-96-011, the patients assessed the adequacy of the anesthetic block and rated the severity of pressure, pulling, and pain.

8.7.4.1 Initial implantation

Following initial insertion, the anesthetic was rated "good" or "very good" by all patients in both groups. Pressure, mostly rated "mild" or "moderate," was reported by 70.4% of Group 1 patients and by 66.6% of Group 2. In Groups 1 and 2, pulling was reported by 11.1% and 12.5% of patients, respectively, and pain was reported by 11.1% and 16.7% of patients, respectively.

8.7.4.2 Reimplantation

At reinsertion, the anesthetic was rated "good" or "very good" by more than 90% of patients in both groups. In Groups 1 and 2, pressure was reported by 44.0% and 54.1% of patients, respectively; pulling by 28% and 37.6%, respectively; and pain by 28% and 16.6%, respectively.

8.7.4.3 Wearing sensations

In Study C-96-011, more than 90% of patients reported that they had forgotten about the implant(s) most of the time by Week 6 in Group 1 and by Week 12 in Group 2. In Study C-97-010, 80.3% of patients at Week 24 and 75.7% at Week 52 reported that they forgot about the implant most of the time.

In Study C-96-011, 100% of Group 1 and 95.4% of Group 2 patients rated comfort with the implant as "very comfortable" or "somewhat comfortable" by Week 2. In Study C-97-010, more than 90% of patients rated the implant "very comfortable" or "somewhat comfortable" at Weeks 24 and 52.

In Study C-97-010, most patients reported that the implant did not affect their daily activities when they were asked at Week 24 (87.3%) and Week 52 (81.4%).

8.8 Reviewer comments on Integrated Summary of Safety

The DUROS™ Leuprolide Implant was well tolerated in 131 men with stage A2, B, C, and D adenocarcinoma of the prostate. 120 patients [91.6%] were exposed to the drug for a duration of 52 to 113 weeks. The mean duration of exposure was 72.6 weeks [range: 8, 113].

Ten deaths occurred in this population. The causes of death were primarily cardiovascular, occurring in patients with known cardio-vascular disease or from disease progression of the patient's adenocarcinoma of the prostate.

- *This reviewer believes that none of the deaths were related to the study medication.*

Forty-one SAEs were identified. The majority of the SAEs were cardio-vascular in nature or related to disease progression from adenocarcinoma of the prostate.

- *This reviewer believes that none of the SAEs were related to the study medication.*

The most common non-serious adverse event was vasodilatation, or hot flashes. This expected effect of testosterone deprivation and was reported by 67.9% of patients. Sixty percent of patients reported this symptom as "mild"; 3.7% described it as "severe". Events associated with the physiologic effects of testosterone suppression, such as gynecomastia and impotence, were reported.

- *Six patients had an AE that may have represented a clinical flare associated with the transient increase in serum testosterone during the first 10 days after the initial implant. Only three of the six reports seem likely to be due to exacerbation of the patient's malignancy. In all six patients, these symptoms were mild to moderate and were managed easily with conservative therapies. This incidence of "flare" is similar to the incidence reported historically with similar GnRH agonist products in this population.*

- *The AEs reported and the incidence rate for these events would appear to be representative of those expected over the study duration in a population of elderly*

men. There is no control group for comparison, but this reviewer believes that the incidence of AEs is acceptable.

Application-site reactions were reported by a little over half of the patients who received a single implant. Most ASRs were mild and over 80% resolved within 2 weeks after insertion. Only four patients required a course of antibiotics and no patient developed a local reaction [abscess or seroma] that required local drainage or implant removal.

Both investigators and patients rated the easy of implantation/removal and wearing tolerability of the device as high.

Spontaneous expulsions of the device were rare, observed in three patients of the 131 receiving an initial implant and no patients in the group receiving a reimplant.

- *The sponsor has offered an explanation for the expulsion in ~~two of~~ three patients, reporting that 1) the location of the implant site was not optimal [i.e. too close to the antecubital fossa or not in the bicepital groove] or the patients were "too active" at their work. This reviewer believes that proper labeling for the insertion instructions can address these issues.*

Two investigators reported difficulty located the device at reimplant and the use of fluoroscopy was required.

In two patients, excessive force was required to penetrate the fibrotic tissue that had formed around the previous implant. In another patient, the implanter handle material interfered with the cannula movement, which caused the investigator to break the actuator during the insertion procedure. The insertion was completed without complication, and the implant was advanced to a satisfactory position with forceps.

Removal was "somewhat difficult" or "very difficult" when the implant was placed too deep in subcutaneous tissue or was encapsulated, or because of large patient size.

- *The placement of implants "too deep" in the subcutaneous space, or beneath muscle fascia has been reported for other implant devices. This issue can best be addressed with appropriate labeling text in the insertion instructions.*

- *The sponsor reports that the inserter device has been re-designed to address the matter of the broken inserter handle described above. New handle molds for the implanter were made to rectify the problem.*

9.0 Overall Assessment of Safety and Efficacy

There are no safety concerns on clinical review of the DUROS™ Leuprolide Implant that would prevent approval of this drug product. Leuprolide acetate for daily subcutaneous

dosing and several depot microsphere formulations have been marketed for over 15 years. The safety profile of this drug product is well established. The safety concerns unique to this product are primarily related to the placement, wearing, and retrieval of the implant over the duration of treatment. The sponsor has provided sufficient supportive safety data with over 130 unique exposures over a 14 to 24 months duration in a population of patients with carcinoma of the prostate. Although no placebo control arm is available for comparison, the data demonstrate an acceptable incidence of adverse events. No unexpected AEs were identified. No serious AEs appear to be related to the study medication or implant system. None of the 12 reported deaths appear to be related to the study medication or the implant system.

There are no efficacy concerns on clinical review of the DUROS™ Leuprolide Implant that would prevent approval of this drug product. The sponsor has provided data in two unique studies of adequate design and implementation to demonstrate the efficacy endpoint recommended to the sponsor by the Division during the IND development process. Compared to historical controls, this drug product and delivery system achieves and maintains medical castration in the target patient population at success rates reported for other leuprolide products.

10.0 Labeling Issues

At the time of completion of this review, labeling negotiations with the sponsor are ongoing. After initial comments from the Division were received by the sponsor, most modifications that were suggested were accepted and incorporated into the label. As noted in the reviewer comments above, the two areas of continued discussion concern:

PSA changes -The sponsor has suggested inclusion of claims about the effect of the drug product on a secondary efficacy variable, PSA.. Other approved leuprolide formulations have been allowed to include a variety of statements about PSA in their labels.

The division has recommended that statements about the relationship of DUROS™ use and PSA outcomes be limited. While the sponsor originally suggested a claim about effects on a subgroup of treatment-naïve patients, the Division prefers that any statement be limited to the entire efficacy population. While the sponsor originally offered a claim about a variety of decreases in PSA values from baseline to several points in time over the 52-week treatment period, the Division prefers that the label reflect the percentage of patients who demonstrate a > 90% decrease in PSA from baseline after six months of treatment.

Explanation for extrusion of device – The sponsor has included in the label the claim that "incorrect placement was a factor in two of these extrusions". The Division believes that the sponsor has not provided substantial evidence to support this claim and has suggested that this statement not be included in the final label.

11.0 Recommendation of medical reviewer

The reviewer concludes that DUROS™ Leuprolide Implant is safe and effective for the palliative treatment of adenocarcinoma of the prostate in patients for whom medical castration is indicated. The reviewer recommends that DUROS™ Leuprolide Implant be approved for the indication noted above.

/S/ 2/15/00

Norman S. Marks,M.D., Medical Officer
HFD-580, Division of Reproductive and Urological Drug Products
CC: Daniel Shames, M.D.
Marianne Mann, M.D.
Janine Best, R.N.
Division File

Concur 2/22/00
/S/
Team Leader

FEB 23 2000

FOUR-MONTH SAFETY UPDATE MEMO
Medical Officer Review

NDA 21 088
Drug substance – leuprolide acetate
Drug product – DUROS™ Leuprolide implant
Trade name – Viadur™
Indication – palliative treatment of advanced prostate cancer
Dose and route – 120 microgram/day administered by continuous subcutaneous infusion over a twelve month period

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The safety database available for review at the time of the 4-month safety update of October 13, 1999 included all 131 patients enrolled and implanted in studies C-96-011 and C-97-010. The reporting period for extent of exposure is through week 104 for patients in study C-96-011 and through week 60 for patients in study C-97-010.

Of the 48 patients from study C-96-011 who completed the 52-week treatment phase and were reimplanted with one implant, 43 patients completed week 104 of safety extension phase. Of the 70 patients from study C-97-010 who completed the 52-week treatment phase and were reimplanted with one implant, all 70 patients remained on-study at the time of the 4-month safety update.

Five deaths were reported in the 4-month safety update. All five deaths occurred in Study C-96-011. Summaries of these patients are included in the primary clinical review document. None were considered by this reviewer to be related to study treatment.

Serious adverse events reported in the 4-month safety update were reviewed. None were considered by this reviewer to be related to study medication.

Adverse events occurring after Month 14 through August 15, 1999 for patients in Study C-97-010 were reported separately in the 4-month safety update. Eight patients experienced serious adverse events, including two deaths. All were considered unrelated to study treatment by this reviewer. The two deaths reported were due to a motor vehicle accident [patient no. 905] and metastatic bladder cancer patient no. 2301].

/S/ 2/22/00

Norman S. Marks, M.D.
Medical officer, Urology HFD-580
CC: Daniel Shames, M.D.
Marianne Mann, M.D.
Janine Best, R.N.

/S/ 2/23/00

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

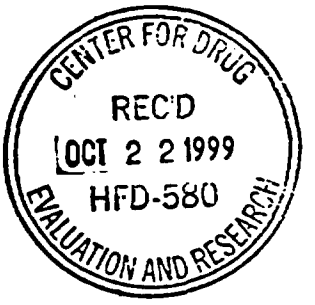
Food and Drug Administration
Office of Device Evaluation
9200 Corporate Avenue

CONSULTATION REVIEW

Date: October 12, 1999

To: CDER/Division of Reproductive and Urologic Drug Products (HFD-580)

Thru: Branch Chief,
Patricia Cricenti
Division Director,
Timothy A. Ulatowski



From: Scientific Reviewer/HFZ-480

Document No: NDA 21-088
Company Name: ALZA Corporation
Device: DUROS™ Leuprolide Implant

Indications for Use:

The controlled delivery of leuprolide acetate over a one-year period for the palliative treatment of advanced prostate cancer.

This is a review of a nonbiodegradable, osmotically driven miniaturized implant device designed to deliver leuprolide acetate over a one-year period at a controlled rate of approximately 0.12ml/day. The implant measures 4mm by 45mm and contains 72 mg of leuprolide acetate (equivalent to 65 mg leuprolide) dissolved in 104mg dimethyl sulfoxide. The device is inserted subcutaneously in the inner aspect of the upper arm using a trocar-like implanter made of plastic and stainless steel. A surgical procedures kit is separately available and recommended for use by the sponsor.

Currently, leuprolide acetate can be administered by daily injections or periodic depot injections at intervals of 1, 3, and 4 months. The efficacy of Leuprolide in the palliative treatment of advanced prostate cancer has been established. The sponsor cited clinical studies in which patients received 20mg of leuprolide acetate daily for two years to support the safety of the device should the full contents of the drug be accidentally administered to the patient. The intent of the Leuprolide implant is to provide consistent, continuous therapy over one year as an alternative to periodic depot injections.

The device is a metal cylinder that is both a drug container and structural component that houses the mechanical elements of the device. The sponsor described the device as an extension of their osmotic drug delivery technology that includes the ALZMET® osmotic pump and the Veterinary Implantable Therapeutic System. The device components and materials of constructions are

The device is intended as a long-term (>30 days) implant. The cylinder, the diffusion moderator, and the rate-

controlling membranes are direct tissue and tissue fluids contact surfaces. The recommended biocompatibility testing for materials intended for long-term implants include Irritation, Sensitization, Cytotoxicity, Acute systemic toxicity, Hemocompatibility, Pyrogenicity, Implantation, Mutagenic, Subchronic toxicity, Chronic toxicity, and Carcinogenecity. The biocompatibility and suitability of these materials were established through testing and the reviews of appropriate literature. Titanium and titanium alloys are materials commonly used in the manufacture of implantable devices, and are used as a negative control implant material. Specifications and physical properties for Ti-6Al-4V have been established and are described in ASTM Standard F 136-96. The diffusion moderator is made of thermoplastic, high-density, polyethylene (HDPE). HDPE is a commonly used material for implantable devices, and is also used as a negative control article in biological reactivity testing. Material testing included subchronic and chronic toxicology, carcinogenicity, 90-day implantation, biological reactivity, cytotoxicity, and genotoxicity.

The rate-controlling membrane is made of polyurethane thermoplastic elastomer. Material testing included cytotoxicity, hemolysis, systemic injection, intracutaneous injection, intramuscular implantation, microsomal assay, 90-implantation, biological reactivity, and genotoxicity. In addition, the sponsor stated that all polymers used in the manufacture of the device were evaluated for safety per the USP XXIII Class VI biological reactivity tests, the Elution cytotoxicity assays, and the MTT assay.

The device uses an "osmotic engine" to push the piston forward to eject the drug through the diffusion moderator into the surrounding subcutaneous tissue. The osmotic engine consists of two salt tablets, designed to absorb water and volumetrically expand. The water, from the fluids in the tissue in which the device is implanted, enters the osmotic engine by permeation across the rate-controlling membrane. The permeation rate is a function of the materials mix that comprises the membrane, specifically the ratio of polyethylene glycol to polytetramethylene glycol.

Performance evaluation of the device included bench testing (release rate assays per sponsor's Analytical Method 1.451f (reverse phase HPLC), dose accuracy and drug release per the USP XXIII General Chapter 724 Drug Release "Extended-release Article - Drug Release Standard, Acceptance Table 4"), animal implant studies (rat, dog, and swine) and clinical trials (single and repeated dose pharmacokinetics).

The device is radioopaque, not affected by MRI, and can be visualized by X-ray, which has no effects on its performance. The device function after implant is determined by monitoring serum levels of testosterone, as well as prostate-specific antigen (PSA).

III. Conclusion:

This review of the ALZA Corporation's DUROS™ Leuprolide Implant did not raise any engineering or performance-related concerns with the Implant as a drug delivery device. The Implant does not raise any new issues in terms of intended uses and technological characteristics, nor does it raise any new questions of safety and effectiveness in its ability to deliver leuprolide acetate over a one-year period at a controlled rate. The device was not evaluated as a drug container/closure.

If you have any questions, please call me

/S/

Von Nakayama