CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER
21-379

MEDICAL REVIEW(S)

CLINICAL REVIEW

NDA-21379

NDA 21-379

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

MEDICAL OFFICER REVIEW OF NDA 21-379

SPONSOR:	Atrix Laboratories, Inc. 2579 Midpoint Drive Fort Collins, CO 80525
DRUG PRODUCT:	**LA 2550,** Eligard™
DOSE:	22.5 MG
ROUTE OF ADMINISTRATION:	Subcutaneous Injection
PHARMACOLOGICAL CLASS:	Gonadotropic Releasing Hormone(GnRH) Agonist
INDICATION:	Palliative Treatment of Advanced Carcinoma of the Prostate.
DATES:	
SUBMITTED:	September 25, 2001
CDER STAMP:	September 27, 2001
PDUFA GOAL:	July , 2002
RELATED IND's:	[redacted] NDA 21-343
MEDICAL OFFICER	Ashok Batra MD
DATE REVIEW COMPLETED:	June 13, 2002

CLINICAL REVIEW

NDA-21379

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Executive Summary

1. Recommendations

1.1. Approvability

This reviewer recommends that ELIGARD™ 22.5 mg should be approved for the proposed indication of palliative treatment of advanced prostate cancer. Some labeling changes will be required to accurately convey the product profile to the prescriber.

1.2. Basis for recommendation regarding approvability (risk/benefit assessment)

Benefits

Androgen withdrawal treatment is a current standard of care in the palliative management for advanced prostate cancer patients since the majority of prostate cancers are androgen sensitive. This is achieved either by surgical (orchiectomy) or medical means. The goal of therapy is to suppress serum testosterone (T) levels to below 50ng/dL.

In support of their claim, the sponsor conducted one pivotal trial (Protocol AGL 9909) . In the intent-to-treat population following treatment with LA-2550 , 22.5 mg, 99% (116/117) of patients reached castrate (≤50 ng/dL for two consecutive time points approximately one week apart) suppression of T concentration. By Day 28, 115 of the 117 (98%) patients achieved castrate T suppression, and by Day 35, 116 of the 117 (99%) patients achieved this measure. One patient received less than half of the study drug dose at the Baseline injection and was withdrawn from the study because he did not achieve medical castrate T levels. The median time to castrate suppression was 21 days, and the mean time to castrate suppression was 21.9 days. All patients who achieved castrate T suppression (50 ng/dL) remained suppressed throughout their participation in the study, with the exception of one patient (#1701). This patient achieved castrate suppression at Day 21 and later experienced a breakthrough at Day 49 (T 112 ng/dL). His T continued to rise until it reached a high of 557 ng/dL at Day 85, one day after his second injection. His T then declined until Day 98, when it was 27.0 ng/dL. His T levels then remained ≤50 ng/dL throughout the remainder of the study.

Risks

Medical castration by GnRH agonist is usually accompanied by an initial rise in serum T level for 1-2 weeks followed by a decline to castrate levels in about one month. This initial rise can occasionally cause a "flare" phenomenon whereby the patient might experience transient worsening of symptoms (bone pain, obstructive urinary symptoms). In rare instances, ureteral obstruction and spinal cord compression have been reported.

While no "flares" were reported in this NDA, this potential adverse reaction is a labeled warning for all drugs of this class.

The sponsor of this NDA also reported such known drug-related adverse events as hot flashes, dizziness/giddiness, malaise/fatigue, testicular discomfort/atrophy, diminished libido, and impotence. The incidences of these events were generally in line with expected incidences in the class.

GnRH analogs can also potentially induce antibody formation and hypersensitivity reactions. These were not reported in this NDA but they are also labeled for the class. Additionally, since ELIGARD is a subcutaneous preparation, local pain, itching, swelling, erythema, induration, and rarely ulceration may occur. While pain, itching, and swelling was a commonly reported adverse reaction, most events were reported as mild in severity and short in duration. All of the reported events resolved spontaneously without sequelae. No patient was discontinued for a local adverse event.

In summary, based on safety and efficacy information contained in NDA 21-379, this reviewer believes that the sponsor has demonstrated that ELIGARD™ is safe and effective for the proposed indication of palliative treatment of advanced prostate cancer.

1.3. Specific recommendations to the sponsor

The Sponsor will be asked to make some labeling changes to accurately describe the product. (Also see section 10)

2. Summary of clinical findings

2.1. Brief overview of the clinical program

2.1.1 Drug product

The drug product used in the clinical trials (ELIGARD 22.5 mg) was manufactured by Atrix Laboratories.

ELIGARD 22.5mg, was supplied in two separate, sterile syringes and was mixed immediately prior to administration. One syringe contained the polymer formulation, ATRIGEL® Delivery System, consisting of [redacted] 75/25 Poly(DL-lactide-co-glycolide) (PLG) and [redacted] N-methyl-2- pyrrolidone. The other syringe contained 22.5 mg lyophilized leuprolide acetate. The syringes were joined via the syringe connections, and the delivery system was passed between syringes until it was thoroughly mixed with the leuprolide acetate. Study drug was manufactured by Atrix Laboratories. The lot numbers of drug product used in the study were 1252 and 1272. The injection volume was 0.375 mL.

2.1.2. Brief overview of the clinical trials conducted

The sponsor submitted data from an open label pivotal study (AGL 9909) in support of NDA 21-379. For the intent-to-treat population, by Month 1 (Day 28) 115 of the 117 (98%) patients achieved castrate testosterone suppression, increasing to 116 patients (99%) by Day 35. The remaining patient (#1801) received less than half his scheduled dose at Baseline and never achieved medical castrate testosterone suppression. He was switched to Lupron™. A very high proportion of patients (84% at Day 28, 92% at Day 42) achieved the more stringent criteria of testosterone suppression using a threshold of ≤20 ng/dL for at least two consecutive time points approximately one week apart. At the end of the study 104 of 111 (94%) patients remaining in the study were at or below this more stringent level.
All patients who achieved castrate testosterone suppression (50 ng/dL) remained suppressed throughout their participation in the study, with the exception of one patient (#1701). This patient achieved castrate suppression at Day 21 and later experienced a breakthrough at Day 49 (testosterone 112 ng/dL). His testosterone continued to rise until it reached a high of 557 ng/dL at Day 85, one day after his second injection. His testosterone then declined until Day 98, when it was 27.0 ng/dL. His testosterone levels remained ≤50 ng/dL throughout the remainder of the study. The median time to castrate suppression was 21 days while the mean time to castrate suppression was 21.9 days. In addition, no acute-on- chronic responses were observed in any patients following any of the post-Baseline study injections.

2.2 Efficacy

2.2.1. Primary efficacy assessments and efficacy endpoints

Prostate cancer is an androgen-dependent tumor in most men at the time of initial presentation. The goal of endocrine therapy in prostate cancer is to suppress serum androgen levels to those normally observed following surgical castration. Based on these considerations, the FDA accepts a surrogate endpoint (T suppression to castrate levels) as primary evidence of efficacy for products indicated for treatment of this disease.

For this NDA, the Division agreed that the attainment of castration levels of testosterone (<50 ng/ dL) by treatment Day 28 and maintenance of these levels through at least 2 dosing cycles (6months) would constitute the primary measure for success.

Therefore, the efficacy objectives in Study AGL 9909 (the single Phase 3 trial) were to determine:

1. The proportion of patients with a serum testosterone of < 50 ng/ dL(i.e., medically castrate) on Day 28.

2. The proportion of patients maintaining castrate levels of serum testosterone from Day 29 through Day 168.
3. The proportion of patients exhibiting "acute-on-chronic" phenomenon upon repeated dosing.

2.2.2. Efficacy results (primary endpoints)

The results of study AGL9909 revealed that following two doses of ELIGARD™ 22 .5 mg, given every 84 days, Most (116/117=99%) of patients reached castrate(< 50 ng/dL) suppression of testosterone concentration. By Day 28, 115 of the 117 (98%) patients achieved castrate testosterone suppression, and by Day 35, 116 of the 117 (99%) patients achieved this measure. The one exception (patient #1801) ,who reportedly received less than half of the study drug dose at the Baseline injection and was withdrawn from the study because he did not achieve medical castrate testosterone levels. The median time to castrate suppression was 21 days, and the mean time to castrate suppression was 21.9 days. In addition, all but one of those patients who achieved castrate testosterone suppression (50 ng/dL) remained suppressed throughout their participation in the study. There was one patient with a break through elevation of Testosterone levels.

2.2.3. Other efficacy issues

There was no evidence of acute rises in the serum testosterone upon repeated dosing (the so-called "acute-on-chronic" phenomenon). This result as well as other secondary measures such as PSA changes, bone pain and performance status are reflected in labeling.

2.2.4. Proposed label indication

The data provided by the sponsor in this NDA, especially the data regarding post-dosing serum testosterone levels, are sufficient to support the claim that "ELIGARD™ 22.5 mg is indicated in the palliative treatment of advanced prostate cancer."

2.3. Safety

2.3.1. Exposure to study drug

As a class, superactive GnRH agonists have been found to be safe and well-tolerated. Based on the data in the present application and the overall experience with leuprolide acetate, the exposure to the ELIGARD™ is considered adequate to assess its general safety for the indication of management of advanced prostate cancer. Additionally the data regarding local site reactions is also considered sufficient to make a determination of the local tolerability of the drug.

In study AGL 9909, 117 patients with carcinoma of the prostate were exposed to at least a single SC injection of study drug. Of these, 113 patients received two SC injections of study drug. Six patients discontinued during the study. Two patients voluntarily withdrew their consent from the study: one patient (#0102) discontinued at Day 71 due to transportation problems and received only one injection; the second (#2002) received two injections and discontinued at Day 134 due to an illness in the family requiring his extended absence. Two patients discontinued due to progression of disease. Patient #2402 experienced increases in bone pain beginning at Day 14 following his Baseline injection. Testosterone levels were 350 ng/dL at Baseline and peaked at 600 ng/dL at Day 3. By Day 7, these values had returned to Baseline levels (362 ng/dL) and by Day 14 were well below Baseline (99 ng/dL). At Day 21 levels were below medical castrate (23 ng/dL) and remained below castrate until the patient was withdrawn (Day 64). He received radiation therapy for his hip pain and metastasis. Patient #2602, shortly after the first injection, went to [redacted] for a second opinion of his prostate cancer. At that time, the cancer was found to be locally recurrent, and [redacted] advised him to start radiotherapy. One patient (#3401) was withdrawn on Day 155 as he was hospitalized for a drug unrelated severe adverse event. The sixth patient (#1801) was withdrawn on Day 74 because of insufficient dosing and lack of T suppression.

2.3.2. General safety findings

The drug-related adverse reactions reported in this NDA for ELIGARD 22.5 mg were comparable to those reported in the currently approved 22.5 mg leuprolide acetate package insert. Common AE's found in the treatment-related categories for this multi-dose study were: hot flashes, fatigue, nausea, urinary frequency and arthralgia.

While there were some reports of mild, transient irritation at the subcutaneous injection site, in the opinion of this reviewer, these local adverse reactions do not outweigh the demonstrated efficacy benefit. Therefore, these reactions should not preclude approval.

2.3.3. Patient deaths

There were no reported deaths in the studies conducted for this NDA.

2.4. Formulation and dosing

ELIGARD™ 22.5 mg is a novel subcutaneous depot formulation of leuprolide acetate administered at three monthly intervals. It is supplied in two, separate, sterile syringes which are mixed immediately prior to administration.

One syringe contained the polymer formulation, ATRIGEL® Delivery System, consisting of [redacted] 75/25 Poly(DL-lactide-co-glycolide) (PLG) and [redacted] N-methyl-2-pyrrolidone. The other syringe contained 22.5 mg lyophilized leuprolide acetate. The system is designed to deliver 22.5 mg of leuprolide.

2.5. Special Populations

2.6.

- Women and children: No women and no children were studied for this indication. The package insert contraindicates use of ELIGARD in these populations.

- Renal and hepatic impairment: There were no special investigations in patients with renal or hepatic impairment and these patients were excluded form the single Phase 3 trial. The label notes these issues.

- Racial differences in efficacy and safety:
  Efficacy results were similar across all races studied.

3. Introduction and background

3.1 Drug established and proposed tradename, drug class, proposed indication(s), dose, regimen

Drug product:	LA-2550 22.5 MG, Eligard™
Drug substance	Leuprolide acetate
Dose:	22.5 mg
Dosing Regimen	Administered once every 3months
Route of administration:	Subcutaneous injection
Pharmacological class:	Gonadotropic releasing hormone (GnRH) agonist
Indication:	Palliative treatment of advanced carcinoma of the prostate

3.2. Overview of disease and treatment options

3.2.1 Carcinoma of the prostate and medical therapy

Cancer of the prostate is the most frequent non-cutaneous malignancy.It is the second most frequent cause of death from cancer in men over 50 years of age. Since majority of prostate cancers are dependent on circulating androgens and are responsive to hormone manipulation, the mainstay of therapy, for non localized disease , is androgen deprivation. Testosterone (T) withdrawal may be produced by surgical orchiectomy or by "medical castration" (via diethylstilbestrol or synthetic gonadotropin releasing hormone (GnRH) agonists) and is associated with a symptomatic improvement in 60-80% of patients.

Synthetic analogues of GnRH have a longer half-life and higher potency than naturally occurring GnRH secreted by the hypothalamus. Chronic administration of GnRH agonists has a biphasic action, acutely increasing gonadotropin and testosterone levels and then suppressing luteinizing hormone (LH) release from the anterior pituitary. Physiological secretion of GnRH is pulsatile and the continuous presence of GnRH down-regulates GnRH receptors and diminishes LH release. The lack of LH stimulation then reduces testosterone production from Leydig cells in the testes. Studies have established that GnRH agonists have equivalent efficacy to surgical castration.

LA-2550 22.5 MG is a novel subcutaneous depot formulation of leuprolide acetate administered at 3-monthly intervals. Leuprolide acetate has been approved for the treatment of advanced prostate cancer for approximately 15 years. It is well recognized

as a safe and effective method of "medical castration". The adverse events directly related to the diminished circulating testosterone include; hot flashes, sweating, impotence, decreased libido, and gynecomastia. Disease "flare" is characterized by an acute and temporary exacerbation of disease-related symptoms during the first few weeks of leuprolide acetate therapy. Flare occurs in susceptible patients resulting from the initial increase in T and LH stimulated during the first 10 days of leuprolide acetate therapy (testosterone "surge"). Overall, patients experiencing flare range from 10%-20%. Post-marketing data on safety and efficacy of these drugs has been favorable when used for the palliative treatment of advanced prostate cancer.

3.2.2. Important issues with pharmacologically related agents

As noted above, a superactive GnRH analog (Lupron) was first approved by the FDA for the treatment of advanced prostate cancer in 1985. Two other GnRH analogs were subsequently approved for this indication. Atrix Laboratories, Inc. received approval for its monthly GnRH product ELIGARD 7.5 mg ™ in January of 2002. Various GnRH agonists have been widely used in urology with an acceptable safety record.

3.3. Important milestones in product development

The first GnRH agonist approved by the FDA for this indication was leuprolide acetate (Lupron™, TAP Pharmaccuticals) in 1985. Other superactive GnRH agonists approved by the FDA for this indication include goserelin acetate (Zoladex™, AstraZeneca Pharmaceuticals) and triptorelin pamoate (Trelstar™ Depot, Debio Recherche Pharmaccutique). Because these peptide agonists are rapidly metabolized and not pharmacologically active if taken orally, they are administered parenterally by means of long-acting biodegradable formulations. These long-acting formulations are currently administered at intervals ranging from 4 to 16 weeks. Atrix Laboratories, Inc. received approval for its monthly GnRH product ELIGARD 7.5 mg ™ in January of 2002. Atrix developed and proposed to administer the dose via the subcutaneous route, using their ATRIGEL ® Delivery System.
The following milestones in Atrix Laboratories, Inc. 's drug development are relevant :

1. An **IND #** [redacted] was filed on January 26, 2000. For AGL 9909, by agreement with the FDA, a total of 100 evaluable patients were required to demonstrate the efficacy and safety of study drug. To assure this minimum was reached, a total of 117 patients was enrolled in the study and received LA-2550 22.5 mg.

2. Essential elements of Phase 3 study design were discussed with the Division at the **End-of-Phase 2 meeting** held on March 10, 2000.

3. Protocol Amendments

The following changes were made to the protocol and are incorporated as Amendment No. 1. dated September 21, 2000.

- In order to enhance enrollment, patients with earlier stages of "advanced prostate cancer" who are candidates for androgen ablative therapy will be eligible for the study.

5. Three letters of clarifications were submitted on ; 8/00, 10/00, 3/02

3.4. Other relevant information

ELIGARD™ 7.5 mg was approved by the FDA for marketing in January, 2002. LA 2550, 22.5 mg is not marketed in any international market. No other research- related information on ELIGARD™, other than that submitted, is available.

4. Clinically relevant findings from chemistry, animal pharmacology and toxicology, microbiology, biopharmaceutics, statistics and/or other consultant reviews

4.1 Toxicology review

According to the primary reviewer (Dr. K.Raheja), there are no pharmtox findings that would preclude the approval of the 3 month formulation of ELIAGARD™ 22.5 mg for the proposed indication of prostate cancer.

4.2 Microbiology review

According to the the Microbiology reviewer , there are no microbiology issues pertaining to the sterility profile of the product that would preclude this products approval .

4.3 Clinical pharmacology and biopharmaceutics review

According to the primary reviewer (Dr. M. Kim), there are no biopharmaceutical findings that would preclude the approval of the 3 month formulation of ELIAGRD™ 22.5 mg for the proposed indication of prostate cancer.

4.4. Chemistry review

According the primary chemistry reviewer (Dr. S. De), some chemistry issues are outstanding but none should preclude the approval of the 3 month formulation of ELIAGRD™ 22.5 mg for the proposed indication of prostate cancer.

5. Human pharmacokinetics and pharmacodynamics

5.1. Pharmacokinetics

5.1.1. Absorption

In a multiple dose study (AGL 9909), a subset of 25 adult male patients with advanced prostate cancer enrolled in the PK analysis group (Group A). Patients in the PK subset had a mean age of 73.2 years (range, 62 – 84 years, with 60% over age 70), and a mean body weight of 185.9 lbs [84.5 kg] (range, 135 – 255 lbs [61.4 – 116 kg]). Patients in this subset were identified as white (76%), black (16%), Hispanic (8%). After the first dose, serum leuprolide concentrations were measured at Hours 0 (pre-dosing), 4 and 8, and on Days 1, 2, 3, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and Month 3 (Day 84) (prior to second dose). After the second dose, serum leuprolide concentrations were measured at Hours 4 and 8, and on Days 1, 3, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and Month 3 (Day 84). Leuprolide concentrations in serum were measured by a validated RIA assay, which was performed after sample purification by [redacted] and [redacted] Data from 22 of the 25 subset patients in this study was evaluable and included in the PK analysis. "Three of the 25 patients enrolled in the PK subset were excluded from the PK analysis. One patient (1801) did not receive a full dose and did not complete the study. The other patient was excluded because the number of leuprolide (L) measurements after Month 3 (Day 84) were insufficient to permit calculation of the required PK parameters. Lastly, serum L was not measured after Month 3 in one patient (1701) who experienced a breakthrough at Day 49 (T 112 ng/dL) after achieving castrate suppression at Day 21. His T continued to rise until it reached a high of 557 ng/dL at Day 85, one day after his second injection. His T then declined until Day 98, when it was 27.0 ng/dL. His T concentrations remained < 50 ng/dL throughout the remainder of the study"

Serum L concentrations rose rapidly after each dose (first dose Cmax: 127 +/- 39 ng/mL at 4.6 +/- 1.6 h, second dose C max 107+/- 50 ng/mL at 4.5+/-1.5 h), and then fell over the several days. Based on the AUC previously reported for a single 1 mg IV injection of L acetate in adult males (126 ng hr mL-1) (Sennello et al. J Pharm Sci 1986;75:158-60), the AUC of a 22.5 mg IV dose of L acetate would be approximately 2,835 ng hr mL-1. The mean bioavailability (F) of LA-2550 22.5 mg injections was > 100% after both doses.

5.1.2. Distribution

The literature reported mean Vdss of L 26.5 +/- 10.1 L following IV bolus administration to healthy male volunteers (Sennello et al. J Pharm Sci 1986;75:158-60). In vitro binding to human plasma proteins ranged from 43% to 49% (PDR 1999).

5.1.3. Metabolism and Excretion

Metabolism:
No drug metabolism study was conducted with LA-2550 22.5 mg. In animals, leuprolide(L) was metabolized to the M-I, M-II, M-III, and M-IV. Within 1 hour of IM injection of L 3.75 depot, a serum M-I concentration of 0.15 ng/mL was detected, increasing to a maximum of 0.86 ng/mL after 3 hours (Ueno & Matsuo. J Chromatograph 1991;566:57-66). In a L recipient, the concentration of this metabolite in the urine reached a peak of 4.97 □g/L within 2 days, and could still be detected (1.74 ng/mL) after 29 days (Ueno & Matsuo. J Chromatograph 1991;566:57-66).

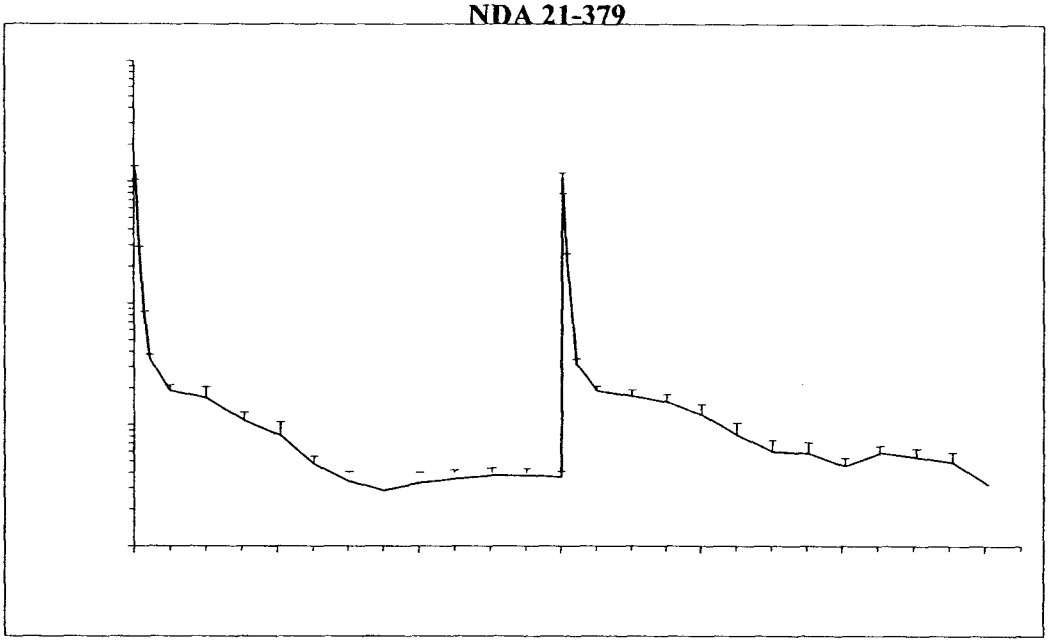
Excretion:
In healthy male volunteers, a 1 mg bolus of L administered IV revealed that the mean systemic clearance was 8.34 L/h, with a terminal elimination t1/2 of 2.9 +/- 0.5 hours based on a two compartment model. Mean elimination t1/2 and clearance were reported to be 3.6 h and 9.1 L/h, respectively, following single SC 1 mg SC injection (Sennello et al. J Pharm Sci 1986;75:158-60).

5.2. Pharmacodynamics

The pharmacodynamic response to ELIGARD, as reflected in serum T concentrations, is quite consistent. (FIG 1). The mean concentration at Baseline was 367.1(— ng/dL, with the middle 50% of the data ranging from — ng/dL. Concentrations increased until a maximum mean concentration of 588.0 (—) ng/dL was reached on Day 2. By Day 14, the mean concentration (99.4 ±5.8 ng/dL) was below the mean Baseline concentration and by Day 21 the mean concentration (31.4 ±2.3 ng/dL) was below the medical castrate threshold. By Day 28, the mean concentration (15.2 ±1.4 ng/dL) was well below 20 ng/dL. Mean concentrations remained well below the 50 ng/dL castrate threshold, but increased transiently and minimally following the second injection from 8.3 ±0.5 ng/dL at Month 3 (Day 84: hour 8) to a mean concentration of 16.3 ±4.6 ng/dL on Day 87, and then decreased consistently throughout the following month. By Month 6 (Day 168), mean T concentrations averaged 10.1 ±0.7 ng/dL. Results were similar across centers.

Figure 1. Pharmacodynamic Response to LA-2550 22.5 mg (AGL 9909)

Pharmacodynamic response to LA-2550 22.5 mg showing serum levels of L (open circles) and testosterone (closed circles) after two consecutive SC injections at 3 month intervals in patients with advanced prostate cancer (n = 22). Doses administered on Days 0 and Month 3 (84 days)

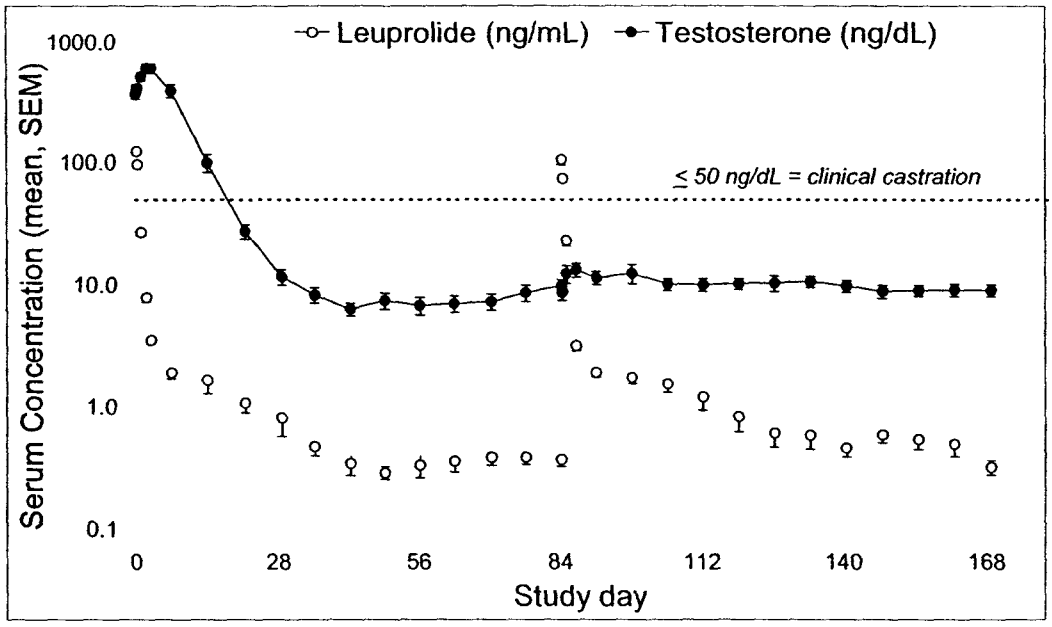


Influence of Intrinsic Factors:
Gender/Pediatric Patients: The indication sought is for the palliative treatment of advanced prostate cancer. Therefore, women and pediatric subjects were not included in the clinical PK studies.

Race: The clinical PK study of LA-2550 22.5 mg (AGL 9909) included white (n=19, 76%), black (n=4, 16%), Hispanic (n=1, 4%) and **Asian** (n=1, 4%). PK of L and T suppression was similar in this population.
Age: Elderly patients made up a substantial portion of the patients studied in the clinical investigation of LA-2550 22.5 mg (n=117, mean age 73.1, range 46-85, 71% over age 70). Patients in the PK subset had a mean age of 73.2 years (range, 62-84 years, with 60% over age 70).

Weight: Patients (n=25) studied ranged in weight from 61.4 to 116 kg with a mean body weight of 84.5 kg. Patients in clinical PK study received a unit dose of 22.5 mg, resulting in weight-normalized doses ranging from 194 to 366.5 □g/kg. Drug exposure varied between individual subjects, tending to be lower in patients with higher body weights. There was no evidence of significant PK variability over this range of doses, with serum L remaining at effective levels in all patients over the course of treatment

Renal Impairment: Slightly higher serum L levels would be expected in patients with pronounced renal dysfunction with no clinical relevance (Wechsel et al Eur Urol 1996;30:7-14). Although none of the patients in the clinical PK study had evidence of severe renal disease, 3 of 22 evaluable patients in the Study AGL9909 PK subset had urea nitrogen > 40 mg/dL and/or creatinine > 2 mg/dL at one or more time points during



the study. Due to the wide therapeutic index of L, the PK variations observed were not of sufficient magnitude to affect the efficacy and safety of LA-2550 22.5 mg.

Drug-Drug Interactions

No PK drug-drug interaction studies were performed with LA-2550 22.5 mg. No drug-drug interactions have been described for other preparations of L acetate which does not appear to be metabolized by Cytochrome P450 or other phase I or phase II pathways that could lead to metabolic interactions. Because L is primarily metabolized via peptidase(s) (Chriap & Sorkin Drugs & Aging 1991;1:487-509), and is less than 50 % bound in the plasma (PDR 1999), PK drug-drug interactions are unlikely to be observed with LA-2550 22.5 mg. The effect of L on CYPs is unknown.

Medical officer's comment:

LA 2550, 22.5 mg suppressed serum total testosterone levels by D28 in over 90% of patients in Study AGL9909. The pK/pD profile is adequate for the indication sought.

6. Description of clinical data and sources

Complete study reports for **Three** clinical trials were submitted in NDA 21-379. These reports were:

a. AGL 9909 (Single pivotal Phase 3 trial for LA 2550, 22.5 mg)
b. AGL9802 (pK study in 8 orchiectomized patients for Eligard 7.5mg)
c. AGL9904 (single pivotal Phase 3 trial for Eligard 7.5 mg)

The main focus of this review centers on AGL9909.

7. Clinical review methods

7.1 How the review was conducted

The review conducted by this medical officer focused on Study AGL 9909. Other studies listed in previous sections were also reviewed. AGL 9802 and 9904 also formed the basis of approval for Eligard™ 7.5 mg in January of 2002.

The accuracy of the sponsor's primary efficacy analyses for maintenance of testosterone suppression and acute changes in serum LH and testosterone levels after repeat dosing were reviewed.

Analyses and summary tables relating to major protocol violations, deaths, serious adverse events, and routine adverse events were reviewed using the data listings or electronic case report forms provided by the sponsor.

7.2. Overview of materials consulted in review

7.2.1. Submissions to NDA 21-379

- Original NDA 21-379; Submission date of September 27, 2001
- Electronic case report forms (CRF' s) and electronic case report tabulations (CRT's)
- Serial submission to NDA 21-379 (Amendments / Updates)

7.2.2. Other materials reviewed

- Various related IND and NDA reviews.

7.3. Overview of methods used to evaluate data quality and integrity

7.3.1 DSI audits of clinical site

One study center that participated in the pivotal clinical trial (AGL 9909) was audited by the Division of Scientific Investigation (DSI) in the spring of 2002. A DSI audit report was submitted describing the inspection results from that site(The inspections found a few minor irregularities, but the report concluded that data from these sites was acceptable for review.

Medical officer's comment:

The information provided to us in the DSI report of the inspection of this clinical site supports the validity of the data submitted in NDA 21-379.

7.3.2 Site monitoring

According to the Final Report for AGL-9909 , the investigators allowed representatives of Atrix to inspect all phases of the study at any time throughout the study. The Atrix monitor kept a record of each visit to the study site. The record included the monitor's name, date of visit, purpose of visit, and study personnel who were present during the visit. The Atrix CRA responsible for each center reviewed the completed CRFs at the

study center and sent them to Atrix. Receipt of the CRFs was documented. Accuracy of data entry into the system was audited by an independent contractor.

Medical officer's comment:

The monitoring process, data entry, and auditing procedures are adequate.

7.3.3 Central laboratories

7.3.3.1 [redacted]

[redacted] was responsible for all laboratory tests with the exception of T, LH and leuprolide acetate. [redacted] is a fully accredited clinical laboratory, maintaining certification by the College of Pathology and Clnical Laboratory Improvement Amendments (CLIA), in addition to holding current licensees for the states of Georgia, Maryland, West Virginia and New York.

[redacted] conducted periodic internal audits of ongoing studies as well as hosting external audits by independent agencies and sponsors. An accreditation certificate for [redacted] was submitted in the NDA.

7.3.3.2 [redacted]

[redacted] was utilized for T and LH analyses. The laboratory has an written Quality Assurance/Preventive Maintenance program which encompasses: calibration of equipment and instruments; preventive maintenance of equipment; inventories of critical reagents; schedules for purification of isotopes; calibration of measuring devices; and other systems which are necessary for long-term maintenance of laboratory performance.

Medical officer's comment:

The overall quality control data submitted by [redacted] were adequate to obtain a general impression of the quality of the laboratories. Based on the quality control data included in this application, the testosterone data submitted in support of NDA 21-379 appear to be acceptable to assess suppression of serum testosterone to values of 50ng/dl.

7.4 Were trials conducted in accordance with accepted ethical standards?

Based on the IRB documents, the protocol design, the conduct and analysis of the trial and the reports of DSI audits and sponsor's internal auditing, it appears that this study was conducted within norms of current standards.

7.5 Evaluation of financial disclosure

Based on information submitted by the sponsor there were no financial conflict-of-interest issue.

8. Integrated review of efficacy

8.1. Efficacy endpoint

The primary efficacy assessment measure in the principal Phase III Study, AGL 9909, was serum total testosterone concentration at various sampling timepoints. Descriptive statistics (e.g., mean, standard error, minimum, maximum) were used to summarize the concentrations at each timepoint as well as to determine the mean and median time to testosterone suppression. Descriptive statistics were also used to evaluate testosterone data for acute-on-chronic and breakthrough responses following initial suppression.

8.1.1. Primary efficacy endpoints

The primary efficacy endpoints were:

1. The proportion of patients achieving castrate levels of serum testosterone (testosterone $\leq$ 50ng/ml) on Study Day 28 (i.e., within 28 days following the initial injection of Study Drug), and

2. The proportion of patients maintaining castrate levels of serum testosterone from the day they actually achieved castrate levels to study end, and

3. The proportion of patients showing acute-on-chronic and breakthrough responses following initial suppression.

Descriptive statistics (i.e., mean, standard error, minimum, maximum) were used to summarize the T concentrations at each time point as well as to determine the mean and median time to testosterone suppression.

8.1.2. Secondary (supportive) efficacy endpoints

Secondary efficacy parameters included evaluation of serum LH concentrations, WHO performance status, bone pain, and urinary symptoms at the various sampling time points. These measures were summarized using descriptive statistics.

8.2. Populations analyzed

Analyses were performed for both the intent-to-treat (ITT) and observed-cases data-sets. These populations were defined as follows:

8.2.1. ITT population

The ITT (Intent To Treat) population included all efficacy data for patients enrolled in the study who received at least one dose of study drug, with one exception: patients with baseline data only (e.g., patients who discontinued before any efficacy information was collected) were not included in the ITT data-set. In addition, in the analysis of testosterone suppression, the intent-to-treat analysis involved carrying forward data to the end of the study for three patients who were withdrawn prior to completing the study.

8.2.2. "Observed-cases" population

This data-set is similar to the ITT data-set used to analyze testosterone suppression, except that the data for the six withdrawn patients was not carried forward past the time that they were withdrawn. In the event of a missing interim value, the last non-missing observations were carried forward.

8.3 Handling of dropouts or missing data

Missing data were handled as follows for the intent-to-treat population: Patients with baseline data only (i.e., no on-study efficacy data) were not included in the analysis. In addition, for any missing interim visits, the value from the previous visit was carried forward to the missing visit (e.g., last observation carried forward). For all other data, no corrections or adjustments were made for missing data.

8.4. Principal clinical trial to support efficacy claim (AGL9909)

8.4.1. Design

This was a six-month, multi center, fixed dose investigation of two doses of LA-2550 22.5 mg administered to patients with Jewett Stage A2, B, C, or D adenocarcinoma of the prostate at three month intervals. A total of 117 patients received at least one, SC injection of LA-2550 22.5 mg. The first was given at Baseline and the second at Month 3 (Day 84). Patients were male, between 46 and 85 years of age.

The Screening visit took place within 3-16 days prior to initial LA-2550 22.5 mg administration. Patients who met all eligibility criteria were given a patient number on Day 0 prior to treatment and entered into the study.On Day 0 (Baseline) patients received a single dose of LA-2550 22.5 mg SC between 6:00 a.m. and 10:00 a.m. Blood samples for various hormone and PK determinations were collected at specific time points. During participation in the study, patients were closely monitored by physical examinations, vital signs, clinical laboratory values, and AE's. At Month 3 (Day 84), patients were given a second dose of LA-2550 22.5 mg. Final assessment and evaluation took place at Month 6 (Day 168).

LA-2550 22.5 mg administration was performed by an individual experienced in giving SC injections. This was an open-label, fixed dose, non comparative study in which all patients received the same treatment. No blinding, randomization or stratification procedures were performed, and no concurrent controls were used.

8.4.2. Patient Selection Criteria

8.4.2.1. Inclusion criteria

The inclusion criteria were intended to select a reasonably healthy study population. Patients entered the study based upon an initial Screening ensuring the following conditions:

1. Patients read , understand and signed the informed consent agreement.
2. Male patients were between 40-85 years of age, inclusive.
3. Patients were outpatients, not currently hospitalized.
4. Patients had histologically or cytologically proven adenocarcinoma of the prostate.
5. Patients had Jewett Stage A2, B, C, or D adenocarcinoma of the prostate or a rising PSA after failed local therapy for prostate cancer.
6. Patients were candidates for androgen-ablative therapy. Hormone-refractory patients were excluded from the study.
7. Patients had a World Health Organization/Eastern Cooperative Oncology Group (WHO/ECOG) performance status of 0, 1, or 2.
8. Patients had a life expectancy of at least one year.
9. Patients had adequate renal function. Adequate is defined by a serum creatinine ≤1.6 times the upper limit of normal (ULN) for the clinical laboratory, and adequate and stable hepatic function as defined by bilirubin ≤1.5 times the ULN and transaminases (i.e., SGOT, SGPT) ≤2.5 times the ULN for the clinical laboratory at Screening.
10. Patients were willing to complete all phases and all procedures of the study.

8.4.2.2. Exclusion Criteria

Patients meeting any of the following criteria were excluded from the study: Disease specific Criteria

1. Patients with evidence of brain metastases.
2. Patients with evidence of spinal cord compression.
3. Patients with evidence of urinary tract obstruction where a flare in disease could put patient at significant risk.
4. Patients with serum testosterone levels below 150 ng/dL at Screening. (Rationale: To ensure they had relatively normal testosterone levels.)
5. Patients under the effects of any of the following treatments for prostate cancer within two months of Baseline: immunotherapy (e.g. antibody therapies, tumor-vaccines), external radiotherapy, brachytherapy, chemotherapy, or biological response modifiers (e.g. cytokines).
6. Patients who had undergone any prostatic surgery (e.g. transurethral resection of the prostate (TURP), radical prostatectomy) within two weeks of Baseline.
7. Patients under the effects of any hormonal therapy, including anti-androgens, (e.g. Lupron®, Zoladex®, Megace®, etc.) for treatment of prostate cancer within three months of Baseline.
8. Patients who had received LA-2500 7.5 mg or LA-2550 22.5 mg previously.
9. Patients who had an orchiectomy, adrenalectomy, or hypophysectomy.

10. Patients who had used any investigational drug, biologic, or device within five half lives of its physiological action or three months, whichever was longer, before Baseline.
11. Patients who had received finasteride (i.e., Proscar® or Propecia®) within three months of Baseline.
12. Patients anticipated to need concomitant hormonal, anti-androgen, radio-, chemo-, immuno-, or surgical therapy for prostate cancer throughout the duration of the study.
13. Patients who had used over-the-counter or alternative medical therapies which have an estrogenic or anti-androgenic effect (i.e., PC-SPES, saw palmetto, Glycyrrhiza, Urinozinc, DHEA) within the three months prior to Baseline.
14. Hematological parameters outside 20% of the upper and lower limits of normal (ULN, LLN) for the clinical laboratory at Screening.
15. Patients with co-existent malignancy or a history of malignancy, with the exception of basal and/or squamous cell carcinomas of the skin.
16. Patients with uncontrolled congestive heart failure within six months before Baseline.
17. Patients who had experienced a myocardial infarction or a coronary vascular procedure (e.g., balloon angioplasty, coronary artery bypass graft) within six months before Baseline.
18. Patients with significant symptomatic cardiovascular disease within six months of Baseline.
19. Patients who had experienced venous thrombosis within six months of Baseline.
20. Patients who had experienced resting uncontrolled hypertension (160/100 mmHg) or symptomatic hypotension within three months before Baseline.
21. Patients with insulin-dependent diabetes mellitus.
22. Patients with a history of drug and/or alcohol abuse within six months of Baseline.
23. Patients with other serious intercurrent illness(es) or disease(s) (e.g., hematological, renal, hepatic, respiratory, endocrine, psychiatric) that might interfere with, or put them at additional risk for, their ability to receive the treatment outlined in the protocol.
24. Patients receiving anticoagulants who had prothrombin and partial thromboplastin times outside of the normal range for the laboratory assays. Patients who were on anticoagulation or antiplatelet medications (e.g., dipyridamole, aspirin, ticlopidine, warfarin derivatives) must have been receiving a stable dose for three months before Baseline. Patients who were receiving warfarin-derivative anticoagulants must have had an International Normalized Ratio (INR) in the therapeutic range for the clinical indication for which the anticoagulant had been prescribed.
25. Patients with a known hypersensitivity to GnRH agonists, ATRISORB® Barrier product, ATRIDOX® product (PLA, NMP), or any excipients of LA-2500 7.5 mg (PLGH, NMP) or LA-2550 22.5 mg (PLG, NMP). (Rationale: To minimize risk of hypersensitivity reaction to study drug.)
26. Patients with a history of the following prior to the study were excluded:

a.Immunization (within four weeks of Baseline)
b. Flu shots (within two weeks of Baseline)
c.Donation or receipt of blood or blood products (within two months of Baseline)
d.Anaphylaxis
e.Skin disease which would interfere with injection site evaluation
f. Dermatographism (Rationale:Decreases the possibility of non –treatment related adverse events being attributed to study treatment.)

Medical officer's comment:

The study design, patient selection and the laboratory measurements are adequate and acceptable.

8.4.3.Study drug and dose selection

Based on the previous marketing experience with 22..5 mg leuprolide in the palliation of advanced carcinoma of prostate, toxicokinetics with ELIGARD, and historical dose-ranging data for leuprolide, a 22.5 mg dose of leuprolide was selected and developed.

All patients were scheduled to receive two doses of LA-2550 22.5 mg (Baseline and Month 3) subcutaneously injected into the upper right or upper left quadrant of the abdomen using a half-inch, 20-gauge hypodermic needle. The specific injection location was an area with soft or loose subcutaneous tissue.

Medical officer's comment:

The proposed dose and method of administration is reasonable.

8.4.4. Assignment to study drug

No patient or investigator-blinding procedures were implemented. This was an open-label investigation.

Medical officer's comment:
This was an open-label study, conducted with prior agreement from the Division.

8.4.5. Treatment compliance

The test article was administered as a SC injection by a trained member of the investigational staff at the investigational center; therefore, patient compliance was ensured. When there was any deviation from study drug administration, Atrix was to be notified and the event documented in the study file. No patient received an injection given at a non-SC location. One patient, #1801, received less than 50% of study drug dose at the Baseline injection and did not reach castrate suppression (50 mg/dL) subsequently. He was withdrawn from the study on Day 74 and treated with commercially available LH-RH agonist. Data from this patient is included in the study database up to the time that he was withdrawn from the study.

Medical officer's comment: There were no compliance issues that had a significant impact on approvability.

8.4.6. Schedule of study assessments

During the screening period, the patient's eligibility for the study was determined according to the inclusion and exclusion criteria described in Section 8.4.2. All blood samples for efficacy and pharmacokinetic assessments were to be obtained in the morning prior to dosing with study drug unless otherwise indicated. After the first injection of study drug on Day 0, patients were to return to the study center periodically for clinical and laboratory assessments and dosing with study drug according to the schedule presented in section 8.5.

Secondary measures of efficacy included serum LH concentrations (taken at the same times as for T), measures of bone pain, urinary pain and symptoms, and WHO performance status scores.

8.5. Efficacy Assesments

Primary efficacy assessments

The primary efficacy variable for this study was serum T concentration. These concentrations were sampled at Baseline (Day 0) before injection of study drug. Post-injection T and LH concentrations were determined at Day 0 (prior to dosing, and 4 and 8 hours post dosing), Days 1, 2, 3, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and Month 3 (Day 84), (prior to dosing, and 4 and 8 hours post dosing), Day 85, 87, 91, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, and Month 6 (Day 168).

8.5.2. Other efficacy assessments

8.5.2.1. Clinical laboratory assessments

Clinical laboratory measurements, including hematology, coagulation, and serum chemistry, were assessed for safety at Screening, Baseline, Day 1, 3, 7, 14, 28, 42, 56, 63, 70, 77, Month 3 (Day 84), 85, 105, 112, 133, 140, 161 and Month 6 (Day 168).

8.5.2.2. WHO/ECOG Performance status assessments

WHO/ECOG Performance status was assessed at Screening, Baseline, and along with the T and LH measurement schedule.

8.5.2.3. Symptomatic assessments

Patient questionnaires, including assessments of bone pain and urinary signs and symptoms, were collected at Baseline, and along with the T and LH measurement schedule.

8.5.2.5Pharmacokinetic assessments

I. 8.5.2.5.1 Special pharmacokinetic and pharmacodynamic assessments

Blood samples for pharmacokinetic analysis were taken from the first twenty five patients enrolled and serum leuprolide acetate levels were measured at the same time points measured for T and LH.

II. 8.5.2.5.2 Laboratory procedures for efficacy and pharmacokinetic assessments

To standardize clinical laboratory measurements, samples obtained from the patients at the investigational center were prepared and shipped to the central clinical laboratory for analyses.

Serum testosterone levels were measured in samples from this study by a radioimmunoassay (RIA) method. Testosterone was first extracted from serum with hexane/ethyl acetate, and then further purified with ——— ——— with ethanol in hexane. The purification had a recovery of approximately — %. Following purification, samples were run in duplicate using an RIA procedure with testosterone calibration standards between —and — pg. The assay has a limit of quantitation (LOQ) of ng/dL, using a serum sample size of — mL. The assay accuracy (% bias) ranged from - — %. Assay precision was within —% for intra-assay, inter-assay, and long-term (24-month) inter-assay determinations. Assay selectivity was determined for 22 naturally occurring and therapeutic steroids. Of these, only dihydrotestosterone had significant (22%) cross-reactivity in the assay.

When duplicate samples demonstrated differing testosterone levels beyond the stablished range of variability of the assay, the samples were re-run to determine the appropriate testosterone level for that sample timepoint.

Serum leuprolide was determined using a validated assay. This method involved ——— of leuprolide from human serum. The extract was further purified by ——— which separated leuprolide from potential cross-reacting compounds. Analysis for leuprolide was by radioimmunoassay. This method was validated with a minimum quantifiable level of ——pg/mL for leuprolide.

Medical officer's comment:

All of these assays are commercially available procedures, verified and monitored by a standard laboratory. Other supportive efficacy assessments are also considered adequate.

8.6 Efficacy results
8.6.1 Demographics
Age, Race , Height and Weight :

The mean age of the 117 patients enrolled in the study was 73.1 years (8.0), ranging from 46–85 years. The largest majority (44.4%) of patients were 70-79 years of age, while 27% were in the 80-85 age group, 23% were in the 60-69 age group, 5% were in the 50- 59 age group, and 1% were in the 40-49 age group. Eighty percent (80%) of patients were white, 11% were black, 6% were Hispanic, and 3% were Asian. The mean height of patients was 68.2 (2.8) inches (5'8") and ranged from 55 to 74 inches. The mean weight of patients was 186 (34.8) pounds, ranging from 130-296 pounds. Demographics were similar across centers.

Medical Conditions:

Seventy-two percent (84/117) of patients enrolled in the study reported a history of urinary/renal conditions. In addition, 69% (81/117) reported a history of musculoskeletal conditions, 62% (73/117) reported a history of gastrointestinal and head, eyes, ears, nose, and throat (HEENT) conditions, 57% (67/117) reported endocrine or metabolic conditions, 44% (52/117) reported allergies, 40% (47/117) reported reproductive conditions, 36% (42/117) reported psychiatric or neurotic conditions, 32% (37/117) reported dermatologic or connective tissue conditions, 23% (27/117) reported respiratory conditions, 17% (20/117) reported hematopoietic or lymphatic conditions, 13% (15/117) reported infectious diseases, and 11% (13/117) reported hepatic conditions. Less than 10% of patients reported conditions in the following systems listed in descending order of frequency: drug/alcohol abuse and general body. Results appeared consistent across centers.

8.6.2. Disposition of patients

Of the 117 patients enrolled, 111 (95%) completed the study and received all SC injections of study drug .

One patient (#3401) was withdrawn due to an adverse event unrelated to study drug on Day 155 Seventy-six (76) days following his second injection he was admitted to the hospital complaining of difficulty with breathing on exertion, orthopnea and paroxysmal nocturnal dyspnea. He was diagnosed with mild congestive heart failure secondary to severe chronic obstructive pulmonary disease. His T levels prior to withdrawal was <3 ng/dL on day 154.

Two patients voluntarily withdrew consent from the study. Patient #0102 was withdrawn due to transportation problems on Day 71 after his first injection. His base line T was 191ng/dL , he achieved castrate T levels on day 7(T=49 ng/dL) and on day 63 his T level was 11 ng/dL.
Patient #2002 moved from the study center area and was withdrawn from the study on Day 134 after his second injection. His baseline T levels were 351 ng/dL. He achieved castrate T levels on day 21 (T =23 ng/dL) . He maintained T suppression and on day 126 his T was 3.1 ng/dL.
Two patients (#2402, #2602) were withdrawn due to progression of disease. Patient #2402 experienced an increase in bone pain on Day 14 following his Baseline study injection. Testosterone levels were 350 ng/dL at Baseline and peaked at 600 ng/dL at Day 3. By Day 7 these values had returned to Baseline levels (362 ng/dL) and by Day 14 were well below Baseline levels (99 ng/dL). At Day 21 levels were well below medical castrate (23 ng/dL) and remained below castrate until the patient was withdrawn (Day 64), before he received his second injection. The investigator determined that the patient had experienced metastatic progression of his prostate cancer to the right hip and received radiation therapy for it. Patient #2602, shortly after his first injection, sought a second opinion from [redacted] regarding his prostate cancer. At that time the cancer was found to be locally recurrent and [redacted] recommended he have radiotherapy. The investigator withdrew him from the study on Day 78, classifying the cause as disease progression. He received one study injection. His last T recorded on day 70 was 7.3 ng/dL.
Patient #1801 was withdrawn from the study because he did not receive a full dose of study drug at the first injection. His baseline T was 515 ng/dL, it peaked to 934 ng/dL on day 2 and reached nadir of 92 ng/dL on day 42 to go back again on day 70 to 555 ng/dL. He was withdrawn from the study on Day 74. He received one partial study injection. See Table 1.

Table 1: Testosterone levels in 6 withdrawn Patients

Patient #	Withdrawn (Day)	Reason	T levels Prior To withdrawal (ng/dL) BL	<50(Day)	Mid value (D)	End Value(D)
3401	155	AE	676(bl)	28(D21)	12(84)	<3 (D154)
0102	71	Voluntary	191(bl)	49(D7)		11 (D63)
2002	134	Voluntary	351(bl)	23(D21)		3.1 (D126)
2402	64	Disease Progression	359(bl)	23(D21)		17 (D56)
2602	78	Disease Progression	223(bl)	29(D21)		7.3 (D70)
1801	74	In sufficient Dose	515(bl)	92(D42)	346(D63)	555 (D70)

Medical Officers Comments:
This study was reported to complete 111 evaluable patients of the 117 enrolled . Of the six patients not evaluable, 4 patients recieved one injection only . These patients were withdrawn on Days 71(#0102), 64 (# 2402), 78 (2602) and 74 (# 1801). Of these Patient # 1801 did not suppress his T levels and therefore

switched to Lupron. The other patients showed T concentrations below castrate levels prior to withdrawal.
The other 2 patients were withdrawn following two injections on Days 155 (#3401) and 134 (#2002). These 2 patients also showed T concentrations below castrate levels prior to withdrawal. These withdrawals did not significantly impact the approvability of the product.

8.6.3. Major protocol violations
There were 292 protocol deviations attributable to 99 patients during the study (Table 2. below.). The majority of protocol deviations (74%) were due to the timing of patients visits being outside visit windows.

Table 2:**Summary of Protocol Deviations**

Deviation	**Frequency**
Out of window visit	218/292 (74%)
Abnormal laboratory value	22/292 (8%)
Abnormal laboratory value	46/292 (16%)
Prohibited Medication	3/292 (1%)
Other admission failure	3/292 (1%)

Medical officer's comment:
Although there were a notable number of protocol deviations, these did not significantly impact the approvability of the product.

Primary efficacy variables

8.6.4 Achievement of castrate T levels on Day 28

For the intent-to-treat population, 115 of the 117 patients (98%) had achieved castrate T suppression by Month 1(Day 28). By Day 35, 99% (116/117) of patients had attained castrate suppression, the only exception being a single patient who received less than half of his scheduled dose at Baseline. This patient (#1801) never achieved castrate suppression level and was withdrawn from the study at Day 74. A very high proportion of patients (84% at Day 28, 92% at Day 42) achieved the more stringent criteria of T suppression using a