CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-343

Medical Review(s)

NDA 21-343

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

MEDICAL OFFICER REVIEW OF NDA 21-343

SPONSOR:	Atrix Laboratories, Inc. 2579 Midpoint Drive Fort Collins, CO 80525
DRUG PRODUCT:	Eligard™
DOSE:	7.5 MG
ROUTE OF ADMINISTRATION:	Subcutaneous Injection
PHARMACOLOGICAL CLASS:	Gonadotropic Releasing Hormone(GnRH) Agonist
INDICATION:	Palliative Treatment of Advanced Carcinoma of the Prostate.
DATES:	
SUBMITTED:	March22,2001
CDER STAMP:	March26,2001
PDUFA GOAL:	Jan.2002
RELATED IND's:	
MEDICAL OFFICER	Ashok Batra MD
DATE REVIEW COMPLETED:	January 23, 2002

CLINICAL REVIEW

NDA-21343

TABLE OF CONTENTS

TABLE OF TABLES

Executive Summary

1. Recommendations

1.1. Approvability

This reviewer recommends that ELIGARD™ 7.5 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 information 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. Medical therapies directed towards this goal achieve castrate T levels in about one month's time.

In support of their claim, the sponsor conducted one pivotal trial (Protocol AGL 9904) and two smaller supportive trials. AGL9904 enrolled 120 patients. The results from this trial demonstrated that after receiving six doses of ELIGARD™ 7.5 mg (given every 28 days), 112 of 119 (94%) patients achieved testosterone suppression of ≤50 ng/dL by Study Day 28 (1 patient withdrew on Day 14). By Study Day 42, all 118 patients remaining in the study had achieved this measure. In addition, all of those patients who achieved castrate testosterone suppression (≤50 ng/dL) remained suppressed throughout the duration of the study. Thus, there were no castrate suppression "breakthroughs" (defined as a testosterone concentration of >50 ng/dL) after achieving suppression. The median time to castrate suppression was 21 days, and the mean time to castrate suppression was 21.6 days.

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 21-343, 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 was asked to make some labeling changes to accurately describe the product and an acceptable changed PI was submitted on January 16,2002. (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 7.5 mg) was manufactured by Atrix Laboratories. The lot numbers used in the pivotal phase 3 trial (AGL9904) were 1144 and 1199. The injection volume was 0.25 milliliters. ELIGARD is designed to deliver 7.5 mg of leuprolide acetate over a one-month therapeutic period.

ELIGARD 7.5 mg 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 % w/w Poly(DL-lactide-co-glycolide) (PLGH) and % w/w *N*-methyl-2-pyrrolidone (NMP). The other syringe contained mg leuprolide acetate. The syringes were joined via the connections on the syringes, and the formulation was passed between syringes until a homogenous mixture was obtained.

2.1.2. Brief overview of the clinical trials conducted

The sponsor submitted data from 3 clinical studies in support of NDA 21-343.

In study AGQ 9706, the sponsor investigated the safety and feasibility of the Atrix delivery system itself by comparing it (n=8) with saline (n=4) in a control population.

That preliminary Phase 1 study was followed by a single Phase 2 study (AGL 9802) in 8 orchiectimized males. The results of AGL 9802 revealed that after an initial "burst phase" characterized by high (>20 ng/mL) serum leuprolide concentrations, the drug product formulation maintained relatively constant mean serum leuprolide levels (0.2–2 ng/mL) over the majority of each dosing interval. The bioavailability of ELIGARD™ 7.5 mg was greater than 90%.

Finally, the sponsor conducted one pivotal Phase 3 (AGL 9904) trial in 120 prostate cancer patients. This was a six-month, two-part, sequential, open-label, fixed-dose study. All patients were males between the ages of 50-85 years and all had advanced adenocarcinoma of the prostate (CaP). Patients were not receiving hormonal therapy and were not anticipated to need hormonal, anti-androgen, radio-, chemo-, immuno-, or surgical therapy for prostate cancer during the course of the study. Of the 120 patients enrolled into the study, 117 received six once-monthly injections of study drug. Of those who did not receive all six per-protocol injections, one patient received three injections, one patient received two injections, and one patient received a single injection of study drug.

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 hormonal 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 these types of products.

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 6 dosing cycles would constitute the primary measure for success.

Therefore, the primary efficacy objectives in Study AGL 9904 (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 AGL9904 revealed that following six doses of ELIGARD™ 7.5 mg, given every 28 days, 112 of the 119 (94%) patients in the study had achieved testosterone suppression of ≤50 ng/dL by Study Day 28 (1 patient withdrew on Day 14). By Study Day 42, all 118 patients remaining in the study had achieved this measure. In addition, all of those patients who achieved castrate testosterone suppression (≤50 ng/dL) remained suppressed throughout the duration of the study. There was no castrate suppression breakthroughs (defined as a testosterone concentration of >50 ng/dL after achieving suppression) observed during the study.

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 is reflected in labeling.

The sponsor purports that a new castrate limit (20 ng/dL) has recently been advocated in the urologic community. The sponsor analyzed the results of

AGL9904 using this new cut-point and found that virtually all patients were below 20 ng/dL at Month 6. The sponsor would like this result noted in the labeling. In essence, this would provide ELIGARD with an "implied superiority claim". While the data from this NDA does confirm this finding, it is not clear to this reviewer that 20 ng/dL represents a clinically significant improvement over 50 ng/dL. Nor is clear whether similar results would be obtained for the currently approved products if such post-hoc data analysis was conducted. Therefore, this claim should not be allowed and it will be removed from the 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™ 7.5 mg is indicated in the palliative treatment of advanced prostate cancer."

2.3. Safety

2.3.1. Exposure to study drug

A total of 128 patients received one or more doses of the to-be-marketed formulation. Of these, 120 patients were in the principal safety and efficacy study, AGL 9904 and 117 of those patients received all six per-protocol doses.

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.

2.3.2. General safety findings

The drug-related adverse reactions reported in this NDA for ELIGARD 7.5 mg were comparable to those reported in the currently approved 7.5 mg leuprolide acetate package insert.

While there were frequent 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™ 7.5 mg is a novel subcutaneous depot formulation of leuprolide acetate administered at monthly intervals. It is supplied in two, separate, sterile syringes which are mixed immediately prior to administration. One syringe contains the polymer formulation, ATRIGEL® Delivery System, consisting of . .% w/w Poly(DL-lactide-co-glycolide) (PLGH) and . .% w/w *N*-methyl-2-pyrrolidone (NMP). The other syringe contained mg . . ! leuprolide acetate. The system is designed to deliver 7.5 mg of leuprolide.

2.5. Special Populations

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

2. 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.

   Nevertheless, it is clear from years of experience that very high concentrations of serum leuprolide are not associated with more frequent or more severe adverse reactions. Thus, this issue is not considered worrisome.

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

   In terms of safety, disturbances of "skin sensation" (e.g. local pain, swelling, redness, itching or induration) were reported in 56 whites (60.9%), six blacks (40%), and three Hispanics (23.1%). In this regard, the difference between whites and Hispanics was found to be statistically significant. Overall, however, no significant racial differences were observed in safety.

Clinical Review

3. Introduction and background

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

Drug product:	Eligard™
Drug substance	Leuprolide acetate
Dose:	7.5 mg
Dosing Regimen	Administered once monthly (every 28 days)
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 and the second most frequent cause of death from cancer in men over 50 years of age. Since approximately 80% of prostate cancers are dependent on circulating androgens and are responsive to hormone manipulation, the mainstay of therapy 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.

ELIGARD 7.5 mg is a novel subcutaneous depot formulation of leuprolide acetate administered at 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 associated with the use of leuprolide in the treatment of prostate cancer are primarily those directly related to the physiological response to

diminished circulating testosterone. These 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"). Estimates of the proportion of patients experiencing flare range from 10%-20%. Overall, 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. 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 selected the 7.5 mg dose of leuprolide for the following reasons:

a. Based on the results from dose-ranging trials previously conducted in the original leuprolide development, there appeared to be a modest trend in objective response favoring a 7.5mg dose over a 3.75mg dose.
b. The currently approved one-month 7.5mg leuprolide acetate depot formulation is widely considered safe and effective.
c. Nonclinical pharmacology and toxicology studies conducted to characterize ELIGARD™ 7.5 mg suggested that the product was an effective LH-RH agonist with a favorable safety profile.

Atrix proposed to administer the dose via the subcutaneous route, using their proprietary ATRIGEL® Delivery System.

The following milestones in drug development are relevant:

1. An **IND** was filed on December 2, 1998. In the opening U.S. IND study, ELIGARD™ 7.5 mg was evaluated in a phase 1 pharmacokinetics study (AGL9802) in 8 orchiectomized CaP patients. This study demonstrated that the treatment with ELIGARD™ 7.5 mg resulted in sustained release of active drug over the proposed one-month dosing interval.

2. Essential elements of Phase 3 study design were discussed with the Division at the **End-of-Phase 2 meeting** held on July 30, 1999.

   The Division agreed that only a single Phase 3 study was required. The Division agreed that the study would be designed to include a minimum of 100 efficacy evaluable patients with Jewett's Stage C or D prostate cancer. To be certain this level was achieved, 120 patients would be enrolled in the study. Twenty-four (24) centers across United States would participate in this pivotal trial. Testosterone suppression would be the primary efficacy endpoint, with medical castration defined as testosterone concentrations of ≤ 50 ng/dl. The study would be divided into two sections, Parts I and II.

   Approximately 36 patients would be enrolled into Part I. These 36 patients would receive two monthly doses of ELIAGRD 7.5 mg. Twenty of these patients (denoted Group A) would have careful post-dosing measurements of serum leuprolide acetate levels as part of a pre-defined pharmacokinetic (pK) analysis. Once all 36 patients in Part I had all completed two injections (Day 42), then serum leuprolide acetate, T, LH, prostate specific antigen (PSA), fractionated alkaline phosphatase, and safety data (including adverse experiences and safety labs) would be collated and summarized. During this analysis and summarization, Part I patients would continue to be treated monthly with ELIGARD™ 7.5 mg and monitored per the protocol.

   The safety and efficacy data from Part I patients would be carefully reviewed before Part II of the study would begin. Following this review, an additional 84 patients would be enrolled. Both Part I and Part II patients would be followed for a total of six months.

3. The preliminary Phase 3 study results and proposed NDA submission were discussed at the **Pre-NDA meeting** held with the FDA on October 3, 2000. Key clinical issues regarding the primary efficacy endpoint and local tolerability were discussed and are listed below:

   The <u>primary efficacy endpoint</u> would be composed of three elements:

   a. Proportion of patients who have serum testosterone ≤ 50 ng/dL at Day 28 (Week 4)

b. Proportion of patients whose serum testosterone level is suppressed at Day 28 and who remain suppressed throughout the study.

c. Proportion of patients/instances in which an acute rise in serum testosterone is observed following repeat dosing of patients who otherwise appear to have adequate suppression prior to next dosing.

Local tolerance data would be compiled and submitted for review.

3.4. Other relevant information

ELIGARD™ 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 the primary reviewer (Dr. K.Raheja), there are no pharmtox findings that would preclude the approval of the 1 month formulation of ELIAGARD™ for the proposed indication of prostate cancer.

4.2. Clinical pharmacology and biopharmacoutics review

According the primary reviewer (Dr. M. Kim), there are no biopharmaceutical findings that would preclude the approval of the 1 month formulation of ELIAGRD™ for the proposed indication of prostate cancer.

4.3. Chemistry review

According the primary chemistry reviewer (Dr. S. De), all the chemistry issues were resolved at the time of the completion of this review.

5. Human pharmacokinetics and pharmacodynamics

5.1. Pharmacokinetics

5.1.1. Absorption

In a multiple dose study (AGL 9904), mean serum leuprolide concentrations following the initial SC injection rose to 25.3 ng/mL (C_{max}) at 4 to 8 hours after injection. A transient rapid release of leuprolide is probably due to leaching from the microsphere surfaces at the injection site. Subsequently, mean leuprolide concentrations decreased rapidly. Thereafter the decline in serum concentrations

occurred more gradually to reach plateau levels and remained relatively constant (0.28 – 1.67 ng/mL). There was no evidence of significant leuprolide accumulation during repeated dosing. Mean serum leuprolide levels, measured 28 days after each of 3 monthly subcutaneous doses, did not differ significantly (0.417 ± 0.389, 0.445 ± 0.199, 0.453 ± 0.192 ng/mL, respectively).

5.1.2. Distribution

There were no specific investigations conducted by this sponsor relevant to distribution of leuprolide. However, the literature reported mean Vd_{ss} of leuprolide 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

Again, there were no specific drug metabolism or excretion studies conducted by this sponsor for this product. However, the literature reports that in animals, leuprolide was metabolized to four major metabolites (M-I, M-II, M-III, and M-IV). Within 1 hour of IM injection of leuprolide 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 second leuprolide recipient, the concentration of this metabolite in the urine reached a peak of 4.97 µg/L within 2 days, and could still be detected at 1.74 ng/mL after 29 days (Ueno & Matsuo. J Chromatograph 1991;566:57-66). In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 8.34 L/h, with a terminal elimination $t_{1/2}$ of 2.9 ± 0.5 hours based on a two compartment model (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 as shown in graphically displayed data from Study AGL9904 (see Figure 1 below).

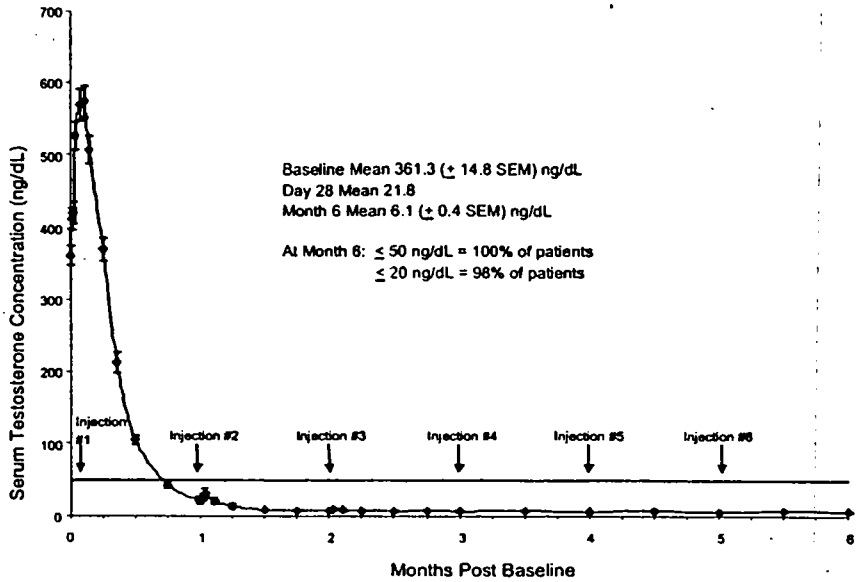

Figure 1. Pharmacodynamic response to ELIGARD in Study AGL9904.

Medical officer's comment:
ELIGARD suppressed serum total testosterone levels by D28 in over 90% of patients in Study AGL9904. The pK/pD profile is adequate for the indication sought.

6. Description of clinical data and sources

Complete study reports for three controlled clinical trials were submitted in NDA 21-343. These reports were:

a. AGL9802 (pK study in 8 orchiectomized patients)
b. AGL9904 (single pivotal Phase 3 trial)
c. AGQ9706 (delivery system versus saline)

The main focus of this review centers on AGL9802 and AGL9904.

7. Clinical review methods

7.1 How the review was conducted

The review conducted by this medical officer focused on Study AGL9904 for was reviewed for the assessment of local tolerability.

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.

The sponsor also provided safety updates that were reviewed.

7.2. Overview of materials consulted in review

7.2.1. Submissions to NDA 21-343

- Original NDA 21-343; Submission date of March 23, 2001; Volumes 1.1 - 1.55
- Electronic case report forms (CRFs) and electronic case report tabulations (CRTs)
- Serial submission to NDA 21-343 (#003 and #004 - Safety updates)

7.2.2. Other materials reviewed

- Annual Report for IND [redacted] (Serial #018)
- Annual Report for IND [redacted] (Serial #006 and 007) – 4-month formulation
- Preliminary filing review for NDA [redacted] – 3-month formulation
- All correspondence submitted to IND [redacted] since submission of the annual report.
- All minutes of regulatory meetings and telephone conferences with sponsor that were located in hard-copy or electronic Division files for INDs [redacted]
- 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 sites

Two study centers that participated in the pivotal clinical trial (AGL 9904) were audited by the Division of Scientific Investigation (DSI) in the fall of 2001. A DSI audit report was submitted on November 28, 2002 describing the inspection

results from those two sites: Drs. Chu and Snoy. 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 these two clinical sites supports the validity of the data submitted in NDA 21-343.

7.3.2 Site monitoring

According to the Final Report for AGL –9904, 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 thoroughly reviewed the completed CRFs at the study center and sent them to Atrix. Receipt of the CRFs was documented.

Data entry was initiated following the validation of data entry screens developed specifically for the protocol. Accuracy of data entry into the system was audited by an independent contractor.

A total of 20 patients were randomly selected, and the case reports for each were compared to data in printouts generated from the database. Discrepancy logs were used to verify changes to the case report forms and/or database content. This audit confirmed the accurate entry of data into the database

Medical officer's comment:
The monitoring process, data entry, and auditing procedures are adequate.

7.3.3 Central laboratories

7.3.3.1

At , the database was constantly monitored to insure that the specifications of the protocol were met. Any modifications or amendments made to the database post launch were validated in a similar manner to the pre-study validation. Control Departments conducted periodic internal audits of ongoing studies as well as hosting external audits by independent agencies and sponsors. An accreditation certificate for was submitted in the NDA.

7.3.3.2 r for Clinical Trials

r was utilized for T and LH analyses. The laboratory has an extensive 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 r and ... 1 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 21-343 appear to be acceptable to assess suppression of serum testosterone to values of 50ng/ml.

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 endpoints

The primary efficacy assessment measure in the principal Phase III Study, AGL 9904, 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 timepoint 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 timepoints. 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 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 three 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 (AGL9904)

8.4.1. Design

This was a multi-center (24), two-part, sequential, open-label, fixed-dose investigation of six monthly dosages of ELIGARD ™ 7.5 mg administered to patients with Jewett's Stage C1, C2, D1, or D2 adenocarcinoma of the prostate (CaP).

A total of 120 patients (36 patients in Part I and 84 patients in Part II) received a single, subcutaneous injection of ELIGARD™ 7.5 mg initially at baseline and then monthly (28 days) for five months. All patients were male, between 50 and 85 years of age.

The study was divided into two sections, Parts I and II. During Part I, 36 patients were enrolled, given two monthly doses of ELIAGARD™ 7.5 mg, and evaluated. Twenty of the patients in Part I (denoted Group A) had serum leuprolide acetate levels measured for pharmacokinetic (PK) analysis.

Once the 36 patients in Part I had completed two injections (Day 42), serum leuprolide acetate, T, LH, prostate specific antigen (PSA), fractionated alkaline phosphatase, and safety data (including adverse experiences and safety labs) were collated and summarized. During this analysis and summarization, Part I patients continued to be treated monthly with ELIGARD™ 7.5 mg and monitored per the protocol. The safety and efficacy data from Part I patients were carefully reviewed before Part II of the study began. Following this review an additional 84 patients were enrolled. Both Part I and Part II patients were followed for a total of six months.

For all patients, the Screening Visit took place within 5-16 days before initial ELIGARD™ 7.5 mg administration. Patients who met all eligibility criteria were given a patient number on Day 0 (Baseline) prior to treatment and were enrolled into the study. On Day 0, patients received a single dose of ELIGARD™ 7.5 mg between 6:00 a.m. and 10:00 a.m. Blood samples for various hormone determinations (and PK determinations for Group A) were collected at specific time points. Patients returned to the investigational center at daily, weekly, semi-monthly, and monthly intervals for assessment and blood sampling. At Months 1, 2, 3, 4, and 5, patients were given another dose of ELIGARD™ 7.5 mg. Final assessment and evaluation took place at Month 6. During participation in the study, patients were closely monitored by physical examinations, vital signs, clinical laboratory values, and adverse events.

8.4.2. Patient Selection Criteria

Patients with prostate cancer who might benefit from hormonal therapy (i.e., reduction in serum androgen levels) were considered for enrollment into Study AGL 9904 if they met the following criteria:

8.4.2.1. Inclusion criteria

1. Patients read and signed the informed consent agreement. If the patient required someone to read and/or interpret any or all of the informed consent, a statement of this fact was included. The signing of the informed consent was witnessed by a staff member at each individual center.
2. Patients were male between 50-85 years of age, inclusive.
3. Patients were not currently hospitalized.
4. Patients had histologically or cytologically proven adenocarcinoma of the prostate.
5. Patients had Jewett's Stage C1, C2, D1, or D2 adenocarcinoma of the prostate
6. 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 at Screening. Adequate was defined by a serum creatinine ≤1.6 times the ULN (upper limit of normal) for the clinical laboratory.
10. Patients had 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.
11. Patients were willing to complete all phases and all procedures of the study.

8.4.2.2. Exclusion criteria

1. Patients with evidence of brain metastases, in the opinion of the investigator, taking into account medical history, clinical observations, and symptoms. (Rationale: To minimize possibility of serious acute flare reactions that would necessitate concomitant administration of other drugs.)
2. Patients with evidence of spinal cord compression, in the opinion of the Investigator, taking into account medical history, clinical observations, and symptoms. (Rationale: To minimize possibility of serious acute flare reactions that would necessitate concomitant administration of other drugs.)

3. Patients with evidence of urinary tract obstruction, where a flare in disease could put patient at significant risk in the opinion of the Investigator, taking into account medical history, clinical observations, and symptoms. (Rationale: To minimize possibility of serious acute flare reactions that would necessitate concomitant administration of other drugs.
4. Patients with serum testosterone levels below 150 ng/dL at screening. (Rationale: To ensure that all patients had relatively normal testosterone for purposes of evaluating the product's efficacy in suppressing serum T.)
5. Certain prostate cancer therapies within two months of Baseline: immunotherapy (e.g. antibody therapies, tumor-vaccines), external radiotherapy, brachytherapy, chemotherapy, or biological response modifiers (e.g. cytokines). (Rationale: These therapies could have altered the patient's androgenic hormonal response and adverse reactions profile.
6. Patients who had undergone any prostatic surgery (e.g. transurethral resection of the prostate (TURP), radical prostatectomy) within two weeks of Baseline. (Rationale: Same as previous.)
7. Patients under the effects of any other hormonal therapy, including anti-androgens, (e.g. Lupron®, Zoladex®, Megace®, etc.) for treatment of prostate cancer within three months of Baseline. (Rationale: These therapies would have altered their androgenic hormonal response.)
8. Patients who had received ELIGARD™ 7.5 mg previously. (Rationale: To prevent previously entered patients from being re-entered.)
9. Patients who had an orchiectomy, adrenalectomy, or hypophysectomy. (Rationale: These surgeries would have altered their androgenic hormonal response.)
10. Patients who had used any investigational drug, biologic, or device within five half-lives of its physiological action or three months, whichever is longer, before Baseline. (Rationale: To prevent adverse effects of another drug being attributed to study drug and to prevent potential interactions.)
11. Patients who had received finasteride (i.e., Proscar® or Propecia®) within three months of Baseline. (Rationale: This alters PSA levels and also alters prostate tissue.)
12. Patients anticipated to need concomitant hormonal, anti-androgen, radio-, chemo-, immuno-, or surgical therapy for prostate cancer throughout the duration of the study. (Rationale: To minimize the number of patients receiving concomitant therapy during the study that could have made it difficult to assess efficacy or safety of the study drug.)
13. Patients who had used over-the-counter or alternative medical therapies which had 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 or lower limits of normal (ULN, LLN) for the clinical laboratory at Screening. (Rationale: To render potential study drug related laboratory abnormalities easier to observe.)
15. Patients who had co-existent malignancy or a history of malignancy, with the exception of basal and/or squamous cell carcinomas of the skin. Patients with basal and/or squamous cell carcinomas were discussed with Atrix on a case-by-case basis. (Rationale: To decrease possibility of disease or associated therapy-caused adverse effects being attributed to study drug therapy.
16. Patients who had uncontrolled congestive heart failure within six months before Baseline. (Rationale: To decrease possibility of disease or associated therapy-caused adverse effects being attributed to study drug therapy.)
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. (Rationale: To decrease possibility of disease or associated therapy-caused adverse effects being attributed to study drug therapy.)
18. Patients who had significant symptomatic cardiovascular disease within six months of Baseline. (Rationale: To decrease possibility of disease or associated therapy-caused adverse effects being attributed to study drug therapy.)
19. Patients who had experienced venous thrombosis within six months of Baseline. (Rationale: Influencing testosterone levels may be associated with increased likelihood of deep venous thrombosis.)
20. Patients who had experienced resting uncontrolled hypertension (≥160/100 mmHg) or symptomatic hypotension within three months before Baseline. (Rationale: To decrease possibility of disease or associated therapy-caused adverse effects being attributed to study drug therapy.)
21. Patients who had insulin-dependent diabetes mellitus. (Rationale: To minimize injection site reactions being incorrectly attributed to study drug due to the fact that these patients often use injection sites on abdomen where the study drug would be administered.)
22. Patients who had a history of drug and/or alcohol abuse within six months of Baseline. (Rationale: These patients were likely to have numerous medical abnormalities and were unlikely to comply with protocol.)
23. Patients who had other serious intercurrent illness(es) or disease(s) (e.g., hematological, renal, hepatic, respiratory, endocrine, psychiatric) that might have interfered with, or put them at additional risk for, their ability to receive the treatment outlined in the protocol. (Rationale: To decrease possibility of disease or associated therapy-caused adverse effects being attributed to study drug therapy.)

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) who were not receiving a stable dose for three months before Baseline. Patients who were receiving warfarin-derivative anticoagulants who did not have an International Normalized Ratio (INR) in the therapeutic range for the clinical indication for which the anticoagulant had been prescribed. (Rationale: To decrease possibility of disease or associated therapy-caused adverse effects being attributed to study drug therapy.)

25. Patients who had a known hypersensitivity to GnRH, GnRH agonists, ATRISORB® Barrier product, ATRIDOX® product, or any excipients of ELIGARD™ 7.5 mg (PLGH, NMP). (Rationale: To minimize risk of hypersensitivity reaction to study drug.)

26. Patients who had a history of the following prior to the study:
    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 (including the rationale provided for each patient selection criterion), and the laboratory measurements are adequate and acceptable.

8.4.3.Study drug and dose selection

Based on the previous marketing experience with 7.5 mg leuprolide in the palliation of advanced carcinoma of prostate, toxicokinetics with ELIGARD, and historical dose-ranging data for leuprolide, a 7.5 mg dose of leuprolide was selected and developed.

All patients were intended to receive six, identical, monthly, subcutaneous, fixed-dose injections of [redacted] 7.5 mg 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. Areas with brawny or fibrous subcutaneous tissue or locations which could be

rubbed or placed under pressure (e.g., with a belt or clothing waistband) were to be avoided.

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 study drug was administered as a sucutaneous injection by a trained member of the staff at each investigational center. In this manner, patient compliance was ensured. When any deviation from study drug administration occurred, Atrix was notified and the event documented in the file. Two patients received less than a full dose of study drug during an injection. Patient #402 received an approximate 50% dose at his Day 84 injection. Patient #1105 also received an approximate 50% dose at Day 28. This had no noticeable impact on efficacy results.

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 8.2.2. After the first injection of study drug on Day 1, 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 Table 1 below.

8.5. Efficacy Assesments

8.5.1. Primary efficacy assessments

All blood samples for efficacy and pharmacokinetic assessments were to be obtained in the morning prior to dosing with study drug unless otherwise indicated.

Serum samples for total T and LH were to be obtained at screening, and on Study Day 0: Hours 4 and 8, Days 1, 2, 3, 4, 7, 10, 14, 21, 28, Day 28: Hour 8, Days 29,

31, 35, 42, 49, 56, 57, 59, 63, 70, 77, 84, 98, Month 4, Week 18, Month 5, Week 22, and Month 6.

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 all visits through Day 14, and then at Days 28, 42, 56, 70, 84, Month 4, Week 18, and Month 6 for all patients.

8.5.2.2. WHO/ECOG Performance status assessments

WHO/ECOG Performance status was assessed at Screening, Baseline, and Days 28, 56, 84, and Months 4, 5, and 6.

8.5.2.3. Symptomatic assessments

Patient questionnaires, including assessments of bone pain and urinary signs and symptoms, were collected at Baseline, Days 1, 2, 3, 4, 7, 10, 14, 28, 56, 77, 84, and Months 4, 5, and 6.

8.5.2.4. PSA assessments

Serum samples for PSA and total acid phosphatase were collected at Screening, Baseline, and Days 14, 28, 42, 56, 70, 84, and Months 4, 5, and 6.

Table 1: Study AGL9904 : Procedures Protocol (INCORPORATING AMENDMENT NO. 1)

	Scr. (5-16 days ↔)	BL (0)	D1	D3	D7 (w1)	D14 (w2)	D21 (w3)	D28 (w4)	D31, 35(w5)	D42 (w6)	D49 (w7)	D56 (w8)	D59, 63(w9)	D70 (w10)	D77	D84 (w12)	M4 (w16)	M5 (w20)	M6 (w24)
Informed consent	X																		
Admission criteria	X																		
Demographics	X																		
Medical history	X																		
Vital signs	X	X			X	X		X				X				X	X	X	X
Physical exam	X															X			X
Height/weight[1]	X	X				X		X				X				X	X	X	X
Pt. Assessments[2]		X	X	X	X	X		X				X			X	X	X	X	X
Performance Status	X	X						X				X				X	X	X	X
Clinical lab[3]/urinalysis[4]	X	X	X	X	X	X		X		X		X		X		X	X	X	X
Testosterone/LH	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry[5]	X	X				X		X		X		X		X		X	X	X	X
Serum leuprolide[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Serum storage	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Reserve prev. injection site								X	X[7]			X	X			X	X	X	X
Administer Eligard 45 mg[8]		X						X				X				X	X	X	
Adverse events/illness		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Height measured at Screening only.
[2] Patient assessments include bone pain and urinary signs and symptoms.
[3] Clinical labs include hematology, coagulation, serum chemistry.
[4] On treatment days, blood and/or urine samples will be collected prior to dosing.
[5] Clinical chemistry includes PSA and total acid phosphatase.
[6] For Group A patients only.
[7] Days 31, 59.
[8] Treatment must be administered between 6-10 a.m. for visits prior to Day 56.

8.5.2.5Pharmacokinetic assessments

I. 8.5.2.5.1 Special pharmacokinetic and pharmacodynamic assessments

Blood samples for pharmacokinetic analysis (serum leuprolide acetate quantitation) were taken at Baseline (Day 0), Hours 4 and 8, Days 1, 2, 3, 4, 7, 10, 14, 21, 28, Day 28: Hour 8, Days 29, 31, 35, 42, 49, 56, 57, 59, 63, 70, 77, and 84 for Group A patients only (N=20).

Blood samples for evaluation of the efficacy variables T and LH were also drawn at each visit for these patients.

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 [redacted] elution with ethanol in hexane. The purification had a recovery of approximately 80%. Following purification, samples were run in duplicate using an RIA procedure with testosterone calibration standards between 5 and 200 pg. The assay has a limit of quantitation (LOQ) of [redacted] g/dL, using a serum sample size of 0.5 mL. The assay accuracy (% bias) ranged from –9% to 6.5%. Assay precision was within 15% 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 [redacted] of leuprolide from human serum. The extract was further purified by [redacted]

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

The mean age of the 120 patients enrolled in the study was 72.8 years, ranging from 52–85 years. The majority (50%) of the patients were 70-79 years of age, while 23% were in the 60-69 age group, 20% were in the 80-85 age group, and 7% percent were in the 50-59 age group.

In terms of race, seventy-seven percent (77%) of patients were white, 12% were black, and 11% were Hispanic.

The mean height of patients was 69 inches (5'9") and ranged from 62 to 75 inches. The mean weight of patients was 185 pounds, ranging from 126-287 pounds.

For age, race, height and weight, results were similar across centers.

In terms of previous medical history, 72% (86/120) of patients enrolled in the study reported a history of urinary/renal conditions. In addition, 71% (85/120) reported a history of dermatologic or connective tissue conditions, 69% (83/120) reported a history of cardiovascular conditions, 68% (82/120) reported gastrointestinal conditions, 64% (77/120) each reported HEENT (head, eyes, ears, nose, and throat) and endocrine or metabolic conditions, 51% (61/120) reported psychiatric or neurologic conditions, 45% (54/120) each reported reproductive or musculoskeletal conditions, 40% (48/120) reported allergies, 27% (32/120) reported hematopoietic or lymphatic conditions, 22% (26/120) reported respiratory conditions, 18% (21/120) reported general body conditions, and 12% (14/120) reported conditions in the infectious diseases body system. Less than 10% of patients reported conditions in the following systems listed in descending order of frequency: hepatic and drug/alcohol abuse. Results appeared consistent across centers.

8.6.2. Disposition of patients

Of the 120 patients enrolled, 117 (98%) completed the study and received all six SC injections of study drug. Three patients voluntarily withdrew. One patient (#2007) withdrew voluntary consent due to changes in the number of blood draws and subsequent reduction in his study compensation. He received three monthly injections. A second patient (#2416), who received two monthly

injections, discontinued because he moved from the area of the study center. A third patient (#2801) discontinued due to his medical insurance provider refusing to pay for study-related costs. He received a single injection and discontinued 14 days later.

8.6.3. Major protocol violations

There were 153 protocol deviations attributable to 73 patients during the study (Table 2 below). The vast majority of protocol deviations (92%) were due to the timing of patient visits being outside visit windows.

Table 2:Summary of Protocol Deviations

Deviation	Frequency
Out of window visit	141/153 (92%)
Abnormal laboratory value	10/153 (7%)
Co-existing malignancy	1/153 (<1%)
Renal condition	1/153 (<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, 112 of the 120 patients (93%) had achieved castrate testosterone suppression by Week 4 (Day 28), and by Day 35, 117 (98%) had achieved castrate suppression (Table 3). By Day 42, 99% of patients had attained castrate suppression; the only exception being a single patient who was withdrawn from the study at Day 14. Ninety-six percent (96%) of patients achieved the more stringent criteria of testosterone suppression using a threshold of ≤20 ng/dL for at least two consecutive timepoints approximately one week apart, at Day 42.

For the observed-cases population, by Week 4 (Day 28) 112 of the 119 (94%) patients remaining in the study had achieved castrate testosterone suppression, and by Day 35, 116 (98%) of the remaining 118 patients had achieved castrate suppression. The remaining two patients achieved castrate suppression by Day 42. Ninety-seven percent (97%) of patients 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 Day 42.

Table 3:Measures of Testosterone Suppression – Intent-to-Treat Population

	Study Day									
Testosterone Suppression Measure	**Day 14 N=120**	**Day 21 N=120**	**Day 28 N=120**	**Day 31 N=120**	**Day 35 N=120**	**Day 42 N=120**	**Day 56 N=120**	**Day 84 N=120**	**Month 4 N=120**	**Month 6 N=120**
(≤ 50 ng/dL)	20 (17%)	93 (78%)	112 (93%)	113 (94%)	117 (98%)	119 (99%)	119 (99%)	119 (99%)	119 (99%)	119 (99%)
Breakthrough above 50 ng/dL	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
≤ 20 ng/dL	4 (3%)	41 (34%)	91 (76%)	102 (85%)	106 (88%)	115 (96%)	114 (95%)	116 (97%)	117 (98%)	115 (96%)

Table 4: Measures of Testosterone Suppression – Observed Cases Population

Testosterone Suppression Measure	**Day 14 N=119**	**Day 21 N=119**	**Day 28 N=119**	**Day 31 N=118**	**Day 35 N=118**	**Day 42 N=118**	**Day 56 N=118**	**Day 84 N=117**	**Month 4 N=117**	**Month 6 N=117**
≤ 50 ng/dL *	20 (17%)	93 (78%)	112 (94%)	112 (95%)	116 (98%)	118 (100%)	118 (100%)	117 (100%)	117 (100%)	117 (100%)
Breakthrough above 50 ng/dL	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
≤ 20 ng/dL	4 (3%)	41 (34%)	91 (76%)	102 (86%)	106 (90%)	115 (97%)	114 (97%)	115 (98%)	116 (99%)	115 (98%)

*Between Day 28 and Day 31, one patient who had achieved castrate suppression was withdrawn and another achieved suppression. (Source: Volume 1.79, page 30)

8.6.5 Maintainence of castrate T levels

Of those patients who achieved castrate testosterone suppression (≤50 ng/dL), **all** remained suppressed throughout their participation in the study. That is, no castrate suppression breakthroughs were observed during the study. The median time to castrate suppression was 21 days, while the mean time to castrate suppression was 21.6 days.

8.6.6 Acute increases in serum T levels following repeat dosing

No acute-on-chronic responses were observed in any patients following any of the post-Baseline study injections.

Medical officer's comments:

1. A superactive GnRH agonist has the potential to increase serum testosterone concentrations on repeat dosing, even in the face of apparent

prior suppression of testosterone. Such increases may be of a source of clinical flare phenomenon. This study did not demonstrate this phenomenon.

2. The pharmacodynamic effects of ELIGARD™ effects are similar to those reported following long-term administration of other superactive GnRH agonists.

3. These efficacy results support the sponsor's contention that the pre-defined efficacy end-points were achieved.

8.6.7 Overall changes in T concentrations

The mean T concentration at Baseline was 361.3 (±14.8) ng/dL, with the middle quartile ranging from . ng/dL. Concentrations increased until a maximum mean concentration of 574.6 (±22.3) ng/dL was reached on Day 3. Concentrations then decreased to a mean of 21.8 (±4.6) ng/dL by Day 28. By Day 10, the mean concentration (212.7 ng/dL) was below the previous mean Baseline concentration and by Day 21 the mean concentration (43.31 ng/dL) was below castrate threshold. By Day 35, the mean concentration (13.4 ng/dL) was well below 20 ng/dL. In addition, a straight line interpolation of the mean data (using Days 21, 28, 35, and 42) serum testosterone decreased below 20 ng/dL by Day 33.

Concentrations remained well below the 50 ng/dL castrate threshold, but increased transiently and minimally following the second injection from 21.8 ng/dL on Day 28 to a mean concentration of 30.9 ng/dL on Day 29, and then decreased consistently throughout the following month.

Following the third leuprolide injection, mean concentrations showed an ephemeral slight increase from 7.7 ng/dL at Day 56 to 9.1 (±0.6) at Day 57, and then decreased to 6.1 (±0.4) ng/dL by Month 6.

At Month 6, testosterone concentrations ranged from <3.0-27.0 ng/dL. Results were similar across centers.

Medical officer's comment:
Review of data-sets submitted affirmed the T profile outlined above by the sponsor.

Secondary efficacy variables

8.6.8 Changes in serum LH concentrations