CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-731

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-731	Submission Date(s): 02/13/2004
	PDUFA Goal Date: 12/17/2004
Brand Name	ELIGARD® 45 mg
Generic Name	Leuprolide acetate
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB Division	DPE II
OND division	Division of Reproductive and Urology Drug Products
Sponsor	Atrix Laboratories, Inc.
Relevant IND(s)	64,779
Submission Type; Code	Standard
Formulation; Strength(s)	Injectable suspension, 45 mg
Indication	Palliative treatment of advanced prostate cancer

OCPB briefing: Optional intra-division level briefing was conducted on November 15th, 2004; Attendees: Drs'. Henry Malinowski, John Hunt, Mark Hirsch, Ameeta Parekh, Julie Bullock, and Sandhya Apparaju.

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1 Executive Summary

ELIGARD® 45mg (Atrix laboratories; NDA 21-731) is a six-month, controlled release polymeric depot injection of leuprolide acetate intended for the palliative treatment of advanced prostate cancer. Leuprolide acetate is a synthetic agonist of the gonadotropin releasing hormone (GnRH or LH-RH). The agency had previously approved the Eligard® 7.5 mg, 22.5 mg and 30 mg formulations for sustained release of leuprolide over one, three and four months, respectively for the prostate cancer indication. The sponsor conducted a pivotal clinical trial in 111 prostate cancer patients dosed with two subcutaneous ELIGARD® 45 mg injections at six month intervals. The PK/PD subgroup of this study involved 27/28 patients with intensive pharmacokinetic sampling. As intended by its design, the ELIGARD® 45mg formulation demonstrated a slow and sustained release of leuprolide acetate over a period of 6 months. There was no evidence of significant accumulation after the second injection. The testosterone suppression (to below castration) was achieved in 100% of the PK/PD patients following the first dose and was maintained at these low levels by the second dose. In vitro release testing method and release specifications have been proposed and reference has been made to previously approved ELIGARD® NDAs to support the safety and efficacy of ELIGARD® 45mg.

1.1 Recommendation

NDA 21-731 is acceptable from a clinical pharmacology and biopharmaceutics perspective.

1.2 Phase IV Commitments

None.

1.3 Summary of clinical pharmacology and biopharmaceutics findings

The sponsor has conducted a phase 3 (pivotal) clinical trial to investigate the safety, pharmacokinetics and efficacy of ELIGARD® 45 mg in prostate cancer patients. Summarized below are the important aspects of this study in the clinical pharmacology & biopharmaceutics perspective:

Pivotal clinical trial (AGL0205): A 12-month, open-label, fixed-dose phase 3 clinical trial was conducted in 111 advanced prostate cancer patients (mean age: 73.2 years) to evaluate the safety, tolerance, pharmacokinetics and endocrine efficacy of two consecutive (six months apart) doses of ELIGARD® 45 mg formulation. The PK/PD subset consisted of 27/28 patients who had intensive blood sampling for the determination of pharmacokinetics (serum leuprolide)/ pharmacodynamics (serum testosterone) following the first and second injections of the drug product.

Pharmacokinetics: ELIGARD® 45 mg injections resulted in a multiphasic leuprolide concentration versus time profiles characterized by a distinctive burst phase and a plateau phase, consistent with the release mechanism of this polymeric drug product. Following the first and second SC injections of ELIGARD® 45 mg formulation, maximum leuprolide concentrations (C_{max}) of 82.0 and 102.4 ng/ml, respectively were observed at a T_{max} of ~ 4.5 hours post-dose. After the initial "burst phase" in which drug concentrations peaked and declined at a rapid rate (0- 3 days), serum leuprolide concentrations then declined gradually and were generally maintained between 0.2-2.0 ng/ml during the "plateau" phase (days 3-168) of the release. The total systemic exposures ($AUC_{0\text{-}6\ months}$) following the first and second doses of ELIGARD® 45 mg SC injection were comparable (5922 versus 5573 ng.hr/ml, respectively) suggesting absence of leuprolide accumulation upon repeated injections.

Pharmacodynamics: Within the PD subset of 28 patients, clinical castration (Testosterone ≤50 ng/dL) was achieved in 100 % of patients by day 28. In response to leuprolide exposure, mean baseline testosterone levels in these patients rose initially to 584.5 ± 48.6 ng/dl on day 3, fell to 30.4 ± 3.0 ng/dL on day 21, and then remained between 5.8 – 11.6 ng/dL for the remainder of the study period. The second injection did not cause acute increases in serum testosterone but in fact maintained the testosterone suppression that was achieved by the first dose. Serum testosterone remained suppressed in all patients for the entire study duration (12-months).

In addition to the changes in serum testosterone concentrations, reduction in serum luteinizing hormone (LH) concentrations and serum prostate specific antigen (PSA) to the desired threshold (secondary measures of efficacy) during the two six month dosing periods provided additional evidence of the pharmacodynamic effect of ELIGARD® 45 mg formulation.

Intrinsic factors: No subpopulation analysis was conducted for ELIGARD® 45 mg. Elderly patients made up a substantial portion of the patients whose pharmacokinetics were evaluated in the pivotal clinical trial of ELIGARD® 45 mg, which included patients between the ages of 50 and 85 years. The clinical pharmacokinetic subset in the ELIGARD® 45 mg phase 3 study included patients identified as white, black, and Hispanic, who ranged in weight from 56 to 121 kg. These patients had a variety of concomitant disease states, took various medications, and exhibited a range of clinical chemistry and hematologic abnormalities during the study. ELIGARD® 45 mg provided sustained leuprolide release and sustained testosterone suppression in all pharmacokinetic subgroup patients.

2 QBR

2.1 General Attributes

2.1.1 Regulatory background

ELIGARD® (leuprolide acetate) formulations for subcutaneous injection have been previously approved by FDA for the palliative treatment of prostate cancer at three different strengths: 7.5 mg, 22.5 mg and 30 mg formulations designed to cause controlled drug release over 1 month, 3 months and 4 months, respectively. The NDA numbers for

these three previously approved formulations are 21-343, 21-379 and 21-488, respectively. The current submission for ELIGARD® 45 mg (NDA 21-731) is fourth in this series and represents the first 6-month formulation of leuprolide acetate for the prostate cancer indication.

2.1.2 Physicochemical properties

The active ingredient of ELIGARD® 45 mg is leuprolide acetate [$C_{59}H_{84}N_{16}O_{12}$•$C_2H_4O_2$; MW of free base: 1209.4]. Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LHRH). Replacement of glycine in position 6 by a D-isomer of leucine renders the GnRH analog resistant to enzymatic cleavage and greatly increases its circulating half-life (around 3.5 hours) compared to native GnRH that has a short half-life of less than 15 minutes. The analog is approximately 80-100 times more potent than the natural hormone. The chemical name of leuprolide acetate is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate with the following structural formula:

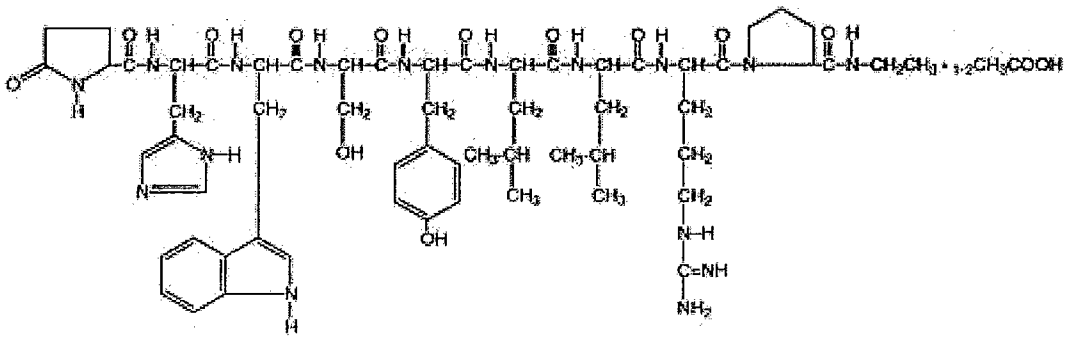


Figure 1: Leuprolide (Glu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-N-EthylAmide) acetate.

2.1.3 Formulation characteristics

ELIGARD® 45 mg is prefilled and supplied in two separate, sterile syringes whose contents are mixed immediately prior to administration. One syringe (syringe A) contains the ATRIGEL® Delivery System and the other (syringe B) contains the active drug, 45 mg leuprolide acetate (equivalent to approximately — leuprolide free base). ATRIGEL® is a biodegradable polymeric delivery system consisting — of 85:15 poly-(DL-lactide-co-glycolide) (PLG) polymer dissolved in —— of biocompatible solvent, N-methyl-2-pyrrolidone (NMP). The approximate weight of the administered formulation is 375 mg. The approximate injection volume is 0.375 mL.

—— Upon subcutaneous injection of the delivery system containing the suspended drug, the water-miscible NMP diffuses into the surrounding tissue as aqueous extracellular fluid permeates into the implant. This process leads to coagulation of the water-immiscible PLG to form an implant in situ. Rapid release of a portion of the leuprolide acetate (LA) solute during the initial diffusion of NMP is termed the burst phase (C_{max}). The remaining LA stays within the PLG implant by physical entrapment, non-polar binding forces and weak hydrogen bonding. Longer-term release (plateau phase) of this portion of the drug content from the implant occurs at a slower, steadier rate via two mechanisms: dissolution and erosion. The dissolution phase involves LA

Because of the compositional and therapeutic similarities of the four ELIGARD® formulations, clinical data on the ELIGARD® 30 mg (four-month), ELIGARD® 22.5 mg (three-month) and ELIGARD® 7.5 mg (one month) formulations that support the safe and effective use of ELIGARD® 45 mg are included in this application.

Table 1: A comparison of the ELIGARD® 45 mg to other ELIGARD® formulations.

Table 2 Comparison of ELIGARD® Formulations for SC Administration				
Formulation	**ELIGARD® 45 mg**	**ELIGARD® 30 mg**	**ELIGARD® 22.5 mg**	**ELIGARD® 7.5 mg**
NDA Reference	21-731	21-488	21-379	21-343
Frequency of Administration	Once every six months	Once every four months	Once every three months	Once per month
Active drug (Dose)	Leuprolide acetate (45 mg)	Leuprolide acetate (30 mg)	Leuprolide acetate (22.5 mg)	Leuprolide acetate (7.5 mg)
Drug loading (w/w)	[redacted]			
Polymer type (lactide/glycolide ratio)	PLG (85/15)	PLG (75/25)	PLG (75/25)	PLGH (50/50)
Polymer Mol. Wt. Acceptance Criteria	16-26 kDa	15-21 kDa	15-21 kDa	23-45 kDa
Polymer (% by wt.)	[redacted]			
NMP Solvent (% by wt.)				
Injection mass	0.375 g	0.500 g	0.375 g	0.250 g

Although the formulations have qualitatively similar components, they differ in the drug load, lactide/glycolide subunit ratio and molecular weight ranges of the polymer in order to achieve the desired rate of drug release.

2.1.4 Mechanism of action

In males, acute administration of leuprolide acetate causes an initial increase in circulating levels of luteinizing hormone (LH) due to the sensitization of the pituitary gonadotropin receptors. The LH surge leads to a transient increase in the gonadal steroids testosterone and dihydrotestosterone. However, continuous release of leuprolide acetate from a long-acting depot formulation such as ELIGARD® 45 mg results in desensitization and down regulation of the receptors, thereby decreasing the production of LH and consequently testosterone, which is reduced below castrate threshold (< 50 ng/dL). This androgen depletion can occur within two to four weeks after initiation of treatment and is reversible upon discontinuation of drug therapy.

2.1.5 Therapeutic indication

The proposed indication for ELIGARD® 45 mg is palliative treatment of advanced prostate cancer. Testosterone is necessary for prostate growth and development, and it also serves as a profound stimulator of malignant progression. Decrease in testosterone to castrate levels (< 50 ng/dL) helps in reducing pain, urinary problems and other symptoms associated with prostate cancer.

2.1.6 Proposed dose and route of administration

ELIGARD® 45 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 45 mg of leuprolide acetate at a controlled rate over a 6-month therapeutic period.

2.2 General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

- Pivotal clinical trial (AGL0205): Atrix laboratories, Inc., has conducted a pivotal phase 3 study entitled: A 12-month, open-label, fixed-dose study to evaluate the safety, tolerance, pharmacokinetics and endocrine efficacy of two doses of LA-2580 45 mg in patients with advanced prostate cancer.

  This multi-center study was conducted in 111 male patients (aged 50-86 years; mean 73.2 yrs) with Jewett stage A2, B, C, or D adenocarcinoma of the prostate. The racial distribution of these patients was as follows: White (75.7 %), Black (17.1 %), Hispanic (5.4 %), Asian (0.9 %), other (0.9 %). While all 111 patients received at least one injection, 106 patients received a SC injection of ELIGARD® 45 mg once every six months for twelve months, for a total of two injections. Pharmacodynamics was assessed in a subgroup of 28 patients and pharmacokinetic data was available and evaluated in 27 patients in this subset during each of the two six-month (168-day) dosing intervals.
- Supportive information: In addition, data from clinical pharmacokinetic studies of ELIGARD® 30 mg (4 months; NDA 21-488), ELIGARD® 22.5 mg (3 months; NDA 21-379) and ELIGARD® 7.5 mg (1 month; NDA 21-343) formulations is also provided in the submission. These formulations have been approved by FDA for use in the palliative treatment of prostate cancer. Because of compositional and therapeutic similarities of these three previously approved ELIGARD® formulations with the proposed formulation (ELIGARD® 45 mg), data from those clinical trials was referenced in the submission as supporting information.

What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

- The primary efficacy endpoint for this study was the proportion of patients in whom the serum testosterone concentration was suppressed to castrate levels by month 1 (day 28). In addition the efficacy was also assessed in terms of the cumulative proportion of patients maintaining castrate testosterone suppression through out the dosing interval (in this case 6 months).

- Because prostate cancers are dependent on circulating androgens, hormonal manipulation using GnRH analogs is the mainstay of symptomatic treatment in contrast to surgical castration that may be undesirable to many patients. Testosterone concentration ≤50 ng/dL is generally accepted as castrate level needed to achieve adequate symptomatic control. The agency accepts a 4-week time frame for the achievement of clinical castration in patients. This has been based upon the fact that most people receiving Lupron depot ("gold standard" for LHRH agonist therapy) achieve castration level by week 4 and also because 4 weeks is a reasonable amount of time for these patients to wait for purposes of treatment.

- Serum testosterone concentrations were determined at screening, and baseline (day 0) before injection of study drug. Post injection testosterone concentrations were determined at day 0: Hours 2, 4 and 8, Days 1,2, 3, 7, 14, 21, 28, 35, 42, 49, 56, 70, 84, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, 168 (month 6): Hours 0 (pre-second dose), 2, 4, 8 following the second injection, days 169, 170, 171, 175, 182, 189, 196, 203, 210, 217, 224, 238, 252, 266, 273, 280, 287, 294, 301, 308, 315, 322, 329, and 336 (month 12). Serum testosterone levels were measured employing a validated radioimmunoassay (RIA) method with a LOQ of 3 ng/dL.
- Other secondary measures of efficacy include serum luteinizing hormone (LH) concentrations (obtained at the same time points as testosterone measurements, except for the screening sample) and serum prostate specific antigen (PSA). While decrease in serum testosterone and LH demonstrate leuprolide-mediated suppression of steroidogenosis (thus confirming the drug-response relationship), PSA levels act as surrogate marker for disease progression. In addition to these surrogate endpoints, direct evidence of efficacy was derived from clinical efficacy endpoints including measures of bone pain, urinary pain and urinary signs & symptoms, and WHO performance status scores.

Are the active moieties in the serum appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Serum leuprolide (PK) and serum testosterone (PD) concentrations following SC injection of ELIGARD® 45 mg were determined using validated analytical methods in order to obtain relevant exposure-response information.

- Concentrations of leuprolide in blood serum, from a subset of patients designated as Group A (n = 27), were assessed from the samples taken at the following scheduled visits: Day 0 (prior to dosing, and hours 2, 4 and 8 post-dosing), Days 1, 2, 3, 7, 14, 21, 28, 35, 42, 49, 56, 70, 84, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, 168 (month 6: prior to dosing and hours 2, 4 and 8 post-dosing), days 169, 170, 171, 175, 182, 189, 196, 203, 210, 217, 224, 238, 252, 266, 273, 280, 287, 294, 301, 308, 315, 322, 329, and 336 (month 12).
- Leuprolide concentrations in serum were measured by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method in which samples were purified using liquid-solid phase extraction. The assay lower limit of quantitation was 50 pg/ml (0.05 ng/ml). The LC-MS/MS assay employed is specific for leuprolide. Four known metabolites of leuprolide (M-I, M-II, M-III and M-IV) were shown not to interfere with a similar LC/MS/MS assay.

- Concentration-response relationship was assessed by correlating the changes in the pharmacodynamic endpoint i.e. testosterone serum concentrations, with serum leuprolide concentrations obtained at the same time points following SC injection of ELIGARD® 45 mg.

2.2.1 Exposure-Response

What are the characteristics of the exposure-response relationships for efficacy?

- Concentration-response relationship: The serum leuprolide concentrations following the first and second doses of ELIGARD® 45 mg administered at six month interval are tabulated below, along with the corresponding changes in serum testosterone concentrations.

Table 2: Serum leuprolide and testosterone concentrations in PK/PD subgroup patients (n = 27/28) following the 1st dose of Eligard® 45 mg. Concentrations are provided as mean ± S.E.M

Time (days)	Leuprolide (ng/ml)	Testosterone (ng/dL)
0 (1st dose)	0.063 ± 0.01	367.7 ±12.98
0.08 (2 h)	66.54 ± 7.81	431.0 ±16.1
0.17 (4 h)	79.45 ± 7.10	434.2 ± 15.4
0.33 (8 h)	63.97 ± 5.11	432.3 ±14.5
1	17.85 ± 1.68	522.7 ±18.7
2	6.42 ± 0.74	588.6 ± 23.9
3	3.56 ± 0.40	569.9 ±23.7
7	1.28 ± 0.12	420.8 ± 20.7
14	0.97 ± 0.15	114.6 ± 6.79
21	0.79 ± 0.08	34.78 ±3.38
28 (M1)	1.25 ± 0.34	16.73 ±3.35
35	1.19 ±0.28	13.11 ±2.73
42	1.77 ±0.67	12.83 ±3.37
49	1.79 ± 0.39	11.94 ±2.75
56 (M2)	1.08 ± 0.23	11.54 ±2.73
70	3.64 ± 2.72	12.23 ±4.12
84 (M3)	0.85 ± 0.21	8.29 ±0.49
98	0.71 ± 0.13	8.75 ±0.49
105	0.87 ± 0.29	9.58 ±0.51
112 (M4)	0.53 ± 0.09	10.05 ±0.49
119	0.50 ± 0.08	9.83 ±0.59
126	0.53 ± 0.10	10.04 ±0.57
133	0.35 ± 0.05	9.39 ± 0.53
140 (M5)	0.31 ± 0.06	10.08 ± 0.52
147	0.23 ± 0.04	9.94 ± 0.49
154	0.19 ± 0.03	8.5 ± 0.43
161	0.19 ± 0.03	9.4 ± 0.50
168 (Month 6)	0.21 ± 0.08	10.4 ± 0.54

Table 3: Serum leuprolide and testosterone concentrations in PK/PD subgroup patients (n = 27/28) following the 2nd doses of Eligard® 45 mg. Concentrations are provided as mean ± S.E.M

Time (days)	Leuprolide (ng/ml)	Testosterone (ng/dL)
168.08 (2nd dose)	80.39 ± 11.15	8.17 ± 0.47
168.16 (4h)	98.16 ± 14.35	8.74 ± 0.48
168.33 (8h)	83.5 ± 9.73	8.2 ± 0.49
169	33.5 ± 4.78	9.94 ± 0.6
170	12.2 ± 1.45	9.68 ± 0.65
171	6.28 ±0.66	9.51 ± 0.6
175	2.09 ±0.15	8.69 ± 0.49
182	1.27 ±0.17	9.47 ± 0.51
189	0.94 ±0.14	10.37 ± 0.53
196 (M7)	0.85 ±0.13	9.48 ± 0.49
203	0.9 ±0.17	9.56 ± 0.64
210	0.71 ±0.11	10.05 ± 0.63
217	0.74 ±0.19	9.04 ± 0.48
224 (M8)	0.63 ±0.17	8.74 ± 0.47
238	1.48 ±0.65	8.35 ± 0.43
252 (M9)	1.05 ±0.41	8.35 ± 0.48
266	0.82 ±0.34	7.97 ± 0.56
273	0.51 ±0.11	6.93 ± 0.4
280 (M10)	0.47 ±0.08	7.48 ± 0.48
287	0.55 ±0.21	7.72 ± 0.55
294	0.35 ±0.05	8.87 ± 0.75
301	0.32 ±0.04	9.63 ± 0.75
308 (M11)	0.31 ±0.04	10.79 ± 1.18
315	0.29 ±0.04	12.4 ± 1.69
322	0.25 ±0.04	11.35 ± 1.84
329	0.2 ±0.04	12.17 ± 1.82
336 (M12;End of study)	0.2 ±0.03	12.56 ± 2.06

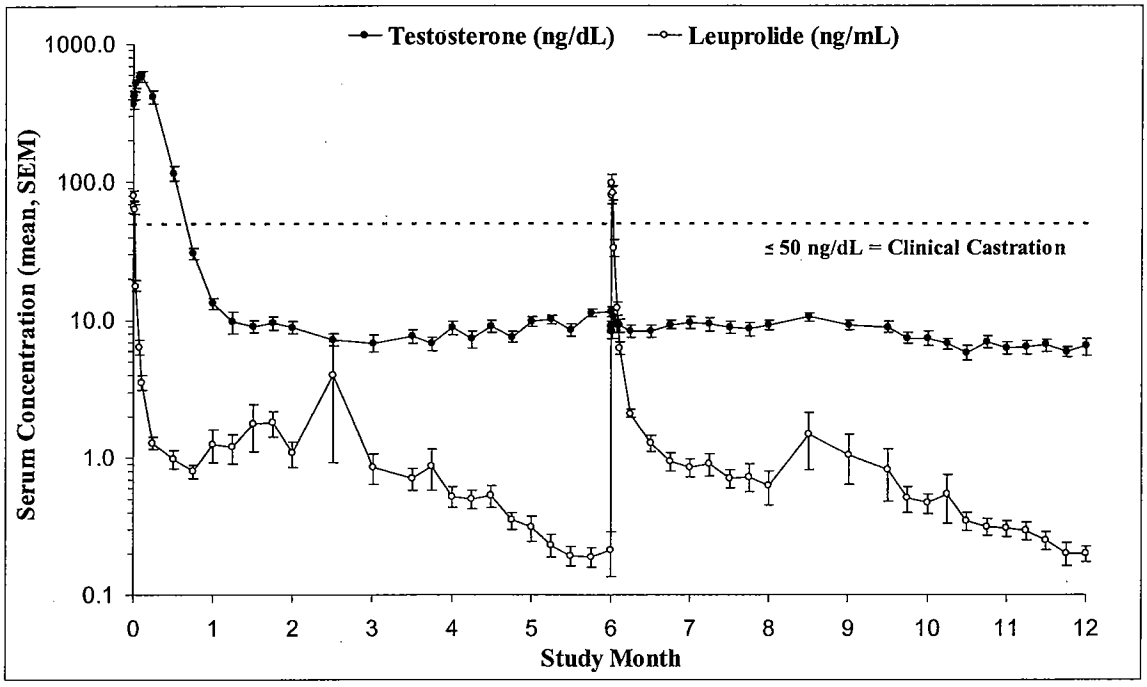


Figure 2: Mean serum Leuprolide and Testosterone after two consecutive SC doses, at baseline (Day 0) and month 6 (Day 168) in patients with advanced prostate cancer (n = 23-28).

- After each SC injection of ELIGARD® 45 mg, mean serum leuprolide levels peaked during the first day (Tmax ~ 4.5 hours), fell rapidly during the next three days, and then declined more slowly, maintaining levels between 0.2-2.0 ng/ml for the remainder of the six month dosing interval.
- In response to this pattern of leuprolide exposure, mean serum testosterone levels in the PK subset (n = 28) rose initially to 584.5 ± 48.6 ng/dl on day 3, fell to 30.4 ± 3.0 ng/dL on day 21, and then remained between 5.8 – 11.6 ng/dL for the remainder of the 336 day study.
- Serum testosterone did not increase in response to the second dose of ELIGARD® 45 mg, but remained suppressed in all patients in the PK subset during the entire second dose interval. This is because the sustained exposure of the pituitary gonadotropin receptors to leuprolide following the first injection has rendered them insensitive to further stimulation by GnRH or its analogs. Therefore a second dose was successful in maintaining the castration that was brought about by the first ELIGARD® 45 mg injection.
- Dose-response relationship: Pivotal study (AGL0205) was a fixed-dose, non-comparative, open-label study. All patients were to receive two identical injections of ELIGARD® 45 mg given once every six months. No dose response was performed with ELIGARD® 45 mg.

What is the time of onset and offset of the desirable pharmacological response or clinical endpoint?

- Within the PD subset of 28 patients, clinical castration (defined as Testosterone concentration of ≤50 ng/dL for two consecutive time points approximately one week apart) was achieved in 100 % of patients by day 28. Serum testosterone remained suppressed in all patients for the study duration (12-months).
- In the pivotal study patients, 108 of the 111 (97 %) enrolled patients who received the first injection achieved castrate suppression by Day 28. Of the three patients that did not achieve suppression, two patients had withdrawn prior to the 28 day assessment and one patient (# 2002) failed to achieve testosterone suppression at any time prior to withdrawing from the study on day 85.
- The median time to castrate suppression was 21 days while the mean time to castrate suppression was 21.2 days.
- No patient experienced breakthrough during the first 6 months of the study. Following the second injection at month 6, testosterone suppression was maintained throughout the study period i.e. month 12, in all but one patient (# 1402). This patient experienced breakthrough (defined as testosterone values above castration when they were previously below castration) on day 308 following the second dose and remained so through the end of the study period (T = 210 ng/dL on day 336).
- Leuprolide serum concentrations are not available for patients # 2002 and # 1402.

Table 4: The time of onset and duration of maintenance of the desired changes in the efficacy variables i.e. decrease in the serum concentrations of Testosterone and LH following two SC injections of ELIGARD® 45 mg given six months apart are tabulated below for all pivotal trial patients (n = 106-111; values indicate Mean ± SEM)

	Testosterone (ng/dL) Desired Threshold for Testosterone : ≤50 ng/dL	**Luteinizing hormone (LH; MIU/mL) Desired LH< 1 MIU/mL**
Baseline (Before 1st dose)	367.7 ± 13.0	6.98 ± 0.48
Initial Surge (Cmax)	588.6 ± 23.9 (day 2)	37.9 ± 2.43 (Hour 8)
Day 7	420.81 ± 20.7	6.85 ± 0.34
Day 14	114.56 ± 6.8	2.54 ± 0.13
Day 21	34.8 ± 3.4	1.137 ± 0.062
Day 28 (month 1)	16.7 ± 3.4	0.538 ± 0.026
Day 56 (month 2)	11.54 ± 2.72	0.111 ± 0.009
Month 6 (2nd dose)	10.4 ± 0.53	0.112 ± 0.024
Month 12 (study end)	12.6 ± 2.1	0.229 ± 0.14

What are the characteristics of exposure-response relationships (dose-response or concentration-response) for safety?

- Common systemic adverse events found in this study were related to the normal physiological response following testosterone suppression and consequent medical castration including: hot flashes, fatigue, weakness, testicular atrophy, gynaecomastia, night sweats and myalgia.

- When testosterone was at its peak concentration during days 0-3 post-dose, no clinically significant increases in the mean scores for bone pain, urinary pain & symptoms etc were observed, suggesting that there were no flare symptoms.
- In general, the drug was well tolerated when given as two consecutive SC injections six-months apart.

Does this drug prolong the QT or QTc interval?

The sponsor has not evaluated the QT interval prolongation potential of ELIGARD® 45 mg. However, it has been observed with leuprolide and other drugs in this class that a prolongation of the QT interval is caused by the use of these drugs. This effect is however attributed to the androgen ablation caused by these drugs (several literature references suggest that androgens have a cardiac protective effect; also suggested by the presence of longer cardiac repolarization intervals in females, compared to males) and not due to the direct action of these drugs on ion channels.

2.2.2 Pharmacokinetics:

What are the single dose and multiple dose PK parameters?

- Following the first dose of ELIGARD® 45 mg SC injection, mean serum leuprolide concentrations rose rapidly to a C_{max} of 82.0 ± 38.2 ng/ml (range 30.4 – 180 ng/ml) at 4.4 ± 1.7 hours (T_{max}). The concentrations then fell rapidly over the next three days, with a day 3 mean concentration of 3.56 ± 0.4 ng/ml. Following this initial "burst" phase, leuprolide concentrations declined slowly over the remaining duration of the dosing interval (day 3-day 168). The serum concentrations during this "plateau" phase (includes data on days 7 to 168) were generally maintained at 0.2-1.8 ng/ml, while individual levels in patients ranged from ——— i.e. BLOQ to ——— (subject # 0201).
- When a second dose of ELIGARD 45 mg SC injection was administered at month 6 (day 168), peak serum leuprolide concentrations of 102.4 ± 72.1 ng/ml (range 28.4 – 376 ng/ml) at a median T_{max} of 4.75 ± 2.0 hours. Concentrations then fell rapidly over the first three days (mean concentration on day 3 was 6.28 ± 0.67 ng/ml) following the second injection and then were maintained in the range of 0.2-2.1 ng/ml during the plateau phase, while individual values ranged from <

Table 5: Summary of PK parameters after the first (Day 0) and second (day 168 or month 6) ELIGARD® 45 mg SC injection

Subject Number	Burst Phase (Day 0-3)			Plateau Phase (Day 3-168)				Total (Day 0-168)	
	AUC ng hr ml^{-1}	Cmax ng/ml	Tmax hr	AUC ng hr ml^{-1}	Cmax ng/ml	Cmin ng/ml	Clast[a] ng/ml	AUC ng hr ml^{-1}	F[b] %
0201	1932.9	64.6	4.08	31109.8				33042.7	5.83
0202	1431.2	84.8	4.08	2968.4				4399.6	0.78
0203	706.3	31.4	8.17	2087.9				3104.2	0.55
0301	2329.24	120	7.65	3744.4				6073.64	1.07
0302	1817.5	73.8	3.88	3844.1				5661.6	1.00
0303	747.5	40.2	3.83	3631.24				4378.74	0.77
0304	1549.1	78.9	3.93	3696.56				5245.66	0.93
0305	2460	160	4.13	2996.8				5456.8	0.96
0306	2970	116	3.87	6794.4				9764.4	1.72
0307	1858.9	96.2	3.80	3736.1				5595	0.99
0308	1329.5	62.4	4.00	4277.07				5606.57	0.99
0701	1317	60.3	3.92	2858.8				4175.8	0.74
0702	2306.3	132	3.67	1187.49				3493.79	0.62
1101	504.2	34	3.95	6861				7365.2	1.30
1401	1004.3	59.4	4.00	2374.64				3378.94	0.60
1501	1816.3	122	2.00	[c]				[c]	[c]
1601	860.2	52.4	4.00	3339.55				4199.75	0.74
1602	856.3	30.4	8.00	3108.3				3964.6	0.70
2001	1725	70.1	7.75	5631.66				7356.66	1.30
2201	1049.3	41.9	7.17	2455.1				3504.4	0.62
2202	1565	105	4.08	1226.27				2791.27	0.49
2203	1790.2	99.7	3.83	4965.4				6755.6	1.19
2401	2861	180	1.83	2285.6				5146.6	0.91
2701	1140.8	88.7	2.00	1213.89				2354.69	0.42
2702	1438.1	71.6	4.08	1625.5				3063.6	0.54
2703	1603.7	81.2	4.00	1499.6				3103.3	0.55
2802	1082.6	56.1	3.83	3898.9				4981.5	0.88
Mean	1557.5	81.97	4.43	4362.2	6.71	0.12	0.21	5921.7	1.04
SD	641.1	38.18	1.74	5667.7	14.75	0.10	0.39	5785.9	1.02
RSD	41.2	46.59	39.3	129.9	220.0	88.58	183.5	97.7	97.7
Median	1549.1	73.8	4	3223.9	2.75	0.072	0.102	4690.6	0.83
Min								2354.7	0.42
Max								33042.7	5.8

[a] Concentration 168 days after dosing.Bioavailability (F) based on reported AUC of intravenous leuprolide.
[b] Bioavailability (F) based on reported AUC of intravenous leuprolide.
[c] Could not be determined, patient withdrew after Day 140.
BLOQ, below assay limit of quantitation

Subject Number	Burst Phase (Day 0-3)[a]			Plateau Phase (Day 3-168)				Total (Day 0-168)	
	AUC ng hr ml^{-1}	Cmax ng/ml	Tmax hr	AUC ng hr ml^{-1}	Cmax ng/ml	Cmin ng/ml	Clast[b] ng/ml	AUC ng hr ml^{-1}	F[c] %
0201	2926.7	84.4	7.58	8982.7				11909.4	2.10
0202	2765.0	111	2.08	2818.1				5583.1	0.98
0203	2171.8	114	3.83	1695.9				3867.7	0.68
0301	2471.6	81	7.50	5251.6				7723.2	1.36
0302	1824.3	83.9	3.80	2680.7				4505.0	0.79
0303	793.8	39.5	4.05	1826.7				2620.5	0.46
0304	599.6	28.4	4.03	3638.1				4237.7	0.75
0305	2793.0	119	3.98	1181.1				3974.1	0.70
0306	2944.4	106	8.07	6238.1				9182.5	1.62
0307	1949.4	88.3	7.97	8957.8				10907.2	1.92
0308	2582.7	96.9	7.85	4281.1				6863.8	1.21
0701	1068.4	39.9	7.92	2386.6				3455.0	0.61
0702	1531.8	52.7	3.75	3143.0				4674.8	0.82
1101	1212.7	72.4	4.03	1737.3				2950.0	0.52
1401	1066.3	50.4	3.75	733.5				1799.8	0.32
1601	1712.2	75.8	4.00	3011.7				4723.9	0.83
1602	2167.6	45.7	8.00	1939.2				4106.8	0.72
2001	4172.0	167	3.75	4840.9				9012.9	1.59
2201	1550.5	41.1	4.00	3379.7				4930.2	0.87
2202	1628.6	68.1	4.00	1415.6				3044.2	0.54
2203	3826.0	185	2.00	2083.5				5909.5	1.04
2401	7237.0	376	3.53	3328.7				10565.7	1.86
2701	3402.0	210	2.00	1172.5				4574.5	0.81
2702	2425.8	107	4.00	2257.7				4683.5	0.83
2703	1590.1	74.1	3.92	1846.5				3436.6	0.61
2802	2867.0	144	4.00	2777.7				5644.7	1.00
Mean	2356.9	102.4	4.75	3215.6	3.37	0.12	0.20	5572.6	0.98
SD	1345.6	72.14	2.01	2142.1	3.19	0.08	0.14	2715.5	0.48
RSD	57.1	70.47	42.39	66.6	94.9	64.8	69.8	48.7	48.7
Median	2169.7	84.15	4	2729.2	2.43	0.111	0.16	4679.2	0.83
Min									
Max									

[a] Days after administration of second dose.
[b] Concentration 168 days after dosing.
[c] Bioavailability (F) based on reported AUC of intravenous leuprolide.
BLOQ, below assay limit of quantitation

Table 6: Comparison of the mean pharmacokinetic parameters of ELIGARD® 45 mg following two consecutive SC injections at six-month intervals in advanced prostate cancer patients.

Parameter[b]	Phase	Dose 1	Dose 2	P-Value[c]
		Mean (± SD)	Mean (± SD)	
AUC	Total	5922 (5786)	5573 (2716)	NS
	Burst	1558 (641)	2357 (1346)	<0.01
	Plateau	4362 (5668)	3216 (2142)	NS
T_{max}	Burst	4.43 (1.7)	4.75 (2.0)	NS
C_{max}	Burst	82.0 (38.2)	102.4 (72.1)	NS
	Plateau	6.7 (14.8)	3.37 (3.2)	NS
C_{min}	Plateau	0.12 (0.1)	0.12 (0.08)	NS
C_{last}	Plateau	0.21 (0.39)	0.20 (0.14)	NS

[a] Patient 1501, who did not receive the second dose, is excluded.
[b] The parameter F, which is a linear transformation of AUCtotal, was not compared.
[c] Determined using the Wilcoxon signed-rank test. NS = Not statistically significant using 2-tailed α=0.05.

Reviewer's comments:

- The ELIGARD® 45 mg formulation resulted in a multiphasic leuprolide concentration versus time profiles characterized by a distinctive burst phase and a plateau phase.
- The serum leuprolide concentrations and the associated pharmacokinetics following the first and second doses of ELIGARD® 45 mg suggest lack of significant accumulation with repeated dosing at 6 month intervals.
- Although the Day 0-3 AUC was about 50 % higher after the second dose in comparison to the first dose (due to high Cmax in one individual as explained below), the overall AUC did not differ between the two doses.
- Following the second dose of ELIGARD® 45 mg, the Cmax in patient # 2401 (376 ng/ml) was 4 times higher than the mean from the other patients (~ 91.5 ng/ml). Following this large initial Cmax, the leuprolide concentrations in this patient remained in the range of 0.3-3.4 during the plateau phase (day 4-day 168). The testosterone levels in this patient remained suppressed below castration and did not exhibit any acute changes.

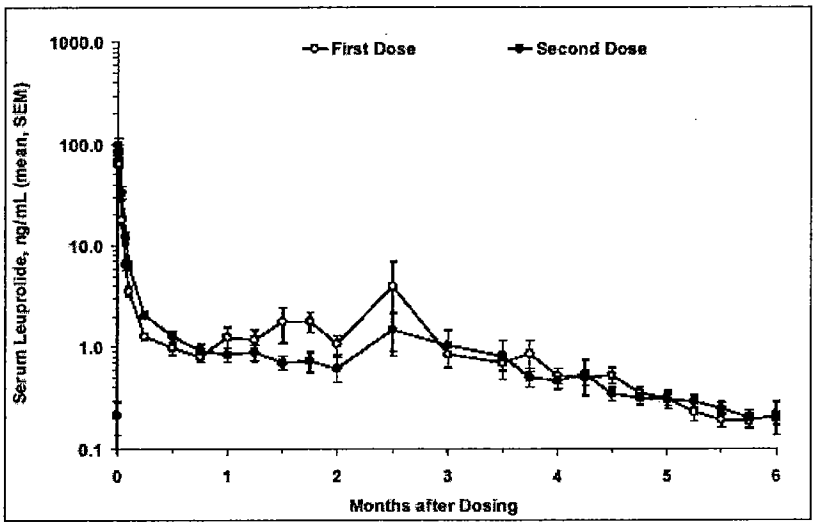


Figure 3: Pharmacokinetic profile of ELIGARD® 45 mg, showing serum leuprolide levels (mean, SEM) after two consecutive SC injections at six-month intervals in advanced prostate cancer patients (n = 26-27).

- The apparent increases in mean plasma leuprolide concentrations observed at 2 to 3 months after the first and second injections were due to very high values in one patient (# 0201) [68.7 ng/ml on day 70 (first dose) and 16.1 ng/ml on day 238 (second dose)]. This patient also contributes to the high CV (> 100 %) observed for the plateau phase Cmax and AUC, while moderate variability was observed for the burst phase (CV < 50 %). The variability associated with the overall AUC (0-6 months) was also very high after the first dose (CV 97.7 %) due to the inclusion of data from patient # 0201. Pharmacokinetic data following the second dose of ELIGARD® 45 mg was less variable compared to the first dose, especially with respect to the plateau phase and the overall AUC over six months. Although

data from patient # 0201 may suggest possible dose dumping from the sustained release formulation, it still doesn't explain why these sudden increases in leuprolide concentration occurred in this patient at around the same time (day 70) after both the doses. However, because the testosterone concentrations in this individual remained castrate at these time points and were not altered by the sudden increase in serum leuprolide concentrations, this observation is not clinically relevant.

- The average plateau phase serum leuprolide concentrations following the first and second doses were 0.69 and 0.81 ng/mL. Based on the reported clearance value of 139 ± 30 ml/min (or 8.3 ± 1.8 L/h) after intravenous injection of a single 1 mg bolus dose of leuprolide in humans, the estimated rate of drug release from the ELIGARD® 45 mg formulation during the plateau phase is 138 and 162 µg/day following the first and second injections (rate = concentration* clearance).
- A single 1 mg intravenous injection of leuprolide acetate in adult males results in an AUC of 126 ± 33 ng.hr/ml (Senello et al; J. Pharm. Sci., 1986). Therefore, the AUC following a 45 mg intravenous dose of leuprolide acetate would be approximately 5670 ng.hr/ml. Based on this estimation, the observed exposure of 5922 and 5573 ng.hr/ml following the first and second doses of ELIGARD® 45 mg SC injections in prostate cancer patients suggests extensive absorption and subsequent mean bioavailability of 104 % (median 83 %) and 98 % (median 83 %) following the first and second doses of the depot formulation.
- The Cmin (minimum serum leuprolide concentration observed during any dosing interval) for many subjects was found to be less than 0.1 ng/ml and in several instances even below the detection limit (i.e. ———— suggesting that sustained exposure to leuprolide concentrations that are less than 0.1 ng/ml may result in adequate testosterone suppression.
- There is no pharmacokinetic data available for those patients who exhibited lack of response to treatment (failure; # 2002) and breakthrough following initial suppression (escape; # 1402).
- This reviewer has compared the PK/PD following the initial injection of Eligard 45 mg to those observed with other Eligard formulations;

    - It appears that the total AUC following the six-month formulation was roughly in the ballpark of what can be expected from administering 6 doses of the 1-month formulation or 2 doses of the 3-month formulation.
    - The Cmax for the 6-month formulation was lower than the 3- or 4- month formulations (desirable from a clinical perspective) and Tmax was similar.
    - In addition, the plateau concentrations were maintained between 0.2-2.0 ng/ml and are consistent with other strengths of Eligard.
    - The formulations also did not vary with respect to the initial surge concentrations of testosterone, the time for castration and the castrate levels during plateau phase.

Table 7: A comparison of leuprolide pharmacokinetics and pharmacodynamic endpoints (i.e. testosterone) following the initial injections of the 1, 3, 4 and 6 month formulations of Eligard.

	Eligard 7.5 mg (1 month)	Eligard 22.5 mg (3 months)	Eligard 30 mg (4 months)	Eligard 45 mg (6 months)
Leuprolide analysis method	RIA	RIA	HPLC/MS	LC-MS/MS
Cmax (ng/ml)	25.3 ± 11.3	127 ± 39	149 ± 77	81.9 ± 38.2
Tmax (hours)	4 to 8	4.6 ± 1.6	3.3 ± 1.2	4.4 ± 1.7
Plateau levels (ng/ml)	0.2 – 2.0	0.2 – 2.0	0.1 – 1.0	0.2 – 2.0
Total AUC (ng.hr/ml)	873 ± 229	3646 ± 1100	3551 ± 990	5922 ± 5786
Delivery rate (µg/day)	140	150 – 190	83-113	138-163
Testosterone peak (ng/dL)	600 ± 74	610 ± 246	588 ± 40	585 ± 49
Time of Testosterone Peak	Day 3	Day 2	Day 3	Day 3
Time for castration (Overall study)	Days 21-42	Days 21-35	Days 21-42	Day 21-28
Castrate levels (ng/dL)	7-18	7-13	6-12	6-12

2.2.2.1 Absorption

Leuprolide is inactive if given by oral route as it undergoes rapid enzymatic degradation by the gut proteases. It is therefore generally administered via subcutaneous or intramuscular routes. Leuprolide acetate is rapidly and completely absorbed after SC administration, as suggested by the observed bioavailability of > 97 % following SC injection of ELIGARD® 45 mg formulation.

2.2.2.2 Distribution

The mean volume of distribution (Vdss) after intravenous administration of leuprolide to healthy male volunteers is reported to be 26.5 ± 10.1 L. The *in vitro* binding of radio labeled leuprolide to human serum, as measured by [redacted] ranged from [redacted], suggesting that leuprolide is only weakly bound to plasma proteins after administration.

2.2.2.3 Metabolism

Metabolites of leuprolide were not assessed in this study. Leuprolide is known to be metabolized by cleavage of its serine-tyrosine peptide bond to form a pentapeptide metabolite (M-I), which is further degraded to several di- and tri-peptide metabolites (M-II, M-III and M-IV). All four metabolites are inactive. The principal metabolite, M-I, is present in serum and urine at lower concentrations than the parent drug.

In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 8.3 ± 1.8 L/h (139 ± 30 ml/min), 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).

2.2.2.4 Excretion

The sponsor did not conduct a drug excretion study with ELIGARD® 45 mg formulation. Animal studies with ^{14}C-leuprolide showed that 49% to 68% of the radioactivity was recovered in the urine, mainly as parent drug and the M-I and M-II metabolites, suggesting that urinary excretion might play an important role in leuprolide elimination.

2.3 Intrinsic Factors

The PK subset of the pivotal trial patients in NDA 21-731 included subjects belonging to various subcategories based on demographic characteristics, disease state etc. However, no formal sub population analysis was conducted. The sponsor states that ELIGARD® 45 mg provided sustained leuprolide release and sustained testosterone suppression in all pharmacokinetic subgroup patients.

Body weight (BW): The clinical pharmacokinetic subset in the ELIGARD® 45 mg phase 3 study included patients who ranged in weight from 56 to 121 kg. When these patients were administered a fixed dose of 45 mg leuprolide acetate (ELIGARD® 45 mg), there was a trend for decreasing Cmax values with increasing BW (significantly different with p=0.002). However, due to the wide safety margin of leuprolide, these observed differences in initial exposure may not be clinically significant. BW did not appear to have an influence on total observed exposure (AUC $_{0\text{-}6\ months}$) following a single dose of ELIGARD® 45 mg (p = 0.5772).

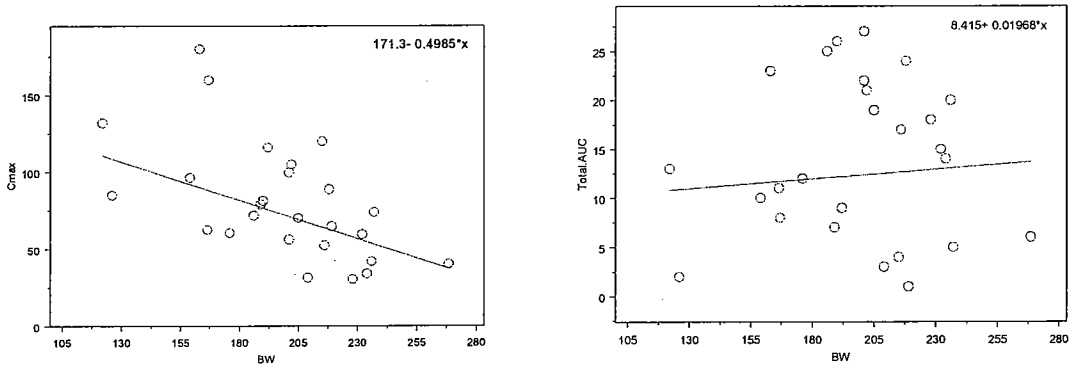


Figure 4: Effect of bodyweight (BW) on Cmax and AUC of leuprolide from ELIGARD 45mg.

Age: Elderly patients made up a substantial portion of the patients whose pharmacokinetics were evaluated in the pivotal clinical trial of ELIGARD® 45 mg, which included patients between the ages of 50 and 85 years. Within the age group studied, Cmax exhibits a slight increasing trend with age (not significant). However, there was no influence of age on total observed AUC (p > 0.05).

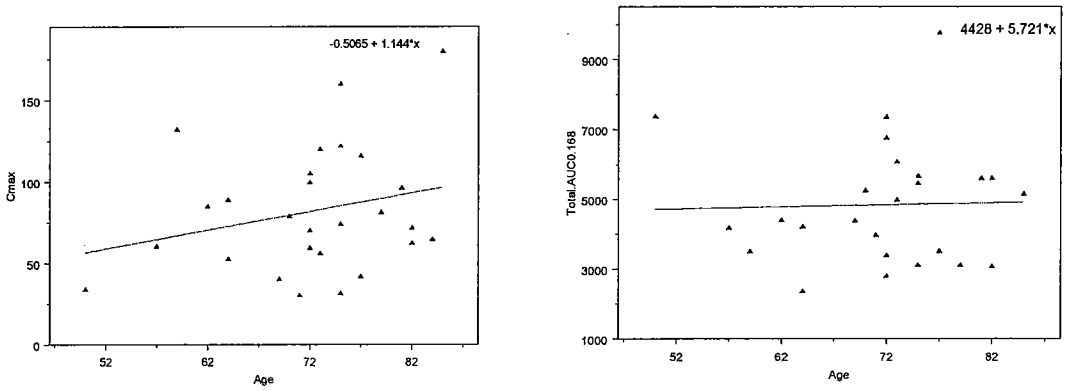


Figure 5: Effect of patient age on ELIGARD 45 mg pharmacokinetics; patient # 0201 was excluded from the right (AUC vs age) plot.

Race: There was no significant impact of race (7 blacks, 17 whites and 3 Hispanics) on leuprolide pharmacokinetics. The mean Cmax values in blacks, whites and Hispanics were 62 ± 24, 89 ± 39 and 87 ± 51 ng/ml, respectively. The mean total AUC(0-6 months) was 4505 ± 1480, 6763 ± 7247 and 4737 ± 1763 ng.h/ml, respectively in the black, white and Hispanic populations following the first dose. None of these differences were statistically significant.

No apparent relationship was observed between the various exposure parameters (Cmax, Cmin, AUC) and pharmacodynamic endpoints (testosterone peak, time for castration) In addition, these patients had a variety of concomitant disease states and exhibited a range of clinical chemistry and hematologic abnormalities during the study. However, the sponsor did not attempt to correlate the observed exposure or response parameters with any of these intrinsic factors.

Women and pediatric subjects were not included in the clinical studies described in this application, which seeks approval to market ELIGARD® 45 mg for the treatment of advanced prostate cancer in men.

2.4 Extrinsic Factors

Drug-drug interactions: No pharmacokinetic drug-drug interaction studies were performed with ELIGARD® 45 mg. No drug-drug interactions have been described for other preparations of leuprolide 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 with other drugs. Pharmacokinetic drug-drug interactions are unlikely to be observed with ELIGARD® 45 mg because leuprolide is primarily degraded by peptidase(s), and is less than 50% bound in the plasma.

2.5 General Biopharmaceutics

Dose selection:

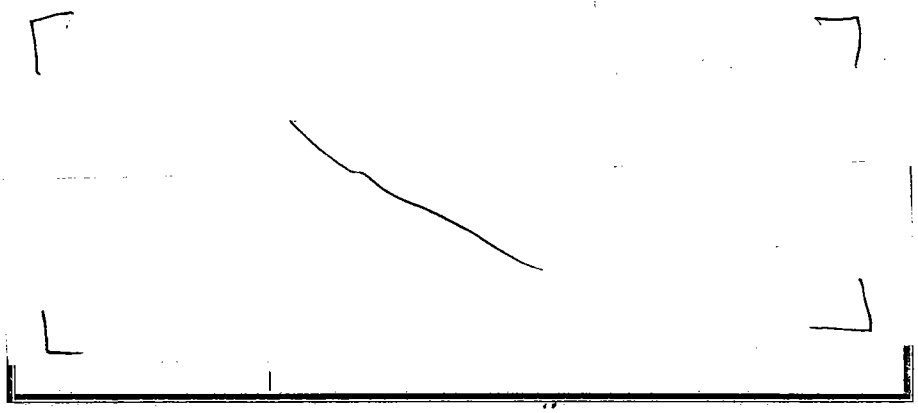
The sponsor provides the following rationale for dose selection in ELIGARD® six month formulation: The dose for the six-month ELIGARD® 45 mg formulation was selected by proportionally increasing the leuprolide acetate dose of the four-month ELIGARD® 30 mg formulation to 45 mg, along with modification of the formulation co-polymer that resulted in a six-month release profile. This resulted in six-month duration of activity in animal models and human clinical trials. Because serum levels below the assay limit of quantitation (0.05 ng/mL) might be associated with incomplete suppression of pituitary gonadotropin secretion, and the wide safety margin of leuprolide acetate, lower doses were not investigated for the ELIGARD ® 45 mg. In addition, a review of the clinical literature found two dose-ranging studies that determined the objective response following monthly treatment with 3.75 mg and 7.5 mg leuprolide acetate. These studies suggested a trend (not statistically significant) toward a better objective response with the larger dose (Akaza et al. *J Int Med Res* 1990; 18(1):90-102 and Akaza et al. *Jpn J Clin Oncol* 1992; 22:177-184). These data supported the selection of a 45 mg dose of leuprolide acetate for the six-month product.

Formulation: The two lots (1522 & 1582) of ELIGARD® 45 mg used in the phase 3 clinical trial (AGL0205) represent the same drug formulation used in the to be marketed product, and no other formulation or significant manufacturing changes were implemented during the clinical trials (Page 221, Volume 2.1).
Although the drug substance (leuprolide acetate) employed in the clinical trials and for the to-be-marketed formulations is from two different sources because the clinical trial employed two lots (1522 and 1582 for the first dose and second dose, respectively) that were manufactured using drug substance from each of the above sources, bridging information in the form of *in vitro* dissolution comparison and clinical (PK/PD) data is available to demonstrate comparable release and pharmacokinetic profiles.

In vitro release testing method (T667): The proposed release testing method for ELIGARD® 45mg is non-physiological in nature with no in vivo relevance and is meant strictly for ensuring quality control. Therefore the release specification setting is being handled by chemistry. Nevertheless a brief description of the method and important results together with CMC's recommendation is given below.

The T667 method employs accelerated release testing designed to produce close to release within a testing period. In method T667, the constituted ELIGARD® 45 mg product (375 mg)

T667 Method Summary



Samples are taken at 6, 24 and — All samples are assayed by — HPLC to determine the cumulative amounts of leuprolide acetate released, which are reported as percentages of the finished product label claim of 45 mg leuprolide acetate. The proposed release specifications for ELIGARD 45mg are shown below:

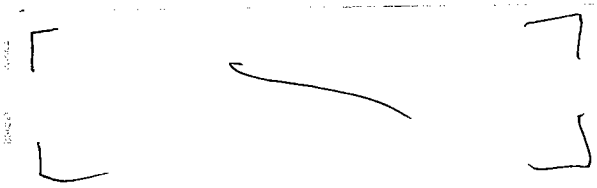
Table 8: Proposed release specifications for ELIGARD® 45mg.

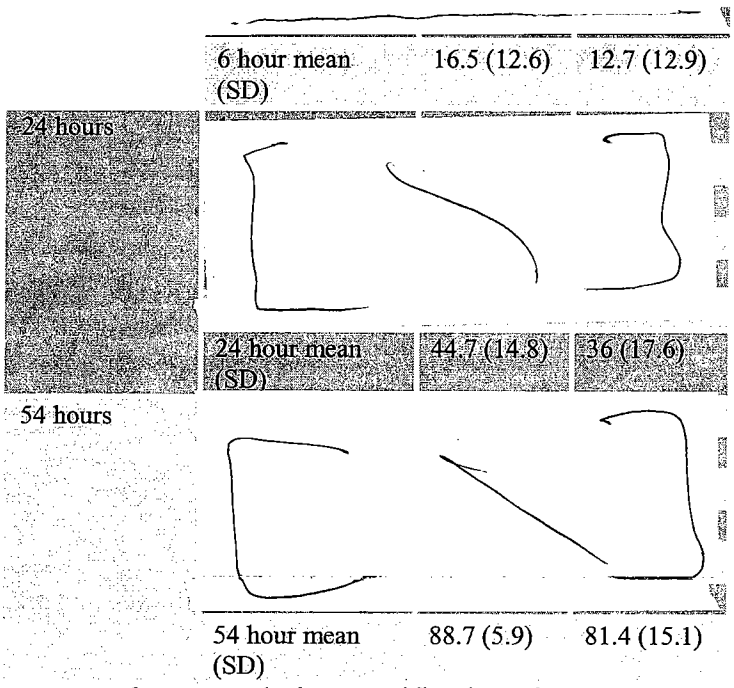
Extended Release (Cumulative % Release) Mean and individual results are reported as whole numbers.	T667	Mean % of Theory 45 mg		Not less than individual unit results are within ± 10% of the acceptance criteria for mean results.		No individual unit result is more than ± 15% of the acceptance criteria for mean results.	
		Min.	**Max.**	**Min.**	**Max.**	**Min.**	**Max.**
6 hour			25		35		40
24 hour		27	62	17	72	12	77
54 hour		75		65		60	
Tier 1: If any acceptance criterion is not met, proceed to —							
Tier 2: An additional — units are tested. Results from — must meet all acceptance criteria.							

The release rates from constituted products of clinical lots 1522, 1582 and 1582A using method T667 are shown below. Note that while the mean release rate was within the acceptance criteria at all time points, individual units fell out of specification at one or more time points during — testing. — testing allows for testing of 6 additional individuals and all individuals need to be within the acceptance criteria to qualify a lot. Although — testing was not done for these initial lots, stability lots that failed — testing have been shown to pass — testing.

Table 9: In vitro release profiles for the clinical lots employed in pivotal trial.

Sampling time	Units	Lot 1522	Lot 1582
6 hours			





The following changes to the mean elution specifications for ELIGARD 45 mg proposed by CMC were accepted by the sponsor:

6 hours: NMT

24 hours:

54 hours: NLT

Additional comments: During the method development it was observed by the sponsor that this method was unable to adequately discriminate between acceptable lots and unacceptable lots i.e. those with polymer MW and solvent content (NMP specifications) outside pre-specified ranges, thereby raising a concern regarding the usefulness of the method in maintaining product uniformity. Changes in polymer molecular weight, lactide-glycolide ratio and solvent content may alter the density, viscosity, porosity characteristics of the delivery system and thereby impact the release characteristics of the final product. The sponsor acknowledges that the method does not discriminate adequately but maintains that this should not be a concern as the method is anticipated to be used in conjunction with other analytical methods that can identify out-of-range polymer and solvent specifications. Because drug release profile from this controlled release long-acting formulation is dependent on the performance of the delivery system, this apparent lack of sensitivity in the release testing method should be adequately addressed by the sponsor. These observations have been conveyed to the CMC reviewer. **The sponsor has accepted Chemistry's recommendation to tighten the acceptable range of polymer MW to**

Manufacturing site considerations (issue identified during filing)

- Eligard® 45 mg final product is comprised of two syringes, A and B. SYRINGE A consists of ATRIGEL polymeric delivery system comprised of poly (DL-lactide –co-glycolide) (PLG) and N-methyl 2-Pyrrolidone (NMP). Atrix Laboratories is the proposed primary site of manufacturing for Syringe A. SYRINGE B consists of the active ingredient, leuprolide acetate. The

manufacturing process for syringe B primarily involves filling of drug solution in water for injection (WFI) into syringes. Atrix laboratories, Inc., (primary site) and alternate site) are the proposed manufacturing sites for syringe B. The two syringes are packed together as the finished drug product at Atrix laboratories Inc.

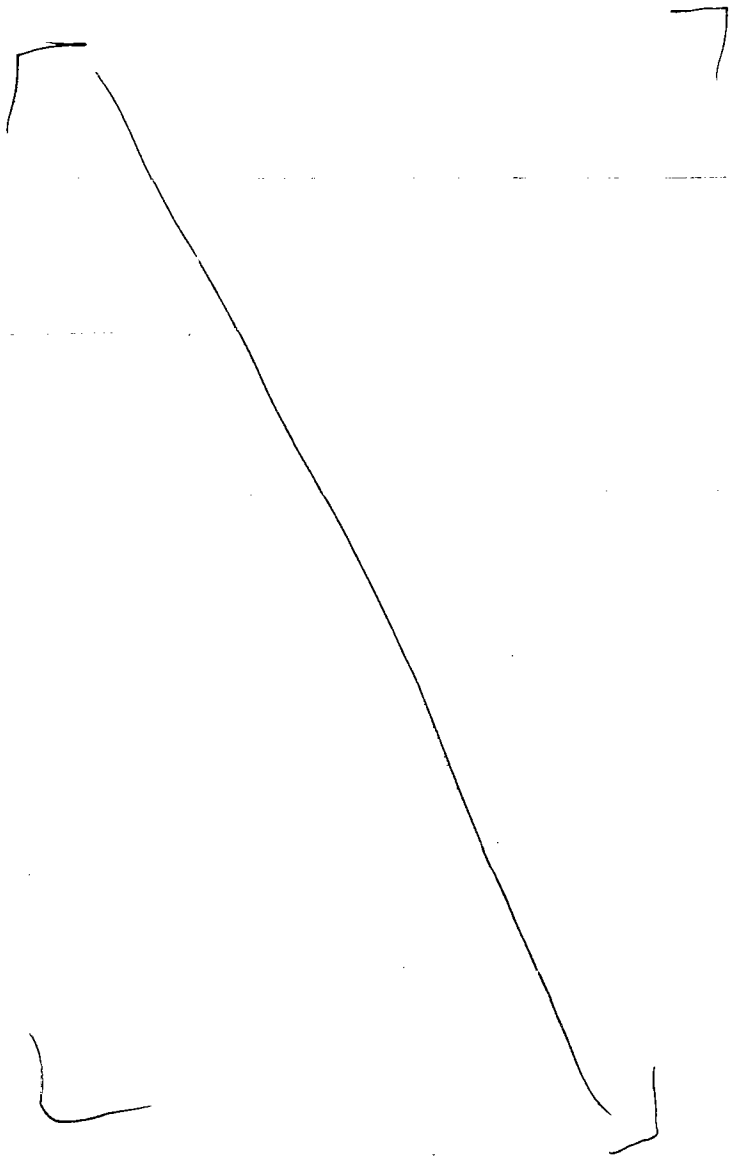
- Clinical trials for ELIGARD® 45 mg employed finished drug products from Lots 1522 and 1582 (manufactured in 2002). These finished products consisted of drug-containing syringes (syringe B) manufactured entirely in the alternate site, No clinical trials were conducted employing drug-containing syringes manufactured in the proposed primary site, Atrix laboratories, Inc.
- The finished drug product for ELIGARD 45 mg is an extended release (ER) formulation that is formed when contents from syringe A and syringe B, are mixed prior to injection. However, the leuprolide acetate contained in syringe B is product prepared from a solution of leuprolide acetate in WFI (immediate release, IR) and therefore variations in the manufacturing site for this syringe may not have an impact on the extended release characteristics of the final

[redacted]

- These possibilities were discussed with and Dr. De (chemistry reviewer) and the sponsor was asked to provide *in vitro* release comparison data for the final drug product obtained after mixing contents of syringe A, with syringe B obtained from the two proposed sites of manufacture (Atrix ε). It was also recommended that the f2 test be used to compare dissolution profiles and confirm similarity.
- The sponsor submitted the requested information in a final amendment to NDA. Three lots were manufactured in the Atrix facility in 2004 (Lots 1847, 1848, 1849) and the release testing was performed using the T667 method. All three Atrix lots demonstrated comparable release profiles with the clinical lots manufactured at (lots 1522 and 1582) as seen from the release profiles and the values of similarity factor, f2 (f2 ≥50 indicates similarity).

Table 10: In vitro release rates (mean%; range) from lots manufactured at two different sites (Atrix . Note that only the lots were used in the clinical trials.

	% In vitro release				
	Atrix lots (new)				
Time (hours)	1847 ( )	1848	1849	**1522**	**1582**
6	12 ( )	6 ( )	8 ( )	**17 ( )**	**13 ( )**
24	38 ( )	34 ( )	33 ( )	**45 ( )**	**36 ( )**
54	89 ( )	89 ( )	86 ( )	**89 ( )**	**81 ( )**



The results of dissolution profile comparison (f2 factor calculations) in general demonstrate acceptable similarity between the release profiles of lots manufactured at Atrix [redacted] Although the above presented information constitutes the most relevant information for this comparison, the sponsor also provided lot to lot comparisons of the Atrix batches with the primary stability lots manufactured in [redacted] Some of the f2 values for release comparison were less than [redacted] but the sponsor notes that this is likely because the lots from Atrix and [redacted] were all not tested for release within the same time frame which would normally take care of potential bias due to assay method variability. The sponsor also notes that for lots manufactured and tested within the same time frame in [redacted] the similarity factors were less than [redacted] on few occasions suggesting apparent difference between product lots manufactured at the same site. However, considering the most relevant lots as seen above i.e. the clinical lots 1522 and 1582 and the new Atrix facility lots, overall it appears that the lots manufactured at the two proposed sites have acceptable similarity.

Delivered mass: ELIGARD® 45 mg formulation is designed to deliver 45 mg of leuprolide acetate subcutaneously within a nominal delivered mass of 375 mg of constituted product. The mean delivered mass for the two phase 3 study lots was determined at various time points during stability testing (Table 11). These studies demonstrated that the mean delivered mass was maintained at approximately 375 mg for both phase 3 clinical lots (# 1522 and 1582) with an individual unit range between 337.3 mg and 387.6 mg and acceptable variability [redacted] as judged by USP mass content uniformity criteria. These data demonstrate the reproducibility of the total mass delivered by the ELIGARD® 45 mg dosing system, and suggest that the actual doses administered to patients in the pivotal study were accurate and consistent.

Table 12: Delivered mass data for phase 3 study lots.

Table 10 Delivered Mass Data for Phase 3 Study Lots

Method	Lot	Time Point (months)[a]	Mean Delivered Mass (mg)	Delivered Mass (% of Nominal)	RSD (%)	Min (mg)	Max (mg)	N
Constitute, Dispense and Weigh[b]	[redacted]							
Constitute, Dispense and Weigh[b]	[redacted]							

2.6 Analytical methods

2.6.1 Leuprolide analysis

Leuprolide ($C_{59}H_{84}N_{16}O_{12}.CH_3COOH$; MW: [redacted] Retention Time: [redacted] concentrations in serum samples obtained during the phase 3 pharmacokinetic evaluation of ELIGARD® 45 mg (AGL0205) were measured by a validated LC-MS/MS method in which samples are purified by solid-phase extraction, separated by HPLC and detected by tandem mass spectrometry. The method uses [redacted] leuprolide or Leuprolide-D_{10} ($C_{59}H_{74}N_{16}O_{12}D_{10}.CF_3COOH$; MW: [redacted] Retention Time: [redacted]) as the internal standard and monitors [redacted]. Calibration was accomplished by weighted linear regression of the ratio of the peak area of leuprolide to that of the added internal standard. The method was found to be specific for leuprolide with no interference from any of the molecules endogenous to serum. No interference was observed for leuprolide with the internal standard.

Validation results:

[redacted]

Reviewer's comments:

The LC-MS/MS method employed for leuprolide analysis in human serum samples appears adequately validated with accuracy and precision values within agency recommended boundaries (± 15 % for all samples, except at LLOQ, where ± 20 % is acceptable).

2.6.2 Testosterone analysis

Serum testosterone levels were measured in samples from the pivotal phase 3 study (AGL0205) by an RIA (radioimmunoassay) method.

Reviewer's comments:

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1 of 1

3 Labeling recommendations

Labeling recommendations have been communicated to the sponsor. The final approved labeling for Eligard 45 mg can be found in DFS.

4 OCPB Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-731**	**Brand Name**	**Eligard® 45 mg**
OCPB Division (I, II, III)	**DPE2**	**Generic Name**	**Leuprolide acetate**
Medical Division	**DRUDP**	**Drug Class**	**GnRH agonist**
OCPB Reviewer	**Dr. Sandhya Apparaju, Ph.D**	**Indication(s)**	**Palliative treatment for Pancreatic cancer**
OCPB Team Leader	**Dr. Ameeta Parekh, Ph.D**	**Dosage Form**	**Suspension(extended release)**
		Dosing Regimen	**Once every 6 months**
Date of Submission	**02/20/04**	**Route of Administration**	**Subcutaneous**
Estimated Due Date of OCPB Review	**12/03/04**	**Sponsor**	**Atrix laboratories**
PDUFA Due Date	**12/17/04**	**Priority Classification**	**3S**
Division Due Date	**12/10/04**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	X			
gender:				
pediatrics:				
geriatrics:	X			
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	X			
PK/PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1	1	Reviewed in detail the PK/PD data from one pivotal study; Referred to supportive information from previous NDAs on a need only basis.
Population Analyses -	X			[redacted]
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	X			
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X			Dissolution data reviewed but final spec setting deferred to chemistry, as the release method is for quality control purposes.
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies	[redacted]			

The clinical trial and the to-be-marketed formulations for Eligard 45 mg are reported to be identical.
Although the drug substance (leuprolide acetate) employed in the clinical trials and for the to-be-marketed formulations is from two different sources, bridging information (*in vitro* and clinical) is provided to demonstrate comparable release and pharmacokinetic profiles.
A specific LC-MS/MS method is used for analysis of leuprolide. The validation report is provided and appears adequate. Testosterone analysis was carried out employing RIA method that shows cross-reactivity with [redacted]. Sponsors claim that [redacted] chromatography procedures prior to RIA increase the specificity of the method for testosterone analysis.
The sponsor has submitted 5 studies that include one pivotal phase 3 clinical study of Eligard 45 mg and four study reports for previously approved Eligard products, as supporting information.
The analyses on subpopulation groups, population PK/PD and bioequivalence issues have been deduced from the pivotal Phase 3 study results and are not submitted as separate studies.
The effect of hepatic and renal impairment on the PK of Eligard 45 mg has not been evaluated.

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	**Sandhya Apparaju, 03/23/04**	
Secondary reviewer Signature and Date		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sandhya Apparaju
12/3/04 03:46:17 PM
BIOPHARMACEUTICS

Ameeta Parekh
12/6/04 01:22:43 PM
BIOPHARMACEUTICS
I concur

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-731**	**Brand Name**	**Eligard® 45 mg**
OCPB Division (I, II, III)	**DPE2**	**Generic Name**	**Leuprolide acetate**
Medical Division	**DRUDP**	**Drug Class**	**GnRH agonist**
OCPB Reviewer	**Dr. Sandhya Apparaju, Ph.D**	**Indication(s)**	**Palliative treatment for Pancreatic cancer**
OCPB Team Leader	**Dr. Ameeta Parekh, Ph.D**	**Dosage Form**	**Suspension(extended release)**
		Dosing Regimen	**Once every 6 months**
Date of Submission	**02/20/04**	**Route of Administration**	**Subcutaneous**
Estimated Due Date of OCPB Review	**12/03/04**	**Sponsor**	**Atrix laboratories**
PDUFA Due Date	**12/17/04**	**Priority Classification**	**3S**
Division Due Date	**12/10/04**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	**X**			
gender:				
pediatrics:				
geriatrics:	**X**			
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	**X**			
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:	X			
Population Analyses -	X			
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	X			
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies	[redacted]			

- The clinical trial and the to-be-marketed formulations for Eligard 45 mg are reported to be identical.
- Although the drug substance (leuprolide acetate) employed in the clinical trials and for the to-be-marketed formulations is from two different sources, bridging information (*in vitro* and clinical) is provided to demonstrate comparable release and pharmacokinetic profiles.
- A specific LC-MS/MS method is used for analysis of leuprolide. The validation report is provided and appears adequate. Testosterone analysis was carried out employing RIA method that shows cross-reactivity with [redacted]. Sponsors claim that [redacted] chromatography procedures prior to RIA increase the specificity of the method for testosterone analysis.
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- The analyses on subpopulation groups, population PK/PD and bioequivalence issues have been deduced from the pivotal Phase 3 study results and are not submitted as separate studies.
- The effect of hepatic and renal impairment on the PK of Eligard 45 mg has not been evaluated.

	"X" if yes	**Comments**
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	**Sandhya Apparaju, 03/23/04**	
Secondary reviewer Signature and Date		

Filing Memo

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-731
Compound: Leuprolide Acetate
Sponsor: Atrix

Date: 04/06/04
Reviewer: Sandhya Apparaju, Ph.D

Background: ELIGARD® 45 mg (also referred to as LA-2580 45 mg) is an injectable polymer-based, extended release formulation of leuprolide acetate, a potent LH-RH agonist. It is designed to deliver a nominal dose of 45 mg leuprolide acetate over a six month period after subcutaneous (SC) injection. As administered, it is a biodegradable polymeric formulation consisting of the polymer 85:15 poly(DL-lactide-co-glycolide) (PLG), the solvent *N*-methyl-2-pyrrolidone (NMP) and the active drug substance leuprolide acetate.
The proposed indication is the palliative treatment of advanced prostate cancer, which is achieved through continuous suppression of gonadal testosterone synthesis.

Phase 3 Clinical Study: Atrix has conducted a pivotal phase 3 study to evaluate the safety and efficacy of Eligard 45 mg in prostate cancer patients (n = 109). The pharmacokinetics of the formulation was assessed in a subset of patients (n=27) who received two injections of Eligard 45 mg at 6 month intervals.
Applicant conclusions: Administration of Eligard 45 mg resulted in a multi-phasic profile of serum leuprolide concentrations. Following the initial burst (C_{max} > 80 ng/ml), the concentrations of leuprolide declined rapidly over the first 3 days, then declined more gradually over the remainder of the dosing interval (3 days to 6 months). During the "plateau" phase the concentrations of leuprolide were maintained between ——— During the plateau phase the average rate of drug delivery from the depot was estimated to be ——— . There was no evidence of accumulation after repeated dosing with ELIGARD® 45 mg in the pivotal phase 3 study. Serum leuprolide concentrations and AUCs following the second dose were similar to those observed after the first dose.
Pharmacodynamics: Following the first dose of ELIGARD® 45 mg, mean serum testosterone concentrations transiently increased, then fell to levels (< 50 ng/dL) associated with medical castration in 99.1% of subgroup patients by Day 28. ELIGARD® 45 mg then maintained testosterone suppression during the remainder of the first six-month dosing interval. There were no acute-on-chronic testosterone responses during the burst phase after the second dose of ELIGARD® 45 mg. One patient did not achieve castrate suppression and one patient demonstrated breakthrough (T > 50 ng/dL after achieving castrate levels).

Formulations: The clinical trial formulation is reported to be identical to the to-be-marketed formulation.

Supporting data: Data from clinical pharmacokinetic studies of ELIGARD® 30 mg, ELIGARD® 22.5 mg, and ELIGARD® 7.5 mg formulations are summarized in the submission. Because of the compositional and therapeutic similarities of these four ELIGARD® formulations, clinical data from the previous formulations (ELIGARD® 30 mg (four-month), ELIGARD® 22.5 mg (three-month) and ELIGARD® 7.5 mg (one month)) is expected to support ELIGARD® 45 mg.

Proposed label: Preliminary review of the proposed label indicates that the subsections pertaining to human pharmacokinetics have been appropriately organized and appear to be based on the information derived from the Phase 3 clinical study and existing literature on the human pharmacokinetics of leuprolide acetate.

Manufacturing site considerations:
Eligard® 45 mg final product is comprised of two syringes, A and B.
SYRINGE A: Consists of ATRIGEL polymeric delivery system comprised of poly(DL-lactide – co-glycolide) (PLG) and N-methyl 2-Pyrrolidone (NMP). ATRIX LABORATORIES, INC. is proposed to be the primary site of manufacturing for Syringe A.
SYRINGE B: Consists of the active ingredient, leuprolide acetate. The manufacturing process for this syringe primarily involves filling of drug solution in water for injection (WFI) into syringes, [redacted] ATRIX laboratories, Inc., is proposed to be the primary manufacturing site for syringe B, while [redacted] (contract facility) is proposed to be the alternate manufacturing site.
The FINISHED drug product (Syringe A plus Syringe B) is packaged at ATRIX laboratories Inc.
Clinical trials with ELIGARD 45 mg employed finished drug products from Lots 1522 and 1582 These finished products consisted of drug-containing syringes (syringe B) manufactured entirely in the alternate site, [redacted] No clinical trials were conducted employing drug-containing syringes manufactured in the proposed primary site, Atrix laboratories, Inc.
The finished drug product for ELIGARD 45 mg is an extended release (ER) formulation that is formed when contents from syringe A and syringe B, are mixed prior to injection. However, the leuprolide acetate contained in syringe B is a [redacted] leuprolide acetate in WFI (immediate release, IR) and therefore variations in the manufacturing site for this syringe may not have an impact on the extended release characteristics of the final product.[redacted]

[redacted] These possibilities were discussed with [redacted] and Dr. De (chemistry reviewer) and it was agreed upon that *in vitro* release comparisons should be requested for the final constituted products that employ drug syringes (B) from the two different sites.
Comments to the sponsor: The sponsor should provide *in vitro* release comparison data for the final drug product obtained after mixing contents of syringe A, with syringe B obtained from the two proposed sites of manufacture (Atrix Laboratores Inc., and [redacted] We recommend that the f2 test be used to compare dissolution profiles and confirm similarity.

Other issues addressed in this submission:
1. Bioavailability/Bioequivalence information: The sponsor states that leuprolide acetate drug substance for the manufacture of Eligard 45 mg will be obtained from two different manufacturers [redacted]. The drug product used for the first dose and second dose of the clinical study were chosen to represent these two batches. Results of the clinical study demonstrate identical pharmacokinetic measures following the first and second doses. The sponsor states that the AUCs with both the batches of the formulation were very close to the expected AUC following intravenous administration, suggesting good bioavailability from the depot produc
2. In vitro dissolution testing: The *in vitro* release profiles of each lot of ELIGARD® 45 mg (Lots 1522 and 1582) used in the clinical pharmacokinetic studies were determined at various times during the dosing period. The test method utilizes accelerated release testing designed

to produce close to ___ , release within a ____ testing period. Mean in vitro release of ~ 90 % was observed during the testing of the 6-month release.

3. Analytical methods for leuprolide (LC-MS/MS) and testosterone (RIA) are reported along with their validation reports. The analysis for leuprolide was specific. RIA employed for testosterone analysis had a cross reactivity potential of ——————————
However, the sponsor claims that due to the solvent extraction and chromatography processes carried out on the samples prior to the RIA of testosterone, the specificity of the method is supposedly increased beyond the low level of interference indicated by the cross-reactions.
4. Special populations: Race (no impact of ethnicity on PK or PD was observed), Geriatrics (majority (71 %) of patients were elderly males; mean age 74 years)
Women and pediatrics need not be addressed due to the proposed indication ————
cancer) which is a disease of adult male patients.
5. Drug-Drug interactions: No drug-drug interaction studies were conducted for Eligard 45 mg. Pharmacokinetic drug-drug interactions are unlikely to be observed with ELIGARD® 45 mg because leuprolide is primarily degraded by peptidase(s), and is less than —— bound in the plasma.
6. Population PK/PD analysis: PK subset included patients of varied races, age, disease state, body weight etc. Inter-individual variability in the PK of leuprolide was observed, but did not appear to influence the efficacy of the formulation. No correlation was seen between body weight and systemic drug exposure.

Recommendation:
The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II find that the Human Pharmacokinetics and Bioavailability section for NDA 21-731 is fileable.

Sandhya Kiran Apparaju, Ph.D., Primary Reviewer ____04/06/04_____

Ameeta Parekh, Ph.D., Team Leader ___04/06/04____

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sandhya Apparaju
4/7/04 02:53:33 PM
BIOPHARMACEUTICS

Ameeta Parekh
4/12/04 04:09:53 PM
BIOPHARMACEUTICS