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APPLICATION NUMBER

21-343

**Clinical Pharmacology and Biopharmaceutics
Review**

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA: 21-343

Drug: Leuprolide Acetate 7.5 mg
ELIGARD™ 7.5 mg

Sponsor: Atrix Laboratories, Inc.

Date of Submission: 03-23-2001

Type of Submission: Original NDA
Class: 3S

Reviewer: Myong-Jin Kim

I. EXECUTIVE SUMMARY

Leuprolide acetate is a potent GnRH agonist used clinically as a palliative treatment for advanced prostate cancer. While single dosing with leuprolide stimulates the release of LH and FSH, repeated dosing reduces circulating levels of LH, FSH and testosterone by decreasing or down regulating GnRH pituitary active receptors and depleting pituitary gonadotropin stores. Leuprolide acts by preventing pulsatile hypothalamic stimulation of the adenohypophysis, which results in reduced gonadotropic hormone release and suppression of gonadal testosterone to levels associated with surgical castration (≤ 50 ng/dL in serum). Currently approved leuprolide are as follow: depot IM (one-month 3.75 and 7.5 mg, three-month 11.25 and 22.5 mg, four-month 30 mg), daily 1 mg SC injection and leuprolide implant designed to deliver for 12 months.

ELIGARD™ (NDA 21-343) is an injectable polymer-based, extended-release formulation of leuprolide acetate designed to deliver a nominal dose of 7.5 mg leuprolide over a one-month period after SC injection. Leuprolide is contained within a biodegradable (lactic and glycolic acids) and biocompatible PLGH which can deliver the drug over a period of about one month.

To seek approval of the palliative treatment of advanced prostate cancer, the sponsor submitted two studies (AGL 9802, AGL 9904) which are included in the human pharmacokinetic section. The sponsor suggested that ELIGARD™ 7.5 mg may provide advantage over currently available leuprolide acetate depot products since lower overall testosterone concentrations and lack of testosterone breakthrough were observed.

A. RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed NDA 21-343 submitted on March 23, 2001. The overall Human Pharmacokinetic Section is acceptable to OCPB. Labeling comments outlined in the labeling section should be conveyed to the sponsor as appropriate.

/S/

Myong-Jin Kim, Pharm.D.

/S/

RD initialed by Ameeta Parekh, Ph.D., Team Leader

FT signed by Ameeta Parekh, Ph.D., Team Leader

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II. Table of Contents

I.	Executive Summary.....	1
	Recommendations.....	2
II.	Table of Contents.....	3
III.	Summary of Clinical Pharmacology and Biopharmaceutics Findings.....	5
IV.	Clinical Pharmacology and Biopharmaceutics Review	
	A. General attributes.....	7
	B. Clinical Pharmacology.....	8
	1. Pharmacokinetic Characteristics.....	9
	a. Absorption	
	b. Distribution	
	c. Metabolism and Excretion	
	2. Variability in Pharmacokinetics.....	10
	a. Single Dose	
	b. Multiple Dose	
	3. Intrinsic Factors	19
	4. Extrinsic Factors	22
	a. Drug Interaction	
	C. Biopharmaceutics.....	22
	1. Analytical Methods	
	2. <i>In vitro</i> dissolution	
V.	Labeling Recommendations.....	25
VI.	Appendices.....	28

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TERMS & ABBREVIATIONS

FSH.....	Follicle Stimulating Hormone
GnRH.....	Gonadotrophin-Releasing Hormone
.....
IM.....	Intramuscular
LH.....	Luteinizing Hormone
M-I.....	Leuprolide (5-9)-Pentapeptide
M-II.....	Leuprolide (5-7)-Tripeptide
M-III.....	Leuprolide (1-3)-Tripeptide
M-IV.....	Leuprolide (1-2)-Dipeptide
NMP.....	N-methyl-2-pyrrolidone
PK.....	Pharmacokinetic
PLGH.....	Poly (DL-lactide-co-glycolide) COOH
RIA.....	Radioimmunoassay
SC.....	Subcutaneous
.....
tldc.....	Time of Last Detectable Concentration

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III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Atrix Laboratories' extended release one-month formulation, ELIGARD™ 7.5 mg, consists of leuprolide acetate in the ATRIGEL® Delivery System and is administered by a different route (SC versus IM) than the currently marketed formulation.

The Human Pharmacokinetics and Bioavailability section included two clinical studies, AGL9802 and AGL 9904. A phase 1 study (AGL9802) evaluated the pharmacokinetics of leuprolide in 8 orchiectomized patients for 56 days after a single dose of ELIGARD™ 7.5 mg. A phase 3 study (AGL9904) evaluated the pharmacokinetics and pharmacodynamics of leuprolide in a subset of 20 patients with advanced prostate cancer during treatment with ELIGARD™ 7.5 mg, given monthly for 3 months.

Absorption: Mean serum ELIGARD™ 7.5 mg concentrations following the initial SC injection was 25.3 ng/mL (C_{max}) at approximately 5 hours after injection. 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 – 2.00 ng/mL). There was no evidence of significant accumulation during repeated dosing.

Distribution: 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).

Metabolism: No drug metabolism study was conducted with ELIGARD™ 7.5 mg. In animals, leuprolide was metabolized to the 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 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 (1.74 ng/mL) after 29 days (Ueno & Matsuo. J Chromatograph 1991;566:57-66).

Excretion: In healthy male volunteers, a 1 mg bolus of 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. Mean elimination $t_{1/2}$ and clearance were reported to be 3.6 h and 9.1 L/h, respectively, following single SC 1 mg SC injection (Sennello *et al.* J Pharm Sci 1986;75:158-60).

Intrinsic factors: NDA 21-343 does not contain population PK study/analysis. Women and pediatric subjects were not included in the clinical PK studies. Elderly patients made up a considerable portion of the patients studied in the clinical investigation (age range, 50 to 85 years). Patients studied ranged in weight from 63 to 109 kg and included both whites and Hispanics.

Extrinsic factors:

Drug Interactions

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. Because leuprolide is primarily metabolized via peptidase(s) (Chriap & Sorkin Drugs & Aging 1991;1:487-509), and is less than 50% bound in the plasma (PDR 1999), pharmacokinetic drug-drug interactions are unlikely to be observed with ELIGARD™ 7.5 mg. The effect of leuprolide on CYPs is unknown.

Biopharmaceutics:

The formulation used in Study AGL-9904 is identical to the to-be-marked formulation.

ELIGARD™ 7.5 mg is prefilled and supplied in two separate syringes, Syringes A (ATRIGEL® Delivery system containing poly polymer formulation dissolved in NMP solvent) and B (leuprolide acetate) whose contents are mixed immediately prior to administration. The two syringes are joined and the single dose product is mixed until it is homogenous. ELIGARD™ 7.5 mg is then administered SC where it forms a solid drug delivery depot.

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IV. Clinical Pharmacology and Biopharmaceutics Review

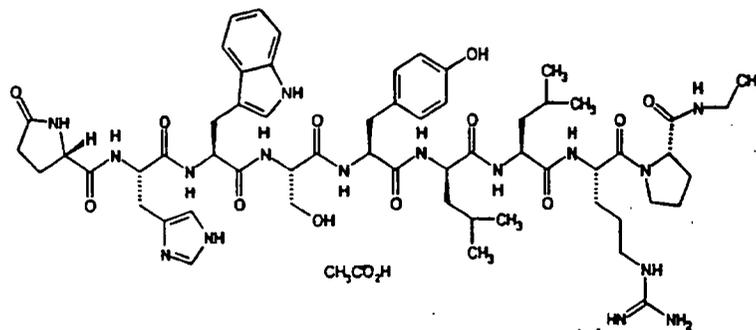
A. General Attributes

1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

a. Physico-chemical properties

Leuprolide acetate is a synthetic nonapeptide analogue of the naturally occurring GnRH. Replacement of the glycine residue at the 6th position in the decapeptide by the D-isomer of leucine and attachment of an ethylamide group to the carboxyl group of proline at position 9 gives the nonapeptide.

- Structural formula:



- Molecular Weight (free acid): 1269.5 (1209.4)
- Molecular Formula: C₅₉H₈₄N₁₆O₁₂·C₂H₄O₄
- IUPAC name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt)
- pK_a (histidine, tyrosine, guanidine groups): 6.0, 10.0, 13.0

b. Formulation

The formulation used in AGL-9904 is identical to the to-be-marked formulation. Study drug was manufactured by Atrix Laboratories. The lot numbers of ELIGARD™ 7.5 mg used in the Study AGL 9904 were 1144 and 1199. Lot 1144 was manufactured using leuprolide acetate supplied by [redacted] (Lot number VI7773), and Lot 1199 was manufactured using leuprolide acetate supplied by [redacted] (Lot number 521101).

Centers were resupplied with study drug as needed during the course of the study. No study drug was used past its expiration date.

Phase I Study (AGL9802): Lot No. 1105

Composition of Syringe A, Atrigel® Delivery System

Component	% w/w	mg/g
PLGH		340
NMP		660
Total Fill Weight: 370 mg		

Composition of Syringe B, Lyophilized Leuprolide Acetate

Component	mg/syringe
Leuprolide acetate	11.4

Composition of Reconstituted Delivery Product

Component	% w/w	mg
Leuprolide acetate		7.5
PLGH		82.5
NMP		160.1
Total Delivered Amount: 250 mg		

Phase III Study (AGL 9904): Lot No. 1144 & 1199

Leuprolide acetate 10.2 mg and ATRIGEL® Delivery System 330 mg were used since less overage was required to deliver 7.5 mg leuprolide acetate. The injection volume was 0.25 mL and the constituted product for these two lots contained w/w leuprolide acetate.

2. What is the proposed mechanism of action?

The therapeutic effects of leuprolide appear to be due to its ability to induce and maintain suppression of testicular androgen synthesis via its effects on pituitary LH release. Leuprolide acts by preventing pulsatile hypothalamic stimulation of the adenohypophysis, which results in reduced gonadotropic hormone release and suppression of gonadal testosterone to levels associated with surgical castration (≤ 50 ng/dL in serum).

3. What is the proposed indication and dose?

ELIGARD™ 7.5 mg SC is indicated for the palliative treatment of advanced prostate cancer.

B. General Clinical Pharmacology

What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Approximately 80% of prostate cancers are dependent on circulating androgens and are responsive to hormone manipulation. Synthetic GnRH agonist, leuprolide acetate, is

often used for obtaining “medical castration” by testosterone suppression. The castrate threshold of testosterone ≤ 50 ng/dL is used by the currently marketed formulation of leuprolide as the primary efficacy endpoint in pivotal clinical studies of GnRH agonists for the treatment of prostate cancer. In addition, testosterone suppression ≤ 50 ng/dL provides clinical benefits equivalent to surgical castration in prostate cancer patients.

Primary endpoint

- The proportion of patients whose serum testosterone concentration was suppressed to castrate levels (≤ 50 ng/dL) by Week 4 (Day 28).

Secondary endpoints

- The cumulative proportion of patients maintaining castrate testosterone suppression.
- The proportion of patients who did not maintain castrate testosterone suppression.

Definitions

- Suppression of testosterone concentration to castrate levels: serum testosterone ≤ 50 ng/dL for at least 2 consecutive time points approximately one week apart.
- Breakthrough: a patient’s testosterone being measured above 50 ng/dL after that patient has achieved castrate testosterone suppression.

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? (if yes, refer to IV. F, Analytical Section; if no, describe the reasons)

Yes. The primary efficacy variable for this study was serum testosterone concentration. Blood samples for pharmacokinetic analysis (serum leuprolide acetate quantitation) and testosterone concentrations 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, 63, 70, 77, and 84.

What are the basic pharmacokinetic characteristics of Leuprolide?

1. Pharmacokinetics (ADME)

a. Absorption

In a multiple dose study (AGL 9904), mean serum ELIGARD™ 7.5 mg concentrations following the initial SC injection rose to 25.3 ng/mL (C_{max}) at 4.6 hr 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: at 24 h they ranged from $\mu\text{g/mL}$ to ng/mL (5.86 ± 2.62 ng/mL). Thereafter the decline in serum concentrations occurred more gradually to reach plateau levels. After the initial increase following each injection, serum concentrations remained relatively constant (0.28 – 2.00 ng/mL). There was no evidence of significant accumulation during repeated dosing. Mean serum leuprolide levels measured 28 days

after each of SC doses administered monthly for 3 months (0.417 ± 0.389 , 0.445 ± 0.199 , 0.453 ± 0.192 ng/mL, respectively) did not differ ($p > 0.05$).

b. Distribution

The literature reported mean $V_{d_{ss}}$ of leuprolide 26.5 ± 10.1 L following 1 mg IV bolus administration to healthy male volunteers (Sennello *et al.* J Pharm Sci 1986;75:158-60). The mean Vd was 33.50 ± 3.54 L using leuprolide depot (TAP 144 SR) 7.5 mg SC (Mazzei *et al* Drugs Exptl Clin Res 1989;8:373-87). In vitro binding to human plasma proteins ranged from 43% to 49% (PDR 1999).

c. Metabolism and Excretion

Metabolites of leuprolide were not measured in this study.

In animals, leuprolide was metabolized to the 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 (1.74 ng/mL) after 29 days (Ueno & Matsuo. J Chromatograph 1991;566:57-66).

No drug excretion study was conducted with ELIGARD™ 7.5 mg SC. 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). The mean systemic clearances of leuprolide was 9.1 L/h with a terminal elimination $t_{1/2}$ of 3.6 h after a 1 mg SC leuprolide administration (Sennello *et al.* J Pharm Sci 1986;75:158-60).

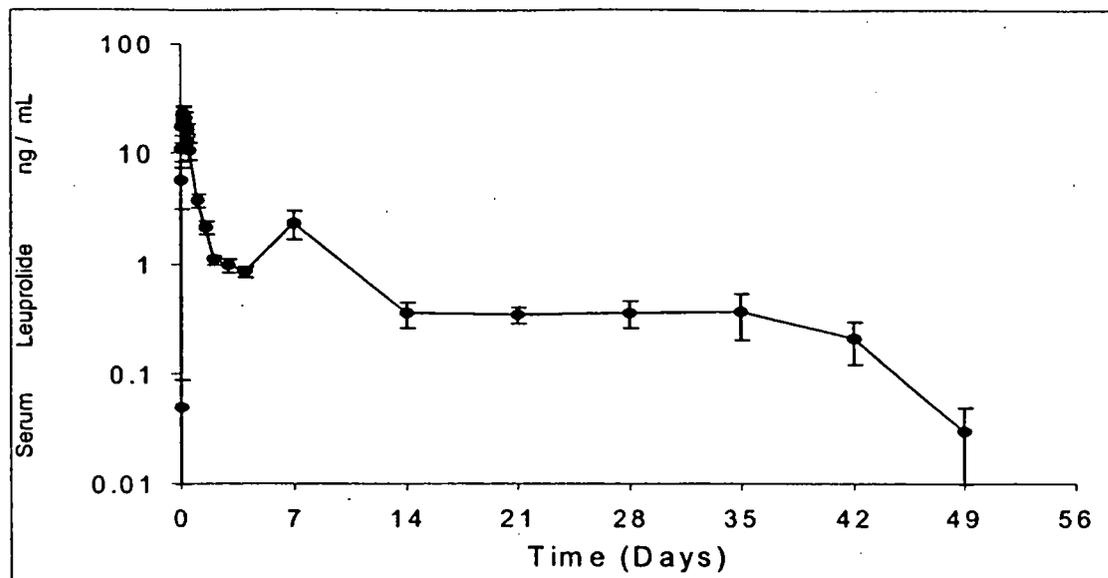
2. Variability in Pharmacokinetics

a. Single Dose PK (Study AGL 9802)

Table 1. Mean Pharmacokinetic Parameters of ELIGRD™ 7.5 mg SC after Single Dose Administration.

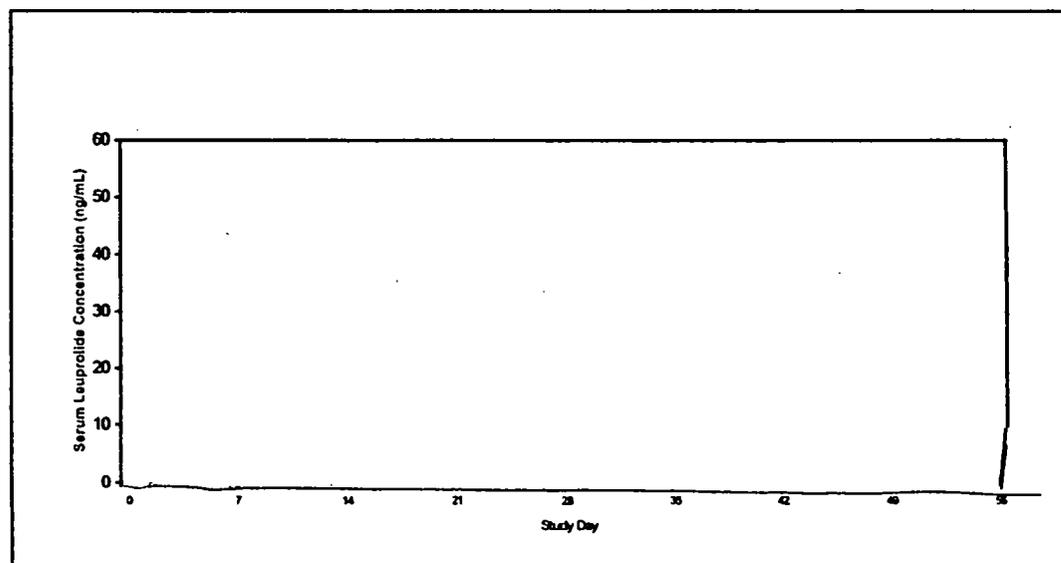
	Single Dose PK Mean ± SD (range)
C_{max} (ng/mL) (Burst Phase, Day 0-2)	26.3 ± 12.6 (11.7-50.7)
T_{max} (hr) (Burst Phase, Day 0-2)	3.79 ± 1.39 (2.00-5.88)
AUC _{0-tlhc} (ng*h/mL)	999 ± 247
AUC ₀₋₂ (ng*h/mL) (Burst Phase, Day 0-2)	351 ± 144
AUC _{2-28d} (ng*h/mL) (Plateau Phase, Day 2-28)	515 ± 266
AUC _{0-28d} (ng*h/mL)	866 ± 241
tlhc (day)	37 (28-49)

Figure 1. Serum Leuprolide Concentrations (Mean, SEM) Following a Single SC Injection of ELIGARD™ 7.5 mg in 8 Orchiectomized Subjects (Study AGL 9802).



Following SC administration of leuprolide acetate, there was an initial rapid absorption phase with maximal concentrations observed at 2-6 hours. The serum leuprolide concentrations fell slowly over 4-6 days and remained detectable for at least 28 days in all subjects. A surge or increase in leuprolide concentration within the first 10 days followed by a plateau period, where concentrations declined very slowly over several weeks was observed. The AUC(0-t_{ldc}) was 999 ± 247 ng·h/mL and was characterized by an inter-subject variability of 24.7%. About 13% of the total AUC was observed after 28 days. Serum levels below quantitation (0.1 ng/mL) were observed in 3/8, 4/8 and 6/8 subjects on Day 35, 42, and 49, respectively.

Figure 2. Serum Leuprolide Concentrations Following a Single SC Injection of ELIGARD™ 7.5 mg in Each Subject (n=8) (Study AGL 9802)



A slight surge or increase in serum leuprolide concentration at Day 7 was seen in 6 of 8 patients. The net increases ranged from _____ ng/mL with a mean of 2.25 ng/mL. Similarly, a second increase in leuprolide concentrations was observed in the majority of the patients at all doses (3.75, 7.5 and 15 mg) of leuprolide depot (TAP-144-SR) tested during the terminal release phase (Day 14 – Day 42) (Mazzei *et al* Drugs Exptl Clin Res 1989;8;373-87).

b. Multiple dose PK (Study AGL 9904)

Table 2. Pharmacokinetic Parameters of ELIGARD™ 7.5 mg SC After Multiple Dose Administration.

No. of Dose given	Multiple Dose PK	
	Mean ± SD	(range)
C_{max} (ng/mL) (Burst Phase, Day 0-2)	25.3 ± 11.3	N/A
T_{max} (hr) (Burst Phase, Day 0-2)	4.6 ± 1.4	N/A
AUC ₀₋₂ (ng*h/mL) (Burst Phase Day 0-2)	435.3 ± 146.3	N/A
AUC ₀₋₂₈ (ng*h/mL)	873.4 ± 228.9	N/A
AUC ₂₋₂₈ (ng*h/mL) (Plateau Phase, Day 2-28)	438.1 ± 185.0	499.6 ± 282

The pharmacokinetics of leuprolide in serum during monthly treatment with ELIGARD™ 7.5 mg were multiphasic (Figure 3). Based on the AUC reported for 1 mg IV injection of leuprolide acetate (125.8 ng*hr mL⁻¹) (Sennello *et al.* J Pharm Sci 1986;75:158-60), the absolute bioavailability of the first dose of SC ELIGARD™ 7.5 mg injection was 93 ± 24%. The average serum concentration of leuprolide during the plateau phase after each three doses was 0.70 ng/mL, suggesting that leuprolide was delivered at a rate of approximately 140 µg/day during this period [(0.7 ng/mL)*(8.34L/hr)].

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Table 3. Summary of ELIGARD™ 7.5 mg SC Pharmacokinetic Parameters After the First of Three Monthly Doses (Study AGL9904, n=20). Bioavailability (F) based on reported AUC of intravenous leuprolide.

Subj. No.	Burst Phase (Day 0-2)			Plateau Phase (Day 2-28)			Total (Day 0-28)	
	AUC ng hr mL ⁻¹	Cmax ng/mL	Tmax Hr	AUC ng hr mL ⁻¹	Cmax ng/mL	Cmin ng/mL	AUC ng hr mL ⁻¹	F fraction
201								
801								
1401			4					
1402			4					
1403			8					
1404			4					
1405			4					
1406			4					
1801			4					
1802			4					
2001			4					
2002			4					
2101			4					
2102			4					
2103			4					
2104			4					
2105			8					
2201			4					
2202			4					
2301			8					
MEAN	435.3	25.3	4.6	438.1	2.68	0.169	873.4	0.93
SD	146.3	11.3	1.5	185.0	0.98	0.11	228.9	0.24
RSD	33.6	44.9	31.9	42.2	36.6	67.3	26.2	26.2
MIN								
MAX								

Table 4. Summary of ELIGARD™ 7.5 mg SC Pharmacokinetic Parameters During the Plateau Phase Following the Second and Third of Three Monthly Doses (Study AGL9904, n=20).

Subj. No.	Second Dose Plateau Phase (Day 31-56)			Third Dose Plateau Phase (Day 59-84)		
	AUC ng hr mL ⁻¹	Cmax Ng/mL	Cmin ng/mL	AUC ng hr mL ⁻¹	Cmax ng/ml	Cmin ng/ml
201						
801						
1401						
1402						
1403						
1404						
1405						
1406						
1801						
1802						
2001						
2002						
2101						
2102						
2103						
2104						
2105						
2201						
2202						
2301						
MEAN	499.6	2.02	0.360	475.7	1.78	0.328
SD	282	1.8	0.15	158.6	1.16	0.14
RSD%	56.4	89	42	33.3	65.1	41.4
MIN						
MAX						

Do PK parameters change with time following chronic dosing?

There was no evidence of significant accumulation during repeated dosing with SC ELIGARD™ 7.5 mg in this study. Mean serum leuprolide levels measured 28 days after each dose did not differ (p>0.05).

	1 st dose of leuprolide	2 nd dose of leuprolide	3 rd dose of leuprolide
serum leuprolide levels measured 28 days after each dose (ng/mL)	0.417 ± 0.389	0.445 ± 0.199	0.453 ± 0.192

Mean leuprolide serum levels during the plateau phases ranged from 0.28 – 2.00, 0.45 – 1.67, and 0.45 – 1.55 ng/mL for the plateau phases from Days 2-28, 31-56 (Days 2-28 from the 2nd dose) and 59-84 (Days 2-28 from the 3rd dose), respectively.

The apparent decrease in C_{max} values in Figures 4 & 5 was a result of the reduced number of sampling time points after the second and third doses. Earliest serum leuprolide concentrations were measured at Hours 4 and 8 post-dosing after the 1st dose; at Hour 8 after the 2nd dose; and Day 1 after the 3rd dose.

Values of C_{max} , C_{min} and AUC during the plateau phase were similar after each of the three doses (Tables 3 & 4). The mean pharmacokinetic parameters after the 1st dose in this Phase 3 study (AGL9904) were nearly identical to those observed in the single-dose Phase 1 study (AGL9802), with burst phase C_{max} values of 25.3 and 26.3 ng/mL, plateau phase C_{max} values of 2.69 and 2.68 ng/mL, plateau phase C_{min} values of 0.175 and 0.169 ng/mL, and AUC_{0-28} values of 873 and 866 ng hr mL⁻¹, respectively.

How long is the time to the onset of the pharmacological response or clinical endpoint?

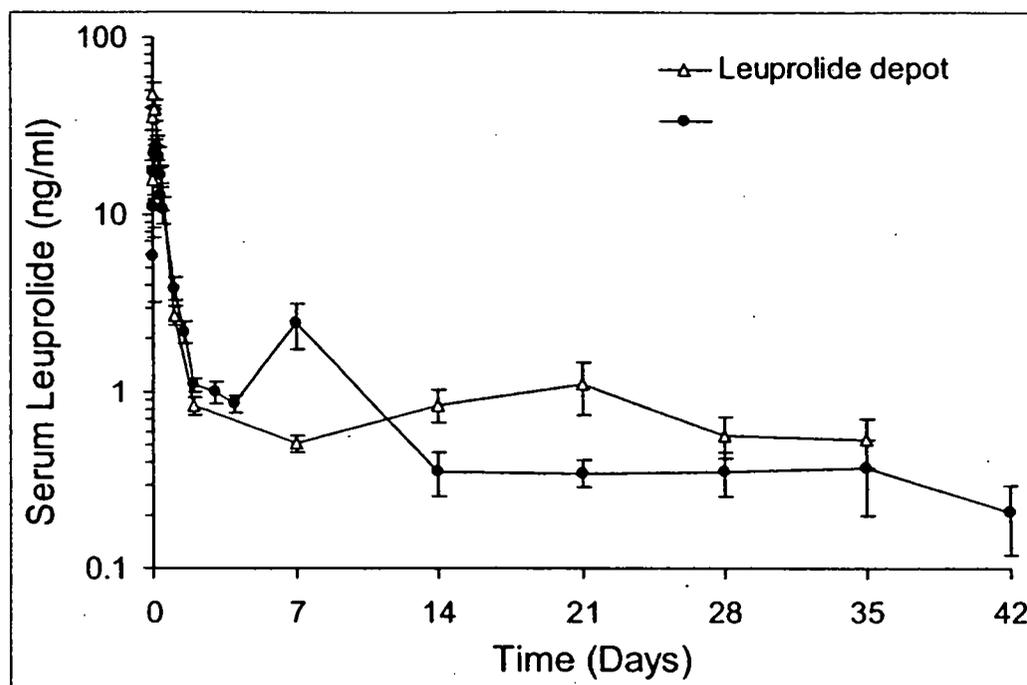
By Day 21, the mean testosterone concentration (43.31 ng/dL) was below castrate threshold (≤ 50 ng/dL). The median time to castrate suppression was 21 days, and the mean time to castrate suppression was 21.6 days. By Study Day 28, 112 of the 119 (94%) patients (Study AGL 9904) had achieved testosterone suppression, and by Study Day 42, all 118 patients had achieved this measure.

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Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response?

Figure 3. Comparison of serum leuprolide concentrations (mean, SEM) after a single SC administration of ELIGARD™ 7.5 mg (Study AGL9802) or a leuprolide depot formulation (TAP-144-SR) at 7.5 mg SC (Mazzei *et al.*, J Int Med Res 1990)



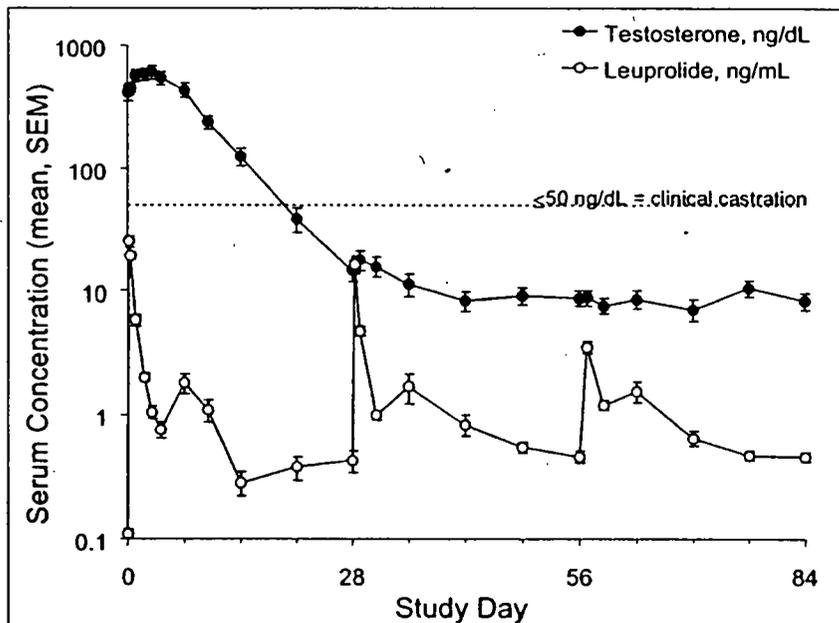
The dose of ELIGARD™ 7.5 mg was selected based on the dose of active drug delivered by other approved effective depot preparations of leuprolide acetate and the proven safety and efficacy of a one-month 7.5 mg approved leuprolide acetate depot formulation currently available.

ELIGARD™ 7.5 is intended for use in single unit dose (7.5 mg SC per month) for all patients. ELIGARD™ 7.5 mg produced a serum leuprolide concentration profile similar to that of the dose shown to be effective in a dose-response study of 1-month leuprolide depot formulations (Mazzei *et al* J Int Med Res 1990;18:42-56) (Figure 3). Patients in clinical PK studies of ELIGARD™ 7.5 mg received a unit dose of 7.5 mg, resulting in weight-normalized doses ranging from 70 to 120 µg/kg. There was no evidence of significant PK variability over this range of doses, with serum leuprolide remaining at effective levels (>0.1 ng/mL) in all patients over the course of treatment.

Administration of ELIGARD™ 7.5 mg provided sustained serum leuprolide levels of > 0.1 ng/mL in patients whose body weights ranged from 63 to 109 kg, with mean serum levels of approximately 0.4 ng/mL at the end of each one-month dosing interval. The threshold for effective leuprolide in the serum is 0.1 ng/mL. Because serum leuprolide levels below 0.1 ng/mL may be associated with incomplete suppression of pituitary gonadotrope secretion (Tunn *et al* Urol Int 1998;60:9-17), and the wide safety margin of leuprolide acetate, lower doses were not investigated by the sponsor.

Two studies which compared 3.75 mg and 7.5 mg leuprolide acetate suggested a trend (not statistically significant) toward a better objective response with the larger dose (Akaza *et al* *J Intl Med Res* 1990;18:90-102, Akaza *et al* *Jpn J Clin Oncol* 1992;22:177-84). In a dose response study, a slow-release depot formulation (TAP-144-SR) by SC injection at doses of 3.75, 7.5 and 15 mg showed no significant differences in the concentrations of testosterone at Days 2, 14, and 35 as a function of dose (Mazzei *et al* *Drugs Exptl Clin Res* 1989;8:373-87). A rapid decline occurred to castration levels within the third week and maintained for the entire observation time, independently of dose. During the terminal release phase, a secondary increase in leuprolide concentrations was observed in the majority of the patients at all doses tested (Mazzei *et al* *Drugs Exptl Clin Res* 1989;8:373-87). Studies with other SC leuprolide formulations have shown dose proportional pharmacokinetics with a depot formulation over a dose range of 3.75 to 15 mg (Mazzei *et al* *J Int Med Res* 1990;18:42-56).

Figure 4. Pharmacodynamic response to ELIGARD™ 7.5 mg showing serum leuprolide levels and serum testosterone reduction after repeated SC administration at one month intervals in advanced prostate cancer patients (n = 20) dosed on Days 1, 28 and 56 (Study AGL9904).



After each injection, mean serum leuprolide levels peaked during the first day, then fell rapidly to sustained levels between 0.2 – 2 ng/mL. In response to this pattern of leuprolide exposure, mean serum testosterone levels rose initially, from 408 ± 60 ng/dL at Baseline to 600 ± 74 ng/dL on Day 3, then decreased to below castrate levels within 3 weeks after the 1st dose (38 ± 9 ng/dL on Day 21). Mean serum testosterone remained relatively constant (7.1 – 17.9 ng/dL) for the rest of the 84-day study. The maximum serum testosterone concentration observed in any patient at any time point after Day 21 was 59 ng/dL (Baseline testosterone, 1173 ng/dL: testosterone suppression at Day 31).

Thus, despite the marked fluctuations in serum leuprolide levels resulting from the burst followed by sustained release profile of once monthly ELIGARD™ 7.5 mg, no clinically significant fluctuations were observed in serum testosterone levels, which remained continuously suppressed once they had fallen to castrate levels.

Figure 5. Serum Leuprolide Concentrations Following Three SC Injections of ELIGARD™ 7.5 mg in Each Subject (n=20) (AGL 9904).

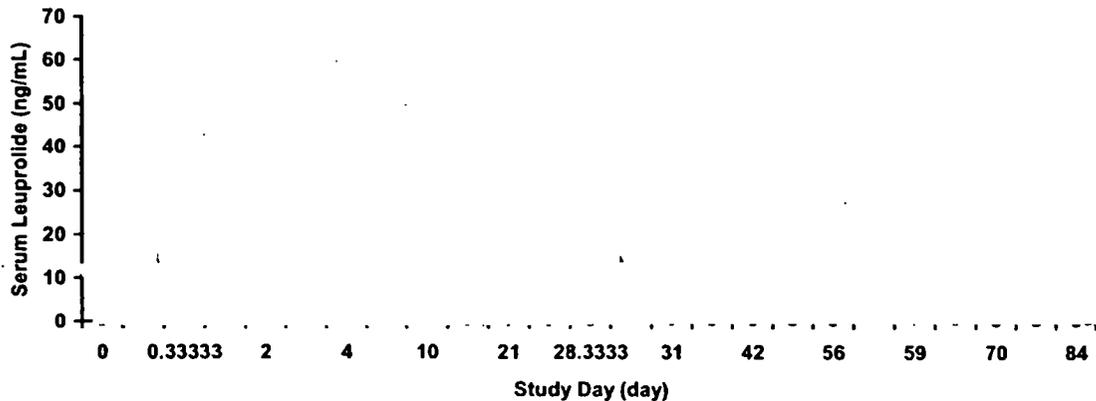
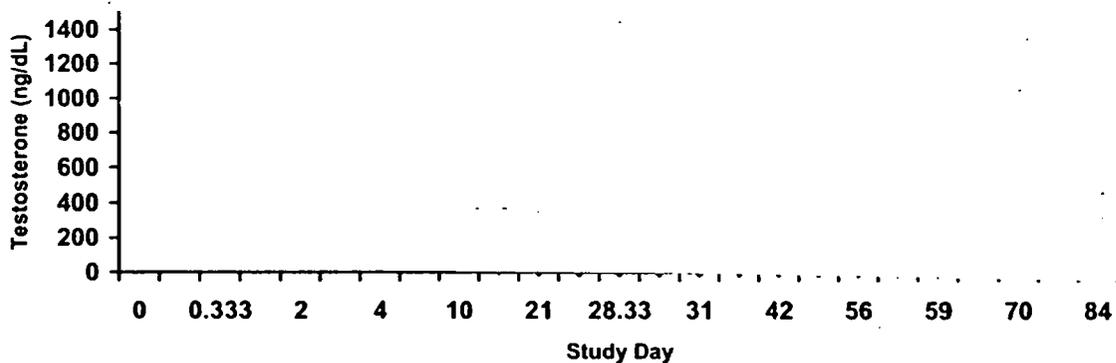


Figure 6. Total Testosterone Concentrations Following Three SC Injections of ELIGARD™ 7.5 mg in Each Subject (n=20) (AGL 9904).

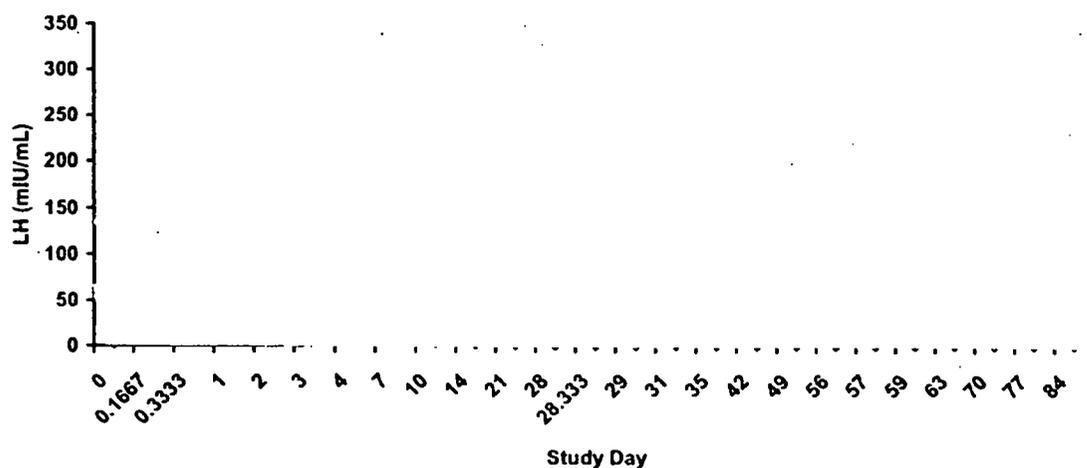


The mean Baseline testosterone concentration of 19 patients in Study AGL 9904 was 407.84 ± 263.15 ng/dL (range, _____ ng/dL). The block of testicular androgens was preceded by a transitory increase within the first week, corresponding to the initial stimulation of the pituitary gonadotrophins.

Analysis of the effect of Baseline testosterone concentration on time to testosterone suppression showed a highly statistically significant positive correlation ($p = 0.002$). Patients with higher Baseline testosterone achieved castrate testosterone suppression more slowly than those patients with lower Baseline testosterone. Seven patients in the observed population ($n=119$, Study AGL 9904) did not attain castrate suppression within 28 days following the Baseline leuprolide injection. Of these patients, 2 had Baseline

testosterone levels greater than two standard deviations above the overall Baseline mean. The remaining 5 patients were within one standard deviation of the Baseline mean.

Figure 7. LH Concentrations Following Three SC Injections of ELIGARD™ 7.5 mg in Each Subject (n=20) (Study AGL 9904).



The mean Baseline LH concentration was 11.60 ± 10.19 mIU/mL (range, mIU/mL). Analysis of the testosterone suppression response related to Baseline LH concentration indicated no effect on time to testosterone suppression ($p > 0.05$).

How does the systemic exposure change with various intrinsic and extrinsic factors? Is there a need for dosage adjustment or contraindication/caution with these factors?

3. Intrinsic Factors

NDA 21-343 does not contain population PK study/analysis.

Slightly higher serum leuprolide levels would be expected in patients with pronounced renal dysfunction with no clinical relevance (Wechsel *et al* Eur Urol 1996;30:7-14). Although none of the patients in the clinical PK studies had evidence of severe renal or hepatic disease, 3 of 20 patients in the phase 3 study (Study AGL 9904) had baseline urea nitrogen > 40 mg/dL and/or creatinine > 1.5 mg/dL. Due to the wide therapeutic index of leuprolide, the pharmacokinetic variations observed were not of sufficient magnitude to affect the efficacy and safety of ELIGARD™ 7.5 mg.

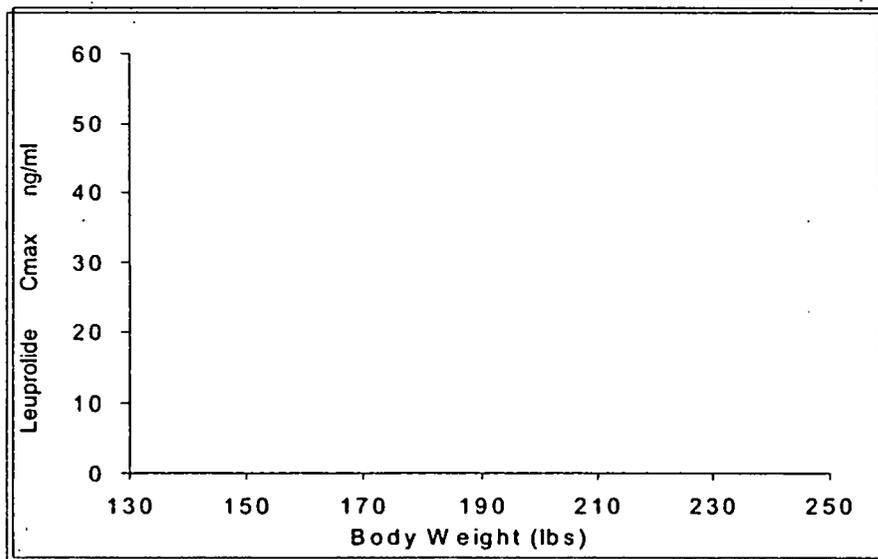
Since the indication sought is for the palliative treatment of advanced prostate cancer, women and pediatric subjects were not included in the clinical PK studies.

Race: The clinical PK study of ELIGARD™ 7.5 mg (AGL 9904) included both white (n=18, 90%) and Hispanic (n=2, 10%) patients. PK of leuprolide and testosterone suppression was similar in this population.

Age: Elderly patients made up a substantial portion of the patients studied in the clinical investigation of ELIGARD™ 7.5 mg. Patients in the PK subset had a mean age of 75.6 years (range, 62-83 years, with 85% over age 70).

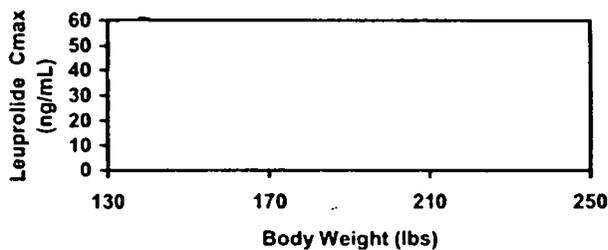
Weight: Patients (n=20) studied ranged in weight from 63 to 109 kg with a mean body weight of 78.9 kg. Patients in clinical PK study received a unit dose of 7.5 mg, resulting in weight-normalized doses ranging from 69 to 119 µg/kg. There was no evidence of significant PK variability over this range of doses, with serum leuprolide remaining at effective levels in all patients over the course of treatment.

Figure 8a. Relationship of PK Parameters to Subject Body Weight (Studies AGL 9802 & 9904, n=26).



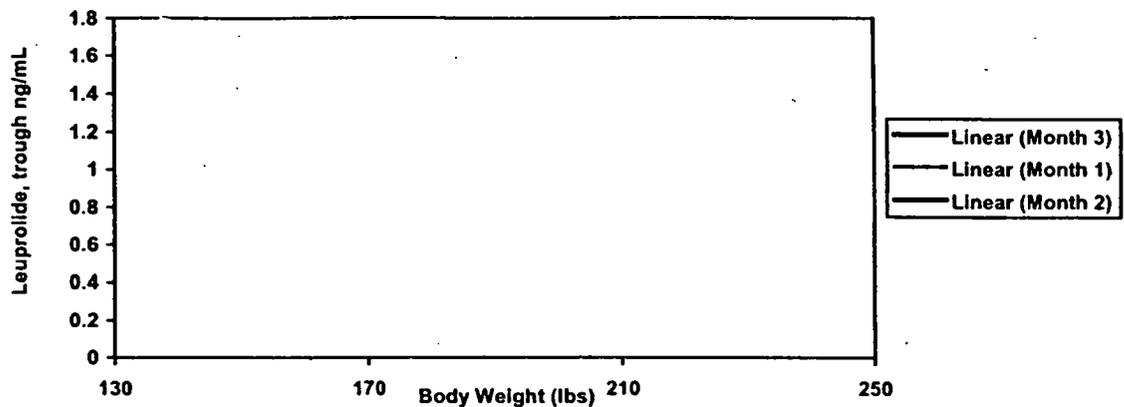
Individual values of leuprolide C_{max} are plotted against body weight for each subject who received ELIGARD™ 7.5 mg in Studies AGL9802 (circles) and AGL9904 (triangles).

Figure 8b. Relationship of PK Parameter (C_{max}) to Subject Body Weight (Study AGL9904, n=20).



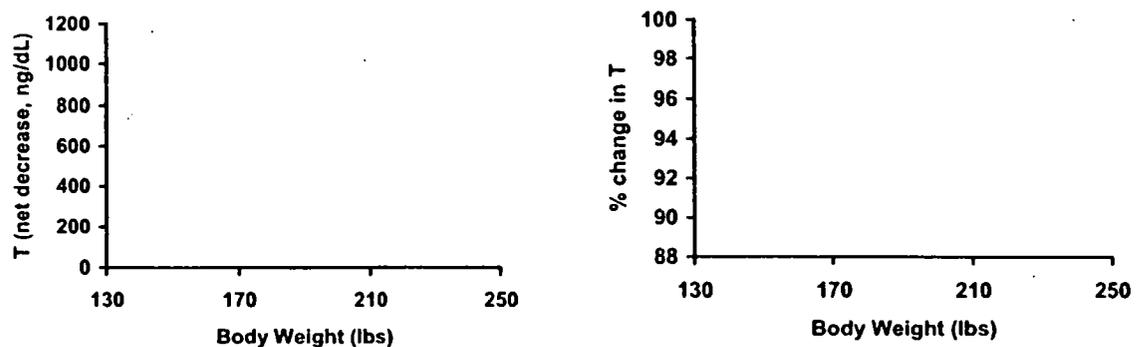
Individual values of leuprolide C_{max} are plotted against body weight for each subject who received ELIGARD™ 7.5 mg in Study AGL9904 (n=20). Serum leuprolide exposures tended to be lower in patients with greater body weights (p=0.005).

Figure 8c. Relationship of PK Parameter (trough) to Subject Body Weight, Study AGL9904 (n=20).



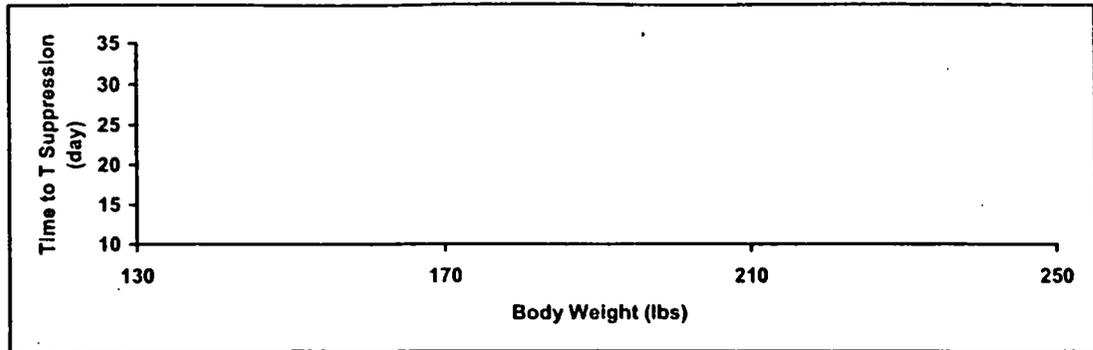
The serum leuprolide concentrations (trough) at Day 28, Day 56, and Day 84 prior to next dose of leuprolide were plotted against body weight for each subject. Analyses of the serum leuprolide trough concentrations related to Baseline weight indicated no effect at Day 28 (p>0.05), Day 56 (p>0.05) and Day 84 (p>0.05).

Figure 9a. Relationship of Response (Testosterone \leq 50 ng/dL) to Subject Body Weight at Day 28 (Study AGL 9904, n=19).



The net decrease of testosterone levels at Day 28 from the Baseline tended to be lower in patients with greater body weights. However, this trend was not observed when the percent (%) changes of testosterone at Day 28 from the baseline were evaluated.

Figure 9b. Relationship of Response (Time to Testosterone \leq 50 ng/dL) to Subject Body Weight at Day 28 (n=19).



Analysis of the testosterone suppression response (testosterone \leq 50 ng/dL) related to Baseline weight indicated no effect on time to testosterone suppression ($p > 0.05$).

4. Extrinsic Factors

a. Drug Interactions

No PK drug-drug interaction studies were performed with ELIGARD™ 7.5 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. Because leuprolide is primarily metabolized via peptidase(s) (Chriap & Sorkin Drugs & Aging 1991;1:487-509), and is less than 50% bound in the plasma (PDR 1999), PK drug-drug interactions are unlikely to be observed with ELIGARD™ 7.5 mg. The effect of leuprolide on CYPs is unknown.

C. BIOPHARMACEUTICS

What are the differences between clinical formulation and to be marketed formulation?

The formulation used in Study AGL-9904 is identical to the to-be-marked formulation.

1. Analytical Methods

	LEUPROLIDE	TESTOSTERONE
Study No.	AGL9802/AGL9904	AGL9904
Type of Biological Fluid		
Assay Method		
Sensitivity (LOQ)		
Recovery		
Linearity		
QC Sample		
Inter-Assay Precision		
Inter-Assay Accuracy		
QC Sample		
Intra-Assay Precision		
Intra-Assay Accuracy		
Selectivity (parent/metabolites)		
Cross-Reactivity		

*(<0.1 ng/mL)

LEUPROLIDE: Serum leuprolide concentrations were measured by a RIA method. To decrease the potential for metabolite cross-reactivity in the assay, serum samples were subjected to a purification procedure, involving , prior to the RIA determination. The validated range of the assay was ng/mL. Samples with concentrations above ng/mL were diluted and re-assayed.

TESTOSTERONE: Testosterone was first extracted from serum with hexane/ethyl acetate, and then further purified with : elution with ethanol in hexane. The purification had a recovery of approximately % . The lower limit QC testosterone sample (ng/dL) had a bias of % . Intra-assay and inter-assay precision for the lower limit QC samples were between and % .

The selectivity of the assay was determined by analyzing samples (ng/mL in water) of four peptides, corresponding to known metabolites M-I, M-II, M-III and M-IV. Metabolite M-I had cross-reactivity to a significant extent with the bioassay. It has been reported that concentrations of metabolite M-I range from 6% to 20 % of serum leuprolide concentrations following administration of a leuprolide acetate depot formulation (TAP Pharmaceuticals, 2000). Thus, the serum concentrations of leuprolide reported in the two clinical PK studies (AGL9802/AGL9904) may be overestimates of the true concentrations by approximately 3 to 10 % as a result of metabolite M-I cross-reactivity in the bioassay. The observed cross-reactivity is unlikely to have a significant effect on the outcome of clinical PK studies.

The assay selectivity was determined for 22 naturally-occurring and therapeutic steroids. Of these, only dihydrotestosterone had significant cross-reactivity in the assay.

2. *In vitro* Dissolution

The extended release test method T452 is a quality control test for a robust product and uses accelerated release conditions and is not intended to correlate with the *in vivo* release profile.

The extended release data from the clinical (Lots 1144 & 1199) and the primary stability lots (Lots 1197, 1268, 1270) demonstrated wide variability between the lots.

Sampling Time	Clinical Lots (1144 & 1199) (Range %)	Clinical & Stability Lots (Range %)
2 hr	6.9 – 11.2	4.4 – 11.2
5 hr	28.1 – 35.1	16.4 – 37.4
8 hr	50.1 – 62.2	32.0 – 64.0
10 hr	58.0 – 68.7	40.6 – 71.7
12 hr	61.9 – 78.2	47.1 – 82.6
24 hr	95.7 – 111.9	88.5 – 111.9

ELIGARD™ 7.5 mg is prefilled and supplied in two separate syringes, Syringes A (ATRIGEL® Delivery system containing poly polymer formulation, PLGH, dissolved in NMP solvent) and B (leuprolide acetate) whose contents are mixed immediately prior to administration within 30 minutes. Therefore, although the *in vitro* dissolution specification is usually set at the mean specification value $\pm 10\%$, mean $\pm 15\%$ at the 10-hour timepoint were proposed after the discussion with the OCPB Division Management and Chemistry. The specification for the acceptance criteria were set based on data from the 10-hour timepoint, and the variability shown between the clinical lots ranged from 58–69%. Therefore, the Division offered the sponsor 2 choices on 12/20/2001:

1. Mean of 58-69% (63) $\pm 15\%$ for a range of 48-78% OR
2. Set the range at 40-70% since there were little data above 70% at this timepoint.

The following *in vitro* dissolution specifications for the acceptance criteria were accepted by the sponsor on 12/21/2001. These acceptance criteria were acceptable to the Division.

In Vitro Dissolution Specification

Extended Release Sampling Time	<i>In vitro</i> dissolution specification
2 hr	NMT %
10 hr	42 – 72 %
24 hr	NLT %

NLT = not less than; NMT = not more than

V. LABELING

The following edited labeling comments (Clinical Pharmacology and Pharmacokinetics sections) were conveyed to the sponsor. The revised labeling was acceptable to DRUDP with some modification and the Atrix Labs accepted the final label on 16/JAN/02.

Draft

2 pages redacted from this section of
the approval package consisted of draft labeling

Atrix Laboratories, Inc. AGL9802
September 23, 1999

SYNOPSIS

Name of Company:	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Atrix Laboratories, Inc.	Volume:	
Name of Finished Product:		
LA-2500		
Name of Active Ingredient:	Page:	
Leuprolide acetate		

Title of Study: A Two-Month, Open-Label, Noncontrolled, Fixed-Dose Study to Evaluate the Safety, Tolerance, and Pharmacokinetics of a Single Monthly Dose of LA-2500 (7.5 mg Leuprolide Acetate SC) in Orchiectomized Subjects with Advanced Prostatic Cancer

Investigator/Study centers: Daniel Robin Saltzstein, MD, Urology San Antonio Research, San Antonio, TX; Lane Clifford Childs, MD; Western Urological Clinic; Salt Lake City, Utah

Publication (reference): N/A

Studied period (years): 2 months

Phase of Development:

Date of first enrollment: 2/10/99

Phase 1 Pharmacokinetic

Date of last completed: 5/26/99

Objectives: The objectives of this study were to evaluate the safety, tolerance, and pharmacokinetic (PK) profile of leuprolide acetate following a single monthly dose of LA-2500 in orchiectomized subjects with advanced prostate cancer.

Methodology: This was a noncontrolled, noncomparative study. All subjects received a single dose of the study drug and were followed for two months thereafter. Subjects received one subcutaneous injection of LA-2500 into the upper right or upper left quadrant of the abdomen using a half-inch, 20-gauge hypodermic needle.

Number of subjects (planned and analyzed): 8 subjects were enrolled and analyzed.

Diagnosis and main criteria for inclusion: All subjects were male, between the ages of 45-85 years, had adenocarcinoma of the prostate, and had been orchiectomized at least two months prior to study start. Subjects 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.

Test product, dose and mode of administration, batch number: The investigational product, LA-2500, 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 of leuprolide acetate. Due to the viscous nature of the formulation, an overage of polymer solution and drug substance was provided to ensure delivery of 250 mg of the formulation and 7.5 mg of leuprolide acetate. Test article was manufactured by Atrix Laboratories. The lot number of the LA-2500 used in the study was 1105.

Duration of treatment: The approximate duration of treatment after the single depot LA-2500 injection, as indicated by measurable serum leuprolide levels, ranged from 28-49 days (mean=37 days).

Reference therapy, dose and mode of administration, batch number: N/A

CRITERIA FOR EVALUATION:

Pharmacokinetics: Blood samples for leuprolide PK analyses were taken at all scheduled visits beginning with the Baseline (pre-dose) visit.

Safety: Clinical laboratory measurements (hematology, coagulation, serum chemistry, urinalysis) were assessed for safety at Screening, Hours 24, 72, Days 7, 14, 28, and 56 for all subjects. Additionally, assessment of safety was measured via the collection of adverse event information at all visits beginning with the Baseline visit. Vital signs, including heart rate, blood pressure, respiratory rate, and temperature were collected for safety at Screening, Baseline, Minute 30, Hours 4, 12, 24, 48, and 72, and Days 28 and 56.

Statistical methods: Serum concentrations of leuprolide were summarized as mean, standard deviation, % relative standard deviation, N, median, minimum, and maximum based upon nominal times. Descriptive statistics were also determined separately for the two study centers. Plots of serum concentration versus time data were prepared using nominal times for mean concentration plots and actual times for individual concentration plots.

Pharmacokinetics parameters included the maximal observed leuprolide concentration (C_{max}), the time of maximal serum concentration (T_{max}), the time of last measured leuprolide concentration in serum (tldc), and area under the leuprolide serum concentration versus time curve (AUC) for various time periods (0-28 days, 0-tldc days, 28-tldc days and potentially other time intervals). The AUC was determined by linear trapezoidal interpolation for the time limits (0-tldc) and (0-28 days), which is the anticipated dosing interval. A third AUC parameter, AUC(28-tldc) was determined as the difference between AUC(0-tldc) and AUC(0-28). Actual times were used for the pharmacokinetic analysis. Summary statistics for pharmacokinetic parameters were performed for all subjects combined and for subjects within the two treatment centers.

Clinical laboratory tests and analysis of adverse events were analyzed using descriptive statistics (mean \pm standard deviation) where possible to assess the safety of study drug, laboratory measurements (hematology, coagulation, serum chemistry, urinalysis), adverse events, and concomitant medications.

SUMMARY - CONCLUSIONS

PHARMACOKINETIC RESULTS: Following subcutaneous administration of leuprolide acetate there was an initial rapid absorption phase with maximal concentrations observed at 2-6 hours. The serum leuprolide concentrations fell slowly over 4-6 days and remained detectable for at least 28 days in all subjects. It was common to observe a "bump" or increase in concentration within the first 10 days, followed by a plateau period where concentrations declined very slowly over several weeks. The mean maximal concentration was 26.3 ± 12.6 ng/ml with a mean T_{max} of 3.79 ± 1.39 hours. Serum leuprolide levels were detectable for a mean of 37 days (range 28-49 days). The AUC(0-tldc) was 999 ± 247 ng*h/ml and was characterized by low inter-subject variability (CV=24%). Only about 10% of the total AUC was observed after 28 days, indicating that accumulation following multiple dosing at 28-day intervals would be small. Pharmacokinetic parameters were similar comparing subjects by study site; however, a statistical comparison was not performed due to the small sample size.

SAFETY RESULTS: No serious treatment-related adverse events were reported during the study. There were no discontinuations owing to adverse events. No trends for clinically relevant abnormalities of laboratory safety tests were noted during the study.

The all-causalities adverse events reported by the most subjects were: discomfort upon injection (7/8), bruise at injection site (3/8), hot flashes (2/8), and gastrointestinal disturbances (2/8).

The total treatment-related, treatment-emergent adverse events reported by the subjects were: mild discomfort upon injection (3/8), mild hot flashes (1/8), and mild erythema at the injection site (1/8).

Discomfort upon injection of LA-2500 was mild and transient, lasting only a few seconds in six subjects, and for less than a few minutes in one subject. One subject reported no discomfort upon injection.

There was no evidence of local hypersensitivity reactions at the site of injection in any subjects. There was no evidence of any acute or chronic systemic hypersensitivity responses in any subject.

CONCLUSION: LA-2500 administered as a single, monthly, subcutaneous dose in orchiectomized subjects with adenocarcinoma of the prostate was associated with a favorable safety and toleration profile.

The course of serum leuprolide concentration over time was consistent between subjects. Leuprolide was detectable in all subjects at Day 28. The overall pharmacokinetic profile of LA-2500 administered subcutaneously indicates that a monthly dosing regimen should be appropriate to provide adequate, measurable serum leuprolide levels throughout the dosing interval time period.

Date of the report: September 23, 1999

SYNOPSIS

Name of Company: Atrix Laboratories, Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: [redacted] 7.5 mg	Volume:	
Name of Active Ingredient: Leuprolide acetate	Page:	

Title of Study: A Six-Month, Two-Part, Sequential, Open-Label, Fixed-Dose Study to Evaluate the Safety, Tolerance, Pharmacokinetics and Endocrine Efficacy of Monthly Doses of [redacted] 7.5 mg in Patients with Advanced Prostate Cancer

Publication (reference): N/A

Studied period (years): 14 months

Phase of Development: Phase 3

Date of first enrollment: September 27, 1999

Date of last completed: November 15, 2000

Objectives: The objectives of the study were: 1) To evaluate the safety and tolerance of monthly doses of [redacted] 7.5 mg in patients with advanced prostate cancer. 2) To evaluate serum testosterone and LH levels following monthly doses of [redacted] 7.5 mg in patients with advanced prostate cancer. 3) To determine the pharmacokinetic (PK) profile of serum leuprolide acetate following three monthly subcutaneous injections with [redacted] 7.5 mg in a subset of patients with advanced prostate cancer.

Methodology: All patients were scheduled to receive six doses of [redacted] 7.5 mg (Baseline and Months 1 through 5; 28-day months) subcutaneously injected into the upper right or upper left quadrant of the abdomen using a half-inch, 20-gauge hypodermic needle. Injections were administered immediately following drug preparation by a person trained to give SC injections. Each patient received the same fixed-dose study drug formulation. The formulation was identical to the to-be-marketed formulation. [redacted] 7.5 mg is designed to deliver 7.5 mg of leuprolide acetate from 250 milligrams of constituted study drug over a one-month (28-day) therapeutic period. The injection volume was 0.25 mL.

The primary efficacy variable in this open-label, fixed-dose study was serum testosterone concentration at the 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.

Number of patients (planned and analyzed): 120 patients were enrolled and analyzed in the intent-to-treat dataset. 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. Testosterone suppression was also evaluated in an analysis of observed cases. In this dataset the data for the three withdrawn patients was not carried forward past the time they were withdrawn.

Diagnosis and main criteria for inclusion: All patients were male between the ages of 50-85 years and had adenocarcinoma of the prostate. 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.

Test product, dose and mode of administration, batch number: The investigational product, [redacted] 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 [redacted] w/w Poly(DL-lactide-co-glycolide) (PLGH) and [redacted] w/w N-methyl-2-pyrrolidone (NMP). The other syringe contained [redacted] mg lyophilized leuprolide acetate. The syringes were joined via the [redacted] connections on the syringes, and the formulation was passed between syringes until a homogenous mixture was obtained. Study drug was manufactured by Atrix Laboratories. The lot numbers of [redacted] 7.5 mg used in the study were 1144 and 1199. The injection volume was 0.25 mL.

Duration of Treatment: [redacted] 7.5 mg is designed to deliver 7.5 mg of leuprolide acetate over one month (28) days following injection. Of the 120 patients enrolled into the study, 117 received six once-monthly injections of study drug. One patient received three injections, one patient two injections, and one patient a single injection of study drug.

Reference therapy, dose and mode of administration, batch number: N/A

CRITERIA FOR EVALUATION:

Efficacy: The primary efficacy variable for this study was serum testosterone concentration. These concentrations were sampled at Baseline (Day 0) before injection of study drug. Post-injection testosterone concentrations were determined at 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. Data for Week 18 and Week 22 timepoints are only available for those patients not effected by Amendment No. 1.

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

Additionally, 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 a subgroup of 20 patients only (Group A). Blood samples for evaluation of the efficacy variables T and LH were drawn at each visit.

Safety: 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.

Assessment of safety was measured via the collection of adverse event information at all visits beginning with the Baseline visit.

Vital signs including heart rate, blood pressure, respiratory rate and temperature were documented at Screening, Baseline, and Days 7, 14, 28, 56, 84, and Months 4, 5, and 6.

Statistical methods: The primary efficacy variable in this study was serum testosterone concentration at the various sampling timepoints. Descriptive statistics (i.e., 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.

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

Clinical laboratory tests and analysis of adverse events were analyzed using descriptive statistics (mean \pm standard error) where possible, to assess the safety of study drug via laboratory measurements (hematology, coagulation, serum chemistry, urinalysis), adverse events, and concomitant medications. Pharmacokinetic parameters were analyzed using descriptive statistics on the maximum leuprolide serum concentration (C_{max}), time of maximum serum concentration (T_{max}), and area under the leuprolide serum concentration versus time curve for various time periods. Observed values were to be used for C_{max} and T_{max} .

SUMMARY-CONCLUSIONS

EFFICACY RESULTS: Following six once-monthly doses of [redacted] 7.5 mg, 100% of patients (observed patients dataset) who continued in the study through at least Day 14 reached castrate suppression of testosterone concentration, defined as testosterone concentration of ≤ 50 ng/dL for two consecutive timepoints approximately one week apart. By Study Day 28, 112 of the 119 (94%) patients remaining in the study had achieved testosterone suppression, and 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. That is, no castrate suppression breakthroughs (defined as a testosterone concentration of > 50 ng/dL after achieving suppression) were observed during the study. The median time to castrate suppression was 21 days, and the mean time to castrate suppression was 21.6 days. Additionally, patient PSA scores were reduced by an average of greater than 90% from Baseline during the study.

Very little change was observed throughout the study in terms of WHO performance status. At Baseline, 88% of patients were classified as fully active and this proportion remained at 88% through the end of the study suggesting no decrease in performance status during the study.

Bone pain, urinary symptoms, and urinary pain were assessed by patients during the study. All measures were low at Baseline and remained low during the study indicating good symptom control was maintained during the six months of the study.

Clinically, it is well recognized that brief symptomatic flare may occur following therapy with leuprolide acetate or other GnRH agonists, sometimes necessitating concomitant medication or other treatment. However, in this study, there was no increase in these symptom scores in the three days post-study drug dosing, suggesting that there were no flare symptoms. Over the course of the study there was a modest reduction in symptom scores from Baseline values. These overall results indicate that good

symptom control was maintained during the six months of the study with no acute-on-chronic response following study injections.

Repeated monthly treatment of advanced prostate cancer patients with [redacted] 7.5 mg, produced serum leuprolide profiles similar to those of other effective leuprolide depot formulations. After an initial burst phase characterized by high (>20 ng/mL) serum concentrations, the formulation maintained relatively constant mean serum leuprolide levels (0.2–2 ng/mL) over the majority of each dosing interval. The bioavailability of [redacted] 7.5 mg was greater than 90% and the rate of delivery of active drug was relatively constant during the plateau phase. There was no evidence of accumulation after repeated administration, with similar serum profiles observed after each dose.

The pattern of leuprolide exposure following monthly [redacted] 7.5 mg administration was associated with suppression of testosterone to castrate levels in 100% of patients (observed-cases population). Thus, monthly [redacted] 7.5 mg maintains constant suppression of testosterone secretion by maintaining serum leuprolide exposure at levels above the minimum required for complete inhibition of gonadotropic hormone release.

All study patients maintained testosterone suppression ≤ 50 ng/dL throughout the study with 97% of patients showing suppression below the more stringent ≤ 20 ng/dL level by Day 42 of the study. At Month 6 mean testosterone values were 6.1 ng/dL compared to 361.3 ng/dL at Baseline.

SAFETY RESULTS: The observed safety profile of [redacted] 7.5 mg was similar to that of other products containing leuprolide acetate.

Common adverse events found in the treatment-related categories for this multi-dose study were: hot flashes, dizziness/giddiness, malaise/fatigue, testicular discomfort/atrophy, and injection site adverse events.

Injection site adverse events were typical of those associated with similar SC injectable products. No patients discontinued the study due to those events. There was no indication that a patient who reported an injection site adverse event would report recurrent events with subsequent injections. There were no trends to increased severity, frequency, or duration with subsequent injections. Injection site adverse events were very brief in duration, mild in severity, and sporadic in nature. No event provoked clinical concern.

Overall, [redacted] 7.5 mg was found to have a favorable safety profile both systemically and locally and was well tolerated for up to six, monthly injections when administered to men with advanced prostate cancer.

OVERALL CONCLUSION: Following six once-monthly doses of [redacted] 7.5 mg, 100% of patients who continued in the study through at least Day 14 reached castrate suppression of testosterone concentration, defined as testosterone concentration of ≤ 50 ng/dL for two consecutive timepoints approximately one week apart. By Study Day 28, 112 of the 119 (94%) patients remaining in the study had achieved testosterone suppression, and 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 remained suppressed throughout the duration of the study. Additionally, patient PSA scores were reduced by an average of greater than 90% from Baseline during the study.

Summaries of WHO performance status, bone pain, urinary symptoms, and urinary pain all indicated good symptom control was maintained during the six months of the study with no evidence of flare responses.

Repeated monthly treatment of advanced prostate cancer patients with [redacted] 7.5 mg, produced serum leuprolide profiles similar to those of other effective leuprolide depot formulations. After an initial burst phase characterized by high (>20 ng/mL) serum concentrations, the formulation maintained relatively constant mean serum leuprolide levels (0.2–2 ng/mL) over the majority of each dosing interval. The bioavailability of [redacted] 7.5 mg was greater than 90% and the rate of delivery of active drug was relatively constant during the plateau phase. There was no evidence of accumulation after repeated administration, with similar serum profiles observed after each dose.

Injection site adverse events were typical of those associated with other injectable SC products. There were no trends to increased severity and duration with subsequent injections. Injection site adverse events did not cause clinical concern. The majority of other adverse events noted—e.g. hot flashes, testicular atrophy, etc.—were those typically associated with testosterone suppression and consequent medical castration. No patients discontinued due to treatment-related adverse events.

Overall, [redacted] 7.5 mg was found to have a favorable safety profile both systemically and locally and was well tolerated for up to six, monthly injections when administered to males with advanced prostate cancer.

Date of the report: February 7, 2001

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/s/

Myong-Jin Kim
1/17/02 11:49:49 AM
PHARMACOLOGIST

Ameeta Parekh
1/18/02 02:09:15 PM
BIOPHARMACEUTICS
I concur

Firm Arix Laboratories, Inc.

Drug [redacted] 7.5 mg

NDA 21-343

BIOPHARMACEUTICS STUDY SUMMARY

Study No.	Route	Dosage Form(s) Study Designs	Dose	Batch No/Date Manufactured	No. of Subj.	Related IND or NDA Numbers	Report Date/ Submission Date	Applicant Conclusion
AGL9802	SC	Single injection	7.5 mg	1105/ 10-98	8	IND [redacted]	9-23-99/ 9-24-99 (Serial #009)	[redacted] 7.5 mg produced a concentration profile similar to other effective depot preparations: burst followed by sustained release. Serum drug levels remained > 0.1 ng/mL over entire dose interval in all patients. Bioavailability was close to 100%.
AGL9904	SC	6 x monthly injection	7.5 mg/ month	1144 8-99 1199 5-00	20	IND [redacted]	2-7-01/ Provided in this NDA	Pharmacokinetics monitored for 3 months in subset of 20 patients. Concentration profile nearly identical to Study 9802, with similar profiles after repeated doses. Bioavailability > 90%. Maintained serum leuprolide > 0.1 ng/mL in all patients at all times, achieving clinical efficacy (testosterone ≤ 50 ng/dL) in 99% of patients in the ITT population over course of study. One patient withdrew at Day 14 before adequate "on study" time had passed to expect T suppression.

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/s/

S.W. Johnny Lau
10/19/01 04:29:35 PM
BIOPHARMACEUTICS

Ameeta Parekh
10/25/01 01:02:10 PM
BIOPHARMACEUTICS
I concur

NDA 21-343
Eligard™ (leuprolide acetate for injectable suspension)
ATRIX Laboratories, Inc.

Abuse/Liability review is NA for this application.

IS/

12/18/04