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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-488

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
(DRAFT January 9, 2003)

NDAs: 21-488
Category: 3S

Submission Date:
April 13, 2002
November 15, 2002

Generic Name	Leuprolide Acetate
Brand Name:	ELIGARD™
Formulations:	30 mg Sustained Release
Route of Administration:	Subcutaneous (SC)
Indication:	Advanced Prostate Cancer
Sponsor:	Atrix Laboratories, Inc., Fort Collins, CO
Type of Submission:	Full New NDA
Reviewer:	Sayed Al Habet, R.Ph., Ph.D.
Dates of Review:	Received for Review: April 26, 2002 First Draft: January 9, 2003 Second Draft: January 23, 2003 Briefing Draft: January 23, 2003 DFS Version:

Synopsis:

This is the third leuprolide formulation that was submitted by the same sponsor within the last 2 years. The previous two depot formulations were approved for 1 month and 3 months SC administration at a dose of 7.5 and 22.5 mg, respectively. These three depot formulations are similar in composition and release technology.

ELIGARD™ 30 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 30 mg of leuprolide acetate at a controlled rate over a four-month therapeutic period. Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH) that, when given continuously, inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis.

ELIGARD™ 30 mg is prefilled and supplied in two separate, sterile syringes whose contents are mixed immediately prior to administration. The two syringes are joined and the single dose product is mixed until it is homogenous. One syringe contains the ATRIGEL® Delivery System and the other contains leuprolide acetate. ATRIGEL® is a polymeric (non-gelatin containing) delivery system consisting of a biodegradable poly(DL-lactide-co-glycolide) (PLG) polymer formulation dissolved in a biocompatible solvent, *N*-methyl-2-pyrrolidone (NMP). PLG is a co-polymer with a 75:25 molar ratio of DL-lactide to glycolide containing carboxyl end groups. The second syringe contains leuprolide acetate and the constituted product is designed to deliver 30 mg of leuprolide acetate at the time of subcutaneous injection.

The proposed recommended dose of ELIGARD™ 30 mg is to be administered subcutaneously once every four months for the palliative treatment of prostate cancer.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics finds the information included in this NDA acceptable. From the PK point of view, the draft label is also acceptable.

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Executive Summary
Clinical Pharmacology and Biopharmaceutics

Background:

ELIGARD™ 30 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 30 mg leuprolide acetate over a four-month period after subcutaneous (SC) injection. It will be available in two separate prefilled sterile syringes whose contents are mixed immediately prior to administration. It is intended to achieve continuous suppression of gonadal testosterone synthesis for the palliative treatment of advanced prostate cancer.

There were two NDAs from the same sponsors that were recently approved by the Division for the same indication. These are ELIGARD™ 7.5 mg (NDA# 21-343) and ELIGARD™ 22.5 mg (NDA # 21-379). The 7.5 mg was approved for SC administration every one month and the 22.5 mg was for every three months.

General Clinical Pharmacology and Pharmacokinetics:

The PK of ELIGARD™ 30 mg was evaluated in a subset of 24 patients with advanced prostate cancer in a pivotal Phase III trial (Study AGL0001). In this study ELIGARD™ 30 mg was administered as two injections each four months apart in 90 patients over 8 months period. The pharmacokinetic of leuprolide and the testosterone (T) suppression were evaluated during each of the two four-month (112-day) dosing intervals.

Administration of ELIGARD™ 30 mg resulted in a multiphasic profile of serum leuprolide concentrations. Serum leuprolide levels start to decline after reaching the peak level within 2-3 hours after the administration. During the plateau phase, mean serum leuprolide levels generally remained between 0.1-1 ng/ml. Serum leuprolide peak concentration after the second dose was slightly higher than after the first dose (**Figure A**). However, the plasma-concentration time profiles of both doses were almost similar with similar half lives and AUCs (**Figure B**).

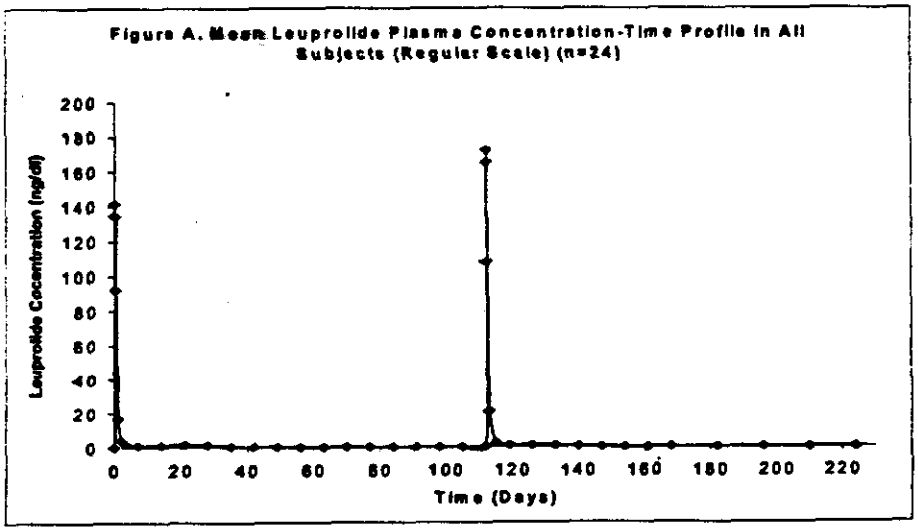
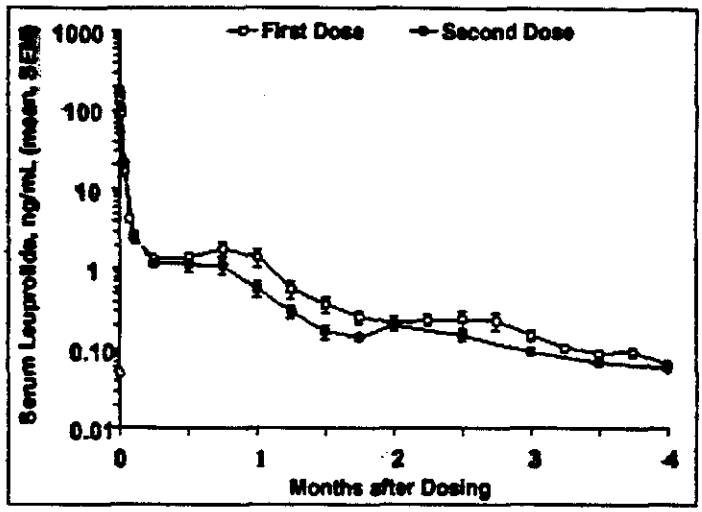
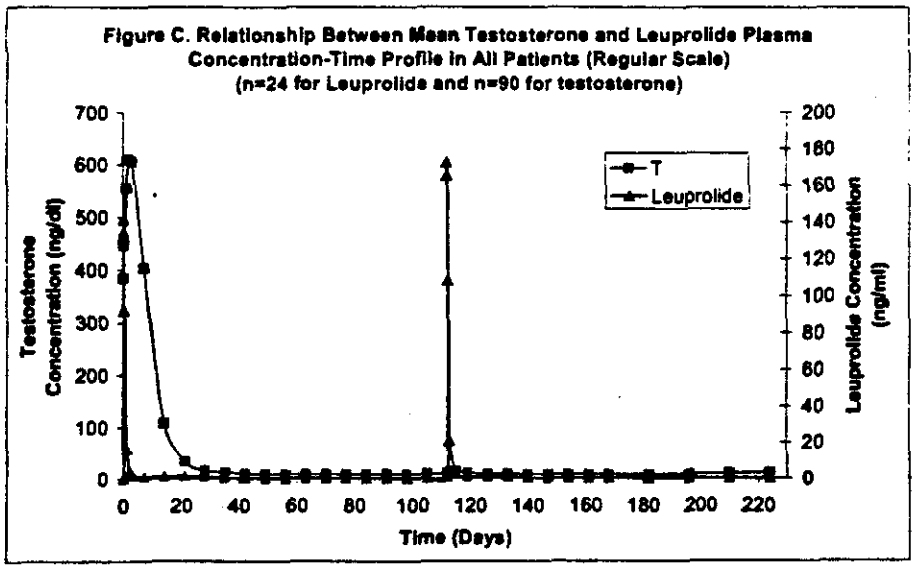
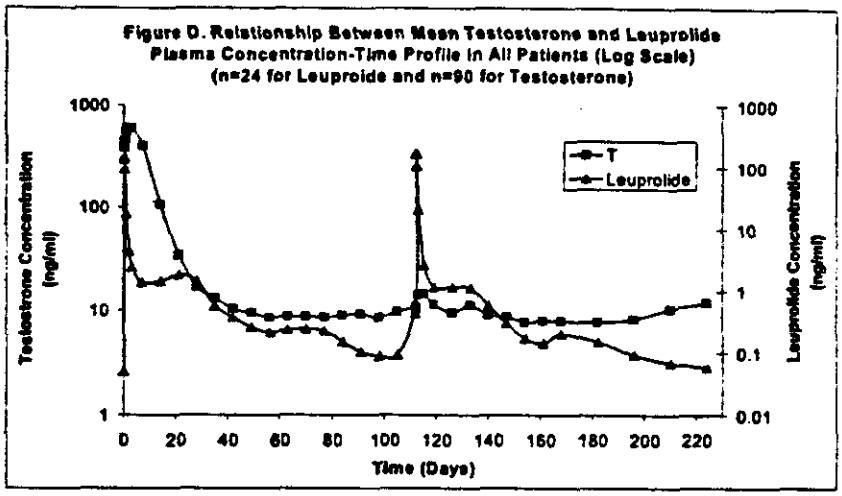


Figure B. Comparison Between Dose 1 and Dose 2 For Leuprolide Serum Concentration-Time Profiles (n=24)



Testosterone serum level rose immediately after the administration of the first leuprolide dose which is a well-known phenomenon called "burst phase". This phase was followed by a rapid decline in testosterone over the next several days (**Figures C & D**). Within 3 weeks of the first dose, testosterone level fell below the medically castrated defined level of **<50 ng/dl**. This level of suppression was maintained throughout the 8 months study. Only 4 out of 90 patients had transient and minor breakthrough in their testosterone suppression at different intervals. All patients who completed the study were completely suppressed by the end of the study. There was no burst phase in testosterone level after the second dose nor was there any significant increase in its level. Continuous testosterone suppression was maintained throughout the entire second four-month dosing interval.





Conclusions:

Leuprolide peak concentration of approximately 150 ng/ml is attained within 2-3 hours after administration and declines rapidly reaching a concentration of approximately 1 ng/ml by the first week. Testosterone undergoes a typical "burst phase" immediately after the first leuprolide dose reaching a peak concentration of approximately 600 ng/dl within 2-3 days and then immediately start to decline to the predefined medically castrated level of <50 ng/dl by Day 28. No burst phase occur after the second leuprolide dose nor there was any change in testosterone level, with a few exceptions.

A total of 85 patients received the two injections in this NDA. Only 7 patients withdrew from the study for various reasons. All 7 patients but two were withdrawn from the study due to personal reasons. The two subjects that were withdrawn from the study experienced hot flashes, fatigue, and loss of libido. No deaths were reported during the trial.

The clinical pharmacokinetic and pharmacodynamic data presented in this NDA support the use of ELIGARD™ 30 mg as a once-every-four-month depot formulation for the sustained suppression of testosterone synthesis to castrate levels for the palliative treatment of advanced prostate cancer. The drug appears to be safe and effective.

SUMMARY REVIEW
OF PHARMACOKINETICS AND BIOAVAILABILITY
(Question Based Review, QBR)

HISTORICAL PERSPECTIVE:

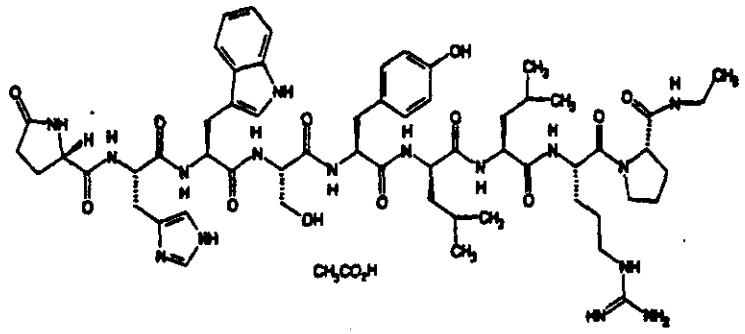
The use of depot formulations to provide sustained release of leuprolide acetate has been extensively investigated, and several polymer-based depot preparations of leuprolide acetate are currently marketed. The pharmacokinetic profiles of several of these leuprolide depot formulations were compared with those of conventional leuprolide injection. These formulations include IM and SC polymer-based depots intended for injection at intervals of one to four months, and an implantable osmotic device intended for twelve-month therapy. Most of these studies were performed in patients with advanced prostate cancer, with serum leuprolide concentrations measured at time points that varied between studies.

Leuprolide depot formulations generally produced a rapid increase in serum leuprolide levels shortly after injection (burst phase), followed by sustained low levels during the remainder of the intended dosing interval (plateau phase). Plateau phase of leuprolide concentrations were in the range of 0.2-1.3 ng/mL for all depot formulations. Treatment with leuprolide depot formulations suppressed testosterone to sub-castrate levels within two to six weeks after the initial dose. Testosterone suppression usually maintained during the course of treatment, with few acute-on-chronic responses reported after subsequent doses. Various types of leuprolide preparations can maintain effective testosterone suppression over long periods by providing sustained release of leuprolide over a range of different concentrations.

BACKGROUND:

What are the Physico-Chemical Properties of Eligard?

Structural Formula of Leuprolide:



ELIGARD™ 30 mg is an injectable polymer-based, extended-release formulation of leuprolide acetate. It is intended to be supplied as two separate prefilled sterile syringes whose contents are mixed immediately prior to administration. The two syringes are joined and the single dose product is mixed until it is homogenous. One syringe contains the ATRIGEL®-Delivery System and the other contains leuprolide acetate. ATRIGEL® is a polymeric (non-gelatin containing) delivery system consisting of a biodegradable poly(DL-lactide-co-glycolide) (PLG) polymer formulation dissolved in a biocompatible

solvent, *N*-methyl-2-pyrrolidone (NMP). PLG is a co-polymer with a 75:25 molar ratio of DL-lactide to glycolide containing carboxyl end groups. The second syringe contains leuprolide acetate and the constituted product is designed to deliver 30 mg of leuprolide acetate at the time of subcutaneous injection.

Clinical Pharmacology and Pharmacokinetics Studies

BIOPHARMACEUTICS:

What Are the Relevant Formulations Used in this NDA?

The formulation components of ELIGARD™ 30 mg are identical to those of ELIGARD™ 22.5 mg (NDA 21-379) approved for SC administration once every three months. The two formulations differ only in the dose and volume of the subcutaneous injection and the frequency of dosing.

The components of the ELIGARD™ 30 mg (four-month) and ELIGARD™ 22.5 mg (three-month) formulations are qualitatively similar to those of the approved ELIGARD™ 7.5 mg (NDA 21-343), a once per month SC formulation of leuprolide acetate in the polymer ATRIGEL Delivery System.

ELIGARD™ 30 mg and ELIGARD™ 22.5 mg contain the same drug substance (leuprolide acetate) and solvent (NMP) as the ELIGARD™ 7.5 mg one-month formulation. However, the copolymer used in the one-month formulation has a different ratio of lactide/glycolide subunits and a different mean molecular weight to achieve the drug release rate required for once monthly treatment. The three-month and four-month formulations have a higher concentration of active drug, and are administered in larger volumes than the one-month formulation, to provide the appropriate drug dose for three or four months duration. A comparison of the three ATRIGEL polymer leuprolide acetate formulations is shown in **Table 1**.

Table 1. Comparison of ATRIGEL Formulation of Leuprolide

Formulation	ELIGARD™ 30 mg	ELIGARD™ 22.5 mg	ELIGARD™ 7.5 mg
NDA Reference	21-488	21-379	21-343
Frequency of Administration	Once Every Four Months	Once Every Three Months	Once Per Month
Active drug (Dose)	leuprolide acetate (30 mg)	leuprolide acetate (22.5 mg)	leuprolide acetate (7.5 mg)
Drug loading	6%	6%	3%
Polymer type (lactide/glycolide ratio)	PLG (75/25)	PLG (75/25)	PLGH (50/50)
Polymer MolWt.	15-24 kD	15-24 kD	23-45 kD
Polymer (% by wt.)	—	—	—
NMP Solvent (% by wt.)	—	—	—
Injection mass	0.500 g	0.375 g	0.250 g

Is there Any Change in Formulation During Development?

The two lots of ELIGARD™ 30 mg administered to patients in the AGL0001 clinical study subset for pharmacokinetic analysis were identical in formulation to the to-be-marketed product (**Table 2**). There were only two lots (# 1276 and 1317) used in Phase III clinical study (AGL0001) and these represent the same formulation of the to-be-marketed product.

Table 2 Drug Formulation Used in Phase III study (AGL0001)

Study No.	Lot No.	Dosage Form and Strength	Batch Size (Units)	PLG Polymer Molecular Weight	Formulation or Significant Manufacturing Change (if any) and Reason for Change
AGL0001 (Dose 1)	1276	Extended release four-month depot, 30 mg	[redacted]	17 kDa	None
AGL0001 (Dose 2)	1317	Extended release four-month depot, 30 mg	[redacted]	18 kDa	None

How Will Leuprolide be Supplied?

Leuprolide will be supplied as two separate prefilled sterile syringes whose contents are mixed immediately prior to administration. One syringe contains 35.8 mg of . —— leuprolide acetate. The other syringe contains 560 mg of a sterile, polymeric delivery system solution of — % 75:25 Poly (DL-lactide-co-glycolide) (PLG) and — % of N-methyl-2-pyrroolidone (NMP). The two syringes are joined and the single dose product is mixed until it is homogenous. One syringe contains the ATRIGEL® Delivery System and the other contains leuprolide acetate. After mixing the total leuprolide dose is 30 mg for a single SC administration.

ELIGARD™ 30 mg is packaged in a pouch that contains two smaller pouches (**Figure 1A**), a needle cartridge and a desiccant pack (**Figure 1B**). Syringe A pouch contains the sterile Syringe A pre-filled with the ATRIGEL® polymer system and a long white replacement plunger rod (**Figure 1C**). Syringe B pouch contains the sterile Syringe B pre-filled with leuprolide acetate powder (**Figure 1D**). The detailed step by step use instructions are shown in **Figure 1 A-N.**

Figure 1 (A-N). Eligard 30 mg Package and Instructions for Use

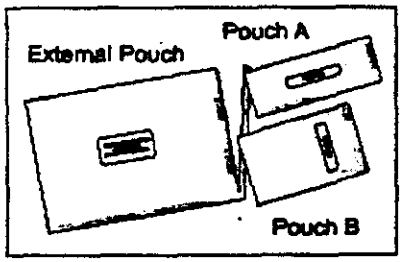


Figure A

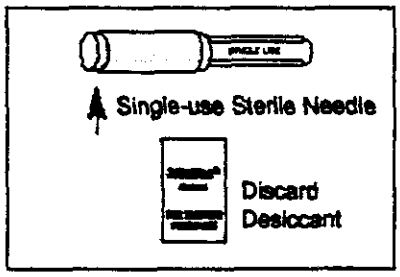


Figure B

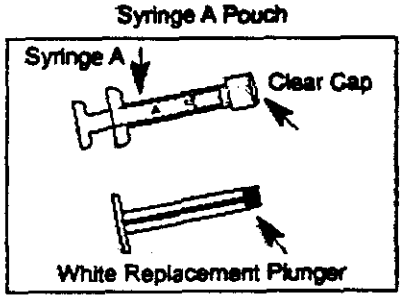


Figure C

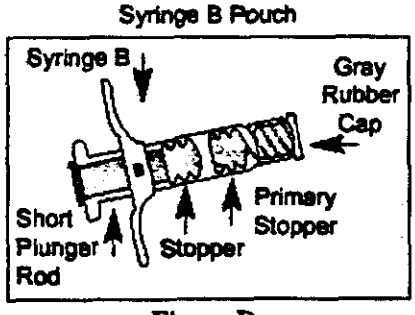


Figure D

How to Use? (Mixing Procedure)

1) Draft

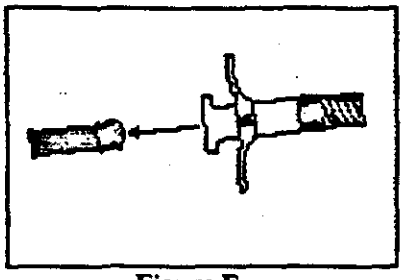


Figure E

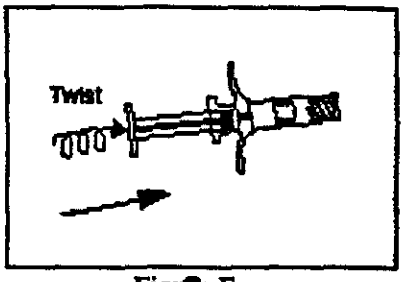


Figure F

2) Pull out the blue-tipped short plunger rod and attached stopper from Syringe B and discard (**Figure E**). Gently insert the long, white replacement plunger rod into the gray primary stopper remaining in Syringe B by twisting it in place (**Figure F**).

3) Unscrew the clear cap from Syringe A (**Figure G**). Remove the gray rubber cap from Syringe B (**Figure H**).

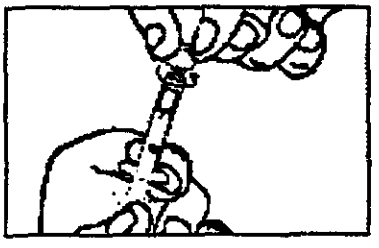


Figure G

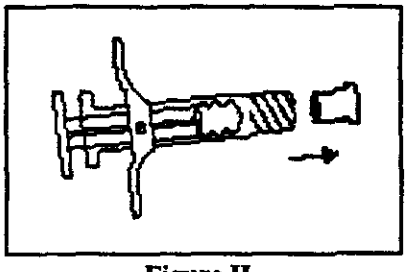


Figure H

4) Join the two syringes together by pushing in and twisting until secure (**Figure I**).

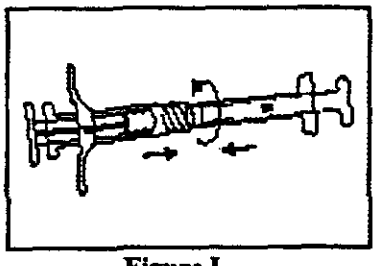


Figure I

5) Thoroughly mix the product by pushing the contents of both syringes back and forth between syringes (approximately 45 seconds) to obtain a uniform suspension (**Figure J**). When thoroughly mixed, the suspension will appear a light tan to tan color. **Product must be mixed as described; shaking will not provide adequate mixing of the product.**

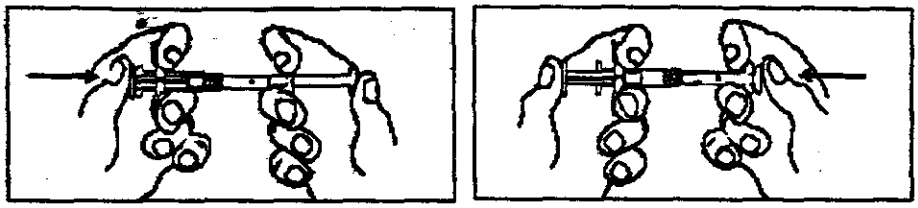


Figure J

6) Hold the syringes vertically with Syringe B on the bottom. The syringes should remain securely coupled. Draw the entire mixed product into Syringe B (short, wide syringe) by depressing the Syringe A plunger and slightly withdrawing the Syringe B plunger. Uncouple Syringe A while continuing to push down on the Syringe A plunger (**Figure K**).

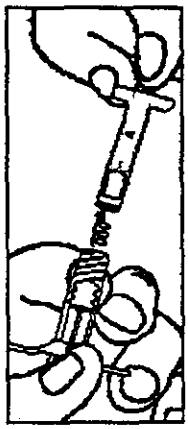


Figure K

7)

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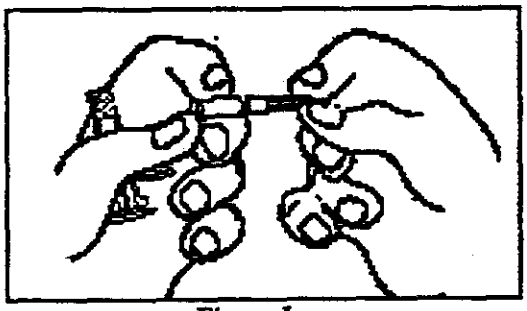


Figure L

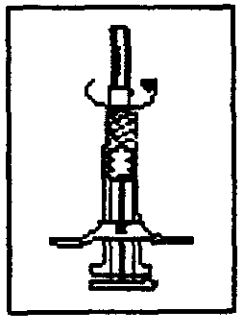


Figure M

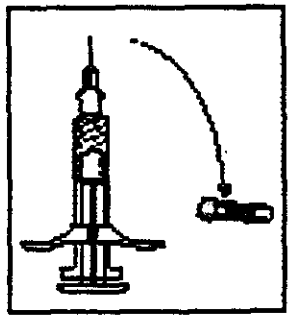


Figure N

What are the Proposed *in Vitro* Dissolution Method and Specifications?

The in vitro release profiles of each lot of ELIGARD™ 30 mg used in the clinical study (Lots 1276 and 1317, Study AGL0001) were determined at various times during the expected shelf life, using test method T553 **(Table 3A)**

The detailed description of the method is provided in the CMC section of this NDA (see chemistry review and **Table 3A and B**). This method is the same as that used for Eligard 22.5 mg product except that the release medium volume was scaled for the differences in leuprolide content of the two products.

Method Description: Briefly, the constituted Eigard 30 mg is initially added dropwise and incubated in purified water at 60 °C in shaking water bath (530 ml). Samples were collected at 6, 18, and 48 hours. The release medium contains 25 mM of 2-morpholino-ethanesulfonic acid MES) buffer (pH 6.0) with 10.0mM zinc acetate and 10% 2-propanol. All samples are assayed by — to determine the cumulative amounts of leuprolide acetate released. **Table 3C and D** shows the mean release for the two clinical batches (#1276 and 1317) and additional batch (data provided by Dr. Swapan De, a Chemistry reviewer). At 48 hours the cumulative release rate ranged from —— . The data are within the range of the proposed and agreed upon specifications with the Agency **(Table 3B)**.

Table 3A. Detailed Description of the *In vitro* Release Dissolution Method (T553)

Method (T553.001)	In vitro extended release test of ELIGARD™ 30 mg is performed to check product's quality and performance. Leuprolide is assayed at three time points from a constituted product samples added to a 530 ml medium that contains 25 mM pH 6.0 2-morpholino-ethanesulfonic acid (MES) buffer with 10.0 mM zinc acetate and 10% 2-propanol. Leuprolide is analized by — **Equipment and solutions:** **Column:** **Mobile phase:** **Extended release test procedure:**

Evaluation:	**parameters:** Column temp: Max Pressure: Flow rate : Run time: Detection: Injection volume: • The method is developed following suggestion from the agency during IND and pre-NDA negotiations for the sponsor's 22.5 mg formulation and is deemed acceptable.

Table 3B. *In vitro* Release Dissolution Method Specifications

CHARACTERISTIC	METHOD	MIN.		MAX.	
Color	Visual	Colorless to pale yellow.			
Appearance	Visual	Viscous suspension. May contain air bubbles, but is substantially free of visible particles and foreign matter.			
Leuprolide Acetate Content (% of Theory 30 mg)	T431	—			—
Extended Release	T553	Mean % of Theory 30.0 mg		Not less than 5 of 6 units are within ± 10% of mean acceptance criteria		No individual unit is more than ± 15% of mean acceptance criteria	
		Min.	Max.	Min.	Max.	Min.	Max.
6 hour							
18 hour							
48 hour							
Tier 1: If any acceptance criterion is not met, proceed to Tier 2.							
Tier 2: An additional 6 units are tested. Results from Tier 2 must meet all acceptance criteria.							

Table 3C. Mean *In vitro* Release Dissolution Data for Different Batches at Long Term Storage Condition (5°C)

Time (hour)	5°C±2°C			
	#1276	#1317	#1352	#1444
	9, 12 and 18 mo.	3, 6, 9 and 12 mo.	3, 6, 9 and 12 mo.	0, 3, 6 and 9 mo.
6	6-10	8-15	6-8	5-7
18	40-48	30-41	27-37	23-36
48	92-95	88-94	90-95	87-96

Table 3D. Mean *In vitro* Release Dissolution Data for Different Batches at Accelarated Storage Conditions (25°C±2°C/60% RH)

Time (hours)	25°C±2°C/60% RH			
	#1276	#1317	#1352	#1444
	None provided	3 and 6 months	2,3 and 6 months	0,1,2,3 and 6 months
6		12-13	6-8	5-9
18		44-45	31-34	25-39
48		87-90	89-92	88-98

What is the Absolute Bioavailability of Leuprolide ?

Leuprolide is poorly absorbed after oral administration. It is rapidly degraded by gut proteases. There was no formal study conducted to determine the absolute bioavailability of Eligard 30mg following SC administration.

What Assay Method Was Used?

A) Leuprolide Assay

Leuprolide concentrations in serum were measured by a validated method in which samples were ——— and quantitated by ——— The assay lower limit of quantitation is — ng/mL. Precision (inter- and intra-assay) is < 11 % over the range of the assay. Accuracy (inter-and intra-assay) is between –4.8% and +8.2%, except at the lower limit of quantitation ———. The presence of the four known metabolites of leuprolide (M-I, M-II, M-III and M-IV) was shown not to cause significant interference with the assay.

B) Testosterone Assay

Serum testosterone levels were measured by validated RIA assay which was performed after — ——— The lower limit of quantitation of the assay is — ng/dL. Of 22 steroids tested, only dihydrotestosterone (DHT) displayed significant (22%) cross-reactivity in the assay. All others were ranged from approximately <0.01 to <1%, except two steroids which were at 2.3% and 5.5%. The physiological level of DHT is usually low or suppressed during leuprolide administration and its interference with testosterone assay would be low or negligible. The inter-and intra-assay precision/reproducibility as defined by %CV was <10% over the range of excepted testosterone physiological serum levels.

C) Luteinizing Hormone (LH) Assay

LH serum levels were determined by a validated two-site immunochemiluminometric assay. The lower limit of quantification of this assay was — mIU/m with a %CV for inter-and intra-assay of <10%.

CLINICAL PHARMACOLOGY:

What are the Indications for ELIGARD?

ELIGARD™ 30 mg is indicated for the palliative treatment of advanced prostate cancer.

What is the Mechanism of Action of Leuprolide?

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).

What is the Proposed Dosage and Administration of Leuprolide?

It is proposed that ELIGARD will be administered subcutaneously once every four months as 30mg dose.

What is the Degree of the Plasma Protein Binding of Leuprolide?

The *in vitro* binding of radiolabeld leuprolide to human serum ranged from 43-49%.

What is the Elimination Pathways of Leuprolide (Metabolism and Excretion)?

The metabolic pathway of leuprolide is well established. Leuprolide is metabolized by cleavage of its serin-tyrosine peptide bond to form a pentapeptide metabolite, which further degraded to several di-and tripeptide metabolites. All four metabolites are inactive.

What Clinical Pharmacology Studies Are Available to Support the Proposed Indication?

The sponsor conducted one pivotal clinical trial on ELIGARD 30 mg (study # AGL0001) and two supportive studies for ELIGARD 7.5 (study # AGL9802) and ELIGARD 22.5 mg (study # 9909). The latter two studies were recently reviewed by the Division and both formulations were approved. ELIGARD 7.5 mg and 22.5 mg are for SC administration once every month and once every three months, respectively. Therefore, only study AGL0001 will be discussed in this review. As appropriate some the data from the previous NDAs may be used to support the discussion and interpretation.

Study AGL 0001 (Eligard 30 mg):

This was an eight-month, multicenter, fixed dose investigation of two doses of Leuprolide 30 mg administered SC to patients with adenocarcinoma of the prostate at four month apart. A total of 90 patients received at least one injection. The first dose was given at Baseline and the second at Month 4 (Day 112). Blood samples for various Testosterone (T), LH, and leuprolide serum determinations were collected over the dose periods from a subgroup of 24 patients. The blood samples time points were as follows: Day 0 (prior to dosing, and 2, 4 and 8 hours post dosing), Day 1, 2, 3, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and Month 3 (Day 84), Day 91, 98, 105, and Month 4 (Day 112); prior to dosing, and 2, 4 and 8 hours post dosing, Day 113, 115, 119, 126, 133, 140, 147, 154, 161, 168, 182, 196, 210 and Month 8 (Day 224).

The primary efficacy parameter in this study was serum testosterone concentration and the secondary parameter is serum LH concentration. Suppression of T concentration to medical castrate levels is defined as serum T <50 ng/dL for at least two consecutive timepoints approximately one week apart. The initiation of castrate suppression is defined as the day upon which the first of these two consecutive samples was drawn. Breakthrough is defined as a patient's T being measured above 50 ng/dL after that patient has achieved castrate T suppression.

Results:

Leuprolide Serum Concentration:

Serum leuprolide concentrations rose rapidly after each dose (**Figure 2**). The mean Cmax (± SD) after the first dose was 149 ± 77 ng/mL occurring at 3.3 ± 1.2 hr and after the second dose was 191.7 ± 107 ng/mL occuring at 2.99 ± 1.0 hr. This was then rapidly declined over the next several days. Serum leuprolide levels then declined more slowly for the remainder of each dosing interval, from Day 3 to Day 112 (plateau phase). During the plateau phase, mean serum leuprolide levels generally remained between 0.1–1.0 ng/ml, while individual levels ranged from <0.05 ng/ml to 5.8 ng/ml (**Tables 4 and 5**).

Figure 2. Mean Leuprolide Plasma Concentration-Time Profile in All Patients (n=24)

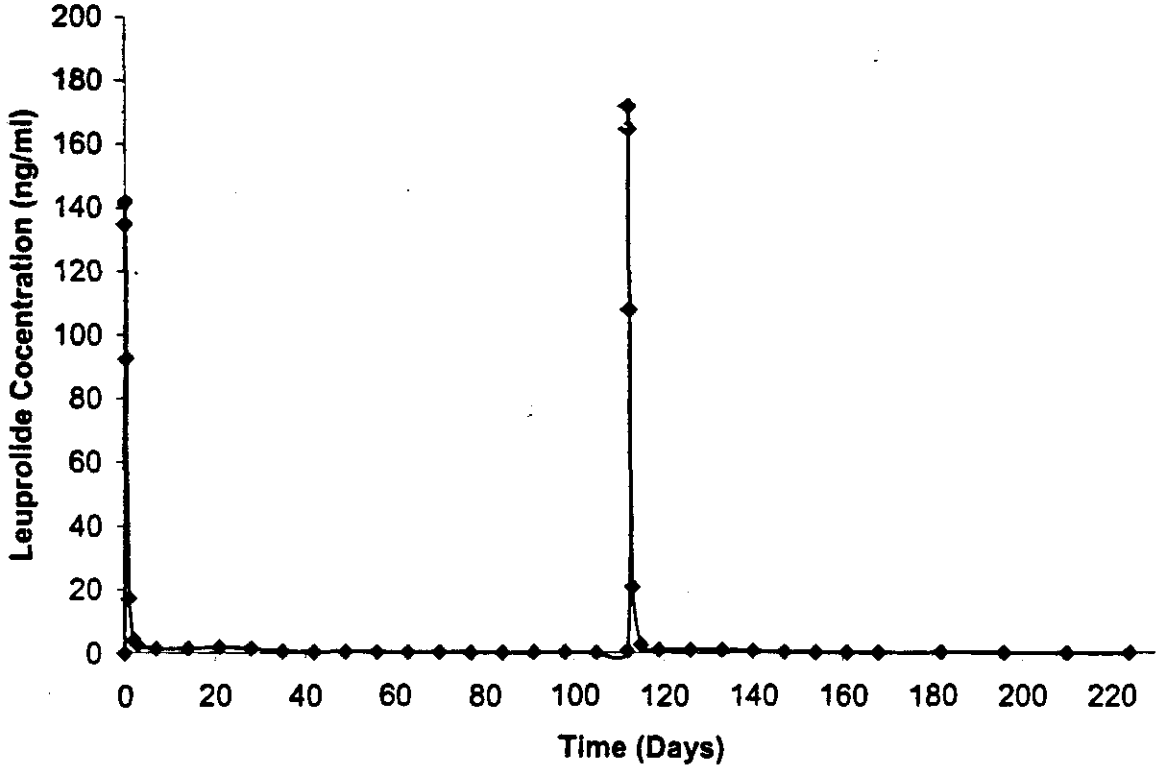


Table 4: Summary of Leuprolide Pharmacokinetic Parameters After the First Dose to Advanced Prostate Cancer Patients (n=24).

	Burst Phase (Day 0-3)			Plateau Phase (Day 3-112)				Total (Day 0-112)	
Subj. No.	AUC ng hr ml^{-1}	Cmax ng/ml	Tmax hr	AUC ng hr ml^{-1}	Cmax ng/ml	Cmin ng/ml	Clast ng/ml	AUC ng hr ml^{-1}	F[a] %
801									
1001									
1002									
1003									
1004									
1601									
1701									
1702									
1703									
1901									
1902									
1903									
1904									
1905									
2001									
2101									
2301									
2302									
2401									
2601									
2602									
2603									
2604									
2701									
Mean	2080.4	149.6	3.31	1471	2.6	0.07	0.078	3551.4	0.940
SD	896	76.5	1.22	680.1	1.5	0.03	0.041	990.4	0.262
RSD	43.1	51.1	36.9	46.2	59.1	45.2	52.93	27.9	27.8
Median	2023.5	139.5	3.67	1378.7	1.9	BLOQ	0.063	3554.1	0.940
Min				——					
Max				——					

[a] Bioavailability (F) based on reported AUC of intravenous leuprolide.
[b] Concentration 112 days after dosing.
BLOQ, below assay limit of quantitation (—— ng/mL).

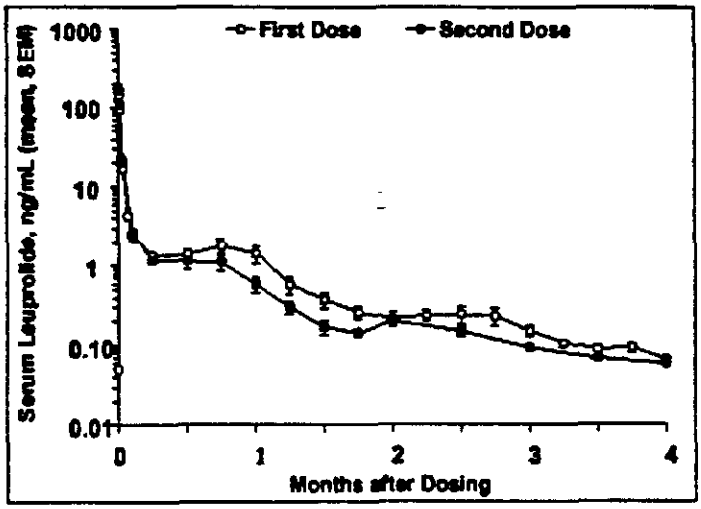
Table 5: Summary of Leuprolide Pharmacokinetic Parameters After the Second Dose to Advanced Prostate Cancer Patients (n=24).

	Burst Phase (Day 0-3)[a]			Plateau Phase (Day 3-112)				Total (Day 0-112)	
Subj. No.	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] %
801									
1001									
1002									
1003									
1004									
1601									
1701									
1702									
1703									
1901									
1902									
1903									
1904									
1905									
2001									
2101									
2301									
2302									
2401									
2601									
2602									
2603									
2604									
2701									
Mean	2659.2	191.7	2.99	1083.4	1.85	0.061	0.07	3742.6	0.99
SD	1186.4	107.4	1.02	500.2	1.37	0.026	0.03	1450.2	0.38
RSD	44.6	56.0	34.1	46.2	74.4	42.2	51.6	38.7	38.7
Median	2390.5	167.2	3.75	974.5	1.40	BLOQ	BLOQ	3604.4	0.95
Min									
Max									

[a] Days after administration of second dose.
[b] Concentration 112 days after dosing.
[c] Bioavailability (F) based on reported AUC of intravenous leuprolide.
BLOQ, below assay limit of quantitation (— ng/mL).

After the first dose, the mean (±SD) total leuprolide serum AUC was 3551 ± 990 ng.hr/mL, of which 1471 ng.hr/mL (41%) occurred during the plateau phase (**Table 4**). After the second dose, the mean total leuprolide serum AUC was 3743 ± 1450 ng.hr/mL, of which 1083 ng.hr/mL (29%) occurred during the plateau phase (**Table 5**). The average serum concentrations of leuprolide during the plateau phases (based on the mean plateau phase AUCs) were 0.56 ng/mL (first dose) and 0.41 ng/mL (second dose). Therefore, the mean serum leuprolide profiles were nearly identical after both doses (**Figure 3**).

Figure 3. Comparison Between Dose 1 and Dose 2 For Leuprolide Serum Concentration-Time Profiles (n=24)



Comparison of PK parameters between the first and second doses revealed a few statistically significant differences (**Table 6**). Leuprolide exposures were about 25% higher during the burst phase (AUC), and about 25% lower during the plateau phase (AUC, Cmax) after the second dose, as compared to the first dose ($P < 0.05$). However the overall AUC, Cmax and Cmin did not differ between the first and the second doses ($P > 0.05$). The magnitude of the observed PK differences was small, suggesting that there is no drug accumulation during repeat dosing.

Table 6. Comparison Between Dose 1 and Dose 2 For Leuprolide PK Parameters

PK Parameter	Phase	Dose 1	Dose 2	
		Mean (± SD)	Mean (± SD)	p-value
AUC	Overall	3551 (990)	3743 (1450)	NS
	Burst Phase	2080 (896)	2659 (1186)	<0.05
	Plateau Phase	1471 (680)	1083 (500)	<0.05
C_{max}	Overall	0.07 (0.03)	0.06 (0.03)	NS
	Plateau Phase	0.07 (0.03)	0.06 (0.03)	NS
C_{min}	Overall	149.6 (76.5)	191.7 (107)	NS
	Plateau Phase	2.6 (1.5)	1.8 (1.4)	<0.05

In terms of the leuprolide PK, it can be concluded that repeat administration of ELIGARD 30 mg to advanced prostate cancer patients produced serum leuprolide profiles similar to those of other effective leuprolide depot formulations. After an initial burst phase characterized by high serum concentrations (>100 ng/mL), **mean** serum leuprolide levels maintained relatively constant over the majority of each four-month dosing interval (0.1–1.0 ng/mL).

What is the Leuprolide PK in Relation to Dose? (i.e., Is there Dose proportionality?):

The **mean** PK data for leuprolide following 7.5, 22.5 and 30 mg are shown in **Tables 7-9**. Considering that the data were from three different NDAs, the overall impression indicates that there was a proportional increase in the burst phase of leuprolide **Cmax** with increase in dose (**Figure 4**). It is noteworthy that the **mean** Cmax value at the plateau phase following all three doses was approximately 2 ng/ml. The total AUC data for each dose were reported for different duration (i.e., up to 28, 84, and 112 days for 7.5 mg, 22.5, and 30 mg doses, respectively (**Tables 7-9**). Overall, the AUC increased with increase in dose, but due the differences in time intervals, it can not be directly used to establish dose proportionality.

Table 7. Mean PK parameters for ELIGARD 7.5 mg (Leuprolide Serum Concentrations)

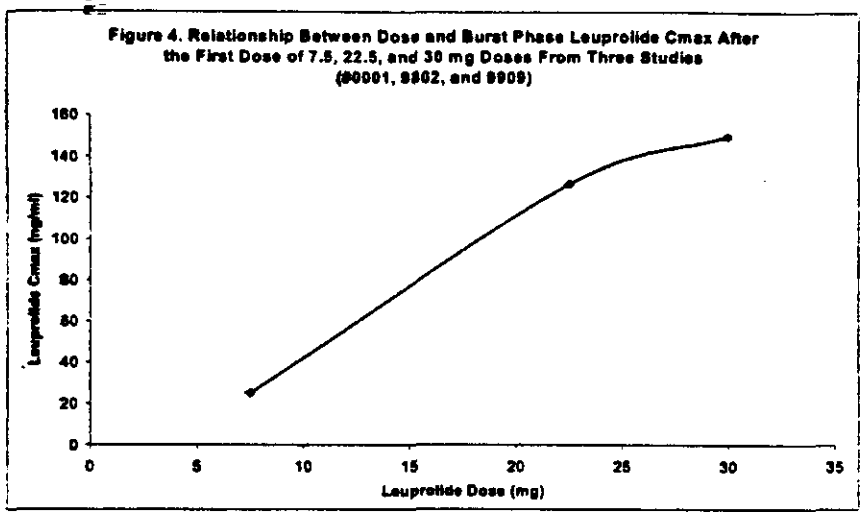
Study No.[a]	Route of Admin.	Dose[b]	Burst Phase Cmax (ng/mL)	Burst Phase Tmax (hr)	Burst Phase (0-48 hr) AUC (ng hr mL^{-1})	Plateau Cmax (ng/mL)	Plateau Cmin (ng/mL)	Plateau (2-28 days) AUC (ng hr mL^{-1})	C last (Day 28) (ng/mL)	Total (0-28 days) AUC (ng hr mL^{-1})
AGL9802	SC	7.5 mg	26.3	4.1	350.6	2.69	0.175	514.9	0.36	865.6
AGL9904										
Dose 1	SC	7.5 mg	25.3	4.6	435.3	2.68	0.169	438.1	0.42	873.4
Dose 2	SC	7.5 mg	ND	ND	ND	2.02	0.360	499.6	0.45	ND
Dose 3	SC	7.5 mg	ND	ND	ND	1.78	0.328	475.7	0.45	ND

Table 8. Mean PK parameters for ELIGARD 22.5 mg (Leuprolide Serum Concentrations)

Study No.[a]	Route	Dose[b]	Burst Phase Cmax (ng/mL)	Burst Phase Tmax (hr)	Burst Phase (0-3 days) AUC (ng hr mL^{-1})	Plateau Cmax (ng/mL)	Plateau Cmin (ng/mL)	Plateau (3-84 days) AUC (ng hr mL^{-1})	C last (Day 84) (ng/mL)	Total (0-84 days) AUC (ng hr mL^{-1})
AGL9909										
Dose 1	SC	22.5 mg	127	4.6	2227	2.4	0.15	1419	0.34	3646
Dose 2	SC	22.5 mg	107	4.5	1955	2.7	0.25	1925	0.30	3880

Table 9. Mean PK parameters for ELIGARD 30 mg (Leuprolide Serum Concentrations)

Study No.	Route	Dose[b]	Burst Phase Cmax (ng/mL)	Burst Phase Tmax (hr)	Burst Phase (0-3 days) AUC (ng hr mL^{-1})	Plateau Cmax (ng/mL)	Plateau Cmin (ng/mL)	Plateau (3-113 days) AUC (ng hr mL^{-1})	C last (Day 112) (ng/mL)	Total (0-112 days) AUC (ng hr mL^{-1})
AGL9908										
Dose 1	SC	30 mg	150	3.3	2080	2.6	0.07	1671	0.38	3751
Dose 2	SC	30 mg	192	3.0	2649	1.9	0.06	1693	0.37	3743

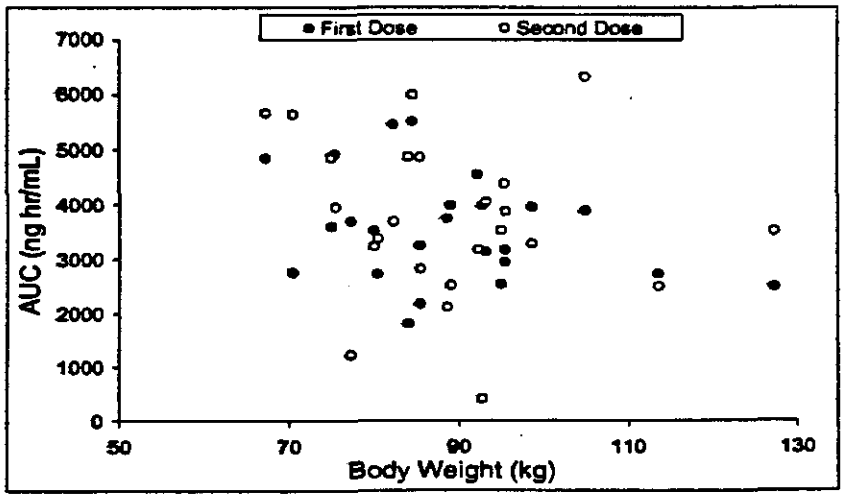


Is There A relationship Between Leuprolide Serum Level and Body Weight?

No formal study was conducted to establish the relationship between leuprolide serum levels and body weight. However, based on population PK there was a small trend for reduction in leuprolide exposure with age (**Figure** 5). It should be noted that there was no difference between the data from dose 1 and dose 3. This trend is typical for leuprolide and is also similar to that observed with Eligard 7.5 mg (see NDA 21-343 OCPB review).

It should be noted the distribution of patients relative to weight in this NDA is as follows: 9 patients were 160 pounds or less, 18 were 161 - 180 pounds, 26 were 181 - 220 pounds and 37 patients weighed more than 200 pounds. Minor side effects such as paraesthesia at the site of injection was noted significantly more often ($p<0.05$) in those weighing less than 160 pounds (27.6% of patients) compared to subjects weighing between 161 and 180 pounds (3.6% of patients).

Figure 5. Relationship Between Individual Leuprolide $AUC_{0\text{-}112\ days}$ and Body Weight (study AGL001)



Testosterone Suppression:

The mean testosterone concentrations at baseline was 385.5 (±18.04) ng/dL ranging from 267-464 ng/dL. Concentrations increased until a maximum mean concentration of 610.0 (±29.5) ng/dL was reached on Day 2. By Day 14, the mean concentration (108.4 ±7.3 ng/dL) was below the mean baseline concentration and by Day 21 the mean concentration (34.9 ±2.2 ng/dL) was below the medical castrate threshold. The mean concentration continued to decline and by Month 1 (Day 28) was below 20 ng/dL (17.2 ±1.4 ng/dL). Mean concentrations remained well below the medical castrate threshold (<50 ng/dL), and increased transiently and minimally following the second injection from 9.3 ±0.8 ng/dL at Month 4 (Day 112). At Month 8 (Day 224), mean T concentrations averaged 12.4 ±0.8 ng/dL. The mean and testosterone concentration-time profiles for both doses are shown in **Figures 6-8**.

Figure 6. Mean Testosterone Plasma Concentration-Time Profile After Eligard 30 mg Over 8 months (224 Days) in All Patients (n=85-90)

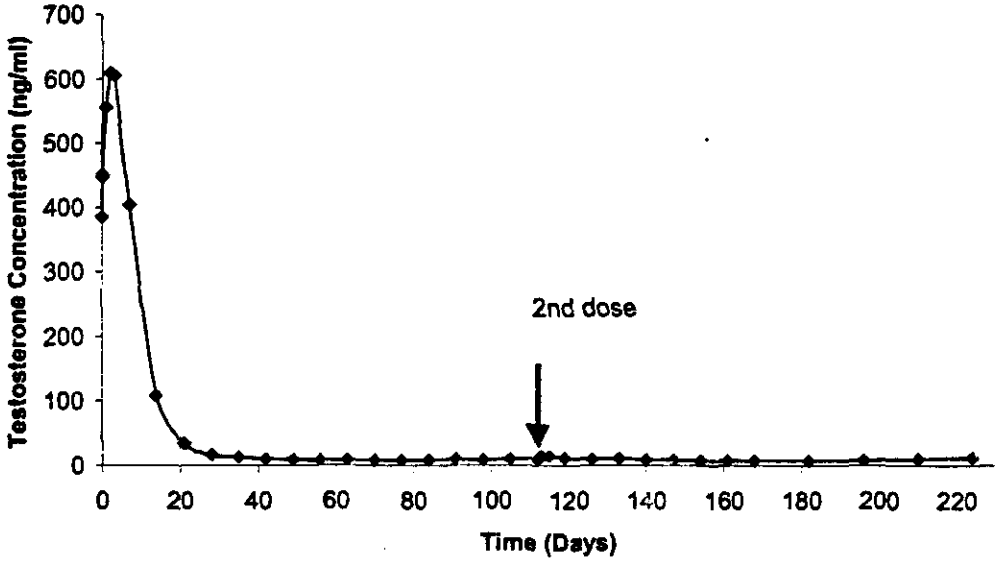


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Figure 7. Relationship Between Mean Testosterone and Leuprolide Plasma Concentration-Time Profile in All Patients (Regular Scale)
(n=24 for Leuprolide and n=90 for Testosterone)

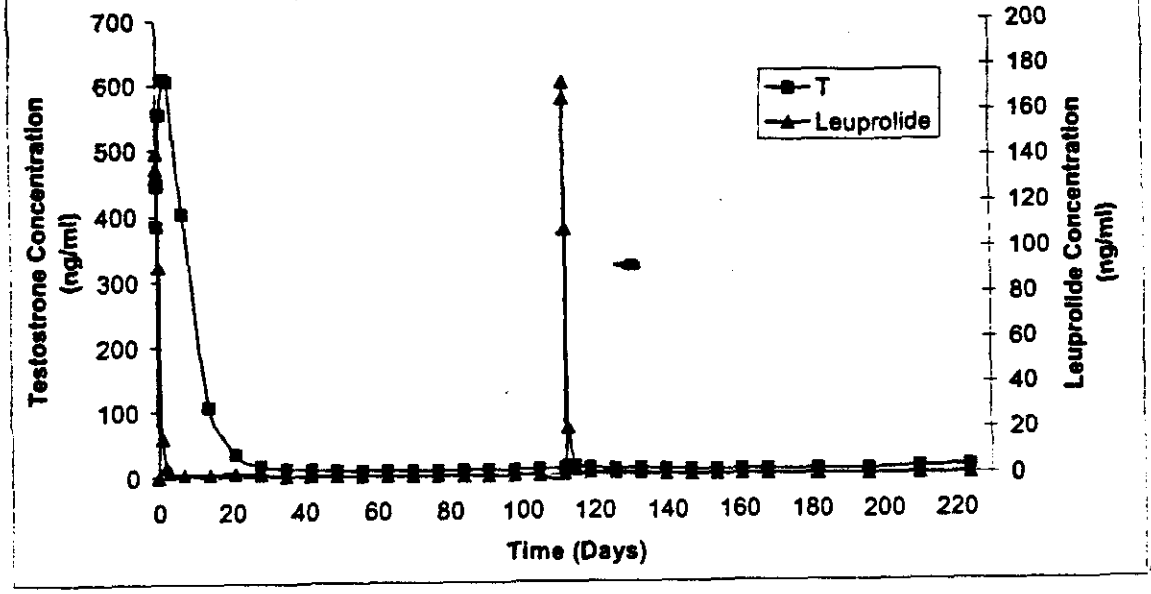
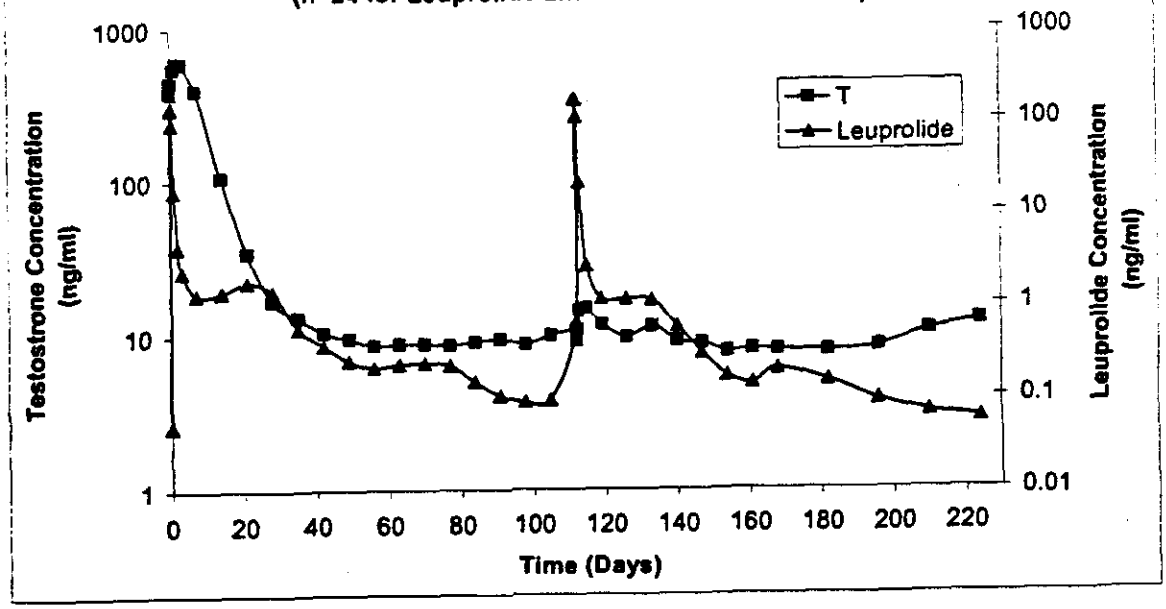


Figure 8. Relationship Between Mean Testosterone and Leuprolide Plasma Concentration-Time Profile in All Patients (Log Scale)
(n=24 for Leuprolide and n=90 for Testosterone)



Individual Suppression Data:

Examining the individual data for all patients in the trial shows that four patients had problems in either maintaining the castrated level or did not achieve the castrated level by Day 28. One additional patient (#2601) had no data for Days 21, 28, and 35. The testosterone level for this patient on Day 42 was 9.9 ng/dl. The individual relative testosterone levels for each patient immediately before and after achieving the castrated levels are shown below:

Subject#	Days	Testosterone (ng/dl)	Leuprolide (ng/ml)
0201 (Age 66 years, Weigh 224 lbs, White)			
	28	62	-
	35	64	-
	36	50	-
	49	28	-
	112	66	-
	112 (4 h)	91	-
	112 (8h)	143	-
	113	147	-
	115	111	-
	119	41	-
0802 (Age 65 years, Weigh 180 lbs, White)			
	21	74	-
	28	58	-
	35	35	-
1002 (Age 80 years, Weigh 185 lbs, Black)			
	112 (8h)	26	126
	113	53	19.6
	115	49	1.9
	119	24	1.5
1604 (Age 69 years, Weigh 135 lbs, White)			
	21	122	-
	28	75	-
	35	39	-
	105	49	-
	112	36	-
	112 (2h)	58	-
	112 (4h)	48	-
	112 (8h)	69	-
	113	94	-
	114	110	-
	119	79	-

126	59	-
133	55	-
140	39	-
210	32	-
224	53	-

2601 (Age 65 years, Weigh 231 lbs, Hispanic)

14	251	1.3
21	-	-
28	-	-
35	-	-
42	9.9	0.35
49	14	0.24

Testosterone suppression data including the number of patients achieving castrate level and those experienced breakthrough are summarized in **Tables 10-12**. For the intent-to-treat population, 85 of the 90 patients (94%) achieved castrate level testosterone suppression by Month 1 (Day 28). By Day 42, 99% (89/90) of patients had attained castrate suppression.

Table 10. Measures of Testosterone Suppression - Intent-to-Treat Population

Testosterone Suppression Measure	Day 21 N=90	M1 (Day 28) N=90	Day 42 N=90	Day 56 N=90	M3 (Day 84) N=90	M4 (Day 112) N=90	Day 168 N=90	M8 (Day 224) N=90
(≤ 50 ng/dL)	72 (80%)	85 (94%)	89 (99%)	89 (99%)	89 (99%)	88 (98%)	89 (99%)	88 (98%)
Breakthrough above 50 ng/dL	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)
≤ 20 ng/dL	18 (20%)	60 (67%)	81 (90%)	85 (94%)	86 (96%)	85 (94%)	86 (96%)	81 (90%)

Table 11. Measures of Testosterone Suppression - Observed Cases

Testosterone Suppression Measure	Day 21 N=89	M1 (Day 28) N=89	Day 42 N=89	Day 56 N=89	M3 (Day 84) N=89	M4 (Day 112) N=88	Day 168 N=84	M8 (Day 224) N=82
≤ 50 ng/dL	72 (82%)	85 (96%)	89 (100%)	89 (100%)	89 (100%)	87 (99%)	84 (100%)	81 (99%)
Breakthrough above 50 ng/dL	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)
≤ 20 ng/dL	18 (20%)	60 (67%)	81 (91%)	85 (96%)	86 (97%)	84 (96%)	81 (96%)	74 (90%)

INTENTIONALLY

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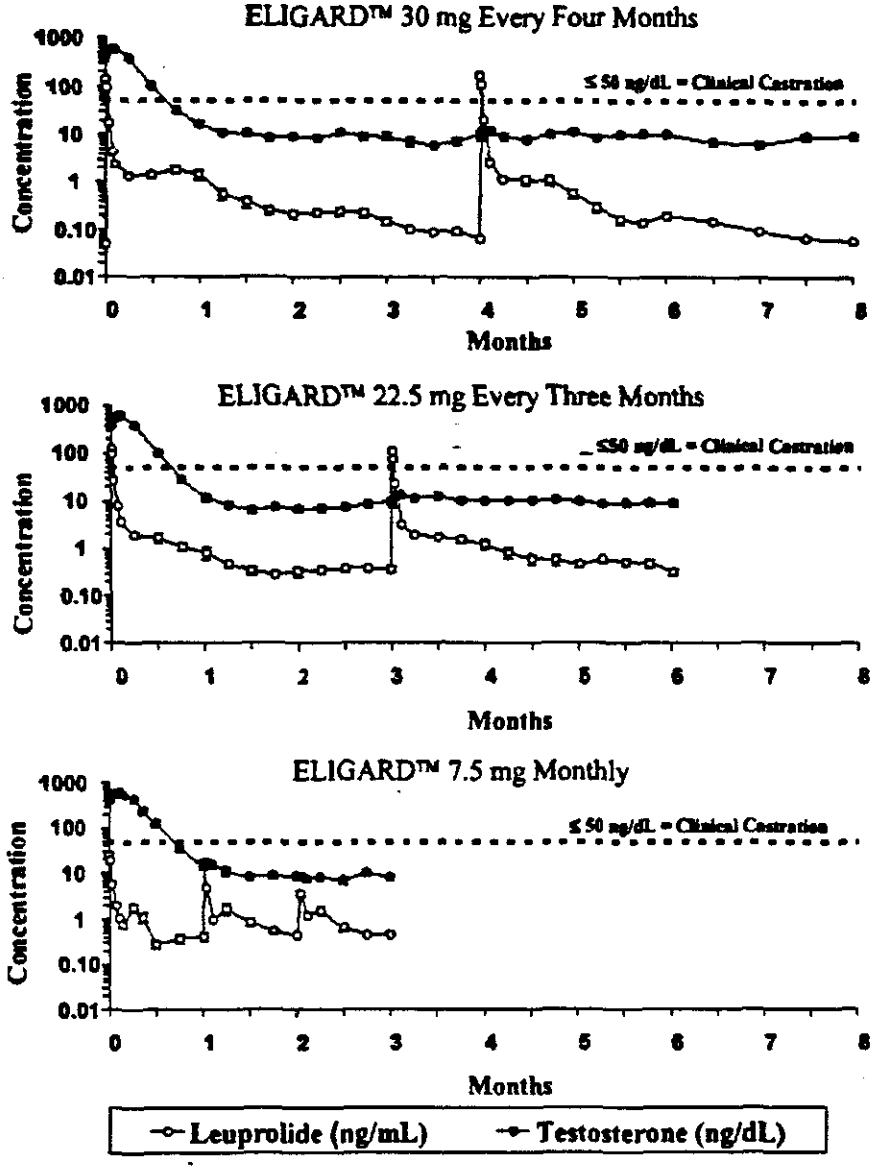
Table 12. Summary of Patients Experiencing Testosterone Breakthrough During the Study

	Patient #201	Patient #1002	Patient #1604
Achieved Initial Suppression	Day 42	Day 14	Day 35
Experienced Initial Breakthrough	Day 112: Hour 2	Day 113	Day 112: Hour 2
Max T During Breakthrough (ng/dL)	147 at Day 113	53 at Day 113	110 at Day 115
Resuppressed	Day 119	Day 115	Day 133
Second Breakthrough	N/A	N/A	Day 224
T Level at Month 8 (Day 224) ng/dL	13.0	7.2	53.0

Is There Dose-Response Relationship?

The pharmacodynamic response to repeat administration of leuprolide at 7.5, 22.5, and 30 mg are shown in **Figure 9.** After both injections for each formulation, mean serum leuprolide levels peaked during the first day, fell rapidly during the next few days, then maintained levels at about 2 ng/ml following all doses. In response to this pattern of leuprolide exposure, mean serum testosterone levels in the PK subset rose initially during and to <50 ng/dl by the third week and remained constantly low until the second dose. It must be emphasized again that no recovery from testosterone suppression was observed prior the second dose in any of three doses. In addition, there was no burst effect in testosterone serum level following any of the second doses. Once testosterone is suppressed it remains suppressed for the remainder of the trial.

Figure 9. PK/PD and Dose-Response relationship for Leuprolide Depot Formulations Given at 1, 3 or 4-Month Intervals for 7.5, 22.5 and 30 mg Eligard Formulations (Data from Studies AGL0001, AGL9909 and AGL9904)



Luteinizing Hormone (LH) Concentrations:

The mean concentration at baseline was 7.5 (0.7) mIU/mL, ranging from 3.3-9.1 MIU/mL. Similar to testosterone, there was a "burst phase" in LH plasma levels. After the first injection LH concentration rapidly increased and within 4 hours achieved a mean peak concentration of approximately 38 mIU/mL (**Figures 10**). Again similar to testosterone response, by Day 7 LH level returned to its mean baseline level of 7.2 mIU/mL. A further suppression of LH level continued and by day 28 a complete suppression of LH was achieved with a constant level of approximately 0.1 mIU/ml throughout the 8 months intervals. It should be noted that after the 2nd injection there was a transient but slight increase in LH reaching a concentration of approximately 0.4 mIU/ml by 4 hours. By Month 8 (Day 224) the mean LH concentration was 0.1 mIU/mL. The relationship between leuprolide and LH response is similar to that discussed for testosterone which is clearly demonstrated in **Figures 11 and 12.**

Figure 10. Mean LH Plasma Concentration-Time Profile After Eligard 30 mg Over 8 months (224 Days) In All Patients (n=90)

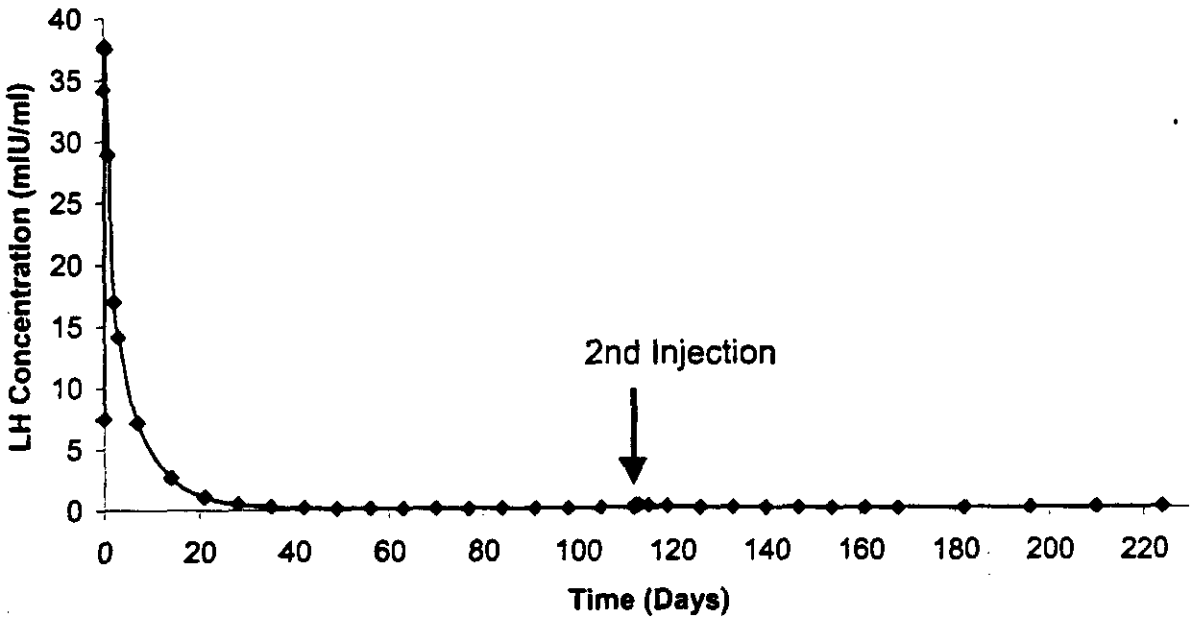


Figure 11. Relationship Between Mean LH and Leuprolide Plasma Concentration-Time Profile in All Patients (Regular Scale)
(n=24 for leuprolide and n=90 for LH)

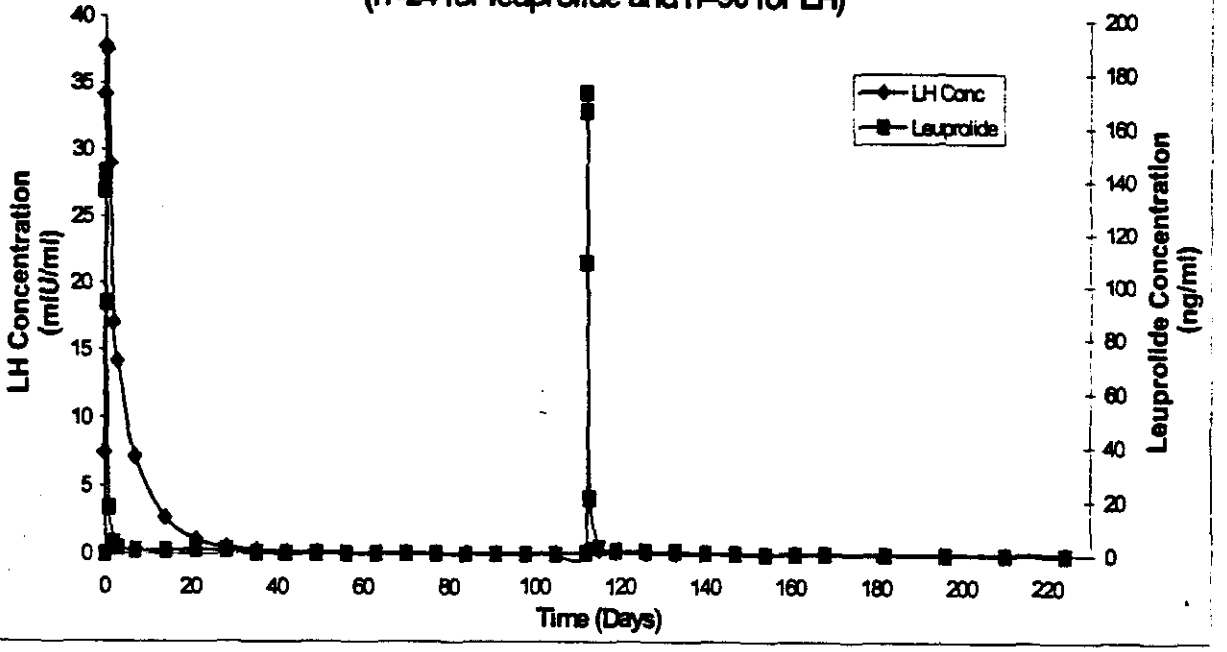
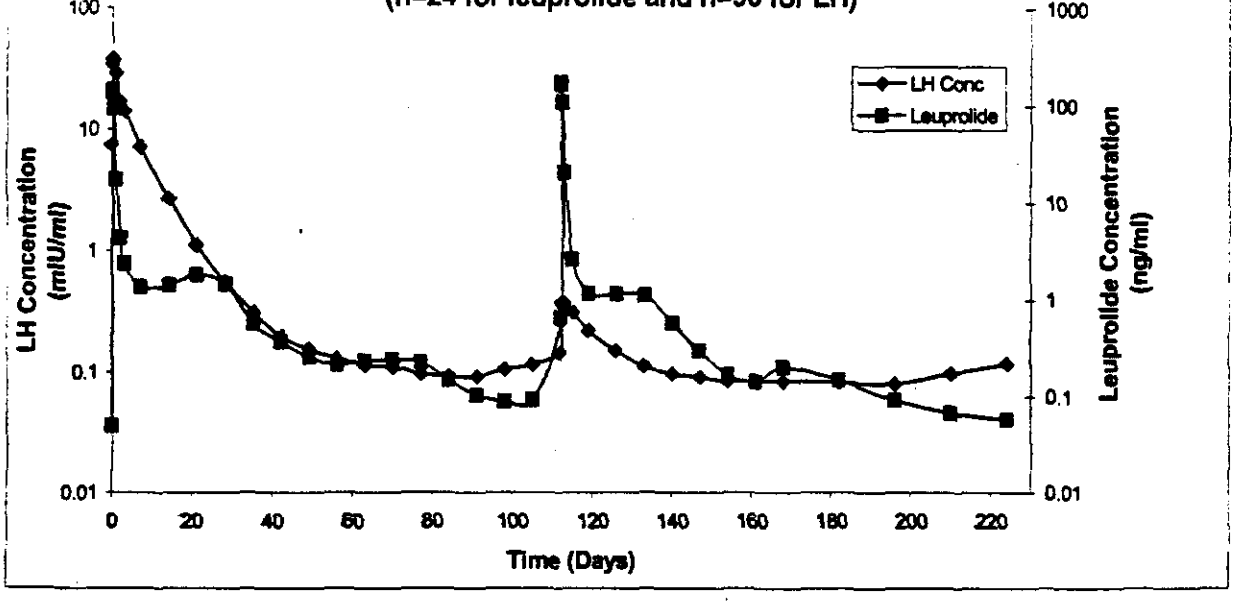


Figure 12. Relationship Between Mean LH and Leuprolide Plasma Concentration-Time Profile in All Patients (Log Sclae)
(n=24 for leuprolide and n=90 for LH)



PSA Levels:

Mean PSA was elevated (defined as PSA >4) at Baseline. PSA values were reduced by 86% from Baseline (13.2 ±2.0) to Month 8 (Day 224) (1.3 ± 0.3 ng/mL). At Baseline 66 of 88 (75%) patients had elevated PSA readings. Patients with elevated PSA declined steadily throughout the study with 4 of 81 (5%) showing elevated levels at Month 8 (Day 224). Of the 60 patients who had elevated PSA levels at Baseline and also had a Month 8 (Day 224) PSA measure, 56 (93%) had normal levels by the end of the study. All patients who had normal PSA levels at Baseline remained at normal PSA levels at the end of the study (see also the Medical Officer Review).

What is the Drop-Out Rate in the Trial?

A total of 90 patients were enrolled and received at least one study injection. Of those, 85 patients (94%) received two study injections. A total of 7 patients withdrew from the study for various reasons and one patient lost to follow. The reasons for the drop out for each patient are summarized in **Table 13.** Please see the Medical Officer's review for further details on the drop out rate and patients safety in the trials.

Table 13. Patients Drop-Out from the Study

Patient #	Day	Reason for drop Out
1909	112	Lose of libido, mild hot flashes, and mild night sweats
0401	14	Suicide intentions
1602	168	Moved out of the area
1606	154	Moved out of the area after being diagnosed with liver metastases
1710	105	Hot flashes and fatigue
1802	98	Study interfering with vacation plans
2304	112	Poor health after undergoing heart valve replacement surgery
1004	182	Lost to follow

Overall Summary:

This is the third NDA from the same sponsor for a similar product. The only difference is that the amount and dose of leuprolide in the new formulation is larger (i.e., 30 mg) than the previously approved formulation of 7.5 and 22.5 mg. The release characteristics and the suppression profiles for testosterone and LH after the three formulations follow similar patterns but they are different in two aspects: 1) the duration of the suppression and 2) the concentration of leuprolide achieved after each formulation. In terms of safety, there is extensive safety data on leuprolide within the Divison and the literature. However, in terms of the efficacy, the drug has been shown to be effective in suppressing testosterone level over the proposed duration of treatment in almost all patients.

ClinPharm/Biopharm Briefing on: Friday January 31, 2003

Briefing Attendees: Drs.

Reviewed by:

Sayed Al-Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD/FT initialed by Ameeta Parekh, Ph.D. _____

cc: NDAs # 21-319: HFD-580, HFD-860 (Al-Habet, Parekh, and Malinowski), and Drug files (Biopharm File, CDR).

Appendix I

NDA Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission			
	Information		Information
NDA Number	21-488	Brand Name	ELIGARD 30MG
OCPB Division 1	HFD-870	Generic Name	Leuprolide acetate
Medical Division	HFD-580	Drug Class	Hormone
OCPB Reviewer	Sayed Al Habet, Ph.D.	Indication(s)	Advance Prostate Cancer
OCPB Team Leader	Ameeta Parekh, Ph.D.	Dosage Form	Sterile Injection
		Dosing Regimen	Once every 3 months
Date of Submission	April 13, 2002	Route of Administration	Subcutaneous
Estimated Due Date of OCPB Review	January 15, 2003	Sponsor	Atrix Laboratories
PDUFA Due Date	February 13, 2003	Priority Classification	3S
Division Due Date	February 1, 2002		

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:	X	1		
multiple dose:	X	1		
Patients-				
single dose:	X	1		
multiple dose:	X	1		
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:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1		
Phase 3 clinical trial:	X	1		
Population Analyses -				
Data rich:	Yes	1		
Data sparse:	Yes	1		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	X	1		
alternate formulation as reference:				

Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X	1		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		5		

Filability and QBR comments		
	"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	There is extensive clinical experience with this drug. In addition, the division has recently approved a similar formulation for a one-month SC injection from the same sponsor (NDA# 21-343). Most of the PK data are crossed reference to NDA #21-343 and will be reviewed when applicable. The application can be filed.	
Primary reviewer Signature and Date	Sayed Al-Habet, Ph.D.	
Secondary reviewer Signature and Date	Ameeta Parekh, Ph.D.	

CC: NDA 21-289, HFD-850 (p. Lee), HFD-580 (Reddy), HFD-870 (Al-Habet, Parekh, Malinowski, Hunt), CDR (biopharm file)

APPEARS THIS WAY
ON ORIGINAL

Appendix II

Sponsor's Proposed Label

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

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

/s/

Sayed Al-Habet
1/31/03 03:36:07 PM
BIOPHARMACEUTICS

Ameeta Parekh
2/4/03 02:43:28 PM
BIOPHARMACEUTICS
I concur