CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-088

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

FEB 24 2000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW	
NDA:	**21-088**
Compound:	65 mg leuprolide acetate implant, Viadur™ (osmotic delivery 120 µg leuprolide acetate/day/implant over 1 year)
Sponsor:	Alza Corporation
Type of Submission:	New Drug Product; Classification, 3S
Date of Submission:	April 30, 1999; B2, July 19, 1999; SU, October 13, 1999; 13B, December 23, 1999; BL, February 16, 2000
Reviewer:	S.W. Johnny Lau, R.Ph., Ph.D.

Background

NDA 21-088 (Viadur™ 65 mg leuprolide acetate implant for palliative treatment of advanced prostate cancer; [redacted] was submitted on April 30, 1999. Viadur™ is a single-use, titanium alloy, implantable, osmotically driven, miniaturized dosage form designed to continuously deliver leuprolide acetate at a nominal rate of 120 µg/day/implant over 1 year. The implant is inserted subcutaneously in the inner aspect of the upper arm. Viadur™ must be removed after 12 months of therapy and another implant may be immediately inserted to continue therapy. Sponsor conducted 2 clinical safety and efficacy studies (C-96-011 and C-97-010), from which clinical pharmacology and biopharmaceutics information is also assessed.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 21-088 dated April 30, 1999. OCPB/DPEII finds that the submitted information supports the "Human Pharmacokinetics and Bioavailability" section of NDA 21-088. The Clinical Pharmacology labeling comments have been communicated to and agreed by the sponsor. The following comments should be communicated to the sponsor:

[redacted]

Time interval (days)	Leuprolide acetate released (mg)
0 - 14	≤ 5.5
14 - 28	1.3 - 2.6
28 - 42	1.4 - 2.5

The proposed Viadur™ in vitro cumulative leuprolide acetate release rate method and specifications are acceptable on an interim basis.

2. Since the proposed in vitro release rate method and specifications only account for the release of about 10 mg of leuprolide acetate in Viadur™ implant (total = 65 mg) up to 42 days, an accelerated in vitro release rate procedure is recommended as a Phase IV commitment to investigate and account for ≥ 80% of the leuprolide acetate content in Viadur™ implant.

3. For future changes on Viadur™ drug formulation, implant components, manufacturing process, and/or manufacturing site, either an in vivo bioequivalence study or acceptable in vitro/in vivo correlations (IVIVC) should be used to support the approval of the changes. Although useful IVIVC assessments have been submitted, namely,
i) both in vitro release and estimated in vivo (humans) input rate data for leuprolide acetate for 7 days
ii) both in vitro and in vivo (humans) cumulative amount of leuprolide acetate released for 12 months
iii) both in vitro and in vivo (rats) cumulative amount of leuprolide acetate released for 3, 6, 9, and 12 months, none of the submitted data address the in vitro/in vivo relationship between 7 days and 12 months in humans. Therefore, to support future changes in Viadur™ drug formulation, implant components, manufacturing process, and/or manufacturing site, in lieu of conducting a classical in vivo bioequivalence study for 1 full year of Viadur™ administration, OCPB recommends that additional in vivo cumulative amount of leuprolide acetate released data for Viadur™ should be collected in humans at 1, 2, and 3 months to better substantiate the IVIVC. Ideally, the clinically tested batch/lot and the new-marketed batch/lot should be compared both in vitro and in vivo in this study.

/S/

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

y 24, 2000

An optional Inter-Division Clinical Pharmacology and Biopharmaceutics Briefing for NDA 21-088 was conducted on February 11, 2000. Participants included N. Marks, S. Huang, J. Hunt, A. Parekh, and J. Lau.

FT signed by Ameeta Parekh, Ph.D., Team Leader /S/ 2/24/2000

cc: NDA 21-088, HFD-870 (S. Huang, A. Parekh, J. Lau), HFD-580 (N. Marks, J. Best), CDR (B. Murphy for Drugs)

The following questions, based on the content of NDA 21-088, guided this review.

1. What is leuprolide (L)?
L is a synthetic gonadotropin-releasing hormone (GnRH) analog (nonapeptide) agonist with about 80 to 100 times the potency of GnRH and is used to treat a wide range of sex-hormone related disorders.

2. How does L work?
L primarily acts on the anterior pituitary. Administration of L causes an initial surge of luteinizing hormone (LH) from the pituitary, which increases testicular testosterone (T) production. With continued use, L causes pituitary GnRH receptors "down-regulation" and desensitization, leading to a decline in LH release and thereby suppression of T synthesis. Lowering T in the body helps to relieve pain, urinary problems, and other prostate cancer symptoms.

3. What is the proposed indication for Viadur™?
Palliative treatment of advanced prostate cancer (PTAPC).

4. What are the adverse effects of L in prostate cancer patients?
Impotence and decreased libido are universal. Hot flushes, usually mild and tolerable, occur in 35 to 71% of patients (Plosker & Brogden *Drugs* 48:930 1994). Exacerbation of symptoms (disease flare: mostly as bone pain) occurs in about 10% of patients.

5. What other L preparations are indicated for the PTAPC?
Lupron® (L acetate aqueous solution as single daily subcutaneous injection), Lupron Depot® 7.5 mg, Lupron Depot®-3 Month 22.5 mg, and Lupron Depot®-4 Month 30 mg (L acetate depot suspensions as single intramuscular injections).

6. What are the clinical safety and efficacy studies that support the approval of NDA 21-088?
NDA 21-088 contains 2 well-controlled randomized studies. Study C-96-011 is a dose-ranging study to evaluate the safety, efficacy, and repeated doses pharmacokinetics (PK) of 1 or 2 Viadur™ implants (120 or 240 µg L acetate/day; Group 1 and Group 2, respectively). Study C-97-010 is a pivotal study to evaluate the safety, efficacy and single dose PK of 1 Viadur™ implant (120 µg L acetate/day). Both studies were conducted in 2 phases (1-year Treatment Phase and then 1-year Safety Extension Phase). After the 1st phase, implants were extracted and replaced with new implants. This NDA includes data from the Treatment Phase through reinsertion for both studies and also from the 1st 2 months following reinsertion for study C-96-011. Serial serum L, T, LH, and prostate specific antigen (PSA) concentrations were quantified for the both phases of both studies.

7. What is the proposed dose for Viadur™? How is this dose determined?
One Viadur™ implant, which delivers at a nominal rate of 120 µg L acetate/day for 12 months.

Subcutaneous injection of 1-month depot suspensions containing 3.75, 7.5, or 15 mg L acetate to 22 prostate cancer patients resulted in maximum serum L concentrations of 13.09, 47.40, and 55.54 ng/mL, respectively, within 3 hours (Mazzei et al. *Drugs Exptl. Clin. Res.* XV:373 1989). Mean

serum L concentrations declined, reaching respective average concentrations of approximately 0.54, 0.84, and 1.10 ng/mL by Day 2. The high serum L concentration observed immediately after injection was due to a rapid and transient release of the drug from the surface of the microspheres. This was followed by a more constant release from Day 28 - Day 35; the estimated L acetate release rates were 2.89 and 4.30 µg/h (69.36 and 103.2 µg/d) following the 3.75 and 7.5 mg depot administration, respectively (Mazzei et al. *Drugs Exptl. Clin. Res.* XV:373 1989). Rapid increases in serum T concentrations resulted and were maintained for approximately 1 week. About 3 weeks postdose, serum T concentrations declined rapidly to castrate concentrations; there were no significant differences in these concentrations as a function of dose (Mazzei et al. *Drugs Exptl. Clin. Res.* XV:373 1989). Serum FSH and LH concentrations followed similar pattern.

Study C-96-011 demonstrated that 1 Viadur™ implant was as effective as 2 Viadur™ implants in suppressing serum T concentrations to castration concentrations (≤ 50 ng/dL; primary efficacy parameter). The nominal delivery rate of 120 µg L acetate/day/implant may not be the lowest effective dose for PTAPC. However, safety is not a concern at this L dose as per discussion with medical officer.

8. What are the bioanalytical methods for L, T, and LH used in NDA 21-088?
Bioanalytical assays including validation for L, T, and LH in serum samples follow (Table 1):

	L ng/mL	T ng/dL	LH mIU/mL
Method	LC-MS/MS	RIA	ICMA
LLOQ	0.1	< 3	0.04
Recovery, %	75.4	> 96	NA
Linearity	0.1 - 20	5 - 200	0.1 - 50
Accuracy, %			
intra-assay	0 - 11.7	NA	-17.3 to 2.2
inter-assay	0.11 - 1.6	4.56 - 5.81	-9.73 to -3.68
Precision, % CV			
intra-assay	1.3 - 11.6	2.94 - 7.98	7.4 ± 2.2
inter-assay	2.2 - 11.1	23.09	7.4 ± 2.3

L = leuprolide
T = testosterone
LH = luteinizing hormone
LC-MS/MS = liquid chromatography-tandem mass spectrometry
RIA = radioimmunoassay (after nonpolar solvent extraction and alumina column chromatography)
ICMA = immunochemiluminometric assay
LLOQ = lower limit of quantitation
NA = not available

Sponsor did not measure any L metabolites in studies C-96-011 and C-97-010.

9. What is the known clinical PK of L (via formulation not related to Viadur™ implant)?

Absorption

Oral L bioavailability is less than 1% (Plosker & Brogden *Drugs* 48:930 1994). Upon subcutaneous administration of 1 mg L acetate (aqueous solution) to 6 healthy men, the absolute bioavailability was 94% with a mean absorption half-life of 10 minutes and peak plasma L concentration of 32.3 ng/mL at 0.6 hours (Sennello et al. *J. Pharm. Sci.* 75:158 1986).

Following a single injection of Lupron Depot® 4 Month (30 mg L acetate suspension) in 16 orchiectomized prostate cancer patients, the mean plasma L concentration was 59.3 ng/mL at 4 hours (PDR 1999). The mean plasma L concentration from 3.5 to 16 weeks was 0.44 ± 0.20 ng/mL (range: 0.20-1.06 ng/mL). Following the onset of steady-state concentrations during week 4, L appeared to be released at a constant rate, resulting in steady plasma L concentrations throughout the 16-week dosing interval. The initial rise in plasma L and rapid decline to a steady-state concentrations is similar in the 1-, 3-, and 4-month depot formulations (PDR 1999).

Distribution

The mean steady-state volume of distribution of L following 1 mg (aqueous solution) subcutaneous and intravenous bolus administrations in healthy male volunteers was 37.1 and 26.5 liters, respectively (Sennello et al. *J. Pharm. Sci.* 75:158 1986). In vitro L human plasma proteins binding was 43 - 49% (PDR 1999).

Metabolism

Intramuscular injection of an 1-month L acetate (3.75 mg suspension) depot to a prostate cancer patient resulted in serum M-I (major metabolite; pentapeptide) concentration of 0.15 ng/mL at 1 hour and maximum serum M-I concentration of 0.86 ng/mL at 3 hours (Ueno & Matsuo *J. Chromatograph.* 566:57 1991). M-I biological activity is unknown. In another prostate cancer patient, urine M-I concentration was 1.74 ng/mL 29 days after the intramuscular depot injection. The detection limit for serum and urine M-I concentrations was 0.05 ng/mL.

M-I in 5 prostate cancer patients reached maximum concentrations 2 - 6 hours postdose (route of administration not specified) with Lupron Depot® (dosage strength and dosage form not specified) and was approximately 6% of the peak parent drug concentration (PDR 1999). One week postdose, mean plasma M-I concentrations were approximately 20% of mean L concentrations.

Elimination

In healthy male volunteers, administration of an 1 mg (aqueous solution) subcutaneous and intravenous bolus injection of L resulted in mean systemic clearances of 151 (43 S.D.) and 139 (30 S.D.) mL/min, respectively. The terminal elimination half-life for each route of administration was about 3 hours based on a two-compartment model (Sennello et al. *J. Pharm. Sci.* 75:158 1986).

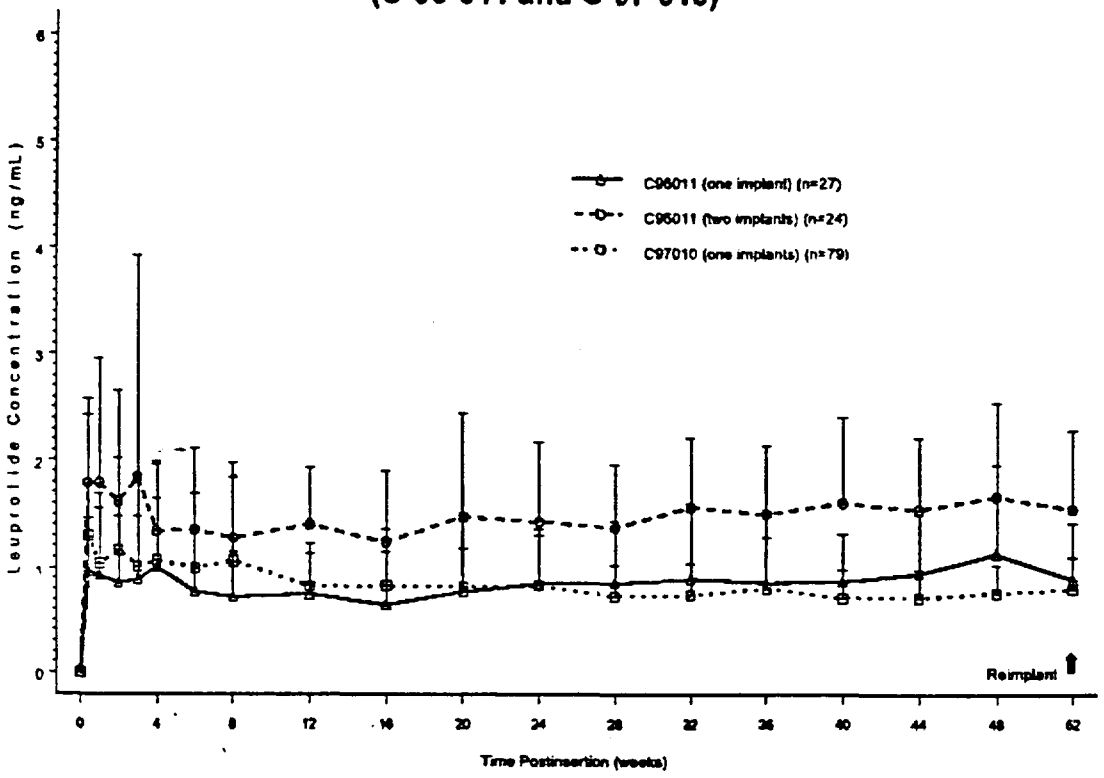
Following administration of Lupron Depot® 3.75 mg (suspension; route of administration not specified) to 3 patients (type of patients not specified), less than 5% of the dose was recovered as parent and M-I metabolite in the urine (PDR 1999).

10. What are the formulations used in the clinical studies for NDA 21-088?

The clinically-tested drug formulation is identical to the to-be-marketed drug formulation. Vendor changes to the quantitative components of the implants occurred but validated.

11. Are Viadur™ doses proportional (1 versus 2 implants)?

Figure A
Mean (SD) Serum Leuprolide Concentrations: Day 3 Through Week 52
(C-96-011 and C-97-010)



Note C96011-two data points excluded - Patient 902 baseline and Patient 304 Week 52
C97010-excluding all data points for Patient 702, Week 52 data point for Patient 804 and baseline for Patient 702 804 905 907 912

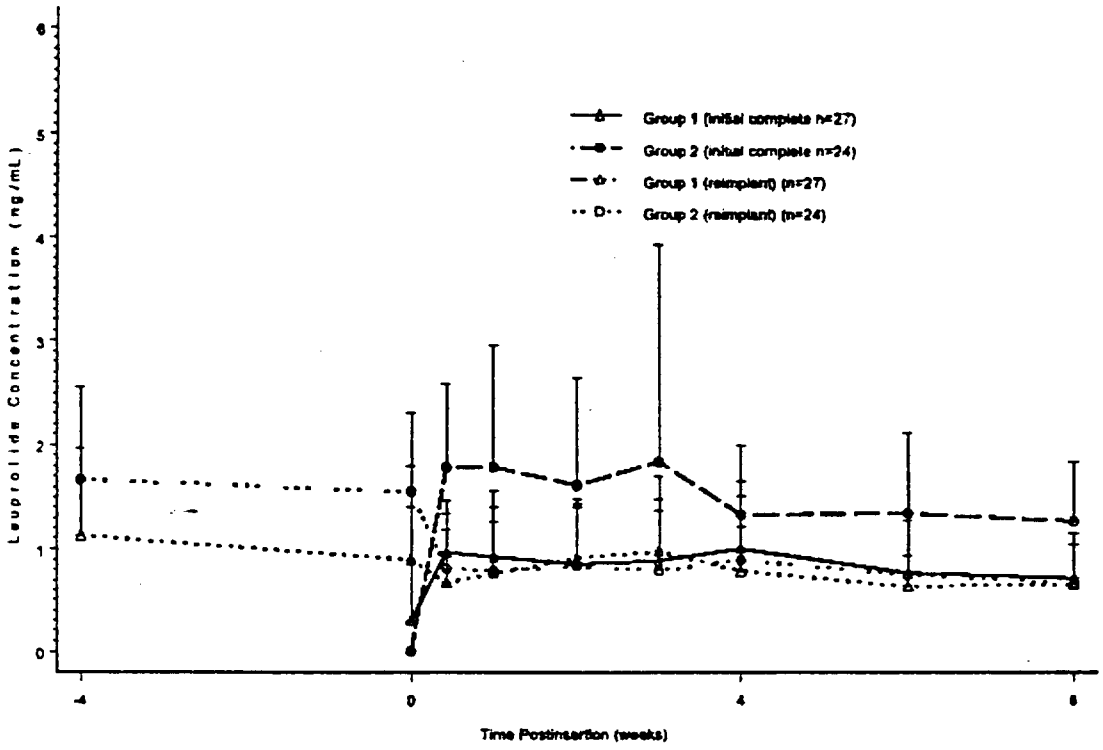
SOURCE: C97010\PKPD\NSPK\CGMMN3.SAS WITH (VER. 02/25/99 9:49)

Figure A shows the mean serum L concentrations versus time plots upon administration of 1 or 2 Viadur™ implant(s) for study C-96-011 and 1 Viadur™ implant for study C-97-010. In study C-96-011, the mean C_{avg} values following administration with 1 or 2 Viadur™ implant(s) were 0.79 ng/mL and 1.28 ng/mL, respectively. C_{avg} is the average serum L concentration maintained over the Treatment Period for an individual patient. In study C-97-010, the mean C_{avg} value following treatment with 1 Viadur™ implant was 0.93 ng/mL. The dose-normalized C_{avg} values were not significantly different between the 2 treatment groups of study C-96-011 ($p=0.09$). Thus, mean C_{avg} was proportional to the number of administered Viadur™ implant.

12. Does Viadur™ accumulate upon multiple dose administration?

Figure B

Mean (SD) Serum Leuprolide Concentrations During the Two Months After Insertion of Initial Implant(s) and During the Month Before and Two Months After Reinsertion of a New Implant (C-96-011)



Note: two data points excluded - Patient 902 baseline and Patient 304 Week 52

SOURCE: C97010\PKPD\SPK\CGMMN2.SAS WITH (VER: 02/25/99 9:44)

Figure B shows the serum L concentrations versus time plots for both treatment groups of study C-96-011 (1 or 2 implants) in the following time periods:

- 2 months after the insertion of Viadur™ implant(s) in the Treatment Phase
- 1 month before and during the 2 months after insertion of the new implant in the Safety Extension Phase.

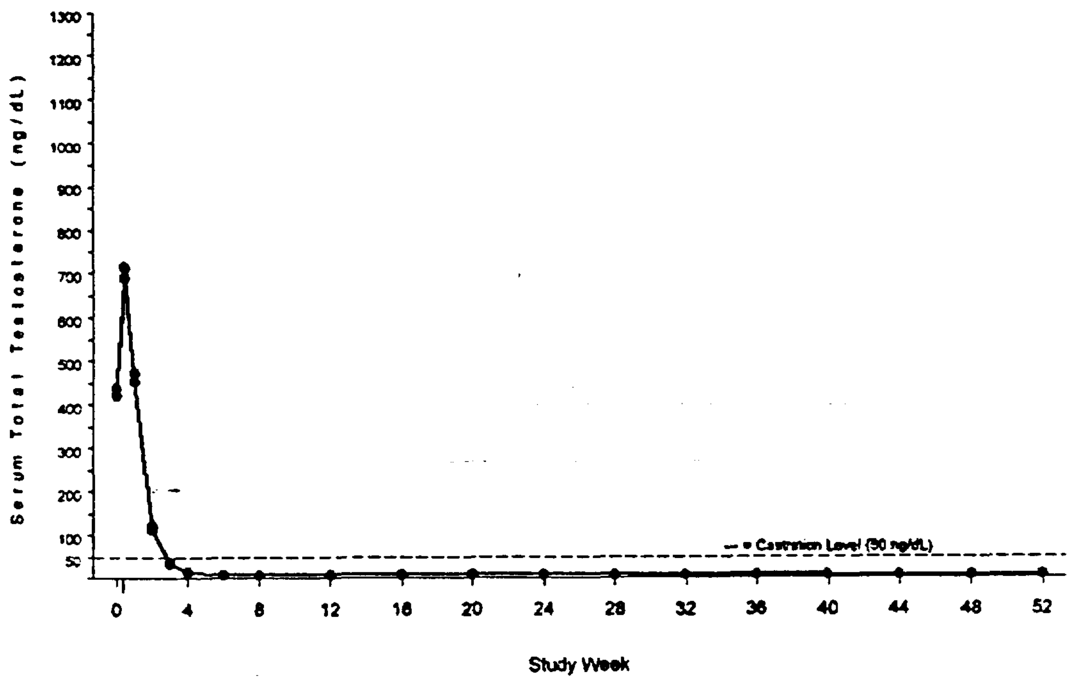
In Group 1, serum L concentrations in the first 2 months of the Treatment Phase and in the 1st 2 months of the Safety Extension Phase are superimposable. In Group 2, serum L concentrations in the 1st 2 months of the Safety Extension Phase (when these patients had 1 implant) are superimposable on the serum L concentrations measured in Group 1 patients during the 1st 2 months of the Treatment Phase. These observations suggest that there was no accumulation of L upon repeated administration, and that the serum L concentration was maintained by reimplantation.

13. **What is the effect of Viadur™ on serum T concentrations?**

Suppression of serum T concentrations to ≤50 ng/dL (castration) is the primary efficacy parameter for studies C-96-011 and C-97-010.

Figure C

Mean (+ SEM) Serum Total Testosterone Concentrations
All Patients Who Received One Implant

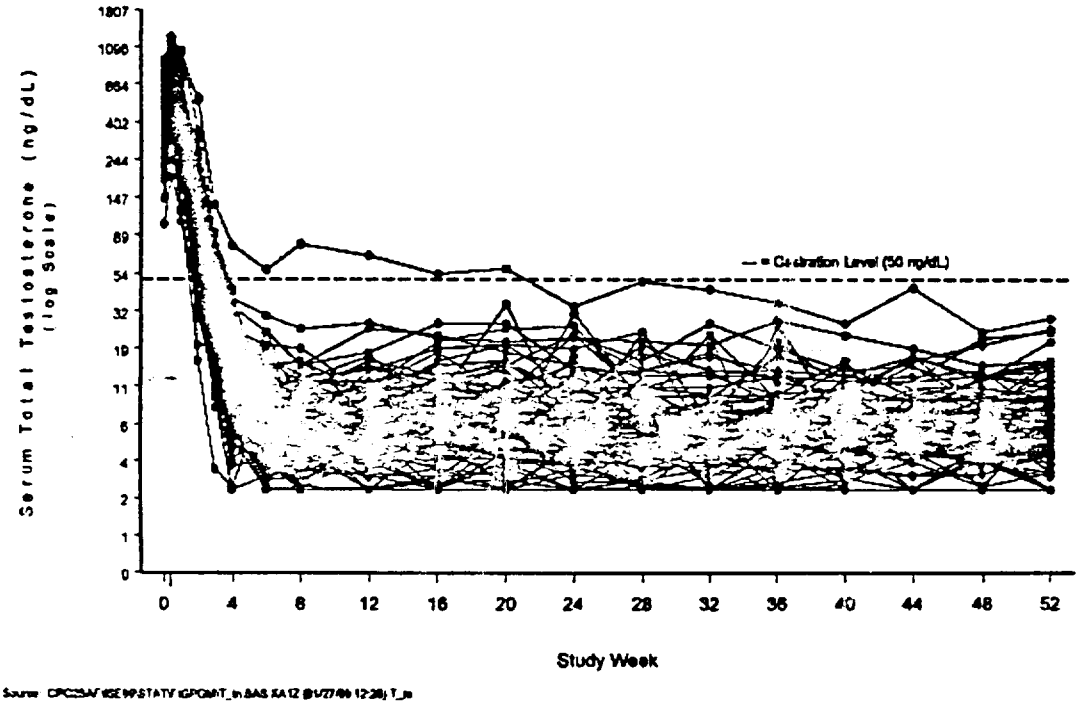


APPEARS THIS WAY
ON ORIGINAL

Upon insertion of 1 Viadur™ implant, mean (±SD) serum T concentrations for all patients increased from 422.7±161.8 ng/dL at baseline to 690.8±251.9 ng/dL on Day 3 (Figure C), and then decreased rapidly, falling below the baseline mean by Week 2 (113.1±91.6 ng/dL). Serum T concentrations fell below the castrate threshold between Weeks 2 and 4 in all but 1 patient (Figure D).

Figure D

Individual Serum Total T Concentrations, Baseline through Month 12: All Patients Treated with One Implant (Logarithmic Scale)

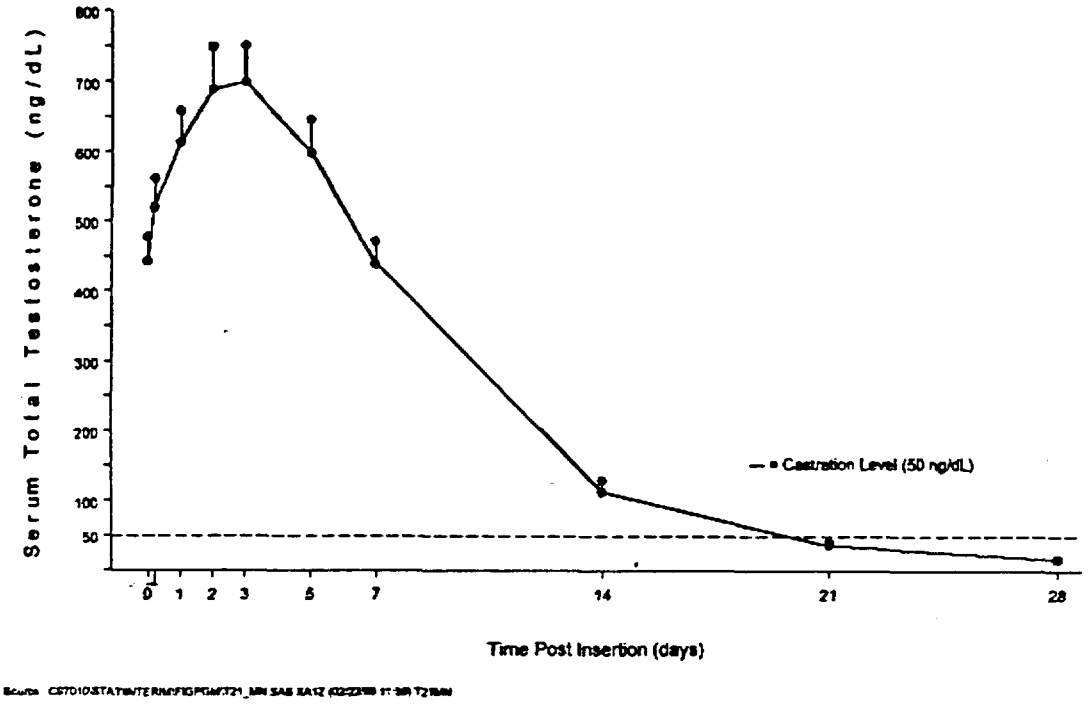


Once T suppression was achieved (even for the 1 patient in whom serum T was not suppressed until Week 28), T remained suppressed below the castrate threshold for the duration of the Treatment Phase (Figure D). Mean T from Weeks 6 through 52 ranged between 6.6 and 8.5 ng/dL.

APPEARS THIS WAY
ON ORIGINAL

Figure E

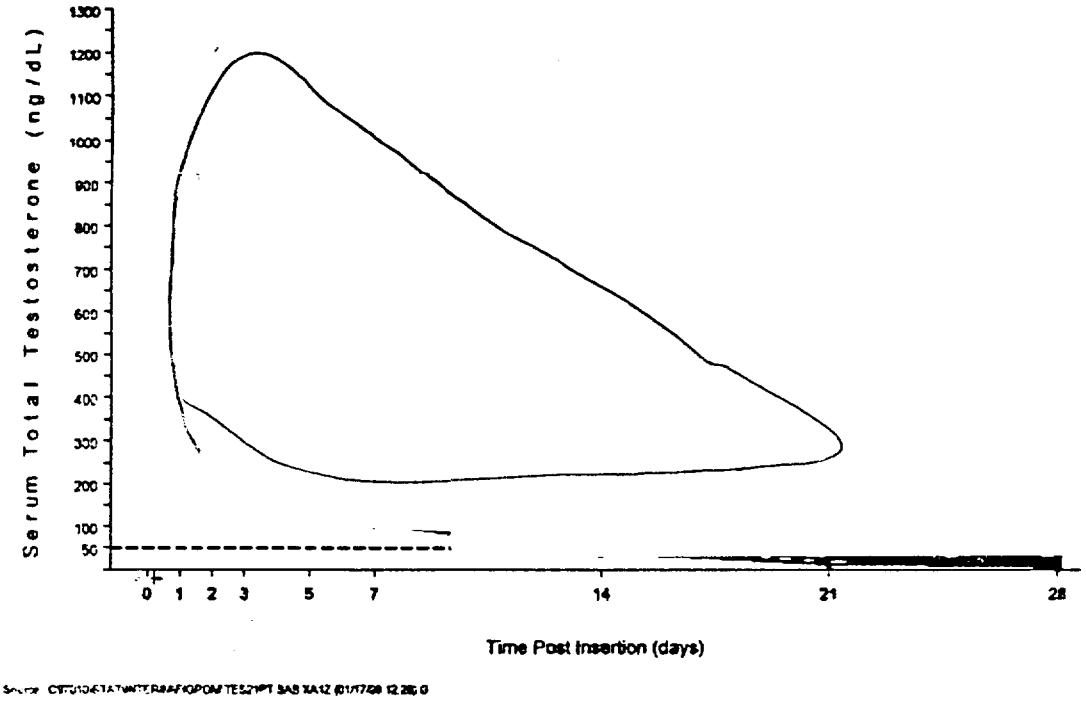
Mean (+SEM) Serum Total T Concentrations, Baseline through Day 28: 21 Patients Included in the Special Pharmacokinetic Assessment (Study C-97-010)



Serum T concentrations in the 21 patients (treated with 1 Viadur™ implant) who underwent frequent blood sampling after implant insertion in Study C-97-010 showed that T rose from a baseline mean (± SD) of 443.1±157.5 ng/dL to 519.9±189.8 ng/dL at 4 hours after implant insertion (Figure E). It peaked on Day 3 (701.4±222.8 ng/dL [range 370–1064 ng/dL]), then decreased, falling below the baseline mean on Day 7 (440.0±153.1 ng/dL) and below the castrate threshold at Week 3 (36.8±23.5 ng/dL).

Figure F

Individual Serum Total T Concentrations, Baseline through Day 28: 21 Patients Included in the Special Pharmacokinetic Assessment (Study C-97-010)

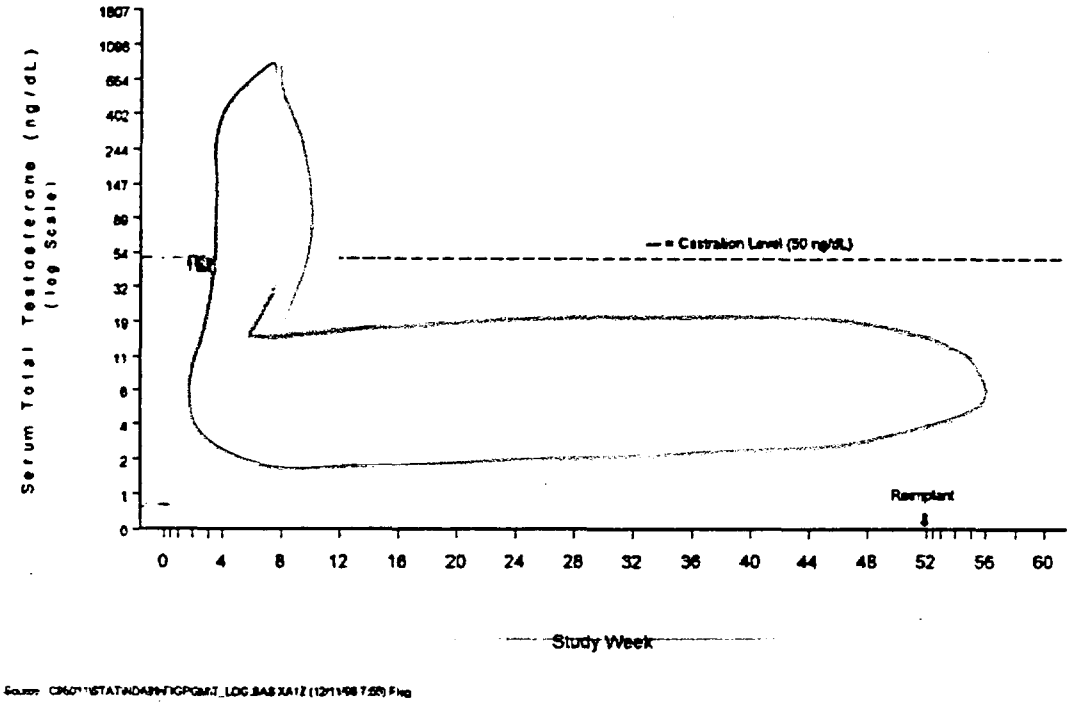


Individual serum T concentrations versus time profiles through Day 28 for the 21 patients in study C-97-010 are in Figure F.

APPEARS THIS WAY
ON ORIGINAL

Figure G

Individual Serum Total T Concentrations, One-Implant Group, Baseline through Month 14: All Randomized and Treated Patients (Study C-96-011)
(Logarithmic Scale)



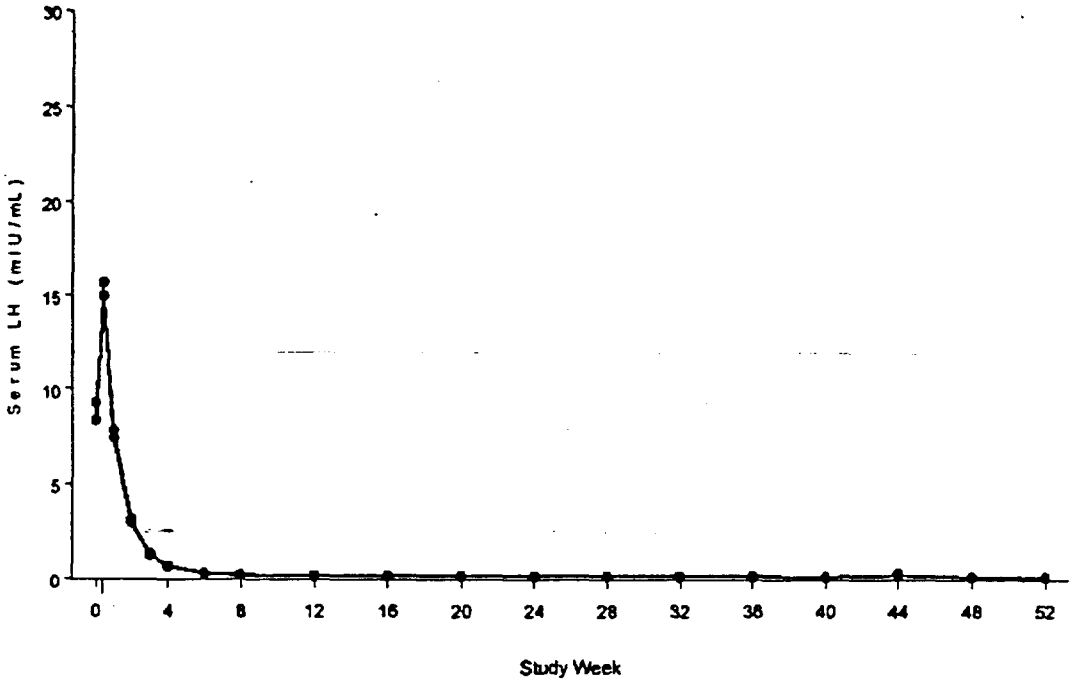
No patient in study C-96-011 had a clinically significant increase in serum T after removal of the initial Viadur™ implant and insertion of a new implant (Figure G—data for 1-implant treatment group only). Suppression of serum T was maintained in all patients throughout the 2-month follow-up period after reimplantation.

APPEARS THIS WAY
ON ORIGINAL

14. What is the effect of Viadur™ on serum LH concentrations?

Figure H

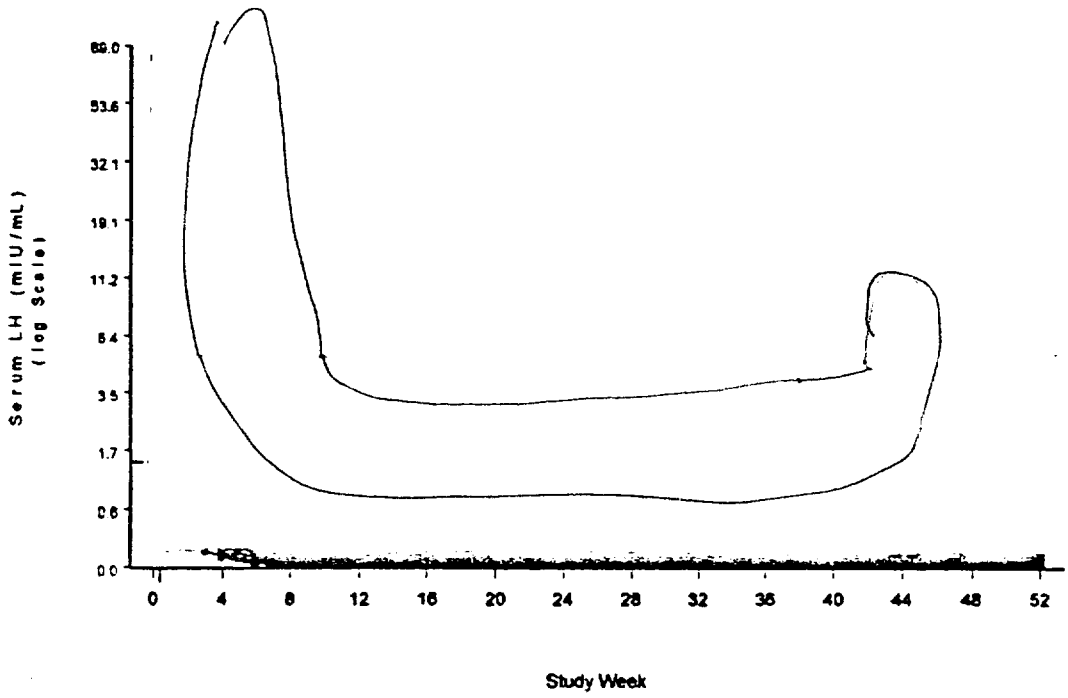
Mean (+SEM) Serum Luteinizing Hormone Concentrations
All Patients Who Received One Implant



Mean serum LH concentrations for all patients who received 1 Viadur™ implant increased from 8.37±9.57 mIU/mL at baseline to 14.98±7.72 mIU/mL at the 1st sampling time, Day 3 (Figure H). Mean serum LH concentrations then decreased, falling below the mean baseline concentration by Day 7 (7.45±4.08 mIU/mL) and below the lower limit of the normal male range (<1.5 mIU/mL) by Week 3 (1.26±0.70 mIU/mL). Once suppressed, mean serum LH concentrations remained suppressed through Week 52, ranging from Weeks 6 to 52 between 0.09 and 0.25 mIU/mL.

Figure I

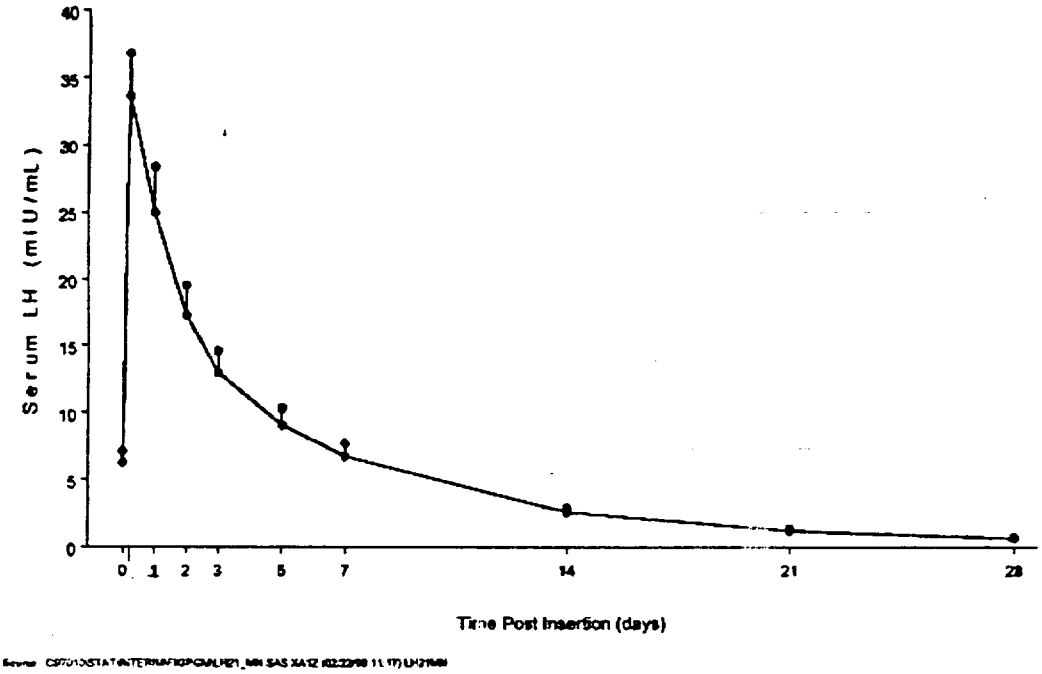
Individual Serum LH Concentrations, Baseline through Month 12:
All Patients Who Received One Implant
(Logarithmic Scale)



In most individual patients, once suppressed, LH remained suppressed well below the lower limit of the normal male range (Figure I). However, occasional transient increases in serum LH were seen in both studies. In study C-96-011, some blood samples were reanalyzed and the repeat values were below the lower limit of the normal range. In study C-97-010, 2 patients demonstrated transient increases in LH. Despite these findings, serum T remained suppressed and serum PSA was below the lower limit of detection in both patients. Generally, once serum LH suppression was achieved, serum LH remained suppressed for the duration of the Treatment Phase.

Figure J

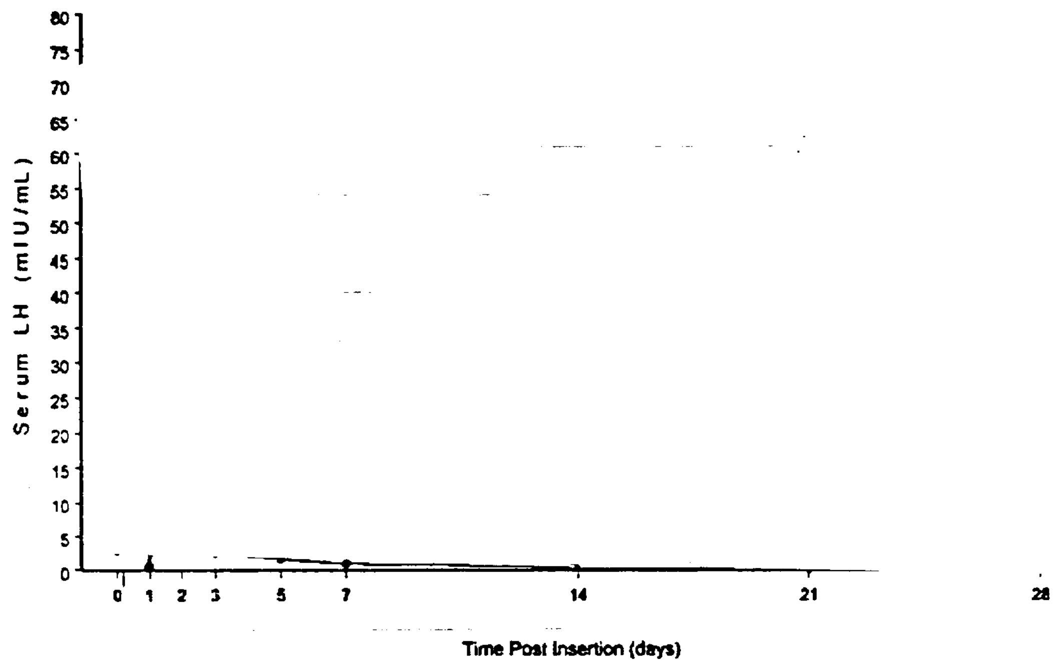
**Mean (+SEM) Serum LH Concentrations, Baseline through Day 28:
21 Patients Included in the Special Pharmacokinetic Assessment (Study C-97-010)**



Mean serum LH concentrations in the 21 patients who underwent frequent blood sampling after implant insertion in study C-97-010 demonstrated rapid increase in serum LH upon insertion of the Viadur™ implant (Figure J). Serum LH in these patients rose from a baseline mean (± SD) of 6.29±3.92 mIU/mL to a peak of 33.62±15.00 mIU at 4 hours after implant insertion. It then decreased, falling below the baseline mean by Week 2 (2.59±1.53 mIU/mL) and below the lower limit of the normal male range by Week 3 (1.19±0.65 mIU/mL).

Figure K

Individual Serum LH Concentrations, Baseline through Day 28: 21 Patients Included in the Special Pharmacokinetic Assessment (Study C-97-010)

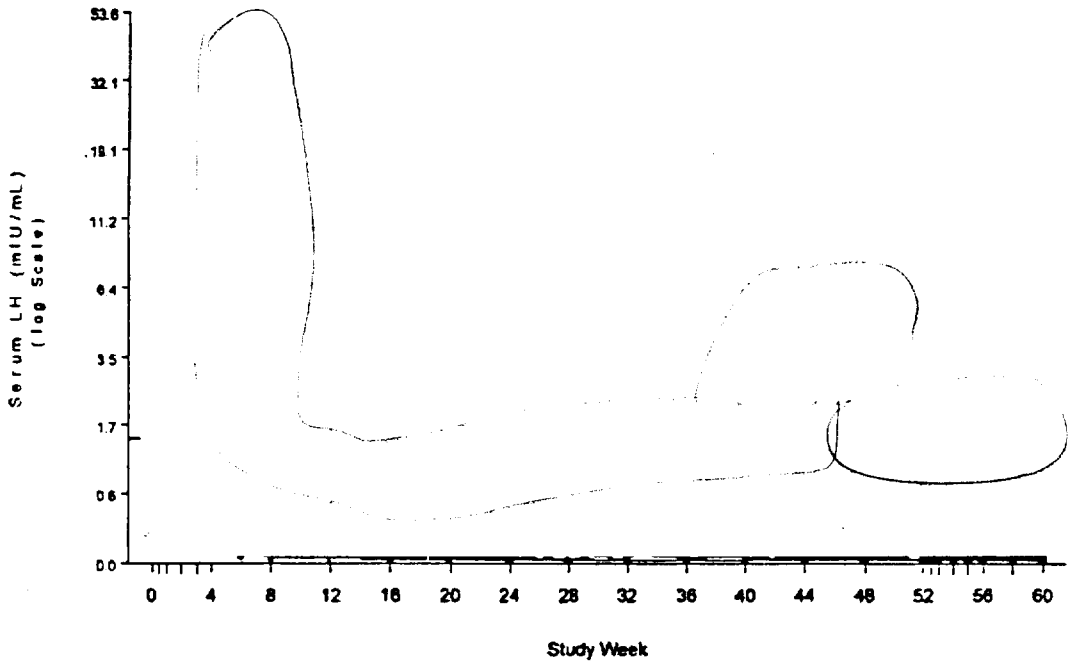


Serum LH concentrations versus time profiles through Day 28 for the 21 individual patients in study C-97-010 are in Figure K.

APPEARS THIS WAY ON ORIGINAL

Figure L

Individual Serum LH Concentrations, One-Implant Group, Baseline through Month 14: All Randomized and Treated Patients (Study C-96-011)
(Logarithmic Scale)



No patient in study C-96-011 had a clinically significant increase in serum LH after removal of the initial Viadur™ implant and insertion of a new implant (Figure L; data for 1-implant treatment group only). Suppression of serum LH was maintained in all patients throughout the 2-month follow-up period after reimplantation.

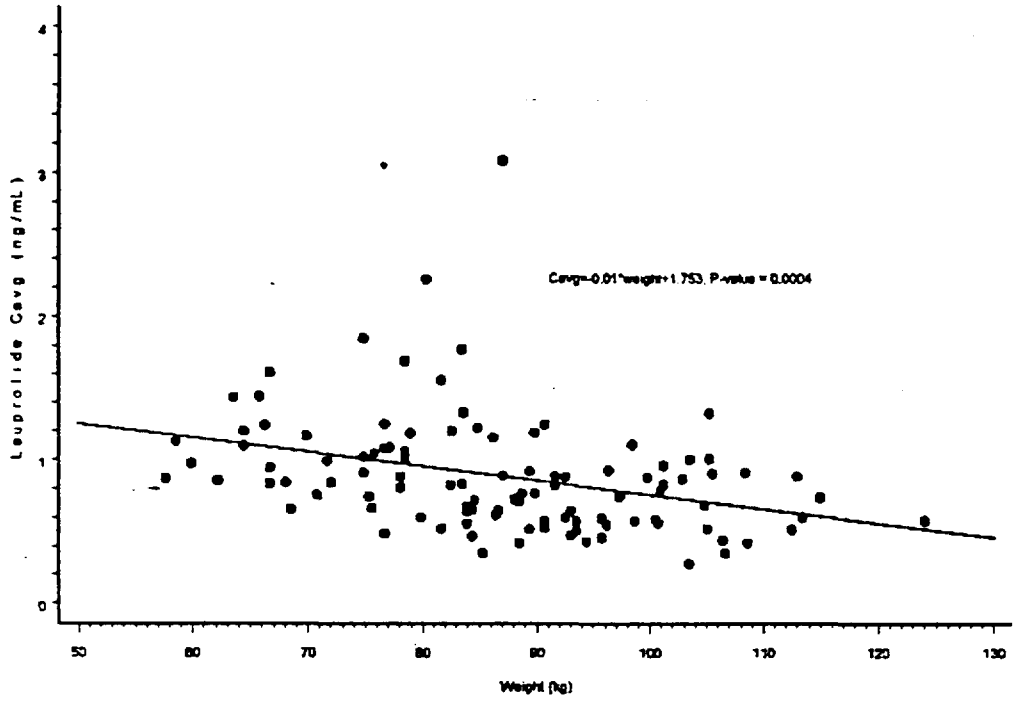
15. How does the PK of Viadur™ differ in special populations?

NDA 21-088 does not contain population PK study/analysis.

The influence of race and age on L C_{avg} values following insertion of 1 Viadur™ implant was examined. C_{avg} is the average serum L concentration maintained over the Treatment Period for an individual patient. Eighty Caucasians, 23 Blacks, and 3 Hispanics patients participated in the 2 clinical studies and their mean (SD) L C_{avg} values were 0.90 (0.45), 0.90 (0.21), and 0.70 (0.48) ng/mL, respectively. Based on these data, there was no significant influence of race on the L C_{avg} values ($p = 0.39$). In addition, there was no significant relationship between L C_{avg} values and age ($p = 0.72$; age range 50 - 88 years old).

Figure M shows L C_{avg} as a function of body weight. The L C_{avg} values decreased with the increase in body weight (p=0.0004); however, all patients were effectively T suppressed. The lowest L C_{avg} value (0.28 ng/mL) appeared in a patient weighing 103 kg; the L C_{avg} value was 0.58 ng/mL appeared in the heaviest patient (124 kg) (p=0.004).

Figure M
L C_{avg} Following Single Viadur™ Implant as a Function of Body Weight



SOURCE C97010/PKPDNSPK/CGMSTAT.SAS WITH (VER 03/10/99 12:03)

16. What are the proposed in vitro L acetate release method and specifications for Viadur™?
No standard FDA or USP in vitro dissolution method is available for implant dosage form.

The release media is 0.75% W/V Dulbecco's phosphate buffered saline + 0.2% W/V NaN_3. Pipet 8 mL of test media solution into each labeled, sterile 15 mL conical polypropylene tubes. Weigh and record the Viadur™ systems. Warm the test tubes in a 37 ± 0.5°C water bath for at least 30 minutes, then carefully place the appropriate Viadur™ systems (orifice pointing up) into the test tubes via sterile tweezers and gloves. A polypropylene tube containing only 8 mL of test media solution is used as a blank. Record the start time when the systems were placed in the 37 ± 0.5°C water bath.

At specified sampling time points, transfer the Viadur™ systems to new labeled, sterile 15 mL conical polypropylene tubes containing fresh media that have been pre-heated to 37 ± 0.5°C for at least 30 minutes. To minimize any temperature change, transfer the systems swiftly via sterile tweezers and gloves. If any of the Viadur™ system accidentally falls into the 37 ± 0.5°C water bath,

rinse the system in an extra test tube containing fresh media before transferring to a new tube. Record transfer times when the systems were replaced into fresh media solution and any observations.

L concentrations of sampled solutions are determined via HPLC with UV detection.

The detailed in vitro release rate method and raw in vitro release data for the clinical lot [redacted], are in Attachment 1.

Viadur™ L acetate implant must meet USP <724> Drug Release, Extended-Release Articles, Acceptance Table 4 - General Drug Release Standard.

The proposed in vitro cumulative release rate specifications for Viadur™ follow (Table 2):

Time interval (days)*	L acetate released (mg)
0 - 14	≤ 5.5
14 - 28	1.3 - 2.6
28 - 42	1.4 - 2.5

*The time intervals were selected to characterize the system in its initial drug release and at steady state.

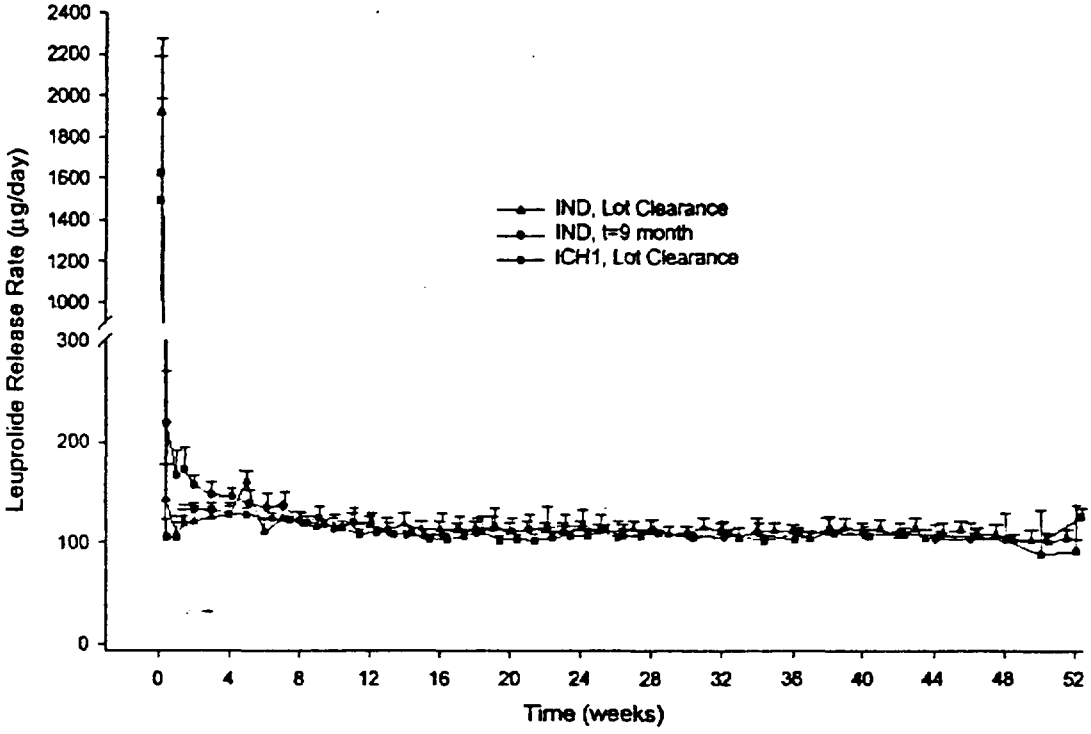
17. What was sponsor's attempt on the in vitro/in vivo correlations (IVIVC) for Viadur™?
Sponsor submitted 3 IVIVC approaches for Viadur™.

1st IVIVC approach:
The in vivo drug input rate was deconvoluted from the observed serum L concentrations following insertion of the Viadur™ L Implant in patients for Studies C-96-011 and C-97-010 via nonlinear regression. Literature L PK parameters (Sennello et al. *J. Pharm. Sci.* 75:158 1986) upon subcutaneous administration to healthy volunteers and a 2-compartment PK model with zero order input rate were used to estimated the in vivo L input rate. However, the average L clearance value (7.25 L/h) between the L clearance values upon 3.75 mg and 7.5 mg L depot subcutaneous administration to prostate cancer patients (6.9 and 7.6 L/h, respectively; Mazzei et al. *Drugs Exptl. Clin. Res.* XV:373 1989) was used in estimating the in vivo L input rate. L clearance in healthy subjects was 9.06 L/h after subcutaneous administration (Sennello et al. *J. Pharm. Sci.* 75:158 1986). All PK parameters were assumed to be same for every patient.

In Study C-96-011, the mean L in vivo input rates following treatment with Viadur™ L Implants over the 12-month Treatment Phase were estimated to be 148 µg/day in Group 1 (1 implant) and 263 µg/day in Group 2 (2 implants; 131.5 µg/day per implant). In Study C-97-010, the mean in vivo input rate was estimated to be 162 µg/day. The mean in vivo input rate for 1 implant system is about 147 µg/day (mean of 132 and 162 µg/day). Figure N shows the in vitro release rate for the lots that were used in the 2 clinical studies. The difference of about 20% between the estimated in

vivo input rate (147 µg/day) and the in vitro release rate (about 120 µg/day) may have resulted from using literature L PK parameters.

Figure N.
In Vitro Release Rate Profiles



Note Release Rate Data in Appendix 1 and 2
Source: C97010\Pkpd\SPK\RR -final.jnb: Data in RR-Final.xls

In the subset of subjects in Study C-97-010 (n=21), the in vivo input rate for Days 0-1, 1-3, and 3-7 were estimated separately. Table 3 presents the mean estimated in vivo input rate in this population and the in vitro release rate at these intervals. The in vivo input rate estimates were 2 - 7% higher than the in vitro release rate.

Table 3
In Vitro Release Rate and In Vivo Input Rate during Week 1

Days	Rate (µg/day) In Vitro* n=6	In Vivo n=21	Ratio
0 – 1	1622.6 (650.7)	1655	1.02
1 – 3	218.3 (51.0)	236	1.08
3 – 7	166.0 (24.8)	180	1.08

* Lot 1 - 0004682/871496, 9-month stability data, since systems that were implanted in these patients (Study C-97-010) were about 9 months old.

2nd IVIVC approach:

The residual L content of in vivo systems (n=71) explanted after the 12-month Treatment Phase in Study C-96-011 were analyzed. The results were compared to residual content of systems that had been used for 12 months in an in vitro release rate experiments (Table 4). In vitro residual L was 94.24% of the in vivo residual L.

TABLE 4
In Vitro versus In Vivo Residual L in Patients' Explants (One Year's Use)

	Mean (SD) Leuprolide (mg)	
	In Vitro	In Vivo
Initial Content	67.5 (0.9)[a] (n= 10)	
Residual	22.9 (2.4)[c] (n= 18)	24.3 (2.8) (n= 71)
Delivered[b]	44.6[c]	43.2

[a]Lot clearance of Lot 1 Code/Control 0004682 / 871496
[b]Delivered = Initial – Residual
[c]Average of t=1, 3, 6 month storage (25 °C) in Stability Study SS-710

The estimated amount of in vivo L delivered (43.2 mg) corresponds to a drug release rate of about 118 µg/day. This was consistent with the in vitro release rate (Figure N). Thus, the in vivo input rate (147 µg/day) as estimated via deconvolution of plasma L concentrations (1st IVIVC approach) was overestimated and may be due to incorporation of L PK values from the literature.

3rd IVIVC approach:

Systems from 3 experimental lots were compared. L content of 10 systems was determined at the beginning of the study in each lot (time=0). Forty systems were implanted into rats for in vivo evaluation, and 40 systems were tested in vitro (37° C in phosphate buffer solution). At 4 time points (t= 3, 6, 9, and 12 months), 10 systems each from the in vitro experiment set and in vivo evaluation were assayed for residual L content.

The residual L content in systems used in these 2 studies is summarized in Table 5. The in vitro and in vivo drug release correlations were comparable between the 3 lots.

TABLE 5
Residual L Content After Delivery in Rats for Various Duration

	Residual Leuprolide (mg)	
Time (months)	In Vitro	In Vivo
Lot 2		
0	69.5 ± 1.6 (n=10)	
3	60.2 ± 1.4 (n=10)	59.3 ± 2.0 (n=9)
6	45.0 ± 1.1 (n=10)	46.8 ± 0.9 (n=10)
9	36.3 ± 1.2 (n=10)	38.0 ± 1.6 (n=9)
12	23.7 ± 1.4 (n=10)	27.0 ± 3.4 (n=9)
Lot 1		
0	68.3 ± 1.6 (n=10)	
3	55.2 ± 2.2 (n=10)	55.0 ± 1.2 (n=10)
6	43.8 ± 2.0 (n=10)	44.9 ± 3.0 (n=11)
9	32.3 ± 1.5 (n=10)	34.2 ± 1.2 (n=9)
12	23.5 ± 1.0 (n=10)	25.1 ± 2.2 (n=9)
Lot 3		
0	72.9 ± 1.9 (n=10)	
3	56.2 ± 1.5 (n=10)	54.3 ± 1.4 (n=10)
6	45.5 ± 0.8 (n=10)	43.7 ± 1.0 (n=10)
9	34.9 ± 1.2 (n=10)	34.2 ± 1.2 (n=10)
12	23.7 ± 1.0 (n=10)	24.8 ± 1.8 (n=9)