CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-320

Clinical Pharmacology and Biopharmaceutics Review

Amendment to Clinical Pharmacology & Biopharmaceutics Review

NDA:	21-320
Product Trade Name:	PLENAXIS [redacted] (abarelix for injectable suspension)
Active Ingredient/s:	Abarelix
Indication:	Palliative Treatment of Prostate Cancer
Submission Dates:	Resubmission in response to NA on 2/25/2003
Sponsor:	Praecis Pharmaceutical, Inc.
Type of Submission/Priority:	Resubmission to Non-approvable regulatory action
Reviewer:	Dhruba J. Chatterjee, Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.

Synopsis

Please refer to the DFS for the reviews on the Original Submission for NDA 21-320 in 2001. This NDA originally received a non-approvable regulatory action in June of 2001. Currently, the sponsor has resubmitted additional information responding to the NA action.

Please refer to the June 2001 OCPB review of the original NDA 21-320. This document is an addendum/amendment to the original NDA review referred to above.

[redacted]

Additionally, the sponsor submitted results from another Phase III clinical safety and efficacy study (Study ABACAS 1) conducted in the European Union. In the safety database of the study, there was evidence of QT prolongation by Abarelix (as well as another comparative treatment employed in another arm of the study). At the request of the clinical review team, the data of the QT prolongation on this study was extensively reviewed by this reviewer, and **this document will contain review of only the QT Prolongation issue** on the ABACAS 1 Study as well as the pooled information from the 2 original Phase 3 studies.

Additionally, labeling comments are included.

Study ABACAS 1 (ECG Aspect Only)

Methodology: This was a multi-center European, open-label, randomized, Phase III study in 2 arallel groups (Abarelix group and Goserelin + Bicalutamide or GB group).

The trial comprised of 3 periods: A – pre-inclusion period, B – from Day 0 (D0) – month 3 (M3) treatment period when randomized patients received either GB or abarelix and C – from M3 – M9 when the same treatments were continued.

Dosing: In the GB group, patients received bicalutamide 50 mg (Casodex® 50 mg) QD (one tablet each evening) from D0 till the end of the study. Patients also received one subcutaneous (SC) injection of 3.6 mg goserelin (Zoladex® 3.6 mg) every 28 days.

In the abarelix group, patients received 100 mg of intramuscular (IM) abarelix 2 times during the first 28 days (D0 and D14), a 50 mg IM injection one D28 (or M1). Thereafter they received every 28 days (M2, M3.... M11):

- one injection of 50 mg *if* serum testosterone (T) level on preceding visit was ≤ 50 ng/dL
- one injection of 100 mg *if* serum testosterone (T) level on preceding visit was > 50 ng/dL
- Once increased to 100 mg, the dose was to be maintained at this level till the end of the study.

Electrocardiographic Safety Assessment Plan: A standard 12 lead ECG was performed on D-14, M3 and M12. All ECGs were directly centrally analyzed by telephonic transmission. Standard calculated parameters were Heart rate, QRS duration, P-R interval, QT interval, QTc using Bazett (QTcB) and Fridericia (QTcF) formulae, QRS axis and ST deviation.

Additionally, ECGs were repeated until recovery when an abnormal reading was observed (i.e., QTcB > 450 msec or PR≥ 240 ms or QRS ≥ 120 ms or HR ≤ 40 bpm on the initial ECG). Withdrawal f study and additional assessments were set meeting criteria where QTb > 500 ms.

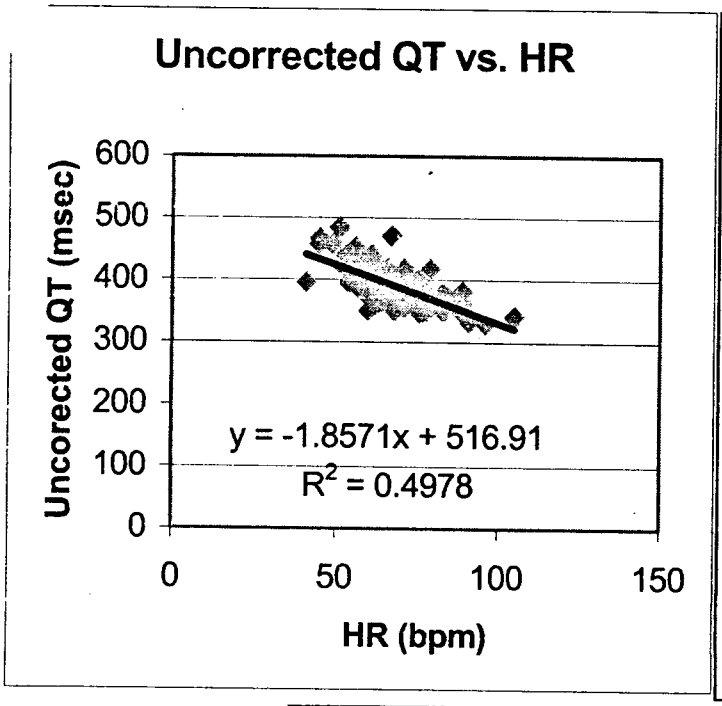
Note: All calculated QT parameters (as mentioned above, but not the ECG tracings) were sent to a consultant cardiologist, Dr. [redacted] report was submitted along with this submission. The same data set was re-analyzed by OCPB and similar (although not exact) findings were obtained (see Results below).

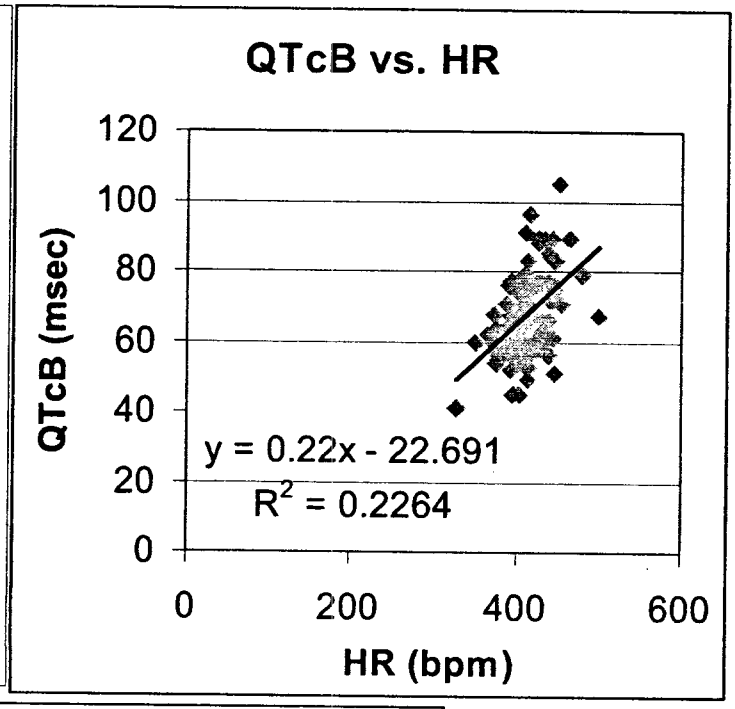
Results:

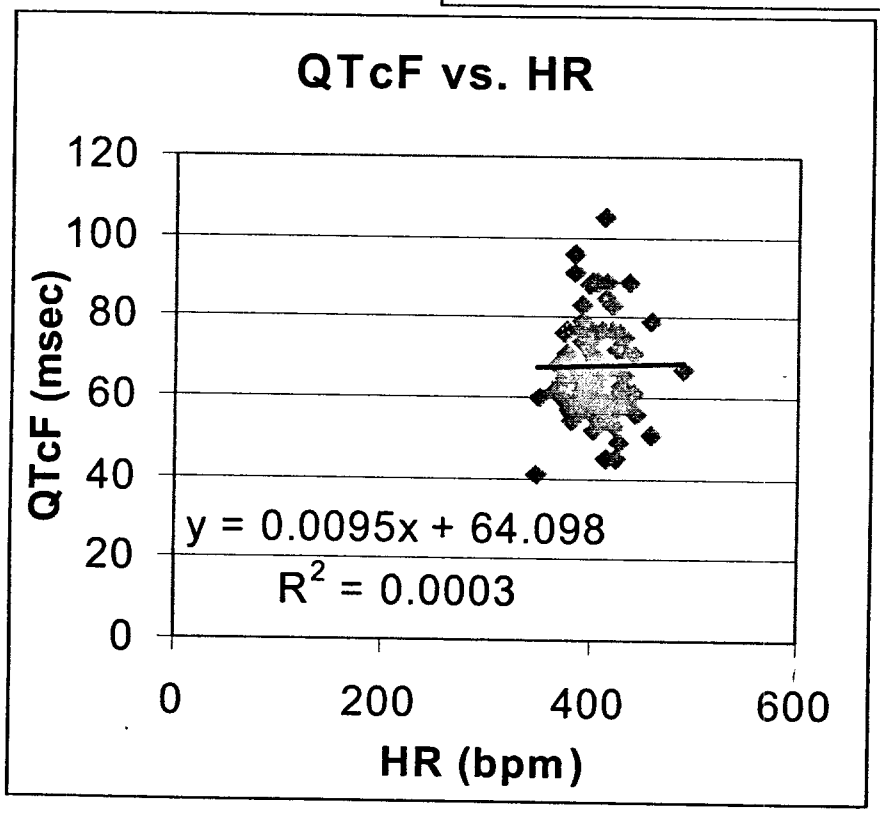
(i) *Abarelix Pharmacokinetics*: Following a single dose of 100 mg IM injection of abarelix, C_{max} of ≈ 30 ng/mL (mean) is generally achieved within the first 1-2 hours. At steady state, the C_{min} (or trough concentration achieved, as in the present ABACAS1 study) is around 10 ng/mL.

(ii) *Method of QT data analysis:* The SAS transport file that was submitted electronically by the sponsor and contained all the calculated ECG parameters were separated into two groups, one each for 1 of 2 treatment arms. Population means of baseline (D -14) and on treatment (all available treatment days) were computed. Additionally, individual patient QTc values on each of the

Figure 1. Fridericia – Preferred Method for Correction of QT for Study ABACAS1







[All the above relationship are at baseline (Day – 14)]

Uncorrected QT vs. heart rate shows that there is a dependence on QT on heart rate, and a method hat abolishes that relationship the best is the method of choice. Here, clearly **the method of choice for QT correction is with the Fridericia formula (Bazett formula over-corrects).**

Delta QTcF in all patients on Treatment Days (dark squares represent means)

Figure 2A:

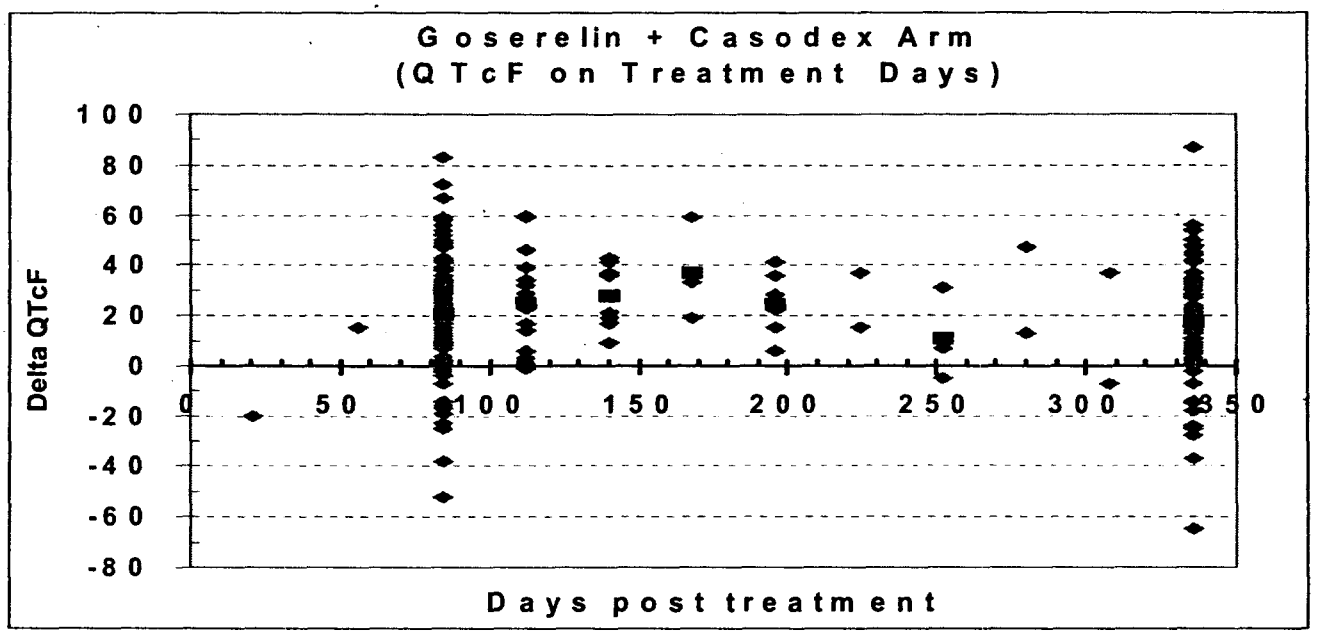


Figure 2B

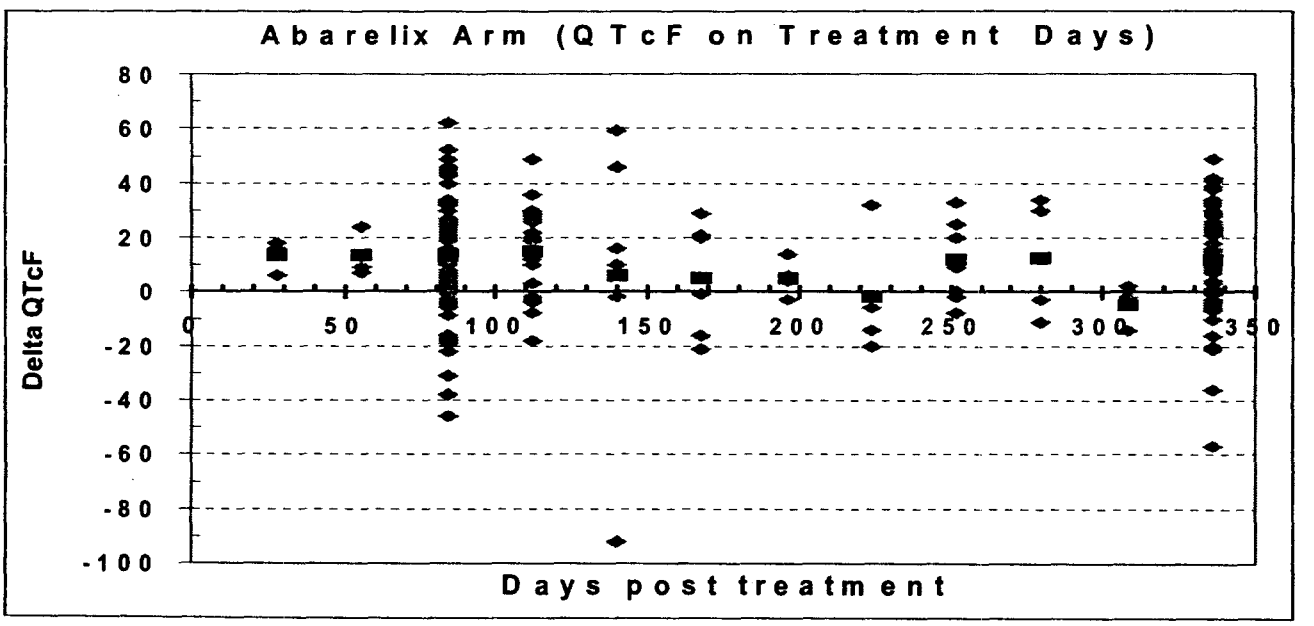


Table 1: QT_C Analysis for Study ABACAS1: Correction methods: Fridericia & (Bazett)

Overall Population Analysis

	Abarelix*	Goserelin + Casodex*
Mean QT_c at Baseline, msec	408 (414)	404 (412)
Mean QT_c on Treatment, msec	426 (434)	428 (434)
Mean QT_c change, msec	18 (20)	24 (22)
Mean HR change, bpm	1.1	-1.5

Individual Patient Analysis

	Abarelix	Goserelin + Casodex
Mean QT_c change, msec	11 (13)	20 (19)

* Data in parenthesis represents comparable values using Bazett correction formula.

Table 2: QT_C Outlier Analysis for Study ABACAS1: Correction methods: Fridericia & (Bazett)

Analysis based on # of ECGs (206 on Abarelix, 214 on Goserelin+Casodex)

	Abarelix*		Goserelin + Casodex*	
# of ECGs with $QT_c \geq 450$ msec; %	40 (57);	19% (28%)	46 (62);	21% (29%)
# of ECGs with $QT_c \geq 500$ msec; %	0 (4);	0% (2%)	6 (7);	3% (3%)
# of ECGs with $\Delta QT_c \geq 30$ msec; %	34 (46);	17% (22%)	70 (72);	33% (34%)
# of ECGs with $\Delta QT_c \geq 60$ msec; %	1 (0);	0.5% (0%)	5 (9);	2% (4%)

Analysis based on # of patients (82 evaluable on Abarelix, 85 on G + C)

	Abarelix*		Goserelin + Casodex*	
# of patients with $QT_c \geq 450$ msec; %	15 (25);	18% (30%)	19 (26);	22% (30%)
# of patients with $QT_c \geq 500$ msec; %	0 (3);	0% (4%)	5 (5);	6% (6%)
# of patients with $\Delta QT_c \geq 30$ msec; %	17 (25);	21% (30%)	39 (43);	46% (51%)
# of patients with $\Delta QT_c \geq 60$ msec; %	1 (1);	0.5% (0.5%)	4 (7);	5% (8%)

* Data in parenthesis represents comparable values using Bazett correction formula.

Reviewer's Comments:

QTc Results:

- Fridericia is the method of choice for this study since it corrected the effect of heart rate on QT better than Bazett.
- Both the arms of the study show significant prolongation in QTc as evidenced by the individual delta QTcF.
- Mean individual delta QTcF was 11 msec for Abarelix and 20 msec for Goserelin + Bicalutamide (an already approved and marketed regimen in advanced prostrate cancer).
- Number of outliers were lower for the Abarelix treatment arm.
- Due to the nature of the study design, no attempt was made to correlate the QT prolongation with plasma concentration.
- Sponsor collected serum trough levels (pre-dose) for abarelix on all visit days. The ECGs were also performed when the drug levels were at a minimum with respect to abarelix and goserelin. Hence, there is at least a theoretical concern that serum drug levels could be 5-6 times higher than that observed at patient visits when patient QTs were prolonged.

Study Design Issues:

- This study was conducted in an elderly prostrate cancer patient population representing the true population for whom the drugs are intended. This is different from a prospectively designed QT Prolongation Study (that we are used to seeing in submissions) in which young healthy volunteers known to have normal QT intervals are recruited to tease out more clearly the effect of a particular drug in prolonging the QT interval.
- This study neither used a placebo or an active control arm (active control for QT with a known QT prolonger, eg. moxifloxacin). In the absence of these arms, the effect of placebo on the QT invterval, or the accuracy of the ECG analysis etc could not be verified/compared.

Once the above results were perceived as cause of concern, the sponsor was requested to send ECG information from the two Phase III studies submitted to the original NDA (Study #s 149-98-02 and 149-98-03). For both these studies, a baseline 12 lead ECG was obtained on Day 0 and on treatment ECGs were obtained on treatment days 169 and 365 (and a few other visits for a very small number of patients). The QT analyses following ECG traces from these two studies were pooled and the results are reported in Table 3 & 4 below. Note that 3 treatment arms (based on the designs of the two studies) are compared in the following table. Delta QTc is based on difference in QTc on Day 0 (baseline) and all treatment days (any available other than Day 0). [Please refer to the Medical Officer Review of the original submission for NDA 21-320 for details on the design and conduct of the two studies.]

Results:

Table 3:

QT_C Analysis for Study 149-98-02 & 149-98-03 (pooled) - Correction methods: Fridericia & (Bazett)

Overall Population Analysis

	Abarelix* (N=191)	Lupron Depot (N = 49)	Lupron Depot + Casodex* (N=34)
Mean QT_c at Baseline, msec	412 (419)	415 (425)	413 (418)
Mean QT_c on Treatment, msec	425 (434)	432 (442)	423 (428)
Mean QT_c change, msec	13 (15)	17 (17)	10 (10)
Mean HR change, bpm	1.4	-0.2	1.4

Individual Patient Analysis

	Abarelix* (N=188)	Lupron Depot (N = 46)	Lupron Depot + Casodex* (N=34)
Mean QT_c change, msec	13 (14)	17 (17)	12 (13)

* Data in parenthesis represents comparable values using Bazett correction formula.

Table 4:

QT_C Analysis for Study 149-98-02 & 149-98-03 (pooled) - Correction method: Fridericia only

[Analysis based on # of patients]

	Abarelix* (N=188)	Lupron Depot (N = 46)	Lupron Depot + Casodex* (N=34)
# of patients with $QT_cF \geq$ 450 msec; (%)	36; (19%)	14; (30%)	4; (12%)
# of patients with $QT_cF \geq$ 500 msec; %	5; (3%)	0; (0%)	0; (0%)
# of patients with $\Delta QT_cF \geq$ 30 msec; %	48; (25%)	19; (41%)	10; (29%)
# of patients with $\Delta QT_cF \geq$ 60 msec; %	5; (3%)	2; (4%)	0; (0%)

Reviewer's Comments:

- Bazett and Fridericia methods of correction were similar in terms of correction of QT for HR when baseline data were pooled in these two studies.
- QTcF values for the abarelix treatment arm in these two studies were in the similar range as the ABACAS1 study indicating that abarelix may be responsible for 10 – 15 msec prolongation of the QT interval in the population it is intended for.
- Sponsor submitted their analysis of the QT effects from the 149-98-02 & 149-98-03 (pooled) on September 12, 2003, and the analysis matched the results presented in Tables 3 and 4 above.

General Comments:

- Taking into account the data in the other comparative treatment arms, it might be worthwhile to investigate the effect of this class of drugs (GnRH agonists or antagonists) in their ability to prolong the QT interval (or the relationship of androgen ablation to QT prolongation).

LABELING COMMENTS

During the initial cycle of review of the original NDA, the labeling comments were not finalized from an OCPB perspective. The following are excerpts of sections of the proposed PLENAXIS label only relevant to OCPB (or, where OCPB related changes were made):

CLINICAL PHARMACOLOGY

Mechanism of Action

Abarelix exerts its pharmacological action by directly suppressing luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion and thereby reducing the secretion of testosterone (T) by the testes. Due to the direct inhibition of the secretion of LH by abarelix, there is no initial increase in serum testosterone concentrations.

Saturation binding studies revealed that [^{125}I]-abarelix has a very high affinity (K_D = 0.1 nM) for the rat pituitary LHRH receptor.

Pharmacokinetics

A single dose (100 mg IM) of Plenaxis™ was given to 14 healthy male volunteers ——— years of age, with body weight of ——— kg, and the pharmacokinetic information is provided in Table 1:

Note to sponsor: Please update the above (underlined) information based on Study # *149-99-01*

Table 1. Mean ± SD Pharmacokinetic Parameter Values of 100 mg of Plenaxis™ Following a Single IM Injection (n = 14)

C_{max} (ng/mL)	T_{max} (days)	$AUC_{0-\infty}$ (ng • day/mL)	CL/F (L/day)	$t_{1/2}$ (days)
43.4 ± 32.3	3.0 ± 2.9	500 ± 96	208 ± 48	13.2 ± 3.2

Absorption

Following IM administration of 100 mg of Plenaxis™, abarelix is absorbed slowly with a mean peak concentration of 43.4 ng/mL observed approximately 3 days after the injection.

Distribution

The apparent volume of distribution during the terminal phase determined after IM administration of Plenaxis™ was 4040 ± 1607 liters, implying that abarelix probably distributes extensively within the body.

Metabolism

In vitro hepatocyte (rat, monkey, human) studies and *in vivo* studies in rats and monkeys showed that the major metabolites of abarelix were formed via hydrolysis of peptide bonds. No significant oxidative or conjugated metabolites of abarelix were found either *in vitro* or *in vivo*. There is no evidence of cytochrome P-450 involvement in the metabolism of abarelix.

Excretion

In humans, approximately 13% of unchanged abarelix was recovered in urine after a 15 µg/kg IM injection; there were no detectable metabolites in urine. Renal clearance of abarelix was 14.4 L/day (or 10 mL/min) after administration of 100 mg Plenaxis™.

Pharmacodynamics:

Effects of Plenaxis™ on Serum Testosterone: The effectiveness of Plenaxis™ in suppressing serum testosterone was studied in two randomized, open-label, active-comparator trials. Patients were not those with advanced symptomatic prostate cancer. They were randomized in a 2:1 ratio to Plenaxis™ 100 mg IM versus LHRH agonist (Study 1) or to Plenaxis™ versus LHRH agonist + nonsteroidal antiandrogen (Study 2). Plenaxis™ was administered IM on Days 1, 15, 29 (Week 4), then every 4 weeks thereafter for at least 6 months (24 weeks). LHRH agonist and nonsteroidal antiandrogen were administered in standard fashion. After completing 6 months of treatment, patients could continue randomized treatment for an additional 6 months.

Avoidance of testosterone surge: In both studies combined, 100% (348/348) of Plenaxis™ patients and 16% (28/172) of comparator patients avoided a testosterone surge.

Attainment of medical castration: The percentage of patients who attained serum testosterone concentration ≤50 ng/dL on Study Days 2, 8, 15 and 29 are summarized in the table below:

2

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

PRECAUTIONS

General

Decreased effectiveness in patients >225 pounds: The decrease in overall effectiveness of Plenaxis™ with increased duration of treatment is greater in patients who weigh more than 225 pounds. Strict monitoring of serum testosterone in these patients is warranted.

Monitoring of liver function: Clinically meaningful transaminase elevations were observed in some patients who received Plenaxis™ or comparator drugs. Serum transaminase levels should be obtained before starting treatment with Plenaxis™ and periodically during treatment (**see Adverse Reactions**).

Decrease in bone mineral density: Extended treatment with GnRH antagonists and LHRH agonists may result in a decrease in bone mineral density.

Drug Interactions

No formal drug/drug interaction studies with Plenaxis™ were performed. Cytochrome P-450 is not known to be involved in the metabolism of Plenaxis™. Plenaxis™ is highly bound to plasma proteins (96 to 99%).

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/s/

Dhruba Chatterjee
11/20/03 02:26:52 PM
BIOPHARMACEUTICS

Ameeta Parekh
11/20/03 03:55:35 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-320	*Brand Name*	PLENAXIS
OCPB Division (I, II, III)	DPE II (HFD 870)	*Generic Name*	Abarelix acetate
Medical Division	DRUDP (HFD 580)	*Drug Class*	GnRH antagonist
OCPB Reviewer	Dhruba J. Chatterjee, Ph.D.	*Indication(s)*	Prostate Cancer
OCPB Team Leader	Ameeta Parekh, Ph.D.	*Dosage Form*	Suspension
Date of Submission	12/12/2000, 3/14/01	*Dosing Regimen*	Once a month injection
Estimated Due Date of OCPB Review	5/10/2001	*Route of Administration*	IM
PDUFA Due Date	6/12/2001	*Sponsor*	PRAECIS Pharma.
Division Due Date	5/14/2001	*Priority Classification*	1P

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	6		
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:	X			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:	X			
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	X			
gender:				
pediatrics:				
geriatrics:	X			
body wt.				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X			

Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	X			
solution as reference:	X			
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies	6			

Filability and QBR comments

	"X" if yes	*Comments*
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)		
Other comments or information not included above	**He Sun, Ph.D. was consulted on the NDA for Pharmacometrics**	
Primary reviewer Signature and Date	**Dhruba J. Chatterjee 5/02/2001**	
Secondary reviewer Signature and Date	**Ameeta Parekh 6/12/01**	

CC: NDA 21-320, HFD-850 (Electronic Entry or Lee), HFD-580 (CSO), HFD-870 (TL, DD, DDD), CDR (B. Murphy)

Clinical Pharmacology & Biopharmaceutics Review

NDA:	21-320
Product Trade Name:	PLENAXIS ——— ™ (abarelix for injectable suspension)
Active Ingredient/s:	Abarelix
Indication:	Palliative Treatment of Prostate Cancer
Submission Dates:	12/12/00 (original NDA), 3/14/01
Sponsor:	Praecis Pharmaceutical, Inc.
Type of Submission/Priority:	Original/1P
Reviewer:	Dhruba J. Chatterjee, Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.
Pharmacometrics:	He Sun, Ph.D.

Table of Contents

Synopsis

Abarelix acetate, a modified decapeptide, is a GnRH analog and antagonist (and a new molecular entity). It binds to and turns off pituitary receptors responsible for the production of gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Unlike GnRH agonists, antagonists such as abarelix do not cause an immediate "flare" (due to receptor stimulation) resulting in initial surges of LH, FSH, testosterone (T) and dihydrotestosterone (DHT) in males. The primary mode of action and main goal of therapy with abarelix is to suppress/inhibit T to castrate levels (< 50 ng/dL) and maintain such lowered levels in the targeted patient population (patients with local, regional or advanced carcinoma of the prostate gland experience difficulty in tolerating T surges). Prior to administration, a single vial of PLENAXIS™ [redacted] (abarelix for [redacted] suspension) containing 100 mg of deliverable dose (expressed as peptide) is intended to be reconstituted with 0.9% Sodium Chloride Injection, USP to provide a 2.0 mL suspension (50 ng/mL) for IM injection. The proposed dosing regimen is one such injection of 100 mg every month (with the first month of therapy having an additional injection on day 15).

In the 2 primary clinical trials conducted (and results presented) in support of this NDA, abarelix leads to fast onset of action and avoidance of a 'T flare'. The percent of patients remaining with castrate T levels appeared to decline over time. It is to be noted that a serious adverse event (anaphylactic reaction) was observed in about 0.5% of the patients exposed to abarelix.

RECOMMENDATION

From an OCPB perspective, the application is acceptable. However, patients on this therapy may experience a reduction in overall efficacy over time. A higher dose of abarelix (provided this is supported by safety data) may lead to higher sustained serum levels of the drug for the longer term resulting in a higher suppression of T and lesser variability in the serum T levels.

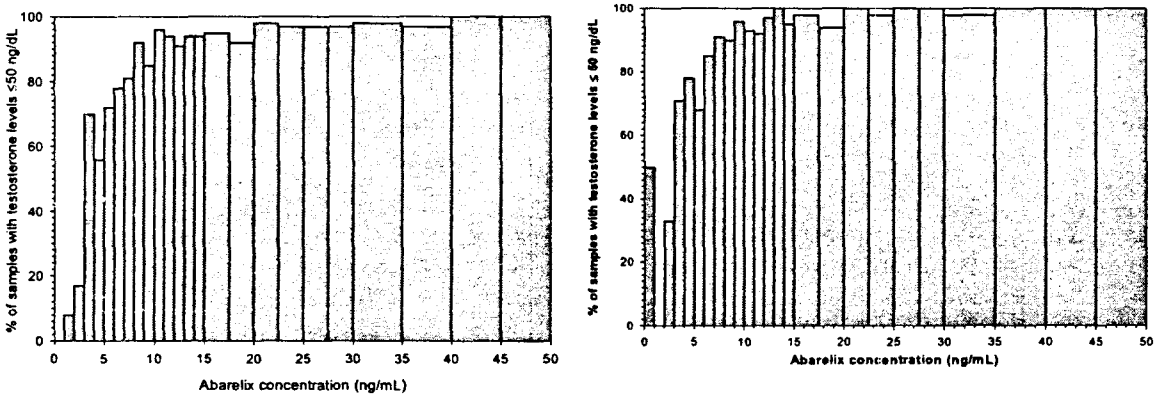
COMMENTS TO SPONSOR

The sponsor may

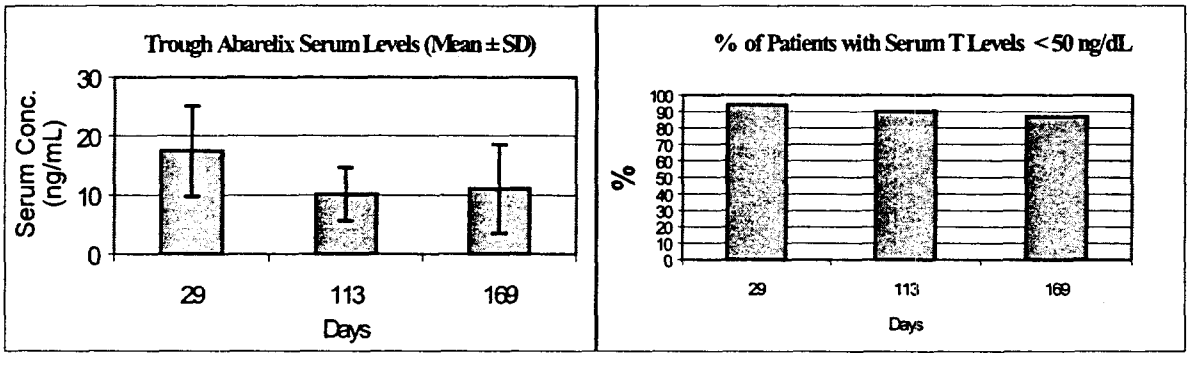
- consider collecting exposure-response information (based on both safety and efficacy) on abarelix from doses higher or more frequent than that currently proposed in this NDA,
- analyze, if possible, archived patient blood samples beyond Day 169 from the primary clinical trials to determine abarelix levels in those samples and correlate that to efficacy,
- address the possibility of the potential of abarelix to affect the metabolism of other medications administered concomitantly,
- investigate possible factors that might have contributed to the high variability of T levels with time (eg. whether there were factors that altered protein-binding of abarelix with time)

Overall Summary of Clinical Pharmacology and Biopharmaceutics Findings

- Following administration of the IM injections (dosing on day 1, 15, 29 and monthly thereafter), the mean trough serum level of abarelix was around 17 ng/mL at day 29 of therapy (day when achievement of efficacy was assessed). Beyond 2 months, the trough levels were around 10 ng/mL. There was no evidence of any significant initial "burst" of drug into the circulation from the formulation. T-suppression may be observed as early as 2 days. There was no evidence of T-surges with abarelix.
- Exposure-response relationship indicates that the serum levels of abarelix need to be > 10 ng/mL for > 90% of samples (patients) below castration levels of T (≤ 50 ng/dL, see Plots I – II below). Towards the end of 6 months of therapy, the trough abarelix levels for patients in the pivotal clinical trials were around 10 ng/mL with significant degree of variability. In some patients, this potentially resulted in T levels above the castration threshold. This phenomenon was a contrast to the active control arms of the pivotal clinical trials (the Lupron and the Lupron + Casodex treatment arms show % of patients maintaining efficacy more effectively than the abarelix arm – please refer to Figure 6A of review).

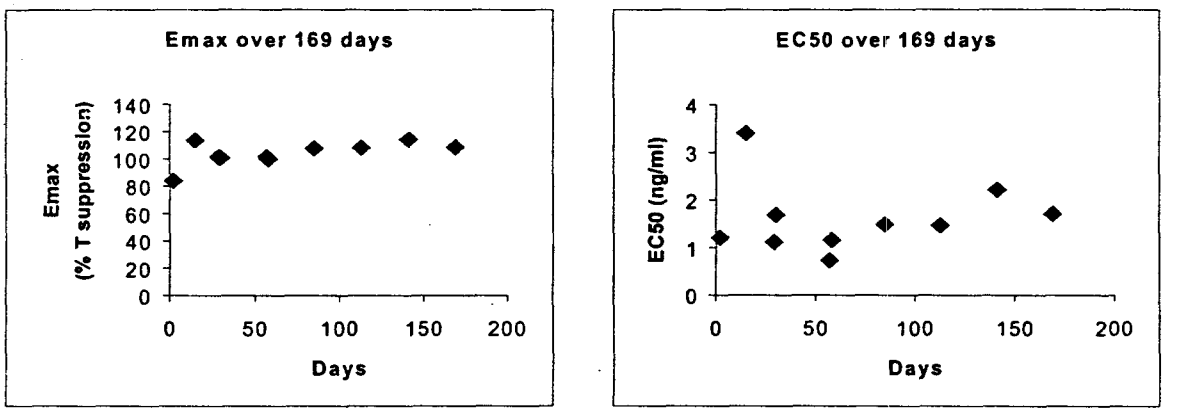


Plot I. Dose Response (From Studies 149-98-02 & 149-98-03)



Plot II. Plots from data pooled from Studies 149-98-02 and 149-98-03 comparing days 29, 113 and 169

- To explain why the efficacy was seen diminishing over time, data from the two pivotal Phase 3 studies were re-analyzed to determine whether,
  (a) there is a development of tolerance to the drug,
  (b) the PK of the drug changed over time, or
  (c) this phenomena could be explained by the exposure-response relationship.



Plot III. Pooled data from Studies 149-98-02 and –03 showing exposure response parameters remaining fairly constant over 169 days

Evidence of tolerance was not detected, as there was no conclusive evidence of changing exposure-response over time (refer to Plot III above). Beyond 2 months of therapy, there was no indication that the mean exposure of the drug was declining. It was therefore concluded that the mean exposure of the drug was at the threshold for optimum efficacy and a wider variability in concentrations at around 6 months may have led to diminished efficacy.

- For the 14 patients identified by the medical officer experiencing serious adverse events (anaphylactic reactions), there was no detectable relationship between the serum drug levels (obtained closest to the adverse events) and the adverse events. All but one of the serum abarelix levels were within 7 – 19 ng/mL. One patient had > 2000 ng/mL as the abarelix level (unexplained outlier, could have been an analytical error).
- It is possible that abarelix doses higher than that currently proposed by the sponsor (if supported by safety data), or administered more frequently, may provide higher sustained serum levels of the drug for the longer term resulting in a higher degree of T suppression and lesser variability in the serum T levels. This may be more effective in maintenance of efficacy for the long term. [Please refer to Appendix 4 for results of simulated Abarelix serum levels following administration of higher or more frequent doses].
- Labeling review for this NDA has been deferred, hence no labeling suggestions are included.

Background

Questions addressed in this section:

- ***What are the highlights of chemistry, formulation and physicochemical properties of the drug and drug product?***
- ***What is the mechanism of action, proposed indication and main goal of therapy?***
- ***What are other drugs available in this class?***
- ***What are some highlights of claims for this product in the proposed label?***

Abarelix acetate, a modified decapeptide, is an amorphous white to off-white powder containing abarelix (the anhydrous free base) with associated water and acetate with a molecular weight of 1416.06. Abarelix acetate is soluble in water and various alcohols. For the drug product, abarelix acetate is converted to an intermediate abarelix carboxymethylcellulose (abarelix CMC) by the formation of a practically insoluble complex with CMC sodium (NaCMC) in an aqueous solution. Abarelix CMC is an amorphous solid, white to off white in color, contains associated water and is practically insoluble in water. The product formulation (no change in formulation between that used in the pivotal trials and the 'to-be-marketed') is as follows:

Quantitative Composition of PLENAXIS™ ——— 100 mg

Material	Quantity per vial	Quantity per mL
Abarelix for depot suspension[a]	100 mg + overage[b]	50 mg
0.9% Sodium Chloride Injection, USP	2.1 mL added to reconstitute	1 mL

[a] Abarelix CMC (carboxymethylcellulose) is named 'abarelix for depot suspension' after the acetate in abarelix acetate is removed during the manufacturing process for abarelix CMC.

Abarelix is a GnRH analog and antagonist. It binds to and turns off pituitary receptors responsible for the production of gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Unlike GnRH agonists, antagonists like abarelix does not cause an immediate 'flare' (due to receptor stimulation) resulting in initial surges of LH, FSH, testosterone (T) and dihydrotestosterone (DHT) in males. This property of GnRH antagonists is viewed as an advantage over agonists in certain clinical scenarios.

The primary mode of action and main goal of therapy with abarelix is to suppress/inhibit T to castrate levels (< 50 ng/dL) and maintain such lowered levels in the targeted patient population (patients with local, regional or advanced carcinoma of the prostate gland). In addition to inhibition of T, suppression of DHT, LH, FSH and PSA (prostate specific antigen) were also monitored. The label for PLENAXIS ——— ™ claims that this product achieves a more immediate suppression of T, DHT, LH, FSH and PSA as compared to a GnRH agonist, Lupron Depot®, and Lupron Depot® plus Casodex® (an antiandrogen) with no evidence of a T surge and that the suppression is comparable to the other two treatment arms through day 169, with a generally acceptable safety profile.

Other GnRH antagonists have been approved by the Agency in recent years indicated for use in females undergoing *in vitro* fertilization and assisted reproductive procedures. Abarelix is the first drug in its class that is currently being considered for use in male patients with prostate cancer. Six study reports have been submitted that summarize clinical pharmacology and biopharmaceutics related information in support of the claims of this application.

This review follows a 'Question-Based' approach.

Clinical Pharmacology

[Note: Although sponsor has submitted CPB information following administration of abarelix solution via the SC and IM routes, majority of CPB discussions in this review will involve the intended mode of administration of this product – IM depot]

Q. ***Were appropriate clinical endpoints, surrogate endpoints or pharmacodynamic (PD) biomarkers selected, adequately measured and used to assess efficacy and safety in clinical pharmacology studies?***

Abarelix is a GnRH antagonist indicated for prostate cancer. It causes rapid reduction of the circulating levels of androgens, hence, suppression of T is the primary biomarker. In addition, the drug is also expected to suppress the levels of DHT, FSH, LH and PSA. Achievement and maintenance of castration is the primary goal for clinical benefit.

The sponsor has determined T levels as the primary biomarker and has also used '% inhibition of T' from baseline in patients as the measurement of PD. In addition, levels of DHT, LH, FSH and PSA were also plotted with time. For the phase 3 clinical trials, achievement of medical castration (testosterone ≤ 50 ng/dL) was based on the patient's T level on study day 29. Patients who were not medically castrate on study day 29 were considered to have failed. A patient was defined as having maintained medical castration if he did not have two consecutive non-castrate levels of testosterone two weeks apart, using values from study days 29, 43, 57, 71 and 85. Adverse reactions were monitored for safety profile of the drug. It is to be noted that the phase 3 trials had an active/comparative treatment arm using another product (GnRH agonist), for comparison of the incidence of initial T-surges between the treatment arms.

In general, the end points and biomarkers selected are acceptable. For CPB purposes, the moieties measured were T, DHT, FSH, LH and PSA.

Q. ***Were metabolites measured?***

Abarelix is a decapeptide. Based on *in vitro* assessments, there are two major metabolites of abarelix (result of hydrolysis). However, *in vivo* in human, those were not detected. Hence, metabolites of abarelix were not monitored for the CPB measurements.

Q. ***For all moieties measured, was free, bound or total measured?***

The total levels of abarelix and all other hormones were measured. The sponsor has submitted data showing that abarelix is highly bound to plasma proteins (96–98 %).

Q. ***Were the methods used to assess concentrations adequate?***

In general, the methods are acceptable. Analytical methods and validations are discussed in more detail in a later section.

Q. ***What are the exposure-related (pharmacokinetic) properties of the drug?***

Sponsor conducted a study [Protocol #149-99-01] to determine PK parameters of abarelix from the 100 mg IM depot in normal volunteers and also compare the bioavailability (BA) relative to a 15 µg/kg solution for IM injection. The following table summarizes the salient PK parameters of abarelix and the relative BA (singe dose with 3-week washout between each treatment phase).

Table 1. Pharmacokinetic (Mean ± SD) characteristics and relative BA of Abarelix

Treatment Period:	**Period 1**	**Period 2**
Dose:	15 µg/kg	100 mg
Route:	**IM injection/solution**	**IM injection/depot**
Number Treated:	**14**	**14**
C_{max} (ng/mL)	57.79 ± 15.25	43.40 ± 32.32
T_{max}	1.0 ± 0.3 (h)	3.02 ± 2.88 (d)
λ_z (day^{-1})	3.30 ± 0.66	0.06 ± 0.01
$t_{1/2}$ (days)	0.22 ± 0.08	13.20 ± 3.23
AUC_{0-1} (ng•day/mL)	11.62 ± 2.09	23.10 ± 10.06
AUC_{0-28} (ng•day/mL)	NA	399.94 ± 105.23
$AUC_{0-\infty}$ (ng•day/mL)	11.96 ± 1.94	500.38 ± 95.66
CL/F (L/day)	104.84 ± 14.05	208.06 ± 47.81
CL/F [(L/day)/kg]	1.29 ± 0.22	2.54 ± 0.53
V_z/F (L)	34.10 ± 14.58	4040.00 ± 1607.13
V_z/F (L/kg)	0.42 ± 0.20	49.14 ± 18.43
MRT (days)	0.22 ± 0.09	17.75 ± 4.37
F_r	NA	0.52 ± 0.11
CL_r (L/day)	13.3 ± 5.7	14.4 ± 2.5
A_e (%)	12.8 ± 5.5	NA

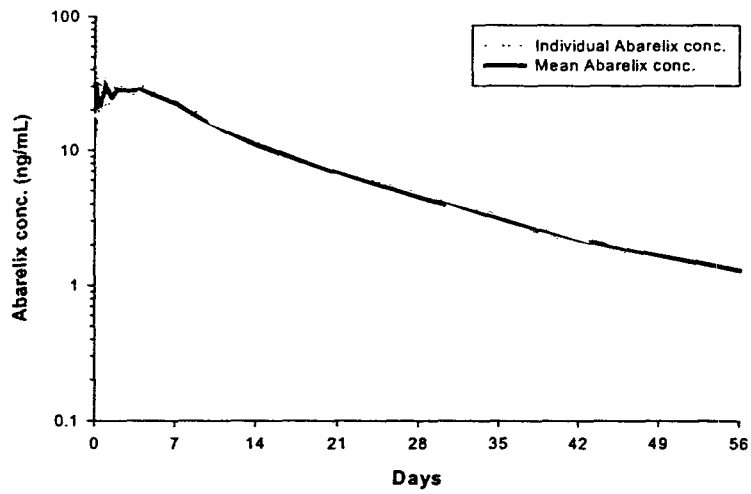


Figure 1. Mean and Individual Abarelix concentrations (ng/mL) following a 100 mg IM (depot) administration of Abarelix in Study 149-99-01

Exposure Response

Q. What are the exposure-response relationships (dose-response, concentration-response)?

In Healthy Subjects:

In study 149-99-01 in 16 healthy men (50-75 years), sponsor has described 2 models to describe the PK (or exposure) of abarelix in different subjects involving a depot site, a "delayed" compartment and either 1 or 2 peripheral compartments.

In order to describe the response (pharmacodynamics) of the drug, the % inhibition of T, DHT, FSH and LH were calculated. The PK/PD data were fit to an indirect-response model. For details of this indirect response PK-PD model and results, please refer to Appendix 1.

In Patients

The inhibitory effect of the post-distributional mean abarelix concentrations on mean testosterone concentrations from Phase II of the study were fit to an inhibitory effect model where:

$$E = E_{\max} \bullet \left(1 - \frac{C}{C + IC_{50}}\right)$$

E (Effect) represents the observed inhibition of testosterone, E_{max} represents the maximal testosterone inhibition effect, IC_{50} represents the concentration of abarelix depot that elicits 50% change of the E_{max}, and C represents the concentration of abarelix.

The inhibitory effect of abarelix on testosterone in Phase II of the study was characterized by an E_{max} of 411 ng/dL (5 %CV) and an IC_{50} of 0.953 ng/mL (26 %CV). These results suggest that abarelix is a potent inhibitor of serum testosterone levels with a rapid onset of action.

The pooled data from the two pivotal phase 3 studies was re-analyzed by this reviewer following a pharmacometric consultation with Dr. He Sun of OCPB using an E_{max} model. In summary, the overall fitted E_{max} and EC_{50}values were 102.5% inhibition of T and 1.2 ng/mL, respectively. The details of the model, the fitted values, the results and statistics are attached in Appendix 2.

Q. Was the selection of dose and regimen appropriate?

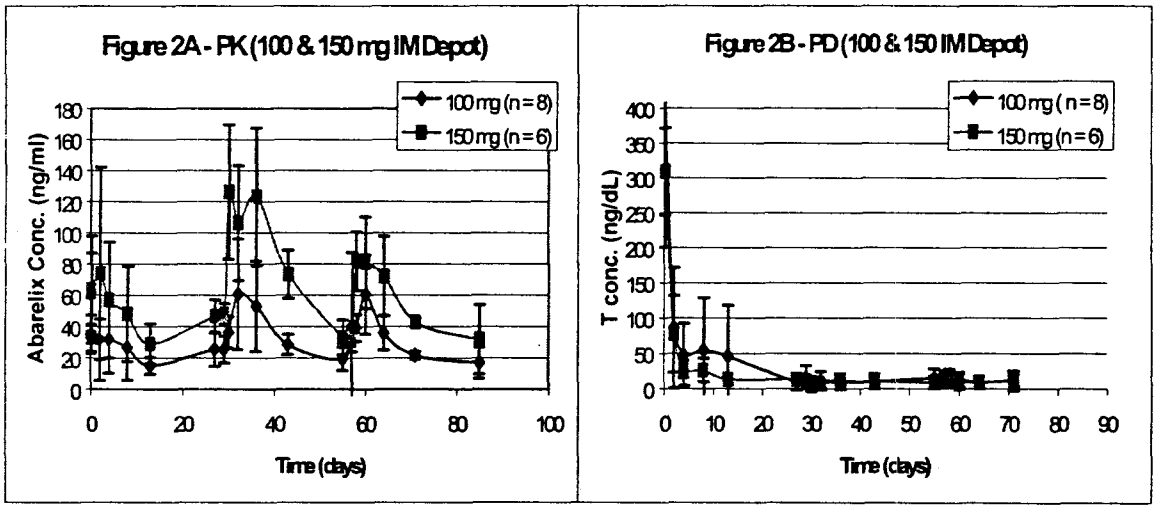
In the Phase II dose selection study # 149-97-04, the sponsor evaluated the PK-PD of the drug in prostate cancer patients. IM or SC doses ranged from 10 – 150 mg. In Phase I, the regimen in Schedule A of the study was dosing on days 1, 15, 29, 57 and 85. Schedule B excluded the dosing on day 15. In phase II of the study, all patients started with a 100 mg dose on day 1, and were titrated to 50 mg or continued on 100 mg doses after a month depending on serum T levels. The Table below shows indication of rapid onset of T-suppression (within day 2)

Table 2. Mean (± SD when n > 2) % Inhibition on Study Day 2

	% Inhibition on Study Day 2

Phase	Schedule	Route	Dose (mg)	n	T	DHT	PSA	LH	FSH
I	A	IM	10	2	-82.12	-58.31	-2.75	-64.18	-36.41
I	A	IM	20	2	-81.37	-66.48	-4.78	-70.02	-28.27
I	A	IM	35	2	-86.79	-60.77	-23.78	-80.88	-50.76
I	A	IM	50	2	-78.15	-59.83	-2.38	-74.06	-31.99
I	A	IM	75	8	-81.28 ± 8.5	-65.16 ± 27.7	-9.06 ± 25.2	-77.05 ± 15.5	-31.81 ± 14.8
I	A	IM	100	8	-85.06 ± 9.4	-73.80 ± 16.8	2.80 ± 23.6	-80.51 ± 11.6	-38.98 ± 7.8
I	A	IM	150	6	-76.72 ± 18.6	-61.28 ± 23.6	-14.53 ± 13.3	-81.09 ± 19.1	-38.17 ± 7.3
I	B	IM	100	6	-87.66 ± 10.8	-68.90 ± 13.0	11.55 ± 58.3	-71.46 ± 10.8	-35.29 ± 10.2
I	B	IM	150	2	-79.95	-64.52	2.76	-65.58	-31.25
I	A	SC	10	2	-63.02	-32.46	-13.47	-40.04	-14.87
I	A	SC	20	2	-75.28	-41.68	-18.48	-55.81	-32.24
I	A	SC	35	2	-73.02	-46.15	-19.47	-61.47	-42.43
I	A	SC	50	2	-83.28	-57.70	-1.44	-82.24	-27.93
I	A	SC	75	6	-69.51 ± 16.7	-68.56 ± 14.4	3.93 ± 10.5	-70.30 ± 20.3	-30.34 ± 4.7
I	A	SC	100	2	-91.08	-77.57	12.63	-85.28	-34.73
II	A	IM	100/50	198	-84.28 ± 10.1	-74.23 ± 18.2	-5.12 ± 21.0	-80.62 ± 16.1	-33.41 ± 21.8

From the above table, it is evident that a choice of the 100 mg was appropriate based on the 2-day T-suppression data. The 150 mg dose was no more effective than the 100 mg. Figures 2A & B indicate that, although in the small population a higher exposure was achieved from the 150 mg as compared to the 100 mg dose, there was no distinction in the response observed between the two doses after 1 month. The following figure summarizes the PD profile in Phase II of the study.



Based on the efficacy information the sponsor obtained in this study, the choice of the 100 mg dose over the 150 mg was justified. However, the data from this study could not shed light as to how the inhibition of T would be maintained over a longer duration of therapy (mimicking actual use of the drug).

Q. In the Phase 3 clinical studies, was clinical efficacy achieved and maintained over the intended period of drug administration?

The sponsor conducted two Phase 3 clinical studies to determine the safety and efficacy of abarelix in successfully lowering T levels leading to an acceptable clinical benefit. They compared the performance of this drug with therapies commonly used in this patient population (Lupron® Depot 1-month, study 149-98-02; Lupron® Depot 1-month + Casodex, study 149-98-03).

According to the Medical Officer revieweing this drug application, the clinical efficacy values (% of patients castrate) were on a diminishing trend generally 4-6 months onwards, and were distinctly lower compared to the active control arm between 6 – 12 months (% of patients castrate were as low as 73 % in certain time points while the values in the Lupron® treated arm remained constant in the range of 95 - 100%).

This CPB review addresses some of the issues related to reduced efficacy for abarelix with time.

1) Exposure-response relationship:

Following the 2 Phase 3 Studies (#s 149-98-02 and 149-98-03), the sponsor presents the following plots:

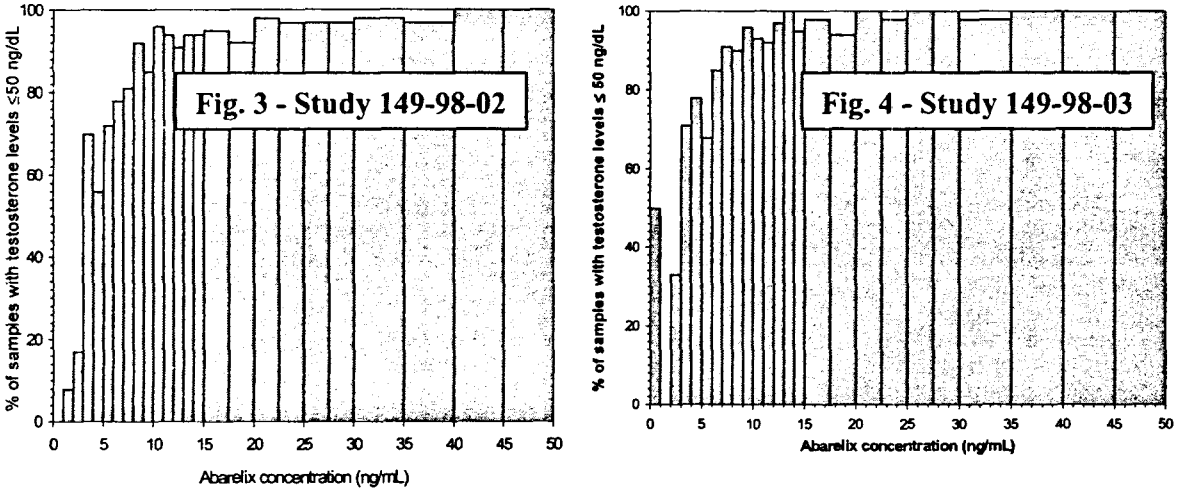


Figure 3 & 4. Percentage of Reported Testosterone Levels ≤ 50 ng/dL at Various Serum Abarelix Concentration Intervals in Clinical Study 149-98-02 (A) and 149-98-03 (B).

From the above data, it may be approximated that the serum levels of abarelix need to be maintained > 10 ng/mL for > 90% of the serum levels to show castration. PK profiles of abarelix were presented from each of the two Phase 3 studies grouped by "responders" (medically castrated as defined by not having 2 consecutive non-castrate levels of T two weeks apart), and "non-responders".

From a review of the data below (Fig. 5) majority of the mean trough serum abarelix levels were around 17 ng/mL at day 29. However, these approached around 10 ng/mL beyond that time point associated with significant variability. On examining individual serum abarelix levels in patients, while a majority of the levels were around 10 ng/mL, several individual levels were as low as 1 – 5 ng/mL. This might be a possible cause for diminished T suppression (based on the

exposure-response relationship that was presented earlier), resulting in a reduction in the % of castrated patients.

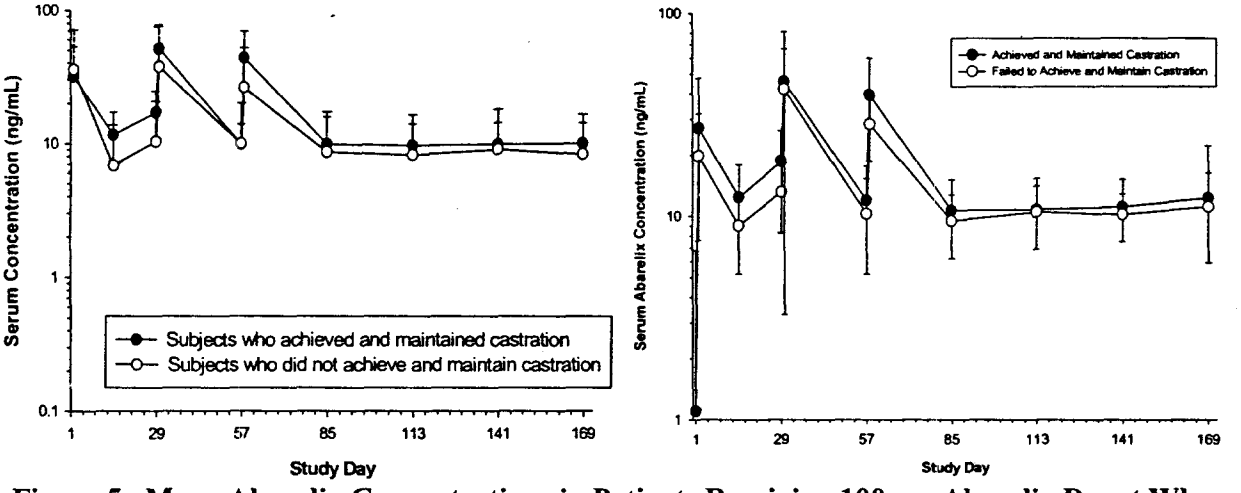


Figure 5. Mean Abarelix Concentrations in Patients Receiving 100 mg Abarelix Depot Who Did and Who Did Not Achieve and Maintain Castrate Testosterone Levels in Phase 3 Clinical Studies 149-98-02 (left) and 149-98-03 (right).

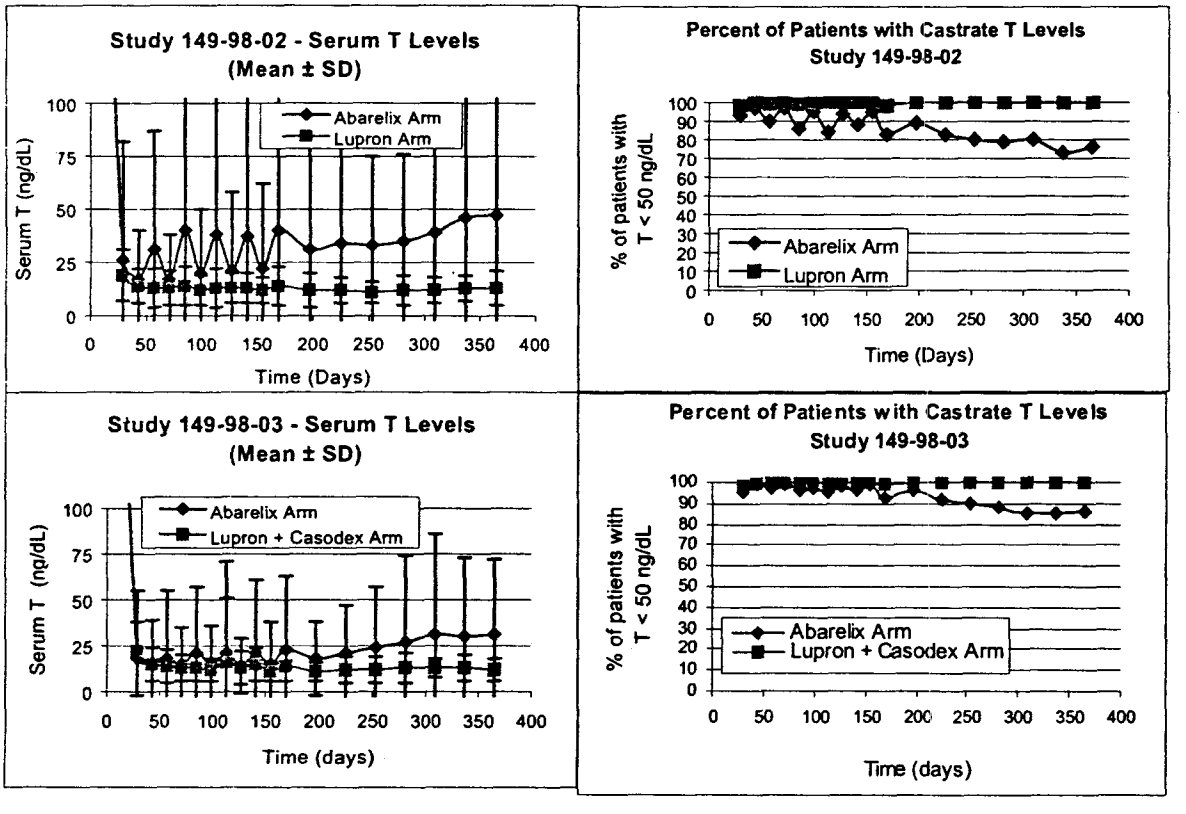


Figure 6A

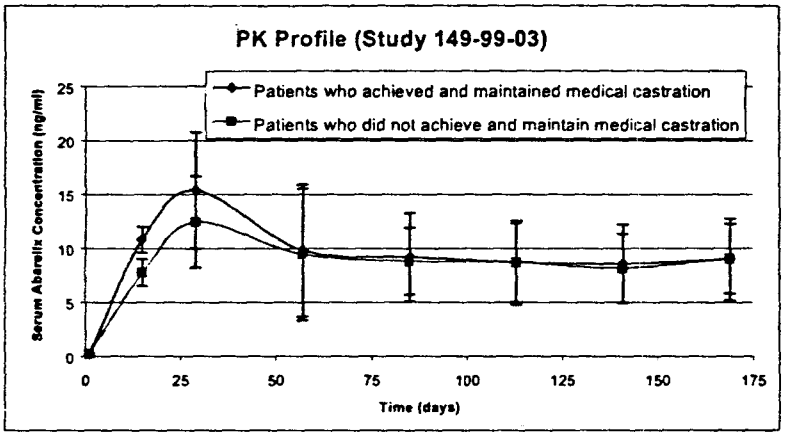
The above plots (Figure 6A, obtained upon further analysis of data provided to the medical officer) depicts the difference in serum T levels following abarelix administration in comparison to the active control arm in each of the two Phase 3 pivotal clinical studies. Note the higher variability of

the serum T levels in the abarelix arm, the gradual elevation of the serum T levels with time in the abarelix arm, and the corresponding reduction in % of patients with castrate T levels in the abarelix arm, all in comparison to the active control arm. The higher values for standard deviation of T levels are distinctly noticeable for the abarelix arm as opposed to the active control arms.

Recently (March 14, 2001), the sponsor submitted the final report of a Study 149-99-03. While the primary objective of the study was determination of safety, a PK summary was also provided. This had an exactly similar study design to the 2 pivotal clinical trials, but involved a larger number of patients (n = 387).

The mean PK profiles from this study was very similar in nature, both qualitatively and quantitatively. The Medical Officer noted, even for this study, a similar trend in diminution of efficacy during prolonged treatment (> 4-6 months). The following Figure 6B describes the mean abarelix PK profiles.

Figure 6B



Q. What are the possible reasons for diminished efficacy of abarelix with time?

The dose-selection was based on the PK and PD information obtained over three months. The primary clinical trials were conducted over one year. If one refers to Figure 2 (from Study 149-97-04), it is evident that the PK and PD profiles of the drug in patients were comparable to that observed in the Phase 3 studies within that time frame. However, based on Plot II (Overall Summary, p. 5 and Appendix 3), it appears that due to higher variability in serum abarelix levels at later time points, there is a lower % of patients with castrate T levels.

On reanalyzing additional data submitted at our request by the sponsor (dated 4/10/01), there was

(i) no evidence of tolerance since the PK-PD relationships remained virtually unaltered over the 6 months (Plot III of Overall Summary, p. 6),

(ii) no obvious indication that the PK (exposure) of the drug appreciably changed over the 6 months (Fig. 6B, however, mean trough serum abarelix concentrations at day 29 were higher due to an additional dose on day 15),

(iii) it may be postulated that the mean exposure of the drug to the patients was just at the threshold for optimum efficacy with a wide variability. This might have led to efficacy failures. [Please refer to Appendix 3 for results following Pharmacometric data analysis].

Q. Do PK parameters change with dose and time?

Fig. 7 describes the PK profile of the drug from different doses.

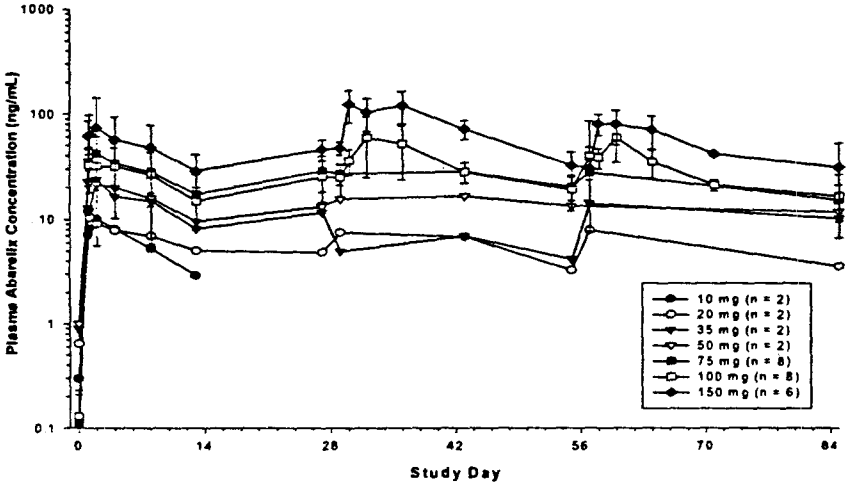


Figure 7. Mean (± SD when n > 2) Abarelix Plasma Concentrations Following IM Administration of Increasing Doses of Abarelix Depot during Schedule A of Phase 1 of Clinical Study 149-97-04

The following figures (8 A&B) may indicate linear PK for abarelix over the dose range of 10 – 150 mg. Figure 8A shows linearity of AUC with dose, while figure 8B shows no significant trend in change of apparent clearance of abarelix with increases in dose (between 10 – 150 mg).

Figure 8A. Mean (± SD) Abarelix AUC_{0-13} Following IM Administration of Abarelix Depot in Clinical Study 149-97-04

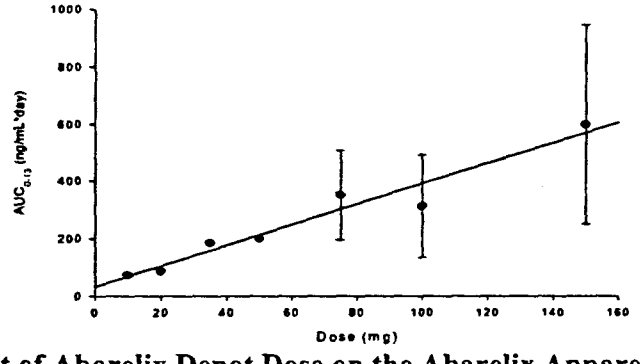


Figure 8B. Effect of Abarelix Depot Dose on the Abarelix Apparent Clearance following IM Administration in Clinical Study 149-97-04

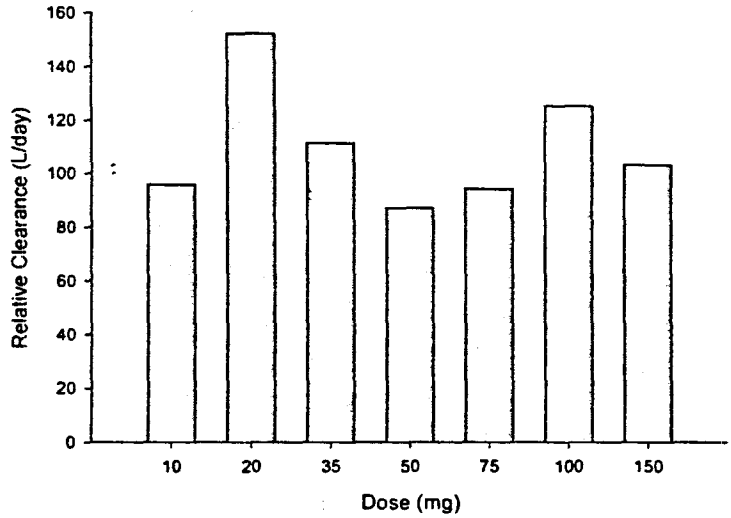
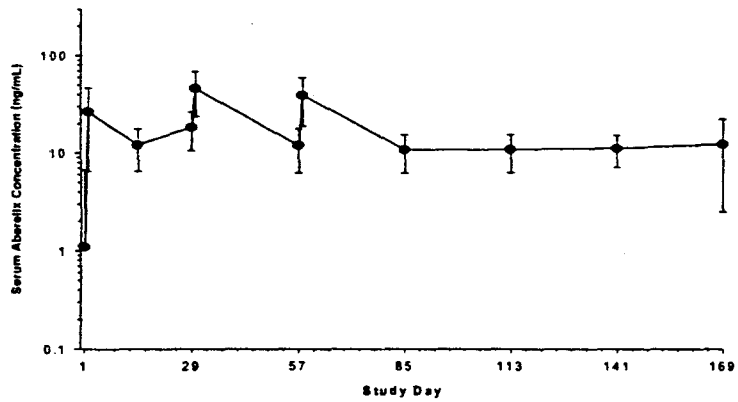


Fig. 9 below indicates the mean apparent clearance virtually remains unchanged over six months.

Figure 9. Mean Abarelix Concentrations for All Patients Receiving 100 mg IM Abarelix Depot in Phase 3 Clinical Study 149-98-03



Q. ***Are PK parameters different in patients than healthy volunteers?***

Comparison of the PK data from the healthy volunteers (Table 1, gray column) with that from patients (gray column in Table 4 on the next page) from the 100 mg dose indicates that clearance appears to be lower in the patient group. This may be attributed to factors such as body weight, age and renal function (refer to covariate analysis results presented later).

Q. What are the inter and intra-patient variability in PK or PD parameters with this drug in patients and normal subjects?

For inter-subject variability in PK parameter (normal subjects), one might refer to Table 1 presented earlier and Figure 1. The apparent clearance was associated with a CV of about 25%.

For inter-patient variability (patients), the sponsor reports a CV of about 10% for apparent clearance following the 100 mg IM dose in Study 149-97-04 (Table 3).

There was an appreciable inter-patient variability of T serum levels following abarelix administration (CV > 200% on majority of the time points based on pooled data from the two controlled pivotal clinical trials).

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Table 3. Mean and %CV Compartmental Parameters for Abarelix in Clinical Study 149-97-04

Phase	Route	Dosing Schedule[a]	Parameter	Units	Dose (mg)															
					10		20		35		50		75		100		150		100 to 50[b]	
					Estimate	%CV	Estimate	%CV	Estimate	%CV	Estimate	%CV	Estimate	%CV	Estimate	%CV	Estimate	%CV	Estimate	%CV
					(n = 2)		(n = 2)		(n = 2)		(n = 2)		(n = 8)		(n = 8)		(n = 6)			
I	IM	A	AUC	(ng•day/mL)	104.4	12.2	131.3	30.6	314.36	17.8	572.9	19.8	795.8	6.5	798.1	10.4	1453.0	5.7		
I	IM	A	$k_a t_{1/2}$	(day)	0.06	19.3	0.10	63.2	0.11	37.7	0.02	508.77	0.03	60.73	0.01	503.2	0.03	62.8	No Cohort	
I	IM	A	$\lambda_z t_{1/2}$	(day)	6.7	15.8	7.4	43.6	9.4	24.3	23.6	32.7	14.9	9.8	18.5	20.0	14.3	11.1		
I	IM	A	CL/F	(L/day)	95.7	12.2	152.3	30.6	111.3	17.8	87.4	19.8	94.2	6.5	125.3	10.4	103.2	5.7		
I	IM	A	V/F	(L)	925.4	6.5	1629.5	23.7	1509.8	13.6	2964.3	21.5	2025.5	7.9	3346.0	13.3	2129.2	7.9		
															(n = 6)		(n = 2)			
I	IM	B	AUC	(ng•day/mL)											928.9	8.8	759.5	20.2		
I	IM	B	$k_a t_{1/2}$	(day)											0.01	276.4	0.01	515.7		
I	IM	B	$\lambda_z t_{1/2}$	(day)	No Cohort		No Cohort		No Cohort		No Cohort		No Cohort		15.8	13.9	35.6	11.2	No Cohort	
I	IM	B	CL/F	(L/day)											107.7	8.8	197.5	20.2		
I	IM	B	V/F	(L)											2448.7	8.8	10142.6	8.8		
					(n = 2)		(n = 2)		(n = 2)		(n = 2)		(n = 6)		(n = 2)					
I	SC	A	AUC	(ng•day/mL)	26.4	62.1	60.1	49.1	241.0	50.9	299.0	22.2	995.6	16.2	731.7	141.9				
I	SC	A	$k_a t_{1/2}$	(day)	0.01	576.4	0.01	472.7	0.01	300.1	0.14	57.6	0.01	443.7	0.01	359.3				
I	SC	A	$\lambda_z t_{1/2}$	(day)	2.6	74.3	4.5	58.4	15.4	58.3	6.8	33.0	37.8	26.1	40.9	151.9	No Cohort		No Cohort	
I	SC	A	CL/F	(L/day)	378.6	62.1	333.0	49.2	145.2	51.0	167.2	22.2	75.3	16.2	136.7	142.1				
I	SC	A	V/F	(L)	1438.6	27.8	2162.1	21.5	3234.0	12.6	1632.3	21.4	4103.3	12.9	8070.8	14.8				
																			(n = 198)	
II	IM	A	AUC	(ng•day/mL)															625.8	3.5
II	IM	A	$k_a t_{1/2}$	(day)															0.01	139.5
II	IM	A	$\lambda_z t_{1/2}$	(day)	No Cohort		No Cohort		No Cohort		No Cohort		No Cohort		No Cohort		No Cohort		16.9	6.4
II	IM	A	CL/F	(L/day)															159.8	3.5
II	IM	A	V/F	(L)															3893.6	4.5

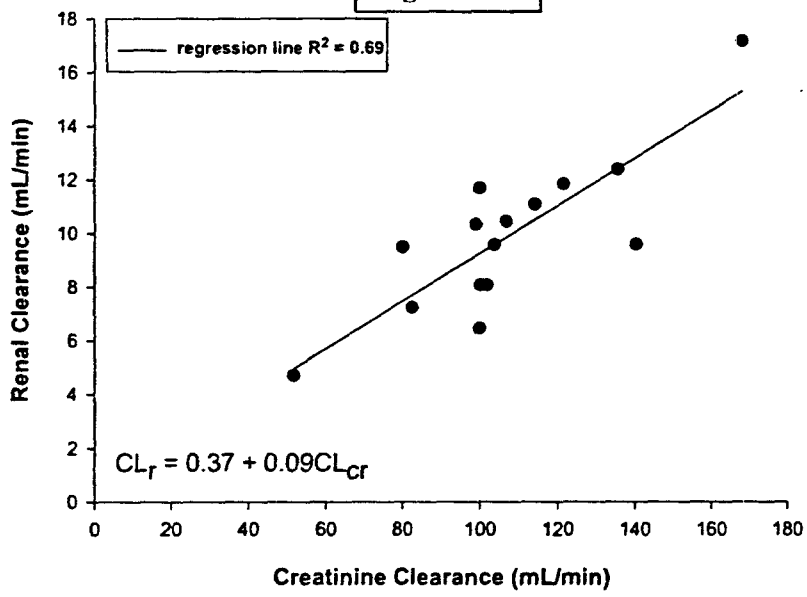
[a] In Schedule A, patients were dosed on Days 1, 15, 29, 57, and 85 depending on their testosterone levels. In Schedule B, patients did not receive a Day 15 dose.
[b] All patients in Phase II that were used in the analyses were dosed with 100 mg abarelix depot until Study Day 29 and thereafter, when they received 50 mg

Q. What are the intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) that influence exposure or response, what is their impact on exposure and/or response? Based upon what is known about exposure response relationships and their variability is dose adjustment recommended depending on any factor/s?

The sponsor evaluated the safety and efficacy of abarelix only from the one regimen, i.e., the 100 mg dose monthly (with one additional dose only on day 15 at the beginning of therapy).

Age: Sponsor evaluated the effect of age on the abarelix concentrations at different time points during the Phase 3 clinical trials. In study 149-98-02, age appeared to be a statistically significant covariate to abarelix concentrations on study days 57, 113 and 169 only. In study 149-98-03, age appeared to be a statistically significant covariate to abarelix concentrations on study days 29, 57, 85, 113, 141, and 169. A positive relationship was shown in which older people had higher abarelix concentrations. In Study 149-99-01 (in 16 normal elderly subjects of mean ± sd age 62 ± 9), there was a correlation between creatinine clearance and renal clearance following the depot dose (Phase 2 of study) as shown in Fig. 10 below:

Figure 10.



Based on the above data, it is concluded that with age and reduced creatinine clearance, the renal clearance of abarelix drops, and that might lead to the higher levels in older patients. No age related safety concerns were reported.

Race: Race was not found to have any significant clinically relevant effect on the PK or PD parameters for abarelix in the primary clinical trials. However, it is to be noted (in the Table below) that the studies might not have been adequately powered to detect PK or PD differences among all the subgroups.

Number of patients in each race in the Primary Clinical Trials

Study #	*Caucasians*	*Blacks*	*Hispanics*	*Asians*	*Others*
149-98-02	159	10	6	5	0
149-98-03	134	21	8	3	2

Body Weight: Body weight appeared to be a statistically significant covariate to the abarelix concentrations in both the pivotal clinical studies, although during the first 2 months of initiation of therapy. In Study 149-98-02, weight appeared to be a significant covariate on study days 2, 15, 29, 30, 57 and 58 only. In Study 149-98-03, the significant of weight as a covariate was observed only on days 2, 15, 30 and 58. There was a negative relationship whereby heavier patients had lower abarelix concentrations. As has been observed with many drugs, heavier people tend to have higher volume of distribution for the drug and hence, lower levels.

According tot he sponsor, in Study 149-98-02, patients that failed to meet the castration criteria (efficacy), were of significantly higher body weight (mean 97.2 ± 18.3 versus 85.8 ± 16.2 kg; $p<0.05$, one-way ANOVA) than those who passed the castration criteria. The same difference was *not* observed in the two groups in Study 149-95-03.

Disease (Renal/Hepatic) Condition: To better understand whether hepatic or renal disease might have an effect on the clinical pharmacology of the drug, it is important to consider the mechanism/s involved in the metabolism and elimination of the drug.

Abarelix is a peptide, and in *in vitro* animal studies the sponsor identified 3-4 metabolites (prior to elimination) as a result of hydrolysis of peptide bonds. In all animal species examined, abarelix appears to be extensively metabolized, followed by fecal excretion of the parent drug and its metabolites. In rats, complete recovery of the radioactive dose was obtained in excreta by 96 hours after both IV (50.1% in urine and 50.4% in feces) and SC (53.4% in urine and 48.5% in feces) dosing of ^{14}C-abarelix. In monkeys, a near-total recovery of the administered radioactivity was obtained in excreta after IV (102% ± 16%), SC (92% ± 3%) and IM (89% ± 3%) routes of ^{14}C-abarelix dosing. In monkey, the urinary and fecal excretion accounted for 17% to 20% and 70% to 81% of the radioactive dose, respectively.

In vivo, human mass balance (^{14}-C) studies were not performed for abarelix depot. Urine from human subjects treated with abarelix-depot in Study 149-99-01 was examined for the known metabolites of abarelix. Abarelix was present in all the urine samples examined. Urinary excretion of abarelix in humans was less than 13% of the total dose, suggesting that the major route of abarelix elimination was non-renal. The 4 known metabolites of abarelix were not detected in any of the samples. Based upon the results of this study, it appears that none of the known metabolites of abarelix are excreted to a significant extent in human urine. This is consistent with observations in monkeys and rats, where urinary radioactivity was predominantly composed of unchanged abarelix. Fecal elimination of abarelix was not monitored in human subjects.

From the above, it may be concluded that abarelix is metabolized primarily by hydrolysis. Hepatic elimination mediated by CYP isozymes might not be primarily responsible for drug disappearance and renal clearance following administration of the injectable solution was only a small fraction of total body clearance (13%). Hepatic or renal impairment are not expected to

significantly alter PK or PD parameters. Clinical pharmacology studies for abarelix were not performed in hepatic and renal impairment.

Q. What are the extrinsic factors (drugs, herbals, diet, smoking, alcohol use) that influence exposure or response? If dosage regimen adjustments across groups are based upon factors other than the exposure-response relationships, please indicate so.

As mentioned above, there is no evidence provided in this application that might indicate the involvement of hepatic CYP isozymes in the metabolism of abarelix. Therefore, a potential of its interaction with other drugs metabolized by CYP isozymes may not be of clinical relevance. No formal drug-drug interaction studies were performed in support of this NDA. In addition, no information is available to determine if there is any effect of herbals, diet, smoking, alcohol use with abarelix. No dose adjustment is either possible, or recommended.

Biopharmaceutics

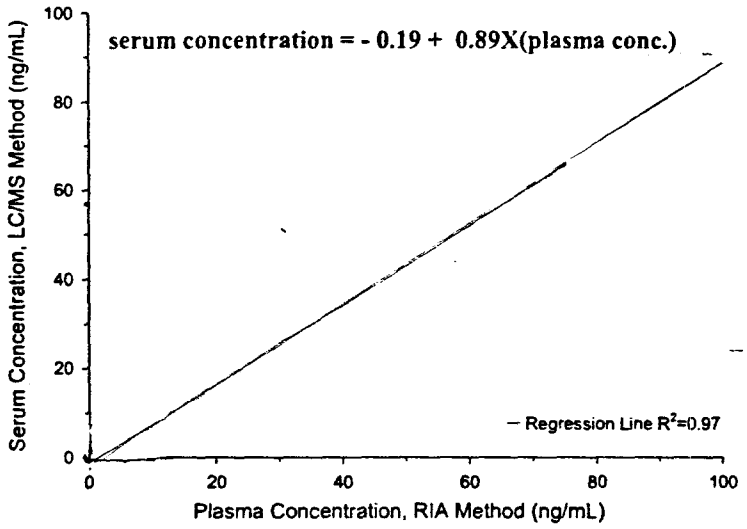
Q. Are the methods used to assess concentrations adequate?

Two broad methods were used to determine the concentrations of abarelix in plasma and urine in the clinical studies. They were the [redacted] (for Studies 149-98-02 and 149-98-03) and RIA (for Study 149-97-04).

The linear range of the [redacted] method was [redacted] ng/mL for abarelix, and the correlation coefficient (concentration versus peak-area ratio) was at least [redacted] when fitted by weighted linear regression. This range covered the typical range observed in the clinical studies. The inter-day precision for the QC samples ranged from 0.99% to 7.27%, while the inter-day accuracy ranged from 97% to 110%. The intra-day precision for the QC samples ranged from 0.84% to 7.85%, while the intra-day accuracy ranged from 94% to 112%. The LLOQ of the assay was defined as the lowest calibration standard concentration ([redacted] ng/mL). Stability study results also demonstrated that abarelix is stable in human serum [redacted] [redacted] before processing. The accuracy for abarelix [redacted] ranged from 96% to 107%. Long term stability of abarelix at [redacted] is not available, and studies are ongoing.

Standard curves for abarelix following the RIA method ranged from [redacted] ng/mL. The lower limit of quantification was [redacted] ng/mL. Dilutions of samples were performed when necessary. The between-day assay coefficients of variation for the QC samples that did not require dilutions were less than 14%. The between-day assay coefficients of variation for the QC samples that required dilutions were less than 25%.

The sponsor performed a cross-validation between the [redacted] and the RIA methods, and showed that the PK parameters were not very different when the same serial samples were used, analyzed with the different methods. The following plot correlates the RIA and the [redacted] methods.



To determine the blood levels of the biomarkers (T, DHT, LH, FSH and PSA), the sponsor has used standard commercial kits. The validation of the methods (as provided by the vendor) has been included in this application. The sponsor has also validated the methods using QC samples. The ranges covered in these assays are within the range obtained in the clinical studies.

The sponsor has included sample (actual) standard curves and chromatograms in the application. Summarizing, the analytical methods utilized in support to this application are acceptable.

Q. Is the pivotal clinical trial formulation identical to the to-be-marketed product?

Yes. This was confirmed by the sponsor via facsimile, and verified with the CMC reviewer.

Q. Are the dissolution conditions and specifications adequately developed to assure in vivo performance and quality of the product?

The formulation consists of a complex of the drug abarelix with carboxymethylcelluose. It is a modified release suspension formulation intended for monthly IM injection. The sponsor argues that with the final depot formulations of abarelix, typically greater than —% of the dose is dissolved within 45 minutes under —— Intramuscular administration of abarelix depot ranging from 10 to 150 mg produces T_{max} values of 0.5 to 3 days after administration. From these observations, it may be assumed that the processes involved in the appearance of abarelix in the systemic circulation from the injection sites are considerably slower than the *in vitro* dissolution rate. The systemic absorption of the drug is depends primarily on the complex mechanisms by which the drug is absorbed from the injection site, and *not* primarily to the dissolution of the product. No *in vitro – in vivo* relationship was established.

Labeling

The review team for NDA 21-230 has decided to defer labeling review for this drug. Hence, a detailed review of this label is not included herewith.

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Appendices

Appendix 1.

Pharmacodynamic Modeling for Abarelix Depot Injection [Study 149-99-01]

For each subject, the measure (endogenous biomarker such as testosterone, DHT, FSH, LH) response to abarelix was modeled using an indirect-response model. The model uses an indirect mechanism in which the production rate of the response variables (testosterone, DHT, FSH, or LH) was inhibited by the serum levels of abarelix. In general, the pharmacodynamic effects can be described by the following differential equations:

$$d[B]/dt = R_{syn} - k_{out} * (B) \quad \text{-------- Equation 1}$$

In Equation 1, R_{syn}, [B] and (B) represent the endogenous production rate, amount of the biomarker in the body and serum concentration of the biomarker, respectively, and k_{out} defines the clearance for the biomarker. When abarelix was injected, it was assumed that abarelix inhibited the production of the biomarkers without changing the clearance of the biomarker and therefore the equation can be modified to:

$$d[B]/dt = R_{syn} * (1 - \frac{C^{\gamma}}{IC_{50}^{\gamma} + C^{\gamma}}) - k_{out} * (B) \quad \text{----- Equation 2}$$

In the above Equation 2, C is the abarelix serum concentration at the time of the inhibition measurement, IC_{50} is the abarelix serum concentration at which 50% of the maximum inhibition is observed, and γ defines the slope and sigmoidicity of the effect-concentration curve.

Table A. Model-Fitted Biomarker IC_{50} (ng/mL) for Subjects[a] Receiving 100 mg Abarelix Depot (Phase 2) in Clinical Study 149-99-01

Subject Number	T	DHT	FSH	LH
1[b]				
2				
3				
4				
5				
7				
8				
10				
11				
12				
14				
15				
16				
N	9	9	12	8
Mean	2.08	3.42	6.43	4.15
SD	1.80	2.15	4.41	3.47
% CV	86.8	62.8	68.6	83.7
Median	1.08	3.90	6.54	3.07
Max				
Min				

All calculations were performed before rounding.
[a] Subject #6 did not complete the study and was therefore excluded from analyses. Subjects #9 and #13 was excluded from this analysis due to lack of best fit.
[b] Subject received 10 □g/kg abarelix injectable solution instead of 15 □g/kg and was therefore excluded from analyses.
[c] No best fit for this parameter. Value excluded from calculation of descriptive statistics.

Table B. Model-Fitted Biomarker K_{out} for Subjects[a] Receiving 100mg Abarelix Depot (Phase 2) in Clinical Study 149-99-01

Subject Number	T (dL/d)	DHT (mL/d)	FSH (mL/d)	LH (mL/d)
1[b]				
2				
3				
4				
5				
7				
8				
10				
11				
12				
14				
15				
16				
N	9	11	12	9
Mean	3.20	2.97	0.95	11.69
SD	2.04	2.92	0.95	14.71
% CV	63.8	98.4	100.0	125.9
Median	2.65	1.90	0.60	7.19
Max				
Min				

All calculations were performed before rounding.
[a] Subject #6 did not complete the study and was therefore excluded from analyses. Subjects #9 and #13 was excluded from this analysis due to lack of best fit.
[b] Subject received 10 µg/kg abarelix injectable solution instead of 15 µg/kg and was therefore excluded from analyses.
[c] No best fit for this parameter. Value excluded from calculation of descriptive statistics.

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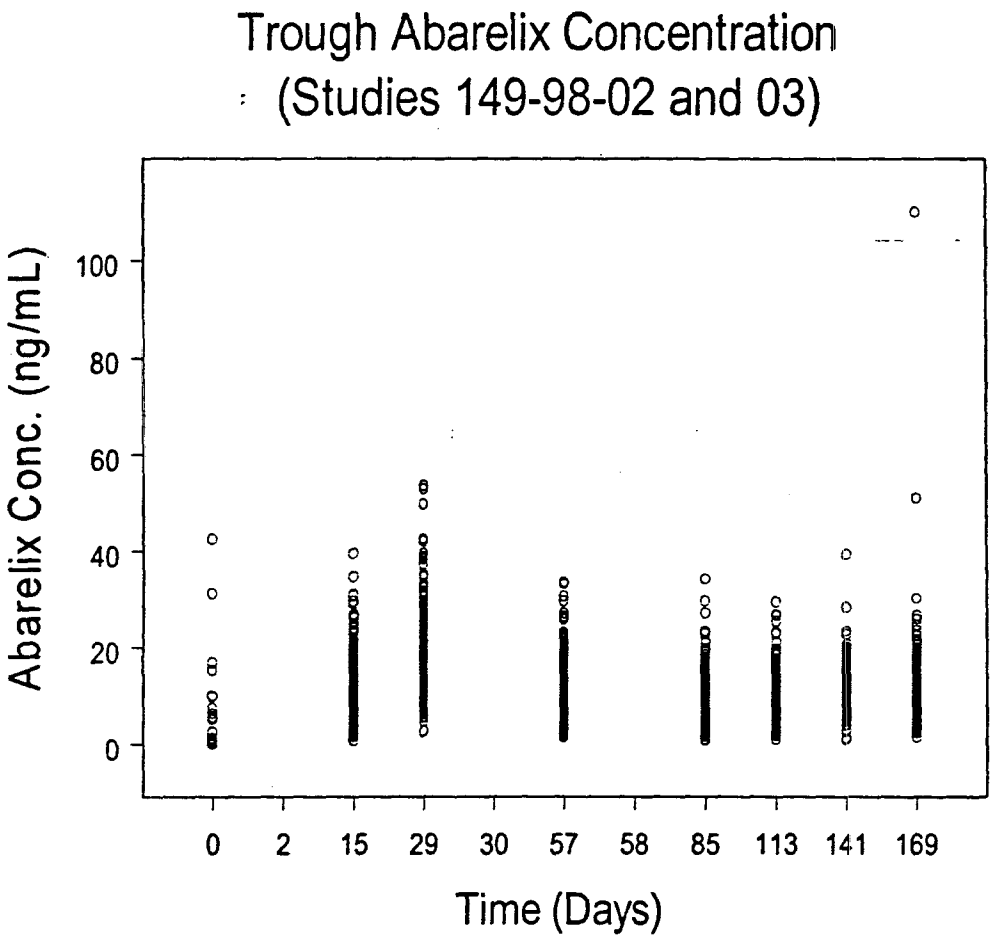
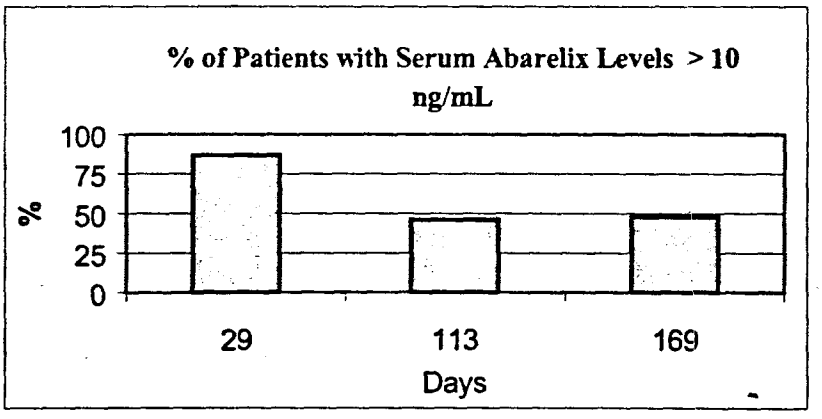
Appendix 3.





[Both the above plots have been created with data pooled from Studies 149-98-02 & -03]

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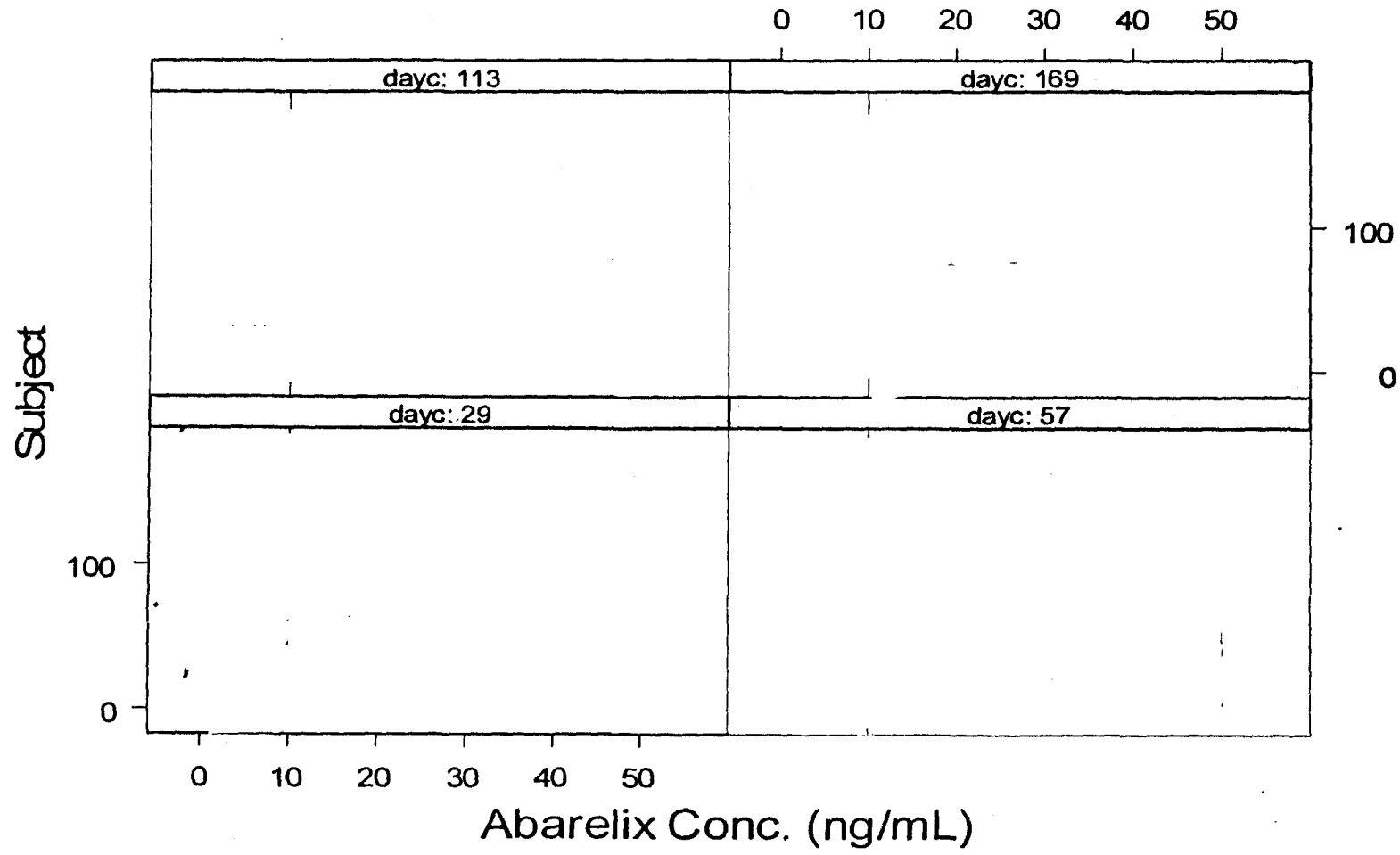
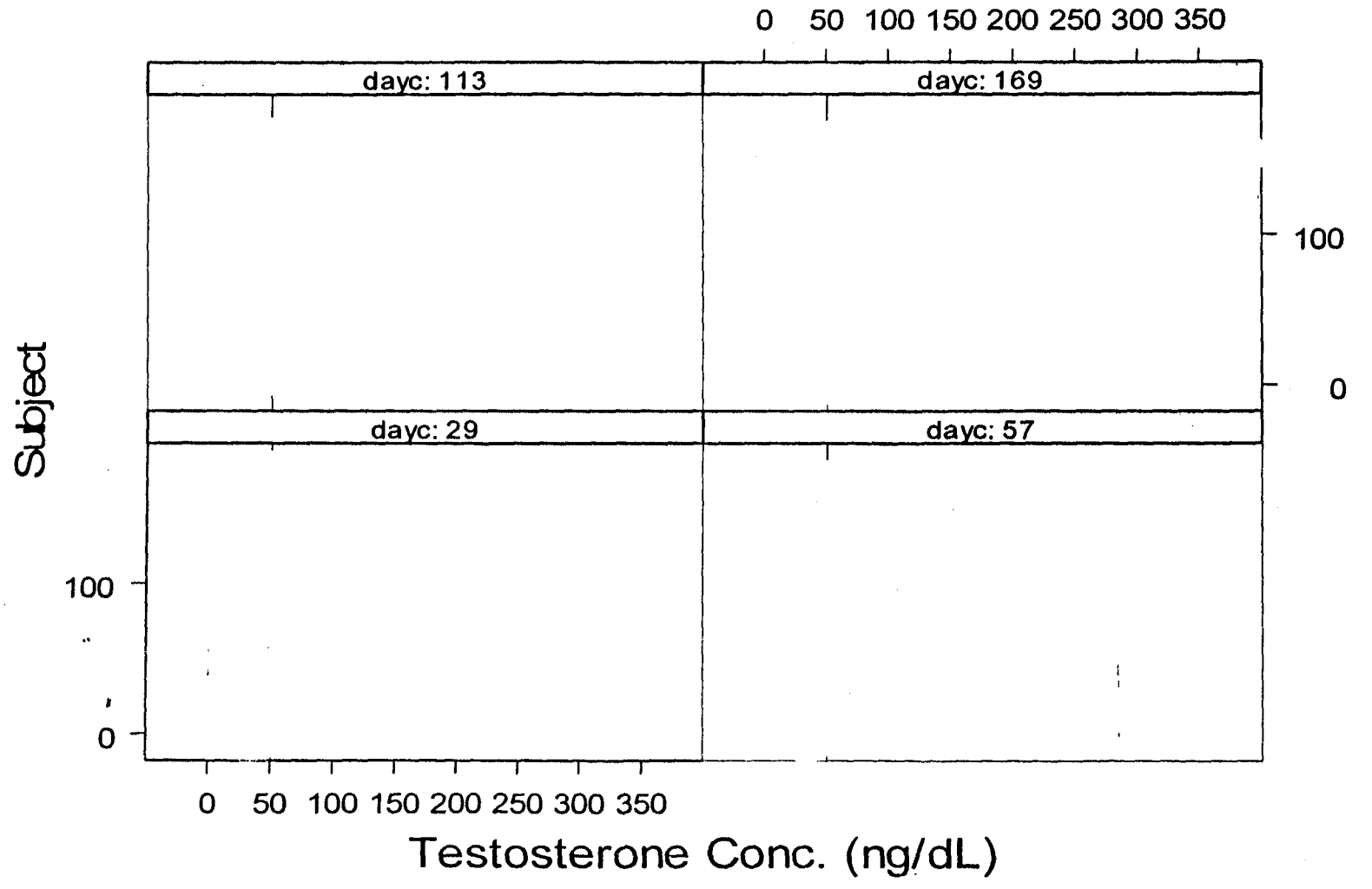
Abarelix Concentration
(Studies 149-98-02 & 03 pooled)



T Concentration Distribution
(Studies 149-98-02 & 03 pooled)



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Appendix 4.

SIMULATION

Method:

1. *Selection of structure model and input function:* A two compartment open model was fitted to concentration-time data observed after single 100 mg dose. There was no available drug input function model to describe the concentration time profile for the depot IM dose. To describe the data, several input functions were tried. An instant input function (bolus) followed by a zero order slow input function (eg. infusion) described the data adequately (see figure below) with the dose divided equally between the instant and the zero order input functions. The total time period of the slow zero order input lasted 4 hours.

2. *Estimation of parameters*: Pharmacokinetic parameters were estimated by fitting the observed mean data to the above selected structure model. The estimated parameters, as compared to those obtained via non compartment method, are listed below:

Table. Comparison of PK parameters obtained using nonparametric (sponsor's) methods versus nonlinear regression method (modeling by reviewer):

	CL	V_c	$T_{1/2}$
Observed (Clinical Study)	208 L/day	4040 L	13 days
Estimated (Modeling)	202 L/day	3484 L	8 days

3. *Simulation*: Population trough concentrations following multiple doses were simulated using nonlinear mixed effect modeling method with NONMEM. Parameters estimated from nonlinear regression were used for the simulation. For each condition, the total number of subjects were 50, variability variables were VarCL=40%, VarVc=20%, VarQ=40%, and VarC2=20% with 15% intra-subject variability. The simulation scenarios included 100 mg monthly (current regimen), 125 mg monthly, 150 mg monthly and 50 mg bi-weekly doses [see following figures for examples of simulated concentration-time profiles].

4. *Results/Conclusions*:

a) Simulated and observed mean trough concentration following 100 mg monthly administration were almost identical (≈ 10 ng/mL) supporting the validity of the model and parameters used in simulation process.

b) With 125 mg dose monthly, mean trough concentration increased to ≈12 ng/mL. The 150 mg monthly dose provided mean trough concentrations of 15 ng/ml with very few concentrations below 5 ng/mL (note, the EC_{50} is 1.21 ng/mL).

c) When profiles following the 100 mg dose divided into two 50 mg bi-weekly doses were simulated, peak to trough concentration ratio was significantly decreased with mean trough concentrations of ≈15 ng/mL.

5. *Conclusion*: Simulations show that increased monthly dose or increased dose frequency may be explored for maintenance of therapy beyond six months.

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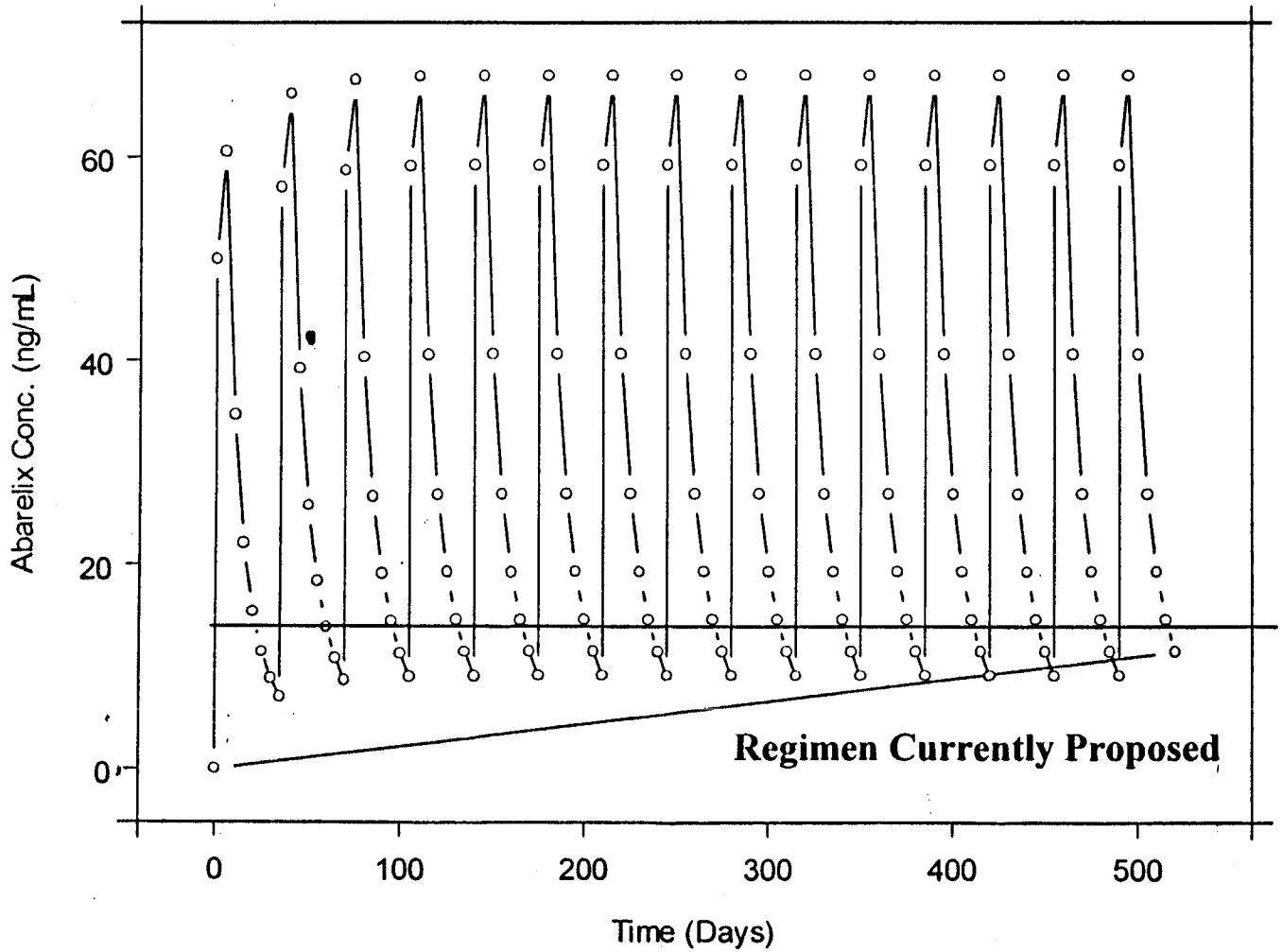
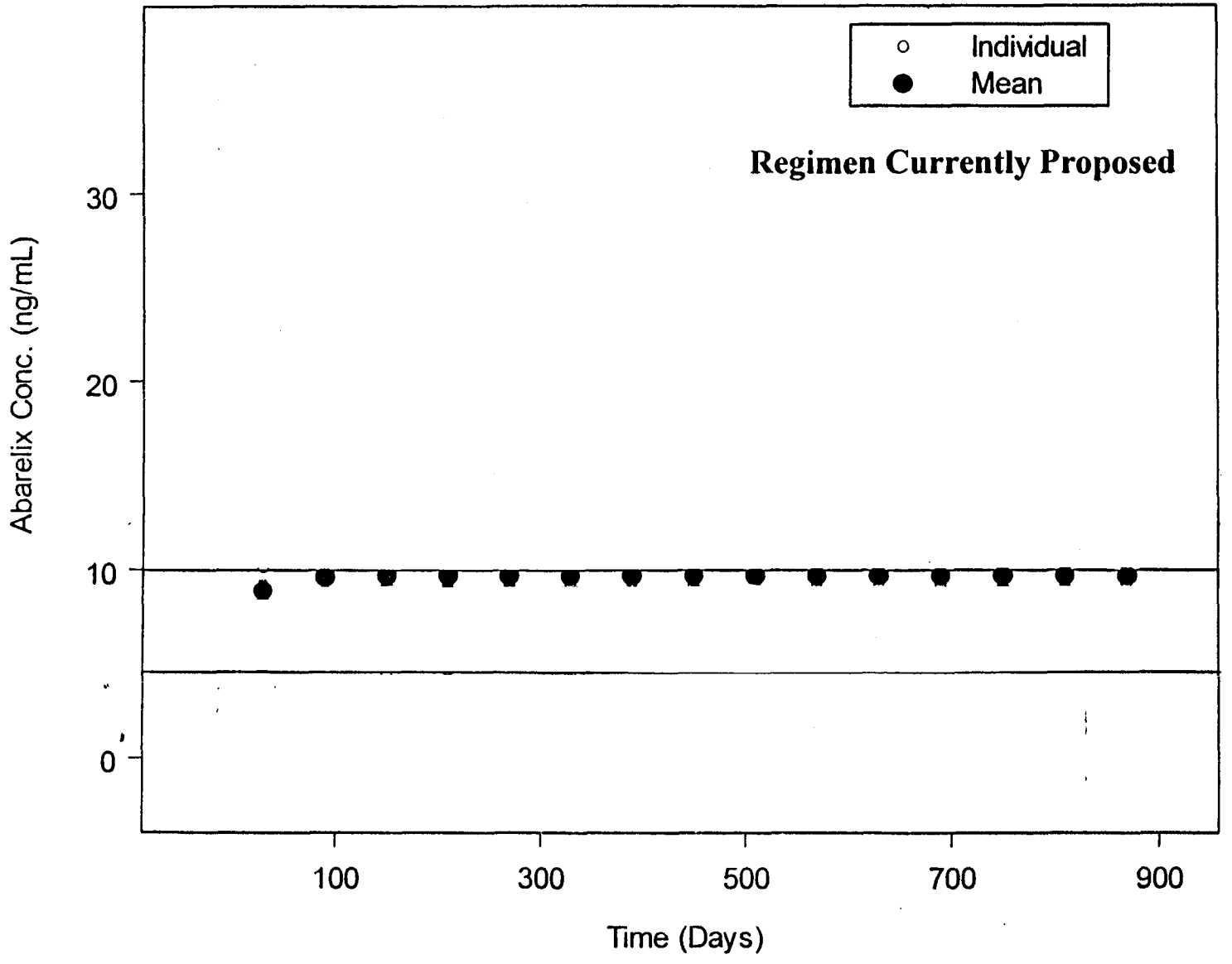
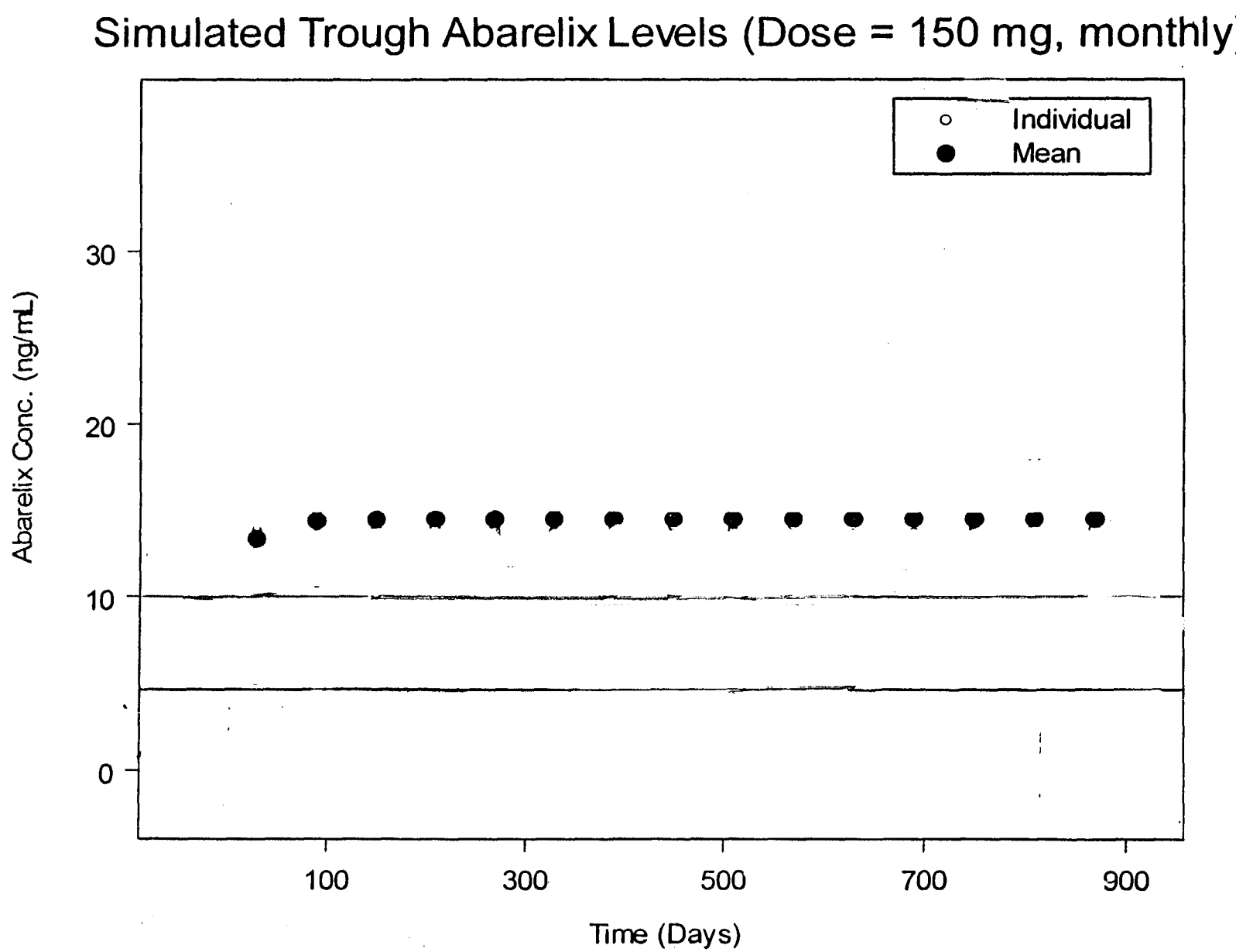
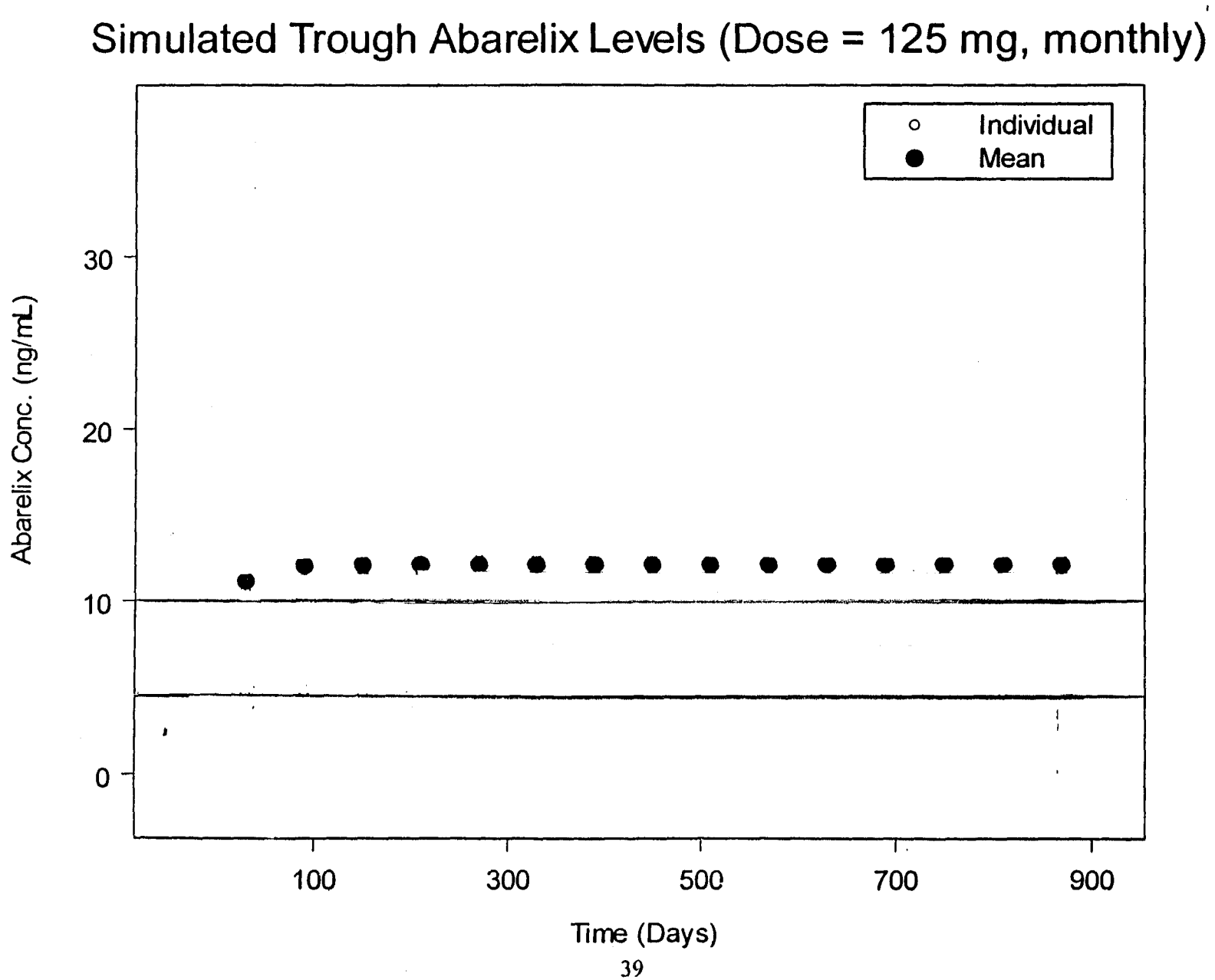
Simulated Abarelix PK Profile (Dose 100 mg, monthly)



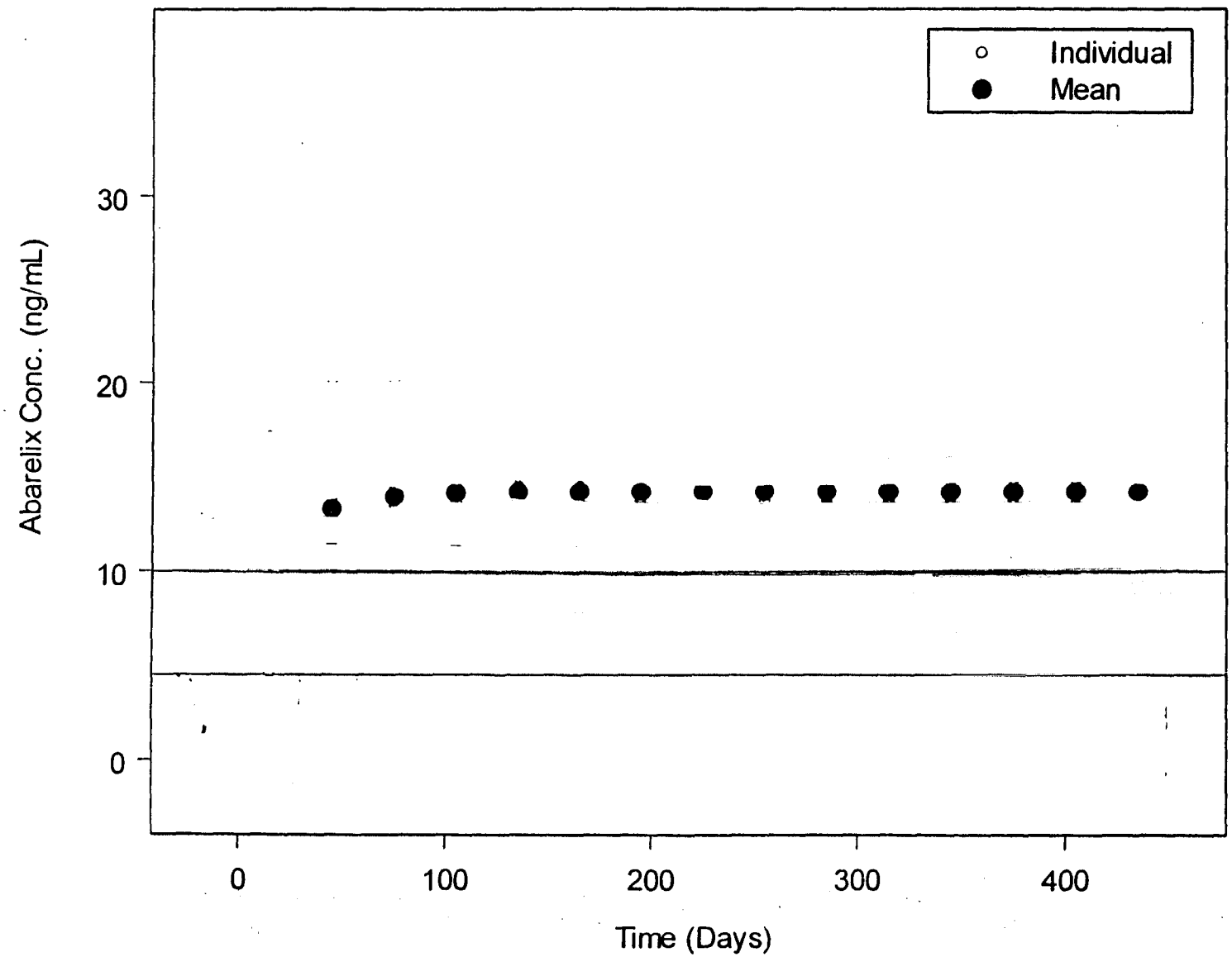
Simulated Trough Abarelix Levels (Dose = 100 mg, monthly)




Simulated Trough Abarelix Levels (Dose = 150 mg, monthly)
Individual
Mean
Abarelix Conc. (ng/mL)
30
20
10
0
100
300
500
700
900
Time (Days)


Simulated Trough Abarelix Levels (Dose = 125 mg, monthly)
Individual
Mean
Abarelix Conc. (ng/mL)
30
20
10
0
100
300
500
700
900
Time (Days)

Simulated Trough Abarelix Levels (Dose = 50 mg, bi-weekly)



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/s/

Dhruba Chatterjee
6/12/01 04:53:43 PM
BIOPHARMACEUTICS
Final version
Ameeta, this is it!

Ameeta Parekh
6/12/01 05:03:41 PM
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I concur