- In patients with cancer-related pain: VAS pain score, analgesic use, pain description
- In patients with bone pain: bone scan, radiation planned (yes or no), risk of pathological fracture (yes or no)
- In patients with impending neurological compromise: spinal computed tomographic (CT) scan or magnetic resonance imaging (MRI), a detailed neurological exam (as applicable)
- In patients with unilateral or bilateral hydronephrosis: pelvic/abdominal CT scan, renal ultrasound, creatinine clearance, presence of stent (yes or no)
- In patients with azotemia: creatinine clearance, BUN

6.5.5 Safety Endpoints

Safety data, including adverse events, laboratory evaluations, and physical findings were collected according to the Schedule of Assessments outlined in Table 5. Safety endpoints included treatment-emergent adverse events, laboratory abnormalities, serious adverse events, and patient withdrawals due to adverse events.

6.5.6 Statistical Methods

Efficacy Analyses. Straight forward proportions for the percentage of patients in the intent-to-treat (ITT) population who avoided bilateral orchiectomy through Day 29 and through Day 85 were calculated with missing observations imputed using LOCF. Descriptive statistics were summarized for androgen and gonadotropin data in the ITT population and for the percentage change in PSA and acid phosphatase in the per-protocol population. Medical castration success rates were provided for the ITT population. Descriptive statistics for pain intensity as measured by the VAS were calculated for per-protocol patients who had cancer-related pain at baseline.

The ITT population was defined as those patients who were enrolled and received at least 1 dose of study medication. This definition was modified to exclude all patients (n = 9) from the single site in Mexico (Site 499) because of inadequate documentation by the study investigator.

The per-protocol (PP) population was defined in the statistical analysis plan as the subset of patients who completed at least 28 days of study drug therapy according to the protocol (i.e., received both the Day 1 and Day 15 injections of abarelix). Patients who at study entry were receiving any concomitant medications or who took any medications that could have influenced the assessment or interpretation of medical castration were excluded from the PP population.

Medical Officer's Comments

- *Only one of the ITT patients was excluded from the PP population. Therefore, the results of the ITT and PP analyses were nearly identical.*

Safety Analyses. The incidence of adverse events was summarized by body system, severity, and relationship to study drug. Descriptive statistics and shifts in hematology and clinical chemistry data were summarized for each planned visit day. Overall shifts in laboratory data were summarized, as were clinically notable results.

6.6 Enrollment, Disposition, and Baseline Characteristics (Study 148-98-04)

6.6.1 Enrollment and Disposition

All enrolled patients. Eighteen centers in the United States and 1 center in Mexico enrolled at least 1 patient in the study. A total of 83 patients were enrolled and 81 (98%) received at least 1 dose of

abarelix (Table 6). The first patient received his first dose of abarelix on 24 February 1999 and the last patient visit occurred on 25 September 2000.

A total of 69 of 83 patients (83%) completed 169 days of treatment. Of the 14 patients who received at least one dose of abarelix and withdrew before Day 169, 2 withdrew for an adverse event (immediate systemic allergic reaction), 4 withdrew voluntarily, 4 died, and 4 withdrew for reasons listed as "other." Of those who continued to receive abarelix depot on or after Day 169, 16 patients withdrew from the study before completion of their course of hormonal therapy as determined by the investigator (1 withdrew for an adverse event (immediate systemic adverse event), 2 died, 10 withdrew because of disease progression, 1 was lost to follow-up, and 2 withdrew for a reason listed as "other"). Fifty-three (53) patients completed their course of abarelix therapy or enrolled in study 149-99-04 to continue abarelix therapy.

Table 6 Summary of Patient Enrollment and Disposition (Study 149-98-04)

Disposition	All Patients N (%)
Enrolled	83
Received at least one dose of study medication	*81 (98)*
Terminated before Day 169	14 (17)
Adverse event	2 (2)
Voluntary withdrawal	4 (6)
Death [1]	4 (5)
Other [2]	4 (5)
Completed through Day 169	*69 (83)*
Terminated on or after Day 169	16
Adverse event	1
Death [3]	2
Disease progression	10
Lost to follow-up	1
Other [4]	2
Completed treatment or enrolled in rollover study 149-99-04	53

[1] The cause of death was reported as progressive prostate cancer in all 4 patients.
[2] One patient did not meet the inclusion criteria and 3 patients were withdrawn by decision of the investigator.
[3] One patient died of respiratory failure caused by pulmonary embolism; the other patient died of progressive prostate cancer.
[4] One patient was withdrawn and placed on alternative hormonal therapy and 1 patient was withdrawn because of rising PSA.

Source: Modified from Table 8-1, pg 50, Final Report for Study 149-98-04, Vol. 19, Submission of February 25, 2003.

ITT Population. All patients (n = 9) treated at the single center in Mexico (Site 499) were excluded from the efficacy analyses because of inadequate documentation by the investigator, resulting in an ITT population of 72 patients. Disposition of the ITT population is presented in Table 7. A total of 60 of 72 patients (83%) completed 169 days of treatment. Of the 12 patients who withdrew before day 169, 2 withdrew for an adverse event (immediate systemic adverse event), 3 withdrew voluntarily, 4 died, and 3 withdrew for reasons listed as "other." Of those who continued to receive abarelix depot on or after day 169, 15 patients withdrew from the study before completion of their course of hormonal therapy (1 withdrew for an adverse event [immediate systemic allergic reaction], 1 died, 10 withdrew because of disease progression, 1 was lost to follow-up, and 2 withdrew for a

reason listed as "other"). Forty-five (45) patients completed their course of hormonal therapy or enrolled in rollover Study 149-99-04 to continue their course of hormonal therapy.

Table 7 Summary of ITT Patient Enrollment and Disposition (Study 148-98-04)

Disposition	ITT Patients N (%)
Enrolled and Received at Least 1 Dose of Study Drug (excluding 9 patients from site 499)	*72*
Terminated Before Day 169	12 (17)
Adverse event	2 (3)
Voluntary withdrawal	3 (4)
Death[1]	4 (6)
Other[2]	3 (4)
Completed treatment through day 169	*60 (83)*
Terminated on or After Day 169	15
Adverse event	1
Death[3]	1
Disease progression	10
Lost to follow-up	1
Other[4]	2
Completed treatment or enrolled in rollover study 149-99-04	*45*

[1] The cause of death was reported as progressive prostate cancer in all 4 patients.
[2] One patient did not meet the inclusion criteria and 2 patients were withdrawn by decision of the investigator.
[3] Patient died of respiratory failure caused by pulmonary embolism.
[4] One patient was withdrawn and placed on alternative hormonal therapy and 1 patient was withdrawn because of rising PSA.

Source: Modified from Table 8-2, pg 51, Final Report for Study 149-98-04, Vol. 19, Submission of February 25, 2003.

6.6.2 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics for the ITT population are shown in Table 8.

Table 8 Baseline Demographics (ITT Population, Study 149-98-04))

Characteristic	ITT Patients N = 72
Race/Ethnicity (n [%])	
Caucasian	62 (87)
African American	6 (8)
Hispanic	4 (5)
Age (yr)	
Median (range)	73 (40 – 94)
Weight (lb)	
Median (range)	170 (112 – 248)
Height (in)	
Median (range)	68 (57 – 76)
Body Mass Index (kg/m^2)	
Median (range)	26.3 (17.5 – 37.9)

Source: Table 8-6, pg 53, Final Report for Study 149-98-04, Vol. 19, Submission of February 25, 2003.

6.6.3 Baseline Disease Characteristics

Baseline disease characteristics in the ITT population are shown in Table 9. At baseline, 50 (69%) of ITT patients were considered by the Investigators to have stage D2 prostate cancer. Thirty-four (47%) of the patients had tumors of Gleason grade 8 to 10. Thirty four (47%) patients had a PSA level ≥ 100 ng/mL. Based on the Investigators' assessments at screening, patients were enrolled for the following conditions: 43% for bone pain from prostate cancer skeletal metastases, 35% for an enlarged prostate gland or pelvic mass causing bladder neck outlet obstruction, 13% for bilateral retroperitoneal adenopathy with ureteral obstruction, and 8% for impending neurological compromise.

Table 9 Disease Findings at Baseline (ITT Patients, Study 149-98-04)

Baseline Disease Characteristic	Abarelix (N = 72) n (%)
Stage of Disease	
T1c	1 (1)
T3	3 (4)
T4	9 (13)
D1.5	6 (8)
D1	3 (4)
D2	50 (69)
Gleason Grade	
2 – 4	6 (8)
5 – 6	8 (11)
7	15 (21)
8 – 10	34 (47)
Unknown	9 (13)
Baseline PSA (ng/mL)	
median (range)	90.5 (0.8-7626)
< 20	14 (19)
≥ 20 and < 100	24 (33)
≥ 100 and ≤ 1000	25 (35)
> 1000	9 (13)
Symptomatic Condition for Study Entry [1]	
Bone pain from prostate cancer skeletal metastases	31 (43)
Impending neurological compromise	6 (8)
Bilateral retroperitoneal adenopathy with ureteral obstruction	9 (13)
Enlarged prostate gland or pelvic mass	25 (35)
Other[2]	1 (1)

[1] Patients may have add more than 1 symptomatic condition at entry
[2] Patient 402-4073 was enrolled for bone pain from skeletal metastases, but was discovered to have bone pain caused by degenerative disease and was withdrawn from the study.
Source: Modified from Table 8-7, pg 54, Final Report for Study 149-98-04, Vol. 19, Submission of February 25, 2003.

6.6.4 Prostate Cancer Signs and Symptoms at Entry

Table 10 summarizes the extent of prostate cancer disease, in terms of entry criteria, that was found in patients at study entry.

Table 10 Extent of Prostate Cancer Disease (ITT Patients, Study 149-98-04)

Bone Pain from Prostate Cancer Skeletal Metastases	BNOO, Pelvic Mass, and/or Enlarged Prostate	Ureteral Obstruction or RPA	Impending Spinal Cord Compression	Number of Patients with Finding
X				22
X	X			7
X		X		1
X			X	6
X	X	X		1
	X			19
	X	X		12
		X		2
			X	2

BNOO = bladder neck outlet obstruction, RPA = retroperitoneal adenopathy
Source: Table 4-11, pg 220, ISE Addendum, Vol. 16, February 25, 2003.

6.7 Efficacy Outcomes (Study 148-98-04)

6.7.1 Primary Efficacy Endpoint

Seventy (70) of 72 patients (97%) in the ITT population were classified as treatment successes per the statistical analysis plan since they avoided bilateral orchiectomy through both Day 29 and through Day 85 (Table 11). Two patients who withdrew for treatment-related adverse events (No. 416-4067 on Day 15 for urticaria and No. 409-4057 on Day 29 for urticaria and pruritus) were considered failures to avoid orchiectomy on Days 29 and 85 as specified in the statistical analysis plan although neither actually underwent orchiectomy.

Five (5) patients withdrew from the study after Day 29 and before Day 85 (2 patients died of progressive prostate cancer, 1 patient withdrew voluntarily, 1 patient was withdrawn by the investigator because his veins were not accessible, and 1 patient was withdrawn by the investigator because he did not meet the inclusion criteria). All 5 patients were considered to have avoided orchiectomy based on LOCF as defined in the statistical analysis plan since none of them had received an orchiectomy or had been scheduled for orchiectomy at the time of study termination and none were withdrawn because of a treatment-related adverse event.

Table 11 Number (Percentage) of Patients Who Avoided Bilateral Orchiectomy per Statistical Analysis Plan Through Day 29 and Day 85 (ITT Patients, 149-98-04)

	Abarelix (N = 72)		
	Avoided Orchiectomy		
	n	(%)	95% Confidence Interval
Through Day 29	70[1]	(97)	(90.3, 99.7)
Through Day 85	70[1]	(97)	(90.3, 99.7)

[1] Two patients were withdrawn because of treatment-related adverse events before Day 29 and were therefore considered failures to avoid orchiectomy as specified in the statistical analysis plan although neither patient actually underwent orchiectomy.
Source: Table 9-1, pg 57, Final Report for Study 149-98-04, Vol. 19, February 25, 2003.

Medical Officer's Comments

- *It cannot be determined from the Sponsor's study report how many patients, if any, chose to undergo orchiectomy after their termination from the clinical trial since the Sponsor did not obtain long-term posttreatment follow-up data. Such information would be of considerable interest since it would help to determine the percentage of patients who truly avoided orchiectomy in contrast to those who merely delayed orchiectomy.*
- *In spite of this deficiency in study design, the study has provided significant information about the efficacy and safety of abarelix in patients who were at increased risk of developing a clinically serious flare of their signs and/or symptoms of prostate cancer. It appears from the adverse event and efficacy data provided by the Sponsor (see Section 6.7.2) that these patients (with one possible exception) did not exhibit any significant acute signs or symptoms of a testosterone-induced clinical flare.*

6.7.2 Secondary and Tertiary Efficacy Endpoints

6.7.2.1 Achievement of Medical Castration

Among the ITT patients, 20 of 67 (30%) evaluated on Day 2 were medically castrate (serum testosterone ≤ 50 ng/dL); 57 of 72 (79%) were medically castrate on Day 8; and 68 of 71 (96%) evaluated on Day 29 were medically castrate (Table 12). Two patients had serum testosterone values of ≤ 50 ng/dL at baseline (Nos. 438-4023 and 416-4067). One patient did not achieve castration levels of serum testosterone at any time during the study (No. 438-4041).

Medical Officer's Comment

- *The percentages of patients who were medically castrate at the various assessments times, were similar to, or somewhat better than those observed in the larger, controlled clinical trials presented later in this review.*

Table 12 Percentage of Patients Medically Castrate at Clinical Visit (Study 149-98-04)

	ITT Patients N = 72	
Study Day	Evaluated n	Castrate [1] n (%)
Baseline	72	2 (3)
Day 2	67	20 (30)
Day 8	72	57 (79)
Day 15	72	63 (88)
Day 29	71	68 (96)
Day 85	65	63 (97)
Day 169	59	55 (93)

[1] Percentages were based on the number of patients evaluated in the treatment group on that day. A patient was considered castrate if his testosterone level was ≤ 50 ng/dL.
Source: Table 9-3, pg 59, Final Report for Study 149-98-04, Vol. 19, February 25, 2003.

6.7.2.2 Achievement and Maintenance of Medical Castration Through Day 85

Achievement and maintenance of castration through Day 85 was defined as castrate levels of testosterone (testosterone ≤ 50 ng/dL) on each of Days 29, 57, and 85. By this definition, 65 of the

72 ITT patients (90.3%) achieved and maintained castration (Table 13). LOCF was used to impute missing values. One patient (No. 402-4073), who received only 1 dose of abarelix because he did not meet inclusion criteria, was considered to have failed to meet this endpoint, and 2 patients (Nos. 409-4057 and 416-4067) were considered to have failed because they were withdrawn for treatment-related adverse events. The remaining 4 patients (Nos. 477-4004, 438-4041, 409-4049, and 409-4060) failed to meet the endpoint because of noncastrate testosterone values on 1 or more of Days 29, 57, or 85.

Table 13 Number (Percentage) of Patients Who Achieved and Maintained Medical Castration (Serum Testosterone ≤ 50 ng/dL) Through Day 85 (Study 149-98-04)

Achieved and Maintained Castration [1] ITT Patients (N = 72)	
n (%)	95% CI [1]
65 of 72 (90.3%)	(81.0, 96.0)

[1] Achievement and maintenance of castration was defined as castrate testosterone levels (testosterone ≤ 50 ng/dL) on each of Days 29, 57, and 85.
[1] 95% confidence interval around the observed point estimate.
Source: Table 9-4, pg 60, Final Report for Study 149-98-04, Vol. 19, February 25, 2003.

Medical Officer's Comments

- *The percentage of patients who achieved medical castration by Day 29 and maintained castrate levels of testosterone through Day 85 in Study 149-98-04 was similar to that observed in a larger number of patients with prostate cancer in the 3 controlled clinical trials (see Section 6.12.2.3).*
- *The wide confidence interval around the observed point estimate is a reflection of the small sample size (n = 72).*

6.7.2.3 Median Testosterone Concentrations

Median testosterone concentrations in the ITT population through Day 169 are listed in Table 14. The medians of the serum testosterone concentrations were reduced from a value of 348 ng/dL at baseline to 70 ng/dL and 26 ng/dL on Day 2 and Day 8, respectively. From Day 29 through Day 169, the medians of the serum testosterone concentration ranged from 9 to 11 ng/dL.

Table 14 Median Serum Testosterone Concentrations (ITT Patients, Study 149-98-04)

Day of Assessment	Number Patients Evaluated	Median Testosterone [1] (ng/dL)
Baseline	72	348
Day 2	67	70
Day 8	70	26
Day 15	72	17
Day 29	71	9
Day 57	65	9
Day 85	65	8
Day 113	61	9
Day 141	60	10
Day 169	59	11

[1] The lower limit of detection of the assay was 8 ng/dL; values below the detection limit were reported as 8 ng/dL.
Source: Table 9-5, pg 61, Final Report for Study 149-98-04, Vol. 19, February 25, 2003.

Medical Officer's Comments

- *Median serum testosterone concentrations in the patients in Study 149-98-04 were similar to those in abarelix-treated patients in the controlled clinical trials (see Table 24). However, median serum testosterone concentrations are not a useful measure of serum testosterone concentrations in the context of this study. A clinically significant number of patients could have non-castrate serum testosterone concentrations with no impact on the median testosterone values.*

6.7.2.4 Serum Prostate Specific Antigen Levels

Table 15 lists the median percentage changes from baseline for serum PSA concentrations. The median change from baseline was -75.3% and -90.5% on Days 15 and 29, respectively. From Day 85 through Day 169, the median percentage changes from baseline PSA were at least -95% or better.

Table 15 Serum PSA: Median Percentage Changes from Baseline (Study 149-98-04)

Assessment Day	Number Patients. Evaluated [1]	Median % Change from Baseline
Day 15	70	-75.3
Day 29	69	-90.5
Day 57	65	-94.8
Day 85	63	-96.4
Day 113	60	-96.0
Day 141	60	-95.9
Day 169	58	-96.5

1 Per Protocol Patients (N = 71).
Source: Table 9-4, pg 60, Final Report for Study 149-98-04, Vol. 19, February 25, 2003.

Medical Officer's Comment

- *Median percentage changes from baseline in serum PSA in Study 149-98-04 were similar to those in abarelix-treated patients in the controlled clinical trials (see Table 34).*

6.7.2.5 Disease Response According to NPCP Criteria

Of the 43 patients included in the disease response evaluation at 12 weeks, 3 patients (7%) had a complete response, 14 patients (33%) had a partial response, and 21 patients (49%) had objectively stable disease. Five patients (12%) had progressive disease (Table 16).

Of the 40 patients included in the disease response evaluation at 24 weeks, 10 patients (25%) had a partial response and 20 patients (50%) had objectively stable disease for an overall objective response rate of 75%. Ten patients (25%) had progressive disease.

Table 16 Disease Response at 12 and 24 Weeks (NPCP Criteria, Study 149-98-04)

Response	12 Weeks N = 43 n (%)	24 Weeks N = 40 n (%)
Complete Response	3 (7)	0
Partial Response	14 (33)	10 (25)
Stable Disease	21 (49)	20 (50)
Progressive Disease	5 (12)	10 (25)
Overall Objective Response [1]	*38 (88%)*	*30 (75%)*

[1] The sum of complete, partial, and objectively stable disease responses.
Source: Table 4-9, pg 218, ISE Addendum, Vol. 16, February 25, 2003.

6.7.2.6 Patients Requiring a Urinary (Bladder) Catheter

The changes in the number of patients with a bladder catheter, compared to baseline, on Days 15, 29, 85 and 169 are presented in Table 17. Patients who no longer required a bladder catheter at the time of the assessment are listed as "improved."

Table 17 Number of Patients with a Urinary Catheter in Place (Study 149-98-04)

Baseline Incidence [1]	Study Day	Number (%) of Patients		
		Evaluated N	Improved [2] n (%)	Unchanged n (%)
13	15	13	1 (8)	12 (92)
	29	13	4 (31)	9 (69)
	85	13	10 (77)	3 (23)
	169	12	10 (83)	2 (17)

1. Number of patients with a catheter at baseline.
2. Number of patients without a catheter at the assessment time.
Source: Table 6-6, pg 54, Addendum to Study 149-98-04 Report, Vol. 18, Submission of February 25, 2003.

6.7.2.7 VAS Pain Score in Patients using Narcotics

The Visual Analog Scale (VAS) for pain was recorded at baseline and on Days 2, 8, 15, 29, 57, 85, 113, 141, and 169. The median VAS pain score for the 18 patients taking narcotic analgesics for

bone pain at baseline are listed in Table 18. The median score decreased from 6.8 at baseline to less than 1.0 at the Day 29, 85 and 169 assessments.

Table 18 VAS Pain Score: Patients using Narcotics at Baseline for Bone Pain (149-98-04)

Study Day	Evaluated n	Median Score[1]	Range	Interquartile Range
1(Baseline)	18	6.8	0.4, 9.8	4.6, 9.1
2	17	5.3	0.9, 8.6	3.7, 7.8
8	18	4.4	0.2, 7.4	0.9, 5.4
15	18	3.4	0.2, 8.2	0.6, 6.2
29	18	0.8	0.0, 8.5	0.3, 2.6
85	15	0.6	0.0, 8.1	0.1, 3.6
169	11	0.8	0.0, 5.2	0.4, 4.7

[1] Score was measured on a continuous scale of 0 to 10, where 0 represented no pain and 10 represented the worst pain imaginable.
Source: Table 6-10, pg 56, Addendum to Study 149-98-04 Report, Vol. 18, Submission of February 25, 2003.

The median changes from the baseline VAS pain score are summarized in Table 19. By Day 8 of abarelix treatment, the median change in the VAS pain score was -3.0 units. Median changes from baseline on Days 29, 85, and 169 were -4.5, -4.2, and -2.7 units, respectively.

Table 19 Change from Baseline VAS Pain Score: Patients with Bone Pain from Prostate Cancer Metastases Using Narcotics at Study Entry (Study 149-98-04)

Study Day	No. Pts. Evaluated	Median Change from Baseline Score[1]	Range	Interquartile Range
2	17	-1.0	-8.2, 3.4	-1.9, 0.7
8	18	-3.0	-7.7, 1.8	-4.3, -0.8
15	18	-2.4	-9.2, 2.1	-4.3, 0.2
29	18	-4.5	-9.2, 1.4	-7.3, -1.9
85	15	-4.2	-9.2, 1.2	-8.6, -1.2
169	11	-2.7	-9.0, 4.4	-7.1, -1.2

[1] Score was measured on a continuous scale of 0 to 10, where 0 represented no pain and 10 represented the worst pain imaginable.
Source: Table 6-11, pg 57, Addendum to Study 149-98-04 Report, Vol. 18, Submission of February 25, 2003.

Medical Officer's Comments

- *Because this was an open label, non-comparative clinical trial, changes in VAS pain scores and narcotic use (see below) cannot be adjusted for placebo effects. In spite of this limitation, it is likely that treatment resulted in a clinically significant diminution in pain intensity in many of the patients, at least through Study Day 85.*

6.7.2.8 Change in Narcotic Analgesic Use

Fifteen of 18 patients taking narcotic analgesics for their bone pain from prostate cancer skeletal metastases were evaluated for change in their narcotic analgesic use at Day 85 (Table 20). According to the Sponsor's analysis, 11 (73%) improved, 2 (13%) were unchanged, and 2 (13%) worsened. Of the 14 patients who were evaluated for change in their narcotic analgesic use at Day 169, 9 (64%) improved, 1 (7%) was unchanged, and 4 (29%) worsened.

Table 20 Change from Baseline Narcotic Analgesic Use for Patients with Bone Pain From Prostate Cancer Skeletal Metastases (Study 149-98-04)

Baseline Incidence	Study Day	Evaluated N	Improved n (%)	Unchanged n (%)	Worsened n (%)
18	85	15 [1]	11 (73)	2 (13)	2 (13)
	169	14 [2]	9 (64)	1 (7)	4 (29)

[1] Patient Nos. 473-4031, 409-4044, and 409-4057, who had bone pain from prostate cancer skeletal metastases at baseline, withdrew from the study prior to Day 85.
[2] Patient 402-4030 died on day 118.
Source: Table 6-13, pg 59, Addendum to Study 149-98-04 Report, Vol. 18, Submission of February 25, 2003.

6.7.2.9 Testosterone Levels for Patients Who Died, Experienced Worsening of Their Disease, or Experienced Disease Progression

To assess whether a failure to maintain castrate levels of testosterone may have been a factor for patients who died, experienced worsening of their disease, or experienced disease progression, the testosterone levels for the 24 patients who met at least 1 of these conditions were reviewed by the Sponsor. According to the Sponsor, testosterone levels were > 50 ng/dL for 3 of the 24 patients who died, experienced worsening of their disease, or experienced disease progression after Day 29. Two of these 3 patients had an isolated testosterone value that probably had little or no impact on disease progression. The third patient had 2 separate testosterone elevations of sufficient magnitude that the potential contribution of these elevations to disease progression could not be excluded.

6.7.3 Overall Assessment of the Effectiveness of Abarelix in the Indicated Population

Abarelix, without concomitant antiandrogen therapy, can be administered to men with advanced symptomatic androgen dependent prostate cancer (the indicated patient population) with little or no risk of a testosterone-induced clinical flare. All patients with advanced symptomatic prostate cancer treated with abarelix (n = 72 in the efficacy analysis) in Study 149-98-04, avoided orchiectomy through study Day 85, the protocol defined primary efficacy endpoint. No patient (with one possible exception) reported a clinically significant adverse event during the initial treatment period suggestive of a testosterone-induced clinical flare. The possible exception was Patient No. 471-4008 who reported severe bone pain within 24 hours after his first dose of abarelix. However, serum testosterone concentrations in this patient, based on reported values, did not increase after administration of abarelix but rather decreased from 237 ng/dL at baseline to 68 and 13 ng/dL on Study Days 5 and 9, respectively.

Part B. Controlled Pivotal Clinical Trials and Other Supportive Data

- **Clinical Trial 149-98-02** – "A Phase 3, Multicenter, Open-Label, Randomized Study of Abarelix 100 Mg Versus Lupron Depot 7.5 Mg in Prostate Cancer Patients Who Were Candidates for Initial Hormonal Therapy"
- **Clinical Trial 149-98-03** – "A Phase 3, Multicenter, Open-Label, Randomized Study of Abarelix 100 Mg Versus Lupron Depot 7.5 Mg Plus Daily Casodex 50 Mg in Prostate Cancer Patients Who Were Candidates for Initial Hormonal Therapy"
- **Clinical Trial 149-99-03** – "A Phase 3, Multicenter, Open-Label, Randomized Study of Abarelix 100 Mg Versus Lupron Depot 7.5 Mg in Prostate Cancer Patients Who Were Candidates for Initial Hormonal Therapy"

6.8 Primary Efficacy Objectives (Controlled Clinical Trials)

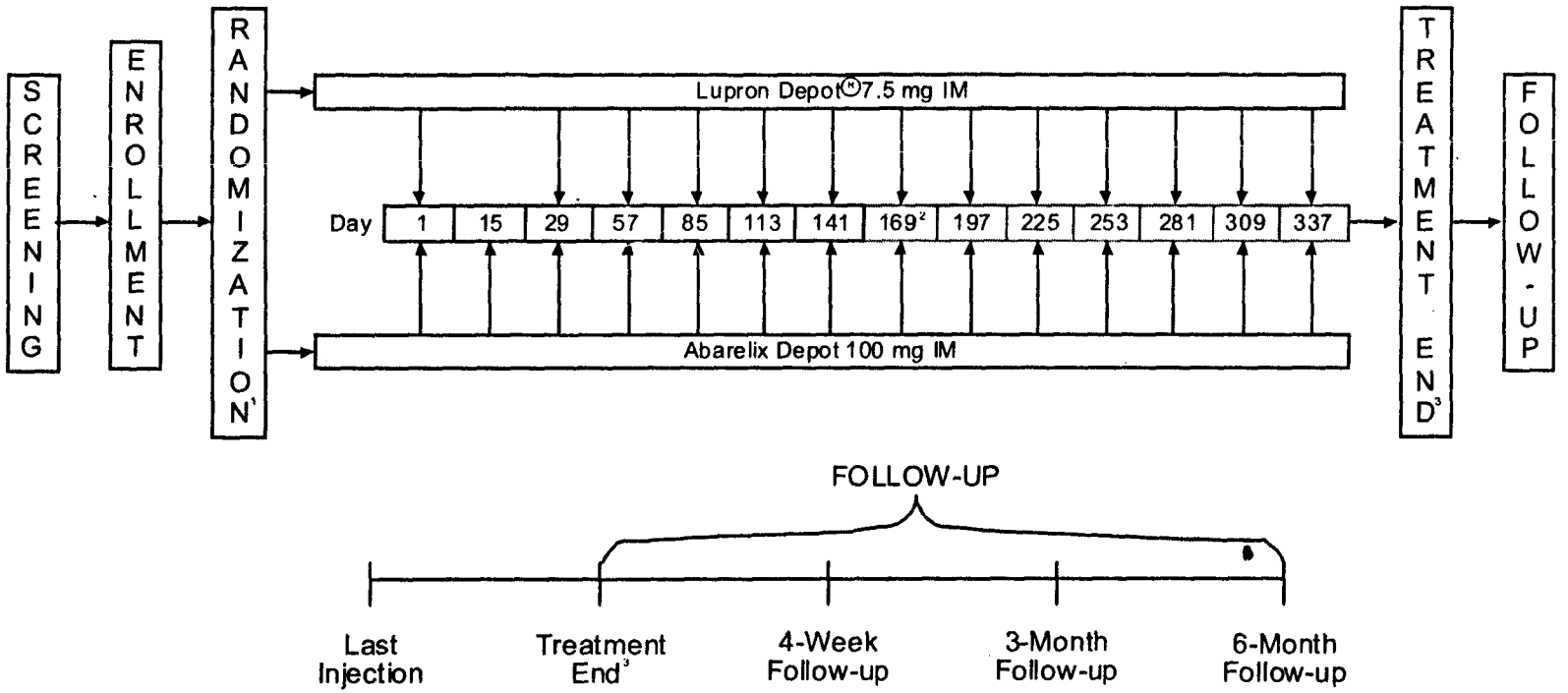
The primary efficacy objective of these studies was to compare abarelix depot to either Lupron Depot (Studies 149-98-02 and 149-99-03) or Lupron Depot plus Casodex (Study 149-98-03) with respect to achievement and maintenance of medical castration (serum testosterone ≤ 50 ng/dL), avoidance of testosterone surge, and rapidity of medical castration during 12 and 24 weeks of treatment in prostate cancer patients who would likely benefit from medical castration.

6.9 Overall Design of the Controlled Clinical Trials

The primary clinical studies conducted by the Sponsor to support the efficacy of abarelix (i.e., rapidity and reliability of testosterone suppression) were Study 149-98-02 and Study 149-89-03. Both were adequately controlled (active comparator), randomized, open label, multicenter clinical trials in which patients with prostate cancer that might benefit from hormonal therapy (i.e., reduction in testosterone levels) were enrolled. The overall study design is summarized in Figure 1. Men with prostate cancer who met the entry criteria were stratified into 1 of 4 strata based on their entry serum testosterone level and body weight. Within each strata, patients were randomly assigned in a 2:1 ratio to treatment with either abarelix or active comparator (Lupron or Lupron + Casodex). All patients were to receive an injection of abarelix or Lupron once every 28 days through Study Day 141. Patients assigned to the abarelix group also received Study Drug on Day 15. Patients, who in the Investigator's opinion had benefited from their initial treatment, were offered the opportunity to continue treatment for an additional 28 weeks (through Study Day 365). The treatment period was defined as the interval from the patient's first injection of Study Drug through 28 days after his final injection. After completion of treatment, patients entered either (1) a follow up period to determine if their serum testosterone levels would return to baseline values or the normal range or (2) a long-term follow on study (Study 149-99-04) in which they continued treatment with abarelix.

A third clinical trial (Study 149-99-03) was conducted primarily to increase the size of the safety database. The enrollment criteria and treatment regimen for this study were identical to those of Study 149-98-02. The schedule of study procedures and assessments for this study also were identical, with some exceptions (described later), to those of Study 149-98-02. Consequently, the critical efficacy endpoint of attainment and maintenance of testosterone suppression in Study 149-99-03 also is reviewed in this section.

Figure 1. Overview of Study Design (Studies 149-98-02 and 149-98-03)



[1] 2:1 randomization – abarelix:Lupron or abarelix:Lupron + Casodex

[2] As clinically indicated, patients in Studies 149-98-02 and 149-98-03 could continue treatment with their randomized Study Drug for up to 1 year, including up to 7 additional injections, beginning on Day 169 and every 28 days thereafter. If continuing in the study, patients in the abarelix group with testosterone > 50 ng/dL on Day 169 received an extra injection of abarelix on Day 183.

[3] Treatment period ended 28 days after the last injection.

6.9.1 Patients

Patients with prostate cancer suitable for initial hormonal therapy (i.e., reduction in androgen levels) were considered for enrollment if they met the following criteria:

Inclusion Criteria Included

- Male ≥ 18 years of age
- Diagnosed with prostate cancer and a candidate for initial hormonal therapy. The categories of disease that were eligible for these studies included
  - Patient with metastatic disease (stage D1 or D2)
  - Patient with rising prostate specific antigen (PSA) levels after radical prostatectomy, radiation therapy, or other local therapy
  - Patient with local or regional disease who were candidates for neoadjuvant hormonal therapy
  - Patients scheduled for their initial course of intermittent hormonal therapy
- Performance status of 0 to 2 on the Eastern Cooperative Oncology Group (ECOG) performance scale
- Life expectancy of at least 6 months
- Adequate hematologic function defined as hemoglobin ≥ 11 g/dL
- Adequate clinical chemistry values, defined as all elements of clinical chemistry panel ≤ 2 x ULN. Patients with chemistry values > 2 x ULN due to underlying medical conditions (e.g., elevated alkaline phosphatase due to metastatic prostate cancer or elevated hemoglobin A_{1c} due to diabetes) were allowed to enter the study at the Investigator's discretion.
- Serum testosterone ≥ 220 ng/dL and ≤ 2 x ULN

Patients were excluded from participation if they met any of the following criteria:

Exclusion Criteria Included

- Known severe bone pain from prostate cancer skeletal metastases, spinal cord compression, bilateral hydronephrosis, bladder neck outlet obstruction, or azotemia from metastatic prostate cancer requiring immediate treatment, where LHRH agonists are known to exacerbate the symptoms
- History of or concurrent secondary cancer, except for basal cell carcinoma or superficial transitional cell bladder carcinoma
- Recent history of clinically significant drug hypersensitivity to LHRH agonists or GnRH antagonists
- Unstable concurrent medical condition
- Prior hormonal therapy for prostate cancer, except for neoadjuvant hormonal therapy. Prior neoadjuvant therapy must have occurred at least 6 months before enrollment.
- Currently taking or planning to take PC SPES® (Botaniclab, Inc.), an herbal therapy for treatment of prostate cancer
- Currently receiving or likely to receive corticosteroids (including inhalants) or other agents know to modify serum androgen levels, or treatment with such agents within 90 days before enrollment
- Currently receiving Proscar (finasteride) or other 5α-reductase inhibitors, or treatment with Proscar or other 5α-reductase inhibitors within 30 days before enrollment.

6.9.2 Study Drugs

6.9.2.1 Dose Selection

In Part 2 of Study 149-97-04 (a Phase I/II pharmacology and safety study of abarelix depot), 209 patients received a 100-mg intramuscular injection of abarelix on Days 1 and 15 followed by 50 or 100 mg on Day 29 and every 4 weeks thereafter for 24 weeks to 2 years. The 100-mg dose was found to be adequate for both induction and maintenance of medical castration (serum testosterone ≤ 50 ng/dL) throughout the assessment period. The 50-mg dose, however, appeared to be suboptimal for maintenance of medical castration after Study Day 85 (per the sponsor). Doses of abarelix higher than 100 mg were not fully evaluated.

Based on the findings from Study 149-97-04, the dose and regimen selected for further investigation in the Phase III studies (both primary and supportive studies) was 100 mg abarelix administered by IM injection on Study Days 1, 15, 29 and every 4 weeks thereafter. Patients enrolled in Studies 149-98-02 and 149-98-03 were treated for up to one year. Patients enrolled in Study 149-99-03 were treated for up to 24 weeks (6 months).

Medical Officer's Comments

- *Based on the findings from the controlled clinical trials (see Section 6.12.3.2), a dose somewhat higher than 100 mg, a formulation with a more uniform release profile, or a shorter dosing interval would likely have provided more reliable suppression of serum testosterone concentrations, particularly after 6-months of treatment.*

6.9.2.2 Choice of Comparator

A placebo control was not deemed ethical because all of the patients required the benefits of medical castration. GnRH agonist therapy, administered alone or in combination with an antiandrogen, and surgical castration are the standard of care for hormonal treatment of androgen sensitive prostate cancer. Lupron is the most frequently used GnRH agonist in the U.S. and Lupron plus Casodex is a frequently used combination therapy. Thus, patients randomly assigned to the comparator group in Study 149-98-02 and Study 149-99-03 (a supportive efficacy study) received an IM injection of Lupron 7.5 mg once every 28 days. Patients randomly assigned to the comparator group in Study 149-98-03 received an IM injection of Lupron 7.5 mg once every 28 days and a 50-mg Casodex tablet orally once each day.

6.9.2.3 Assignment to Study Drug

Before randomized assignment to a treatment group was made, patients were stratified by baseline testosterone level and body weight into 1 of the 4 strata described in Section 6.11.3.1 Within each strata, patient were assigned to abarelix or active control treatment according to a 2:1 randomization scheme (2 abarelix : 1 Lupron or 2 abarelix : 1 Lupron + Casodex).

6.10 Study Procedures and Conduct (Controlled Clinical Trials)

6.10.1.1 Schedule of Study Assessments

During the screening period, the patient's eligibility for the study was determined according to the inclusion and exclusion criteria. After their first injection of Study Drug on Day 1, all patients returned to the clinic for study assessments according to the schedule presented in Table 21.

For all patients, the posttreatment follow up period began 28 days after their last injection. Recovery of testosterone was monitored during the posttreatment period. Based on Protocol Amendment 4, follow-up was complete when testosterone was ≥ 220 ng/dL, the patient had completed 6 months of follow-up, or the patient was receiving alternative hormonal therapy.

6.10.1.2 Efficacy Assessments

- **Primary assessment.** The primary efficacy assessment was the measurement of serum testosterone concentrations. Serum testosterone levels were measured at screening, baseline (Day 1), each scheduled visit during treatment, the end of treatment, the 4-week posttreatment follow-up, and if necessary for monitoring of recovery, 3-months and 6-months posttreatment.
- **Secondary Assessments.** Secondary efficacy assessments included:

  — The measurement of serum levels of DHT and gonadotropins (LH and FSH) at screening, baseline (Day 1), each scheduled visit during treatment, end of treatment, and at the 4-week posttreatment follow-up. Serum PSA levels were measured at screening, baseline, Day 15, Day 29, every 28 days thereafter during treatment, the end of treatment, and 4-weeks posttreatment.

  — Three quality-of-life questionnaires were administered at regular intervals during the study: the EuroQoL (EQ-5D Health Questionnaire), the Southwest Oncology Group (SWOG) 9039, and the Visual Analog Scale (VAS) for pain. Disease response also was assessed in patients with a baseline metastatic evaluation of stage D1 or D2. Quality of life and disease response assessments are not discussed in this review.

Laboratory procedures for efficacy assessments. Serum testosterone levels were measured with the ——— assay, a ——— using a testosterone-specific antibody. Serum DHT levels were measured by a ——— ——— Serum LH and FSH levels were each measured with the ——— using anti-LH or anti-FSH antibody-coated microparticles. Serum PSA levels were measured with the ——— PSA assay, ——— ——— All of these assay methodologies were validated and performed by ——— ———

Medical Officer's Comments

- *The assays that were employed for the measurement of serum hormone and PSA concentrations were adequate for the objectives of the clinical trials.* ——— *is used by many pharmaceutical companies for laboratory support of clinical trials.*

6.10.1.3 Pharmacokinetic Assessments

Blood collection for the measurement of serum abarelix concentrations was performed on Days 1, 2, 15, 29, 30, 57, 58, 85, 113, 141, and 169. On the days when abarelix was to be administered (Days 1, 15, 57, 85, 113, 141, and 169), blood samples were collected before dosing. Specimens were shipped to ——— . and subsequently shipped to ——— for analysis. (See the Biopharmaceutical Review for details concerning the abarelix assay procedure.)

Table 21. Schedule of Study Assessments (Studies 149-98-02 and 149-98-03)

	Study Day																				
	-14 to -1	1	2 30 58	4	8	15	29 57	32 60	36 64	43	71	85	99 127 155	113 141	127	169	197 225 281 309	253 337	365	End of Tx[1]	FU[2]
Informed consent	x																				
General medical history	x																				
Prostate cancer history	x																				
Metastatic evaluation[3]	x											X				x		x			
ECG	x																				x[4]
Physical exam	x	x					x					X		x		x					x
Hematology	x	x[5]					x					x[5]		x		x[5]	x	x[5]	x	x	x
Clinical chemistry	x	x[5]				x	x			X		x[5]		x		x[5]	x	x[5]	x	x	x
Acid phosphatase		x		X	X	x	x		x	X		X		x		x	x	x	x	x	x
Androgens, gonadotropins[6]	x	x	X	X	X	x	x	X	x	X	x	X	x	x	x	x	x	x	x	x	x[7]
PSA	x	x				x	x					X		x		x	x	x	x	x	x
Serum abarelix concentrations[8]		x	X			x	x					X		x							
Anti-abarelix antibodies[8]	x											X				x		x			x
Baseline signs/symptoms	x	x																			
EuroQoL		x					x					X				x			x		x
SWOG 9039		x				x	x					X				x			x		x
Endocrine questionnaire		x			X	x	x		x	X	x	X		x		x	x	x	x	x	x
VAS for pain		x			X	x	x					X				x			x		x
Abarelix depot dosing		x				x	x					X		x		x	x	x			
Lupron Depot 7.5 mg dosing[9]		x					x					X		x		x	x	x			
Adverse events, concomitant Rx	Recorded and monitored throughout the study																				

[1] 28 days after the last injection.
[2] 56 to 63 days (8 to 9 weeks) after the last injection.
[3] Only in patients with D1/D2 disease or baseline PSA ≥ 10 ng/mL.
[4] Only if clinically significant change from baseline to the end of treatment
[5] Fasting blood samples.
[6] Androgens: testosterone and DHT; gonadotropins: LH and FSH.
[7] Patient was required to return for additional follow-up visits 2 months and 5 months later if testosterone was still < 220 ng/dL.
[8] Abarelix depot patients only (predosing sample).
[9] Patients in Study 149-98-03 also received a daily 50 mg tablet of Casodex..

6.11 Efficacy Endpoints (Controlled Clinical Trials)

6.11.1 Primary Efficacy Endpoints

The primary efficacy assessment in the controlled Phase III clinical trials was the patient's serum testosterone concentration during treatment with Study Drug. There were 3 primary efficacy endpoints for the controlled Phase III studies. All three were based on serum testosterone concentrations and were as follows:

1. **Achievement and maintenance of serum testosterone concentrations of ≤ 50 ng/dL from Study Day 29 through Study Day 85 (based on Protocol Definition No. 2)**
   Based on Protocol Definition No. 2, a patient was **classified as a failure** for this efficacy endpoint if (a) his serum testosterone was > 50 ng/dL on Study Day 29 or (b) his serum **testosterone was > 50 ng/dL on 2 consecutive measurements obtained 2 weeks apart** on any of Study Days 29, 43, 57, 71, and 85. The time of failure was the earlier of (a) Study Day 29 if his serum testosterone was > 50 ng/dL on that day or (b) the first of the 2 consecutive measures on which serum testosterone was > 50 ng/dL. A patient who was terminated from the clinical trial before Study Day 85 because of an adverse event also was classified as a treatment failure for this endpoint.
2. **Avoidance of a testosterone surge**
   A patient was considered to have experienced a testosterone surge if 2 of his serum testosterone measurements between Study Days 2 and 8 (inclusive) exceeded his study baseline measurement by 10% or greater. The 2 visits did not need to be consecutive. If a patient did not have enough data between Study Days 2 and 8 to determine if a testosterone surge had occurred, he was counted as not having experiencing a testosterone surge (i.e., a success).
3. **Rapidity of medical castration (attainment of serum testosterone ≤ 50 ng/dL)**
   Rapidity of medical castration was based on the patient's serum testosterone level on Study Day 8. A patient who (a) had a serum testosterone > 50 ng/dL on Study day 8 or (b) was missing a testosterone value on Study Day 8 because of an early withdrawal or another reason was considered a failure.

A successful outcome in each clinical trial required that (1) abarelix was not inferior to treatment with the active control for Endpoint No. 1 and (2) abarelix was superior to treatment with the active control for Endpoint Nos. 2 and 3. Achievement of Endpoint No. 1 was mandatory for marketing approval. Achievement of Endpoint Nos. 2 and 3 was required to support a labeling claim.

6.11.1.1 Rationale for Surrogate Endpoint of Reduction and Maintenance of Serum Testosterone of ≤ 50 ng/dL (Castrate Levels) and Avoidance of Testosterone Surge

Surgical castration remains the standard against which all therapies for the palliative management of advanced prostate cancer have been and continue to be compared. To date, no other therapy used either alone or in conjunction with surgical castration has been shown to increase survival time beyond that achieved by surgical castration. It is accepted that surgical castration exerts its therapeutic effect by markedly reducing serum androgen levels. A serum testosterone of ≤ 50 ng/dL is also generally accepted as being within the range of concentrations observed following castration. The goal of hormonal therapy in prostate cancer is to suppress serum testosterone concentrations to castration levels. Based on these considerations, the FDA has accepted for this application, and prior applications for GnRH agonists, attainment of castration levels of testosterone (i.e., ≤ 50 ng/dL) by Day 29 and maintenance of these levels through at least 3 dosing cycles as a surrogate efficacy endpoint in clinical trials of the treatment of advanced prostate cancer. Absence of a testosterone

surge (and presumably avoidance of symptoms of flare) and rapidity of testosterone suppression are reasonable co-primary endpoints in the context of this NDA.

6.11.2 Secondary (Supportive) Efficacy Endpoints

6.11.2.1 Alternative Definitions of Maintenance of Testosterone Suppression

In addition to **Protocol Definition No. 2** described above in Section 6.11.1, the sponsor described 5 additional definitions for the successful maintenance of castrate levels of serum testosterone during treatment with Study Drug. A successful outcome by these alternative definitions was more difficult to achieve in that they (a) included a longer treatment period (Study Day 29 through Study day 169), (b) defined failure as 1 serum testosterone concentration > 50 ng/dL (instead of 2 consecutive values > 50 ng/dL, or (c) both a and b. These additional definitions are listed below:

Definition 1. A patient was classified as a treatment failure if one or more serum testosterone concentrations between Study Day 29 through Study day 85 was > 50 ng/dL.

Definition 3. A patient was classified as a treatment failure if one or more serum testosterone concentrations on any of Study Days 29, 57, or 85 (days on which patients received their next dose of Study Drug) was > 50 ng/dL.

Definition 4. This definition was identical to Definition 1 but considered the treatment period from Study Day 29 through Study Day 169. For this analysis, Study Days 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169 were considered.

Definition 5. This definition was identical to Definition 2 but considered the treatment period from Study Day 29 through Study Day 169.

Definition 6. This definition was identical to Definition 3 but considered the treatment period from Study Day 29 through Study Day 169. For this analysis, Study Days 29, 57, 85, 113, 141, and 169 were considered.

6.11.3 Overview of Statistical Analyses for Primary and Secondary Efficacy Endpoints

Statistical issues are discussed in detail in the separate Statistical Review for the original submission of December 2000. A brief overview of the most important statistical analyses is presented in this Section.

6.11.3.1 Primary Efficacy Endpoints

The intent to treat (ITT) population was used in the primary analysis of each of the 3 primary endpoints.

- **Avoidance of a testosterone surge**

The number and percentage of patients who experienced a testosterone surge were summarized in a table. The percentage of patients who experienced a testosterone surge was compared across the treatment groups using Fisher's exact test.

- **Rapidity of medical castration (attainment of serum testosterone ≤ 50 ng/dL)**

The number of patients achieving castrate levels of testosterone on planned visit Day 8 was tabulated for each treatment group. The percentage of patients who had castrate levels of testosterone on planned visit Day 8 was compared across the treatment groups using Fisher's exact test.

- **Achievement and maintenance of serum testosterone concentrations of ≤ 50 ng/dL from Study Day 29 through Study Day 85**

Primary analysis. Point estimates of the incidence rates based on Definition No. 2 (achievement and maintenance of serum testosterone concentrations of ≤ 50 ng/dL from Study Day 29 through Study Day 85 with no 2 consecutive values > 50 ng/dL) were determined by 2 methods: straightforward proportions and Kaplan-Meier estimates. Missing data were completed using last observation carried

forward (LOCF) and straightforward proportions. A noninferiority limit of -10% was applied to the lower bound of the 95% confidence interval (CI) of the difference between the rates in each of the treatment groups. A CI with a lower bound no less than -10% (based on a 2-sided test with $\alpha = 0.05$) was the criterion for success (i.e., noninferiority).

Secondary analyses for the primary efficacy endpoint (subset analyses). The primary analysis was repeated for the per-protocol population. Two additional definitions for maintenance of suppression (Definitions 1 and 3) also were used in analyses based on the per-protocol population. Point estimates for the primary endpoint (based on Definition No. 2) also were calculated for patients in each of the 4 protocol defined strata (baseline testosterone level of 220 ng/dL to 500 ng/dL or > 500 ng/dL and body weight of < 200 pounds or ≥ 200 pounds).

6.11.3.2 Supportive Efficacy Endpoints

Selected analyses related to supportive efficacy endpoints that are discussed in this review are described below. Other analyses performed by the Sponsor are not included in this section.

- **Maintenance of testosterone suppression beyond Day 85**

The period for testosterone suppression described in the primary endpoint for achievement and maintenance of castration levels of testosterone was from Study Day 29 through 85. Additional analyses were performed, based on the period from Study Day 29 through Study Day 169. The analyses were conducted using both LOCF and Kaplan-Meier procedures. Two-sided 95% confidence intervals for the differences between rates were calculated.

- **Androgen, gonadotropin, and PSA levels**

Descriptive statistics (mean, median, standard deviation, minimum, maximum, and number of patients) for androgen, gonadotropin, and PSA data were calculated for all planned visit days for the per-protocol population. PSA levels were compared between the treatment groups using the Wilcoxon rank sum test at study baseline and at planned visit days 15 and 29. In addition, descriptive statistics for the percentage changes in PSA from study baseline for all planned visit days were presented.

6.12 Results (Controlled Clinical Trials)

6.12.1 Demographics and Baseline Disease Characteristics

Twenty-six US sites (Study 149-98-02), 22 US sites (Study 149-98-03), and 49 US/7 Canadian sites (Study 149-99-03) each enrolled 1 or more patients. Baseline demographic characteristics for each of these 3 studies are summarized in Table 22. The majority of patients in each of the trials were Caucasian and ranged from 80% in Study 149-98-03 (abarelix group) to 88% in Study 149-98-02 (abarelix group). The second largest ethnic group was comprised of African Americans, ranging from 6% in Study 149-98-02 (abarelix group) to 13% in Study 149-98-03 (abarelix group). Median treatment group ages ranged from 72 to 74 years while individual ages ranged from 46 to 97 years. Median treatment group weights ranged from 181 to 190 pounds while individual weights ranged from 99 to 365 pounds.

Table 22. Baseline Demographics (Studies 149-98-02, 149-98-03, and 149-99-03)

	Study 149-98-02		Study 149-98-03		Study 149-99-03	
	Lupron N = 89 n (%)	Abarelix N = 180 n (%)	Lupron + Casodex N = 83 n (%)	Abarelix N = 168 n (%)	Lupron N = 194 n (%)	Abarelix N = 388 n (%)
Race/Ethnicity n[%])						
Caucasian	73 (82)	159 (88)	69 (83)	134 (80)	159 (82)	327 (84)
African American	8 (9)	10 (6)	10 (12)	21 (13)	20 (10)	40 (10)
Hispanic	6 (7)	6 (3)	2 (2)	8 (5)	10 (5)	9 (2)
Asian	2 (2)	5 (3)	2 (2)	3 (2)	3 (2)	5 (1)
Other	0	0	0	2 (1)	2 (1)	7 (2)
Age (yr)						
Median (range)	74 (49 – 89)	73 (49 – 88)	74 (49 – 93)	73 (51 – 97)	73 (51- 87)	72 (46 - 89)
Weight (lb)						
Median (range)	184 (130 – 300)	190 (132 – 365)	176 (125 – 290)	183 (119 - 279)	184 (102 - 291)	181 (99 - 321)

Intent-to-treat population.
Source: Derived from Table 12.2.1 in the 149-98-02, 149-98-03, and 149-99-03 clinical study reports.

Pretreatment testosterone levels and baseline prostate cancer history are shown in Table 23. Median pretreatment testosterone levels ranged from 338 ng/dL (Study 149-98-02, Lupron group) to 389 ng/dL (Study 149-99-03, abarelix group). More than 50% of the patients in each of the 3 studies had early to moderately advanced disease (Disease Stages T1 to T3). The most common reasons for enrollment in each of the studies was neoadjuvant therapy or a rising PSA level. The least common reason for enrollment was for treatment of D1/D2 stage disease.

Table 23. Baseline Disease Characteristics (Studies 149-98-02, 149-98-03, and 149-99-03)

	Study 149-98-02		Study 149-98-03		Study 149-99-03	
	Lupron N = 89 n (%)	Abarelix N = 180 n (%)	Lupron + Casodex N = 83 n (%)	Abarelix N = 168 n (%)	Lupron N = 194 n (%)	Abarelix N = 388 n (%)
Testosterone (ng/dL)						
Median (range)	338 (112 – 834)	350 (162 – 818)	353 (149 - 787)	341 (119 – 738)	383 (155 - 929)	389 (152 – 859)
Stage of Disease[1]						
T1	13 (15%)	26 (14%)	13 (16%)	28 (17%)	43 (22%)	86 (22%)
T2	31 (35%)	50 (28%)	27 (33%)	59 (35%)	85 (44%)	149 (38%)
T3	12 (13%)	32 (18%)	4 (5%)	11 (7%)	15 (8%)	40 (10%)
T4	1 (1%)	0	1 (1%)	2 (1%)	3 (2%)	0
D0	3 (3%)	1 (1%)	0	0	1 (1%)	5 (1%)
D1.5	22 (25%)	53 (29%)	33 (40%)	56 (33%)	34 (18%)	67 (17%)
D1	4 (4%)	8 (4%)	1 (1%)	7 (4%)	3 (2%)	21 (5%)
D2	3 (3%)	10 (6%)	4 (5%)	5 (3%)	10 (5%)	20 (5%)
Baseline PSA (ng/mL)[1]						
0 to < 4	15 (17%)	30 (17%)	18 (22%)	46 (27%)	36 (19%)	63 (16%)
4 to 10	32 (36%)	60 (33%)	38 (46%)	51 (30%)	83 (43%)	157 (40%)
> 10 to 20	20 (22%)	37 (21%)	17 (20%)	30 (18%)	33 (17%)	80 (21%)
> 20	21 (24%)	47 (26%)	9 (11%)	39 (23%)	40 (215)	79 (20%)
Unknown	1 (1%)	6 (4%)	1 (1%)	2 (1%)	2 (1%)	9 (2%)
Reason for Treatment (Tx) [1]						
D1/D2 Stage [2]	7 (8%)	15 (8%)	4 (5%)	11 (7%)	13 (7%)	41 (11%)
Rising PSA	29 (33%)	67 (37%)	36 (43%)	60 (36%)	51 (26%)	81 (21%)
Neoadjuvant Tx	32 (36%)	67 (37%)	33 (40%)	67 (40%)	102 (53%)	204 (53%)
Intermittent Tx	21 (24%)	30 (17%)	10 (12%)	28 (17%)	28 (14%)	62 (16%)
Other	0	1 (1%)	0	2 (1%)		

Intent-to-treat population.
[1] Percentages are based on the number of patients in each treatment group.
[2] N may be smaller than the combined number of patients with D1 and D2 stage disease because in some cases an alternative primary reason for treatment had been noted on the case report form.
Source: Derived from Tables 12.2.2 and 12.2.4 in the 149-98-02, 149-98-03, and 149-99-03 clinical study reports.

Medical Officer's Comments

- *The treatment groups, both within each study and across the 3 studies, were generally well balanced in terms of both demographics and baseline disease characteristics. The percentages of African American patients in Study 149-98-03 were slightly higher than in the other 2 studies but were well balanced across the 2 treatment groups in Study 149-98-03.*
- *Although medical castration is approved by the FDA only for the treatment and management of advanced prostate cancer, less than 10 % of patients in each study had D1/D2 stage disease. The findings from these clinical studies that pertain to testosterone suppression during treatment with abarelix, however, should be applicable to men with all stages of disease, including those enrolled in Study 149-98-04 (the indicated population with advanced symptomatic disease).*

- *One or more patients in each treatment group in each of the 3 studies appeared to have had a baseline serum testosterone level below 220 ng/dL, the minimum testosterone level for study entry. Since the overall number of such patients is likely to be small, this protocol violation should not affect the validity of the study findings.*

6.12.2 Primary Efficacy Endpoints

The 3 primary efficacy endpoints are dependent upon changes in serum concentrations of testosterone following administration of Study Drugs. Table 24 lists the median serum testosterone concentrations from baseline through Study Day 169 in Studies 149-98-02 and 149-98-03. Figure 2 shows the median serum testosterone levels during the first 4 weeks of treatment in the Lupron group, the Lupron plus Casodex group, and the abarelix groups combined across both Studies 149-98-02 and 149-99-03. Serum testosterone levels in Study 149-99-03 were similar to those in Study 149-98-02 although measurements were not obtained on Study Days 2 and 4.

Within 24 hours of administration of abarelix, median serum testosterone levels had declined from baseline values of 350 and 340 ng/dL to 59 and 58 ng/dL and were less than 50 ng/dL by Day 4. In contrast, median testosterone levels in the Lupron and Lupron plus Casodex groups increased by about 70% and 45%, respectively, following initial dosing. Maximal testosterone levels were observed on Day 4 in both active control treatment groups. Median testosterone levels in the active control groups then gradually declined, reaching castrate values by Day 29. In both groups, once median testosterone values had reached castrate levels, they remained ≤ 50 ng/dL through Day 169.

Medical Officer's Comments

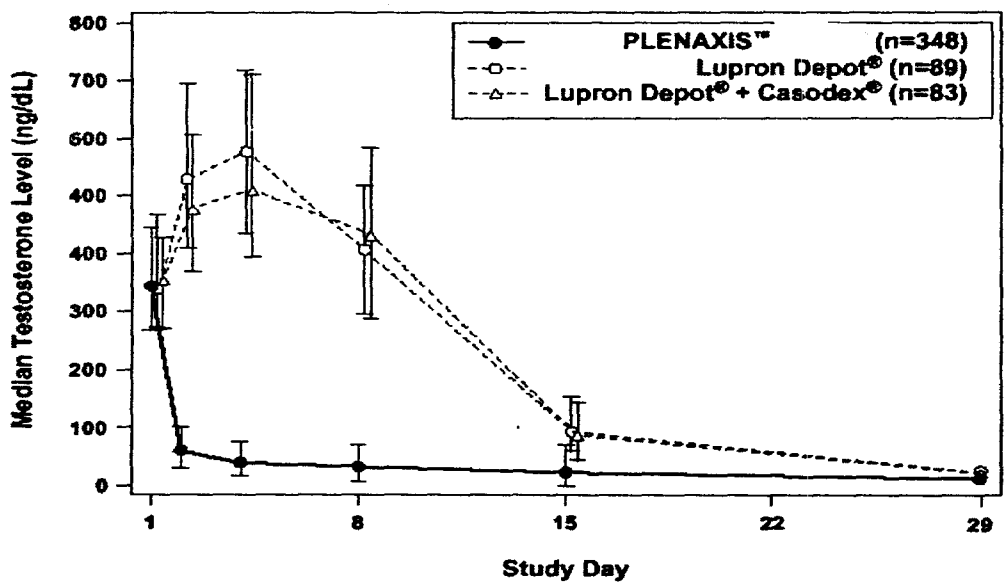
- *Representing serum testosterone levels only in terms of median values may present a misleading picture as to the efficacy of abarelix since the goal of medical therapy in men with prostate cancer is to reduce serum testosterone levels to ≤ 50 ng/dL in all patients, not merely more than half of the patients. Median values, however, accurately convey the major pharmacodynamic differences, in terms of changes in serum testosterone levels that occur in the first 2 weeks after initial dosing with a true GnRH antagonist (abarelix) compared to a GnRH agonist (Lupron).*

Table 24. Median Serum Testosterone Levels (Studies 149-98-02 and 149-98-03)

	Study 149-98-02				Study 149-98-03			
	Lupron N = 89		Abarelix N = 180		Lupron + Casodex N = 83		Abarelix N = 168	
Study Day	n	Median[1] (ng/dL)	N	Median (ng/dL)	N	Median (ng/dL)	n	Median (ng/dL)
Baseline	89	338	180	350	83	353	167	340
Day 2	87	529	178	59	81	480	166	58
Day 4	84	578	173	37	79	512	160	40
Day 8	82	406	175	29	79	435	164	35
Day 15	88	94	179	20	81	90	168	23
Day 29	88	15	179	11	81	16	168	10
Day 57	85	10	174	12	80	10	167	9
Day 85	86	9	176	15	80	10	164	14
Day 113	84	8	173	11	76	8	161	9
Day 141	83	8	169	13	70	11	157	11
Day 169	81	9	166	15	69	10	155	11

Intent-to-treat population
[1] The lower limit of detection of the assay was 8 ng/dL; values below the detection limit are reported as 8 ng/dL.
Source: Derived from Table 12.5.7 in the 149-98-02 and 149-98-03 clinical study reports.

Figure 2. Serum Testosterone Concentrations During the First 4 Weeks of Treatment with Abarelix, Lupron, or Lupron Plus Casodex (Studies 149-98-02 and 149-98-03)



Bars represent the interquartile range.

Source: Proposed label for Plenaxis (Vol. 1.1, December 2000 submission).

6.12.2.1 Avoidance of Testosterone Surge

In Study 149-98-02, 82% of the patients in the Lupron group and none (0%) of the patients in the abarelix group experienced a testosterone surge ($p < 0.001$) (Table 25). Similarly, in Study 149-98-03, 86% of the patients in the Lupron plus Casodex group and none (0%) of the patients in the abarelix group experienced a testosterone surge ($p < 0.001$). Thus, across the 2 studies, all of the abarelix patients avoided a testosterone surge, while only 18% and 14% of the patients in the active control groups avoided a surge.

Medical Officer's Comment

- *Results from both of these controlled efficacy studies support the Sponsor's claim that patients treated with abarelix did not experience the testosterone surge that occurs in a high percentage of patients at the onset of treatment with a GnRH agonist.*

Table 25. Number (%) of Patients Who Avoided/Experienced a Testosterone Surge (Studies 149-98-02 and 149-98-03)

Study Endpoint	Treatment Group: Lupron		Lupron plus Casodex		Abarelix Depot		
	N [A]	n (%) [B]	N	n (%)	N	n (%)	P-value [1]
149-98-02							
Avoided Surge[2]	89	16 (18%)	—	—	180	180 (100%)	
Experienced Surge [2]	89	73 (82%)	—	—	180	0 (0%)	< 0.001
149-98-03							
Avoided Surge[2]	—	—	83	12 (14%)	168	168 (100%)	
Experienced Surge [2]	—	—	83	71 (86%)	168	0 (0%)	< 0.001

Intent-to-treat population

[A] Number of patients in treatment group.

[B] Number (%) of patients experiencing a testosterone surge.

[1] Fisher's exact test.

[2] Testosterone surge is defined as testosterone value that exceeded baseline by ≥ 10% on any 2 of days 2, 4, or 8. Avoidance of surge was defined as the absence of testosterone surge.

Source: Derived from Table 12.4.2.1 in the 149-98-02 and 149-98-03 clinical study reports.

6.12.2.2 Rapidity of Medical Castration

The endpoint for rapidity of medical castration was defined as a serum testosterone value ≤ 50 ng/dL on Study Day 8. No patients in the active control groups were medically castrate on Day 8 compared with 72% and 68% of the patients in the abarelix group in Studies 149-98-02 and 149-98-03, respectively ($p < 0.001$; Table 26). Twenty-four percent (24%) of the patients in each of the abarelix groups were medically castrate by Study Day 2. No patients in the active control groups in either study were medically castrated on Study Day 2.

Medical Officer's Comment

- *Results from both of the pivotal efficacy studies support the Sponsor's claim that serum testosterone levels are suppressed to ≤ 50 ng/dL within 8 days of the onset of treatment in a statistically significant greater proportion of patients treated with abarelix compared to patients treated with Lupron or Lupron plus Casodex.*

Table 26. Percentage of Patients with Testosterone ≤ 50 ng/dL (Medically Castrate) on Study Days 2, 8, 15, and 29 (Studies 149-98-02 and 149-98-03)

	Treatment Group						
	Lupron		Lupron plus Casodex)		Abarelix		
	N	Castrate n (%)	N	Castrate n (%)	N	Castrate n (%)	P-value[1]
			Study 149-98-02				
Day 2	87	0	—	—	176	43 (24)	< 0.001
Day 8	89	0	—	—	180	129 (72)	< 0.001
Day 15	88	9 (10)	—	—	179	134 (75)	< 0.001
Day 29	88	86 (98)	—	—	179	167 (93)	ND
			Study 149-98-03				
Day 2	—	—	80	0	163	39 (24)	< 0.001
Day 8	—	—	83	0	168	114 (68)	< 0.001
Day 15	—	—	81	17 (21)	168	119 (71)	< 0.001
Day 29	—	—	81	79 (98)	168	160 (95)	ND

Intent-to-treat population.
[1] Fisher's exact test.
Source: Table 12.4.3.1 (days 2-8) and Table 12.4.4 (days 15 and 29) in the 149-98-02 and 149-98-03 clinical study reports.

6.12.2.3 Achievement and Maintenance of Medical Castration From Day 29 Through Day 85

The primary efficacy endpoint for the achievement and maintenance of medical castration in the pivotal studies required a serum testosterone concentration of ≤ 50 ng/dL on Day 29 with no 2 consecutive testosterone measurements > 50 ng/dL 2 weeks apart between Days 29 and 85, inclusive (Protocol Definition No. 2). The analysis for this endpoint was based on the ITT population using straightforward proportions with the LOCF. In Study 149-98-02, medical castration was achieved and maintained by 95.5% of the active control group and 91.7% of the abarelix group. In Study 149-98-03, medical castration was achieved and maintained by 95.2% of the patients in the Lupron plus Casodex group and 92.9% of those in the abarelix group (Table 27). The point differences between successful achievement of the primary efficacy endpoint in each of Studies 149-98-02 and 149-98-03 were –3.8% and –2.3 %, respectively, both in favor of the active control treatment. The lower bounds of the two-sided 95% confidence intervals for the differences in achievement and maintenance of medical castration were -9.7% in Study 149-98-02 and -8.4% in Study 149-98-03. The upper bounds of the confidence intervals for both differences crossed 0. Thus, treatment with abarelix met the agreed upon criteria for noninferiority compared to treatment with Lupron or Lupron plus Casodex in the pivotal efficacy studies.

In Study 149-99-03 (a supportive but not a pivotal efficacy trial per the Sponsor), medical castration was achieved and maintained by 97.4% of the patients in the Lupron group and 89.7% of the patients in the abarelix group, a difference of –7.7%. The lower bound of the two-sided 95% confidence interval for this difference was -11.5%, slightly outside of the predefined lower bound of -10.0% required for noninferiority.

Table 27. Percentage of Patients Who Achieved and Maintained Medical Castration From Day 29 Through Day 85 (No Two Consecutive Testosterone Values > 50 ng/dL)

	Treatment Group							
	Lupron		Lupron plus Casodex		Abarelix		Percent Difference	
	N	Percent	N	Percent	N	Percent	Value	95% CI [1]
149-98-02	89	95.5	—	—	180	91.7	-3.8	(-9.7, 2.1)
149-98-03	—	—	83	95.2	168	92.9	-2.3	(-8.4, 3.7)
149-99-03	194	97.4	—	—	388	89.7	-7.7	(-11.5, -4.0)

Intent-to-treat population; last observation carried forward (LOCF)
[1] 95% two-sided confidence intervals for the between-group difference in proportions
Source: Table 10-1, pg 95, Vol. 1.77, Table 9-1, pg 234, Vol. 1.44, and Table 9-1, pg 75, Vol. 1.60 of the December 2000 submission.

Medical Officer's Comments

- *Based on the agreed upon criteria for achievement and maintenance of suppression of serum testosterone levels, abarelix was not inferior to either of the active treatments in the 2 primary controlled trials. In Study 149-99-03 (a primary supportive study), the lower bound of the 95% CI was –11.5% and the upper bound was -4.0% (i.e., it did not cross 0). Thus, in this clinical trial, abarelix was inferior to Lupron. This observation, per se, is not particularly worrisome since the lower bound is only slightly beyond the agreed upon lower limit of –10%, and the success rate for Lupron in this study (97.4%) was extremely high.*

6.12.3 Secondary (Supportive) Efficacy Analyses and Endpoints

6.12.3.1 Achievement and Maintenance of Medication Castration From Day 29 Through Day 169 (Assessed by Protocol Definition 5)

Testosterone data obtained in Studies 149-98-02 and 149-98-03 also were analyzed by the Sponsor for achievement and maintenance of medical castration from Study Day 29 through Study Day 169 in accordance with Protocol Definition No. 5 (Table 28). In Study 149-98-02, medical castration was achieved by Day 29 and maintained through Day 169 by 92.1% of the ITT patients in the Lupron group and 87.2% of patients in the abarelix group. In Study 149-98-03, medical castration was achieved by Day 29 and maintained through Day 169 by 84.3% of the patients in the Lupron plus Casodex group and 90.5% of the patients in the abarelix group. The point estimates of the differences between successful achievement and maintenance of medical castration were 4.9% better in the Lupron arm in Study 149-98-02 and 6.1% better in the abarelix arm in Study 149-98-03. The lower bounds of the two-sided 95% confidence intervals for the difference in achievement and maintenance of medical castration were –12.3% in Study 149-98-02 and –2.9% in Study 149-98-03.

Medical Officer's Comments

- *In this secondary analysis, one of the 2 studies (Study 149-98-03) supports the Sponsor's claim that treatment with abarelix is not inferior to treatment with a GnRH analog in terms of achieving medical castration within 29 days of the onset of treatment and maintaining medical castration through Day 169. The lower bound of –12.3% for the 95% CI for the difference between treatment groups in Study 149-98-02, however, is slightly below –10.0%.*
- *All patients who were withdrawn from the clinical trial because of an adverse event were classified as a treatment failure by the Sponsor. The higher withdrawal rate for adverse events in the Lupron plus Casodex arm of Study 149-98-03, and not better maintenance of testosterone*

suppression in the abarelix arm, is the primary basis for the difference of 6.1% in favor of the abarelix group.

- *It also should be noted that a treatment failure (in accordance with Protocol Definition No. 5, a definition analogous to Protocol Definition No. 2 [see Section 6.11.2.1]) requires 2 successive serum testosterone values > 50 ng/dL. If other, more rigorous definitions of success are used to analyze the serum testosterone data through Day 169 (i.e., definitions 4 or 6), the percentage of patients who meet the definition of success is numerically greater in both the Lupron group and the Lupron plus Casodex group compared to the respective abarelix treatment groups (see Section 6.12.3.2).*

Table 28. Percentage of Patients Who Achieved and Maintained Medical Castration From Day 29 Through Day 169 (No Two Consecutive Testosterone Values > 50 ng/dL)

	Treatment Group							
	Lupron		Lupron plus Casodex		Abarelix		Percent Difference	
Study	N	Percent	N	Percent	N	Percent	Value	95% CI[1]
149-98-02	89	92.1	—	—	180	87.2	-4.9	(-12.3, 2.5)
149-98-03	—	—	83	84.3	168	90.5	6.1	(-2.9, 15.1)

Intent-to-treat population; last observation carried forward.
[1] 95% two-sided confidence intervals for the between-group difference in proportions.
Source: Table 9-4 in the 149-98-02 and 149-98-03 clinical study reports.

6.12.3.2 Achievement and Maintenance of Castration From Day 29 Through Days 85, 169, and 365 (Assessed by Other More Rigorous Definitions of Success)

The Sponsor provided supplemental calculations for "achievement and maintenance of medical castration" by secondary definitions of success that were more rigorous than primary Definitions 2 and 5 (see Sections 6.12.2.3 and 6.12.3.1, respectively. A successful outcome by these alternative definitions required that (a) all serum testosterone values were ≤ 50 ng/dL (Definitions 1 and 4) or (b) that all testosterone values at the end of each 28-day treatment period were ≤ 50 ng/dL (Definitions 3 and 6). (See Section 6.11.2 for a complete description of these alternative definitions.) For these secondary analyses, the Sponsor elected to use the per protocol population and Kaplan-Meier estimates of the cumulative probability of success rather than the ITT population and simple proportions with the LOCF.

Table 29 summarizes the cumulative probability of achieving and maintaining medical castration using the criteria of no serum testosterone value > 50 ng/dL (Definitions 1 and 4). By these definitions, the cumulative probability of success was numerically lower in the abarelix groups in each of the 3 studies. The largest difference in the cumulative probability of achieving a successful outcome was –15.2% (95% CI: -21.38, -9.03) in Study 149-99-03 for the interval from Day 29 through Day 169.

Table 29. Cumulative Probability of Achieving and Maintaining Medical Castration (No Serum Testosterone Value > 50 ng/dL – Definitions 1 and 4)

	Treatment Group				
	Lupron	Lupron + Casodex	Abarelix	Difference	
Study	Cumulative Probability (%)			Value	95% CI
Day 29 through Day 85					
149-98-02	89.4		83.1	-6.3	(-14.91, 2.32)
149-98-03		90.0	88.9	-1.2	(-9.35, 6.96)
149-99-03	95.7		83.0	-12.7	(-17.59, -7.90)
Day 29 through Day 169					
149-98-02	85.6		74.7	-11.0	(-21.04, -0.90)
149-98-03		83.0	82.8	-0.3	(-10.59, 10.07)
149-99-03	90.9		75.7	-15.2	(-21.38, -9.03)

PP Population; Kaplan Meier analyses.

Source: Table 12.4.1.3, pg 296, Vol. 1.44, Table 12.4.1.3, pg 143, Vol. 1.60, and Table 12.4.1.2, pg 119, Vol. 1.77, Submission of December 2000.

Table 30 summarizes the cumulative probability of achieving and maintaining medical castration using the criteria of no serum testosterone value > 50 ng/dL at the end of each 28-day treatment period (Definitions 3 and 6). By these definitions, the cumulative probability of success also was numerically lower in the abarelix groups in each of the 3 studies. The largest difference in the cumulative probability of achieving a successful outcome was –15.6% (95% CI: -21.69, -9.49) in Study 149-99-03 for the interval from Day 29 through Day 169.

Table 30. Cumulative Probability of Achieving and Maintaining Medical Castration (No Testosterone Value > 50 ng/dL at End of Each Monthly Treatment Course)

	Treatment Group				
	Lupron	Lupron + Casodex	Abarelix	Difference	
Study	Cumulative Probability (%)			Value	95% CI
Day 29 through Day 85					
149-98-02	95.3		84.3	-11.0	(-18.11, -3.99)
149-98-03		95.1	90.0	-5.1	(-11.67, 1.49)
149-99-03	95.7		84.0	-11.6	(-16.42, -6.87)
Day 29 through Day 169					
149-98-02	88.8		76.4	-12.4	(-21.86, -2.88)
149-98-03		85.3	83.9	-1.4	(-11.67, 8.48)
149-99-03	91.5		75.9	-15.6	(-21.69, -9.49)

PP Population; Kaplan Meier Analyses.

Source: Table 12.4.1.3, pg 296, Vol. 1.44, Table 12.4.1.3, pg 143, Vol. 1.60, and Table 12.4.1.2, pg 119, Vol. 1.77, Submission of December 2000.

Medical Officer's Comments

- *A successful outcome is more difficult to achieve by the criteria of these alternative definitions in that a patient is considered a treatment failure if only a single (and not 2 consecutive) serum testosterone value is > 50 ng/dL. Assessed by these more rigorous definitions, abarelix was statistically inferior to Lupron in Studies 149-98-02 and 149-99-03.*

At the request of the Medical Reviewer, the sponsor provided additional analyses for the achievement and maintenance of medical castration from Day 29 through Day 365. In these new analyses, (1) treatment failure was based on the serum testosterone concentration at the end of each 28-day treatment cycle, (2) withdrawals for adverse events (regardless of relationship to treatment with Study Drug) were not classified as a failure unless the patient's serum testosterone concentration was > 50 ng/dL), and (3) LOCF was used for missing data. The results of these analyses are listed in Table 31

Table 31 Percentages of Patients Who Attained and Maintained Medical Castration (No Serum T > 50 ng/dL) Prior to Dosing on Day 29 and Every 28 Days Thereafter

	149-98-02		149-98-03	
Day	abarelix (n=180)	Lupron (n=89)	abarelix (n=168)	Lupron + Casodex (n=83)
85	84%	98%	92%	95%
169	76%	96%	87%	93%
365	68%	96%	78%	93%

Source: Submission of 9 April 2001, pg 39-49.

Medical Officer's Comments

- *By these alternative analyses that based the determination of success or failure (1) only on observed serum testosterone values, (2) adjusted for missing data by LOCF and (3) used all available testosterone values obtained every 28 days just prior to each dosing, abarelix was clearly less effective than the active comparators in terms of reliable, long term suppression of serum testosterone concentrations to ≤ 50 ng/dL.*

6.12.3.3 Mean Serum Testosterone and Percentage of Patients with Serum Testosterone ≤ 50 ng/dL

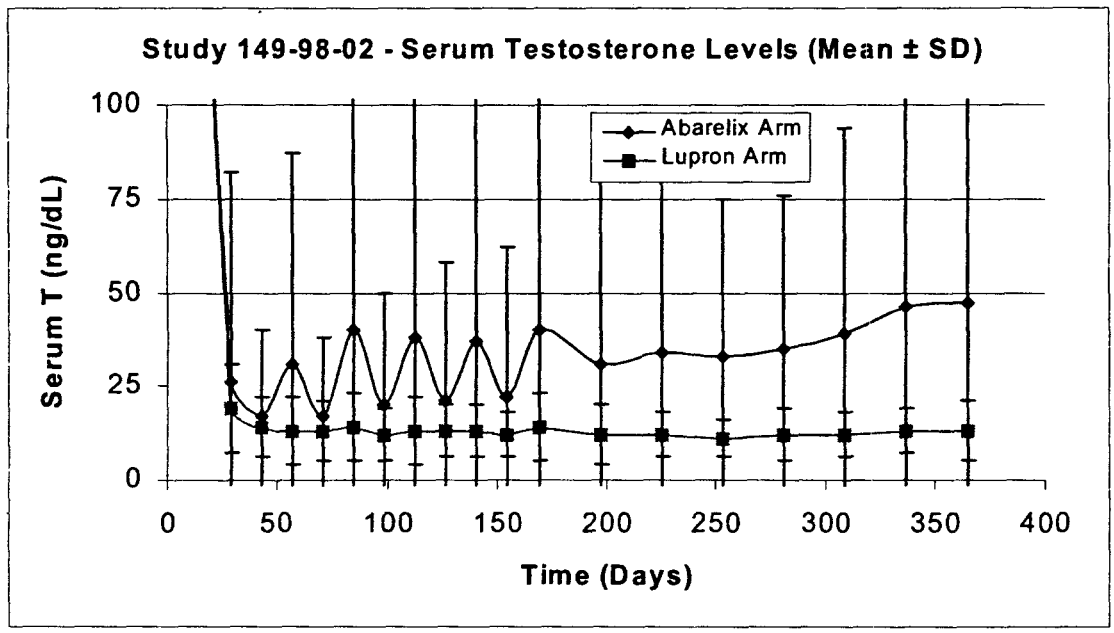
The sponsor did not present in the main body of the Study Reports information on either the mean serum testosterone levels during treatment or the percentages of patients who were medically castrate (serum testosterone ≤ 50 ng/dL) at each protocol defined assessment time after Study Day 29. Such information, however, was available in Data Listings provided in the respective Study Reports.

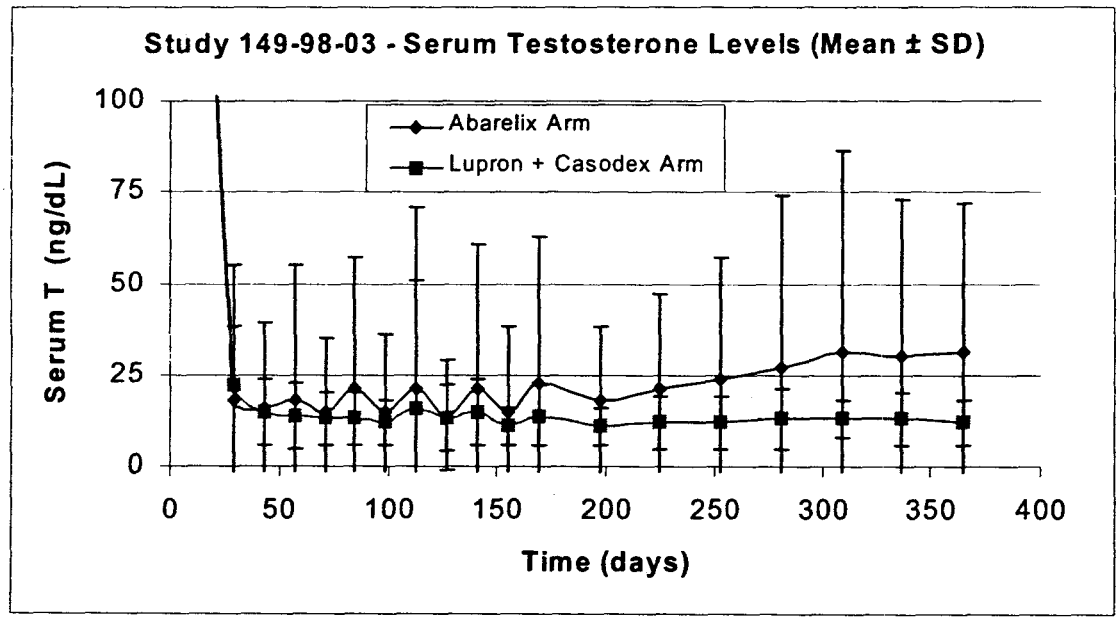
Mean (±SD) serum testosterone concentrations at each protocol-defined assessment time from Day 29 through Day 365 (end of study participation) are graphically represented for Studies 149-98-02 and 149-98-03 in Figure 3. Serum testosterone measurements were obtained at least once every 14 days through Study Day 169 and once every 28 days (immediately prior to dosing) thereafter. In both Studies 149-98-02 and 149-98-03, mean serum testosterone concentrations were generally numerically higher in the abarelix groups compared to the respective active control group. The difference in mean serum testosterone values was most apparent in samples obtained just prior to dosing, particularly after Study Day 169. The standard error associated with each assessment time was greater in the abarelix treatment groups, a reflection of the variability in serum testosterone values in the abarelix groups.

The percentages of patients with a serum testosterone ≤ 50 ng/dL (i.e., medically castrate) at each assessment time from Day 29 through Day 365 (end of study participation) are graphically represented for Studies 149-98-02 and 149-98-03 in Figure 4. Assessments were obtained at least once every 14 days through Study Day 169 and once every 28 days (immediately prior to dosing)

thereafter. In both Studies 149-98-02 and 149-98-03, nearly 100% of patients in the active control groups had serum testosterone concentrations of ≤ 50 ng/dL at each assessment. The percentage of patients with serum testosterone values ≤ 50 ng/dL in the abarelix groups was numerically lower than that in the active control groups at most assessments. Eighty percent (80%) or less of the patients in Study 149-98-02 had serum testosterone values of ≤ 50 ng/dL (i.e., were medically castrate) at each monthly assessment from Study Day 253 onward.

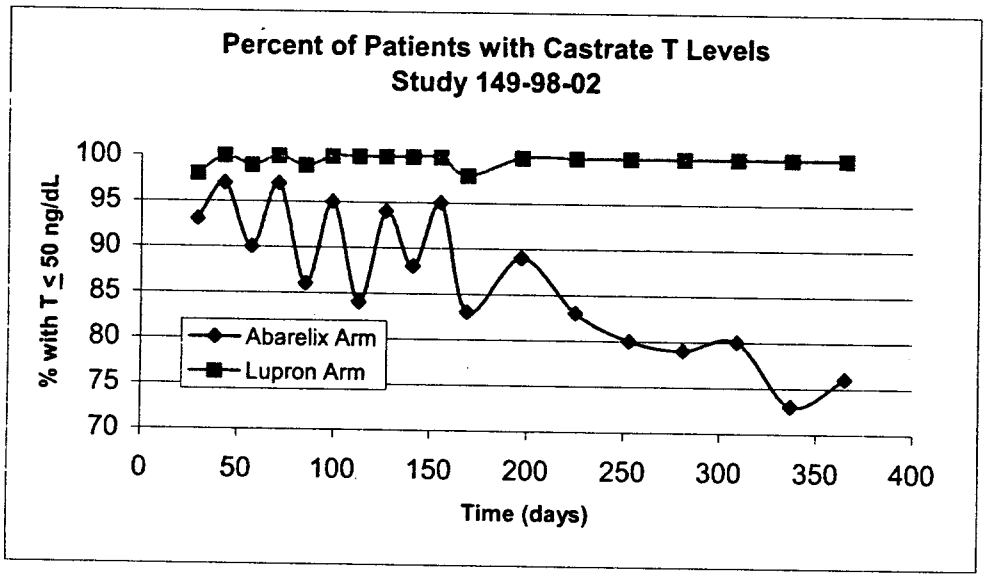
Figure 3. Mean (±SD) Serum Testosterone Concentrations (Studies 149-98-02 and 149-98-03)

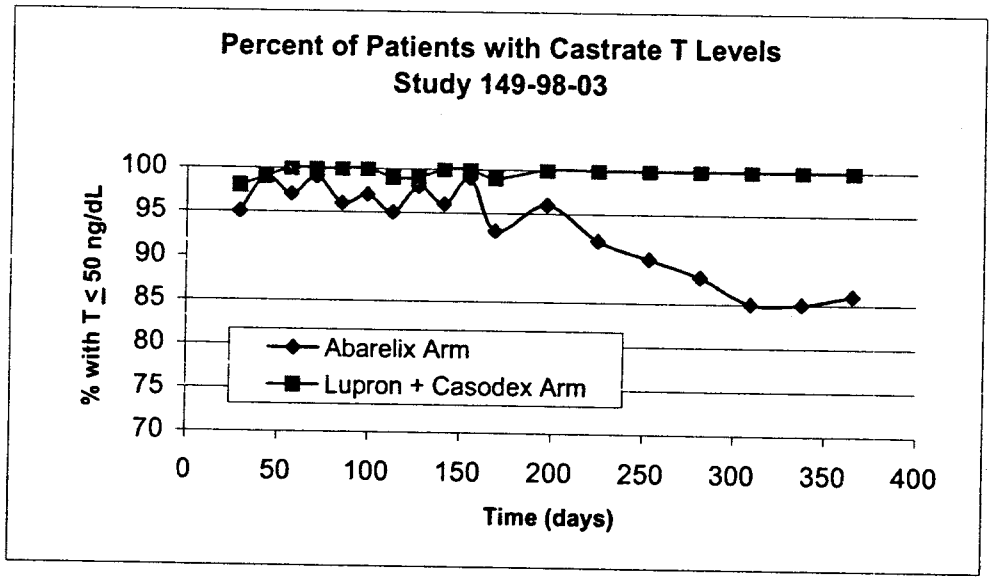




Source: Table 12.5.7, pg. 87, Vol. 1.52 and Table 12.5.7, pg. 92, Vol. 1.67, December 2000 submission.

Figure 4. Percent Of Patients with Serum Testosterone ≤ 50 ng/dL (Studies 149-98-02 and 149-98-03)





Source: Table 12.4.4, pg. 84, Vol. 1.52 and Table 12.4.4, pg. 89, Vol. 1.67, December 2000 submission.

Medical Officer's Comments

- *The descriptive analyses presented in Figure 3 and Figure 4 indicate that abarelix suppresses serum testosterone levels to a lesser extent and less reliably than Lupron or Lupron plus Casodex. This difference is most apparent in assessments made just prior to each dosing with Study Drug (i.e., 28 days after the prior dosing), particularly after Study Day 169.*
- *The difference between abarelix and Lupron in terms of suppression of testosterone might be reduced or eliminated by administering a monthly dose of abarelix greater than 100 mg, administering abarelix more frequently (e.g. every 3 weeks), or modifying the formulation so that a greater percentage of the administered dose is released during the latter part of each 28-day dosing cycle.*
- *The analyses presented in Figure 4 are probably of most relevance to the clinical management of patients with prostate cancer since they provide information about the adequacy of testosterone suppression for all patients while they are receiving treatment with abarelix. These data indicate that regular monitoring of serum testosterone levels will necessary for patients receiving abarelix under the dosing regimen employed in Studies 149-98-02 and 149-98-03.*
- *It is not known if this difference in degree and reliability of suppresses of serum testosterone is clinically important. It is possible that the long-term clinical outcome may be comparable in men with a lesser degree of testosterone suppression (i.e., testosterone values ≤ 75 ng/dL instead of ≤ 50 ng/dL) as observed in the abarelix groups. However, in the absence of such data, one needs to assume that failure to reliably suppress serum testosterone values to those observed in men following surgical castration may have an adverse effect on long term clinical outcomes.*

6.12.3.4 Changes in Serum Concentrations of Pituitary Gonadotropins

Median serum concentrations of LH and FSH in Studies 149-98-02 and 149-98-03 through Study Day 169 are presented in Table 32 and Table 33, respectively. Median serum concentrations of LH and FSH increased 2 to 5 fold after administration of Lupron with maximal values observed on Day 2. Thereafter, median values for both LH and FSH declined, with maximal suppression observed by Day 15 for FSH and Day 29 for LH. In contrast, there was no increase in median serum concentrations of LH or FSH following administration of abarelix. In the abarelix groups, median serum LH concentrations were suppressed to 1 IU/L (the limit of assay sensitivity) by Day 2. Median serum concentrations of FSH declined more slowly, reaching lowest values by Study Day 29.

Medical Officer's Comments

- *Although median LH values were reduced to 1 IU/L by Study Day 2 in the abarelix groups, the decline in serum testosterone values was more gradual. Serum testosterone levels were reduced to ≤ 50 ng/dL in only approximately 24% and 70 % of patients by Study Days 2 and 8, respectively (see Table 26).*
- *Abarelix suppresses serum FSH to a greater degree (median nadir values of 1-2 IU/L) than does Lupron (median nadir values of 5 IU/L). The significance of this difference in terms of potential clinical benefit to patients is not known.*

Table 32 Median Serum Luteinizing Hormone (LH) Levels (Studies 149-98-02 and 149-98-03)

	Study 149-98-02				Study 149-98-03			
	Lupron N = 89		Abarelix N = 180		Lupron + Casodex N = 83		Abarelix N = 168	
	n	Median (IU/L)	N	Median[1] (IU/L)	n	Median (IU/L)	n	Median (IU/L)
Baseline	88	7	180	6	83	6	168	6
Day 2	88	30	179	1	80	33	166	1
Day 4	85	14	173	1	80	13	162	1
Day 8	82	7	177	1	79	6	164	1
Day 15	88	2	179	1	79	2	167	1
Day 29	88	1	179	1	81	1	168	1
Day 57	85	1	174	1	78	1	165	1
Day 85	86	1	175	1	80	1	164	1
Day 113	84	1	171	1	76	1	161	1
Day 141	82	1	169	1	70	1	157	1
Day 169	81	1	166	1	69	1	156	1

Intent-to-treat population.
[1] The lower limit of detection of the assay was 1 IU/L; values below the detection limit are reported as 1 IU/L.
Source: Tables 12.5.9 in the 149-98-02 and 149-98-03 clinical study reports.

Table 33. Median Serum Follicle-Stimulating Hormone (FSH) Levels (Studies 149-98-02 and 149-98-03)

	Study 149-98-02				Study 149-98-03			
	Lupron N = 89		Abarelix N = 180		Lupron + Casodex N = 83		Abarelix N = 168	
	n	Median (IU/L)	n	Median[1] (IU/L)	n	Median (IU/L)	n	Median (IU/L)
Baseline	88	9	180	8	83	8	168	8
Day 2	88	21	179	5	80	17	166	5
Day 4	85	10	173	3	80	9	162	4
Day 8	82	4	177	3	79	4	164	3
Day 15	88	3	179	2	79	3	167	2
Day 29	88	3	179	1	81	3	168	1
Day 57	85	4	174	1	78	4	165	1
Day 85	86	5	175	2	80	5	164	1
Day 113	84	5	171	2	76	5	161	1
Day 141	82	5	169	2	70	5	157	1
Day 169	81	5	166	2	69	5	156	2

Intent-to-treat population.
[1] The lower limit of detection of the assay was 1 IU/L; values below the detection limit are reported as 1 IU/L.
Source: Tables 12.5.10 in the 149-98-02 and 149-98-03 clinical study reports.

6.12.3.5 Changes in Serum Concentrations of Prostate Specific Antigen (PSA)

Table 34 lists the median percentage changes from baseline for prostate specific antigen (PSA). Serum PSA levels declined significantly from baseline in all treatment groups. In Study 149-98-02, these decreases were numerically greater in the abarelix group on Days 15 and 29 compared to those

observed in the Lupron group. In Study 149-98-03, the rate of PSA decrease tended to be greater in the Lupron plus Casodex group. Median serum PSA levels decreased by more than 90% in all treatment groups by Day 85.

Table 34. Median PSA Percent Change From Baseline (Studies 149-98-02 and 149-98-03)

	Study 149-98-02				Study 149-98-03			
	Lupron N = 89		Abarelix N = 180		Lupron + Casodex N = 83		Abarelix N = 168	
	n	Median % change	n	Median % change	n	Median % change	N	Median % change
Day 15	86	-15.0	173	-50.0	76	-45.6	161	-48.5
Day 29	85	-60.9	175	-75.4	78	-81.4	163	-74.5
Day 57	84	-87.1	168	-89.9	75	-96.3	160	-89.1
Day 85	80	-92.6	166	-91.7	71	-97.8	150	-92.3
Day 113	77	-93.8	158	-92.9	65	-98.3	148	-93.4
Day 141	73	-95.8	155	-94.8	64	-98.4	146	-94.7
Day 169	70	-97.2	153	-95.9	58	-98.5	140	-95.8

Per-protocol population.
Source: Table 12.5.11.2 in the 149-98-02 and 149-98-03 clinical study reports.

Medical Officer's Comment

- *Prostate specific antigen is an indicator of the activity of prostate epithelial cells and is used as a clinical biomarker in the management of men with prostate cancer. Median serum PSA levels were significantly reduced during the first 6 months of treatment in all groups.*

6.13 Conclusions Regarding Demonstrated Efficacy in Controlled Clinical Trials

6.13.1 Achievement of Protocol-Defined Primary Efficacy Endpoints

The abarelix treatment groups in the 2 primary efficacy studies successfully achieved each of the protocol-defined primary efficacy endpoints. The primary efficacy studies demonstrated that treatment with abarelix, compared to treatment with Lupron alone (Study 149-98-02) or Lupron plus Casodex (Study 149-98-03), resulted in the following:

1. Avoidance of a testosterone surge

No patients in the abarelix treatment groups experienced a testosterone surge while 82% (Study 149-98-02) and 86% (Study 149-98-03) of patients in the active control groups experienced a testosterone surge ($p < 0.001$).

2. More rapid attainment of medical castration

No patients in the active control groups were medically castrate on Day 8 compared with 72% (Study 149-98-02) and 68% (Study 149-98-03) of the abarelix-treated patients ($p < 0.001$).

3. Comparable proportion of patients achieving and maintaining medical castration from Day 29 through Day 85 (no two consecutive testosterone values > 50 ng/dL)

Medical castration was achieved and maintained by 95.5% and 95.2% of the active control patients and 91.7% and 92.9% of the abarelix patients, respectively, in Studies 149-98-02 and 149-98-03. Based on a prior agreement with DRUDP regarding efficacy endpoints, treatment with abarelix was declared to be noninferior to that of Lupron or Lupron plus Casodex through Study Day 85 since the lower bound of the 95% CI for the differences between the treatment groups was not less than –10%.

However, the lower bound of the 95% CI for primary supportive Study 149-99-03 was slightly below the limit of -10% and the upper bound of the 95% CI was –4.0%.

Percentage of patients achieving and maintaining medical castration from Day 29 through Day 85 (no two consecutive testosterone values > 50 ng/dL)

	Treatment Group							
	Lupron		Lupron plus Casodex		Abarelix		Percent Difference	
	N[1]	Percent[2]	N	Percent	N	Percent	Value	95% CI
149-98-02	89	95.5	—	—	180	91.7	-3.8	(-9.7, 2.1)
149-98-03	—	—	83	95.2	168	92.9	-2.3	(-8.4, 3.7)
149-99-03	194	97.4	—	—	388	89.6	-7.7	(-11.5, -4.0)

[1] Number patients in the ITT population.
[2] Percentage of patients who achieved and maintained testosterone suppression.
Source: Table 10-1, pg 95, Vol. 1.77, Table 9-1, pg 234, Vol. 1.44, and Table 9-1, pg 75, Vol. 1.60, December 2000 submission.

6.13.2 Statistician's Assessment of Efficacy (Protocol-Defined Primary Endpoints)

The validity of the sponsor's analyses in support of the primary efficacy endpoints in the controlled clinical trials was confirmed by the FDA statistician. See the separate FDA Statistical Review of the Sponsor's original submission of December 2000 for further information.

6.14 Medical Officer's Overall Assessment of Efficacy

Absence of clinical flare in symptomatic, advanced prostate cancer patients. In Study 149-09-04, 81 men with symptomatic, advanced prostate cancer were treated with abarelix. The protocol defined primary endpoint was the avoidance of orchiectomy through study Day 85. Although this endpoint is of limited clinical significance in terms of the long-term treatment of these patients who have an anticipated life expectancy of 2 to 3 years, the clinical trial provided meaningful and significant information about the potential benefits of abarelix (a pure GnRH antagonist) in this population. All patients enrolled in the study (both the 72 patients included in the efficacy analyses and the 9 patients not included in the formal efficacy analysis because of inadequate documentation by the Investigator at 1 site) avoided orchiectomy by the Sponsor's definition. Since symptoms of a clinical flare secondary to a GnRH-induced surge of testosterone would have occurred within the first few weeks of treatment, it appears from the outcome of Study 149-98-04 that abarelix, without concomitant treatment with an antiandrogen, can be administered to men with advanced symptomatic prostate cancer with little or no risk of causing a testosterone-induced clinical "flare" (i.e., a testosterone induced increase in the signs and/or symptoms of prostate cancer).

Suppression of serum testosterone concentrations (controlled clinical trials). The sponsor has demonstrated with high statistical probability that treatment with abarelix suppresses serum testosterone levels more rapidity than does treatment with Lupron (a GnRH agonist) and does so without initially producing a testosterone surge. Both of these aspects of treatment with abarelix are of clinical benefit, particularly the absence of a testosterone surge, in certain patients with advanced symptomatic disease, such as those that were enrolled in Study 149-98-04. Based on criteria agreed to by both the Sponsor and DRUDP for achievement and maintenance of suppression of serum testosterone concentrations (Protocol Definition No. 2), abarelix also was found to be noninferior to either of the active treatments through Treatment Day 85 in the 2 controlled, primary efficacy trials.

Failure to maintain suppression, based on Protocol Efficacy Definition No. 2, required that serum testosterone concentrations in 2 successive blood samples taken 2 weeks apart be > 50 ng/dL. This liberal definition thus did not classify a patient who had a serum testosterone > 50 ng/dL at the end of

any 28-day dosing cycle as a treatment failure. This situation occurred more frequently with abarelix treatment than with Lupron treatment. In the 2 controlled efficacy trials, abarelix was not noninferior to Lupron over the period from Day 29-85 and was somewhat inferior to Lupron over the period from Days 29-169 if maintenance of testosterone suppression was assessed by more rigorous criteria (i.e. no testosterone values >50 ng/dL or no predosing values > 50 ng/dL, see Table 29 and Table 30, respectively). Abarelix was clearly less effective than the 2 active comparator treatments, in terms of maintaining serum testosterone < 50 ng/dL throughout 1 year of treatment, when failure was based on (1) the occurrence of any serum testosterone >50 ng/dL just prior to each dosing and (2) premature terminations for adverse events were not classified as failures in the absence of a serum testosterone > 50 ng/dL (Table 31).

The descriptive analyses presented in Figure 3 and Figure 4 also indicates that abarelix is not as effective as Lupron or Lupron plus Casodex in reliably maintaining testosterone suppression to ≤ 50 ng/dL, especially after treatment Day 169. However, Lupron or Lupron plus an antiandrogen should not be administered to patients with impending spinal cord compression due to a metastatic lesion and must be used with caution in men with impending urinary tract obstruction or bone pain requiring narcotic analgesia.

It is not known if the differences in degree and reliability of suppression of serum testosterone seen in Studies 149-98-02 and 149-98-03 (abarelix versus Lupron and Lupron plus Casodex) are clinically important. It is possible that the long-term clinical outcome will be comparable in men with a lesser degree of testosterone suppression as observed in the abarelix groups. However, in the absence of such clinical data, one needs to assume that failure to reliably suppress serum testosterone concentrations to those observed in men following surgical castration may have an adverse effect on long term clinical outcomes.

Conclusion regarding efficacy. Abarelix, without concomitant antiandrogen therapy, can be administered to men with advanced symptomatic androgen-dependent prostate cancer (the indicated patient population) with little or no risk of a testosterone-induced clinical flare. All patients with advanced symptomatic prostate cancer treated with abarelix in Study 149-98-04 avoided orchiectomy through study Day 85, the protocol defined primary efficacy endpoint. No patient (with one possible exception) reported adverse events during the initial treatment period suggestive of a testosterone-induced clinical flare.

In the controlled clinical trials, in which serum testosterone concentrations were more closely monitored, no patient experienced an increase in testosterone values after the initial administration of abarelix. In these trials, approximately 25% and 70% of patients were medically castrate (serum testosterone ≤ 50 ng/dL) by Days 2 and 8, respectively. Approximately 90% (point estimate) of men in the controlled clinical were medically castrate by treatment Day 29 and maintained medical castration through Day 85 by the Sponsor's protocol defined criteria of medical castration (i.e., no 2 consecutive serum testosterone values > 50 ng/dL). However, if maintenance of testosterone suppression was assessed by more rigorous criteria in the 2 controlled efficacy trials (i.e., no testosterone values >50 ng/dL), abarelix was not noninferior to Lupron over the period from Days 29-85 and was somewhat inferior to Lupron over the period from Days 29-169 (Study 149-98-02). After treatment Day 169, the difference between abarelix and Lupron or Lupron plus Casodex, in terms of maintenance of serum testosterone concentrations to ≤ 50 ng/dL was more pronounced (i.e., abarelix was less effective).

Based on these observations, regular monitoring of serum testosterone concentrations will be necessary for patients receiving long term treatment with abarelix under the dosing regimen employed in the controlled clinical trials. The differences between abarelix and surgical castration or GnRH agonist therapy, in terms of producing long term and reliable suppression of serum testosterone, will need to be addressed in labeling.

7 INTEGRATED REVIEW OF SAFETY

7.1 Brief Summary of Safety Findings

All patients in Study 149-98-04 avoided orchiectomy through study Day 85, the protocol defined primary efficacy endpoint. No patient (with one possible exception who reported severe bone pain) had a clinically significant adverse event suggestive of a testosterone-induced clinical flare following the onset of treatment. Six of 81 patients (7%) died during their participation in Study 149-98-04 and an additional 4 patients died during their participation in the safety extension study. None of the deaths was attributed to treatment with abarelix. Excluding premature withdrawals due to disease progression (n = 10) and deaths, 3 of 81 patients (4%) in Study 149-98-04 were withdrawn prematurely because of an adverse event. The adverse event in each instance was a systemic allergic reaction that occurred within minutes of dosing on Study Days 15 (urticaria), 29 (urticaria and pruritus), and 141 (syncope and hypotension), respectively. Of the spontaneously reported adverse events, hot flashes, sleep disturbances due to hot flashes, pain, breast enlargement, breast pain, back pain, constipation, and peripheral edema were the most frequently reported events. Among patients with baseline ALT and AST values that were not > ULN at baseline, 25 of 75 (33%) and 21 of 74 (28%) had increases to >ULN while on-treatment. Two patients (ALT) and 3 patients (AST) had elevations > 2.5 x ULN, respectively.

Abarelix, without concomitant antiandrogen therapy, can be administered to men with advanced symptomatic androgen dependent prostate cancer (the indicated patient population) with little, or no risk of a testosterone-induced clinical flare.

7.2 Safety Studies

Data from 19 clinical studies (either complete clinical reports or limited data) were submitted by the Sponsor. Seven of the studies were either PK studies (n = 3), ——— or conducted with a daily SC formulation of abarelix (n = 2). The remaining 12 clinical studies were conducted in men with prostate cancer using the depot formulation of abarelix (n = 10) or were immunologic studies to investigate the possible mechanisms of the serious systemic allergic adverse events (n = 2). The study identifier and a brief description of each of these latter 12 studies are provided in the following listing. A more detailed description of each of these studies is provided in Table 2.

- *One uncontrolled study of abarelix in the indicated prostate cancer population:*
  - **149-98-04**, a multicenter study of abarelix 100 mg IM in 81 patients with advanced symptomatic prostate cancer in whom the use of a GnRH agonist, without concomitant use of an antiandrogen, was likely to induce a "clinical flare" (i.e., an increase in the patient's prostate cancer-related signs and symptoms)
- *Three active comparator, controlled studies of abarelix in men with prostate cancer that provided a data set of 735 patients treated with abarelix 100 mg and 321 patients treated with Lupron or Lupron plus Casodex*
  - **149-98-02**, a phase 3, multicenter, open-label, randomized study of abarelix 100 mg versus Lupron Depot 7.5 mg in prostate cancer patients
  - **149-98-03**, a phase 3, multicenter, open-label, randomized study of abarelix 100 mg versus Lupron Depot 7.5 mg plus daily Casodex 50 mg in prostate cancer patients
  - **149-99-03**, a phase 3, multicenter, open-label, randomized study of abarelix 100 mg versus Lupron Depot 7.5 mg in prostate cancer patients

- *Six supportive studies of abarelix in men with prostate cancer*
  - **149-97-04**: a Phase 1/2, multicenter, dose-escalation study of abarelix 10 to 150 mg administered by SC or IM injection
  - **149-99-04**: a rollover study that enabled continued treatment of patients who had received abarelix in Studies 149-97-04, 149-98-02, 149-98-03, 149-98-04, or 149-99-03
  - **ABACAS 1** (a European study originally sponsored by ——— and not conducted under the U.S. IND): a Phase 3, multicenter, open-label, randomized study of abarelix 100 mg IM versus Zoladex 3.6 mg plus Casodex 50 mg
  - **ABACAS 1 Extension** (a European study originally sponsored by ———) and not conducted under the U.S. IND): a rollover study that enabled continued treatment of patients who had received abarelix in Study ABACAS 1
  - **149-01-03**: a multicenter, open-label study of abarelix 100 mg IM vs Lupron Depot 7.5 mg in patients with prostate cancer who planned to undergo brachytherapy or external-beam radiation therapy
  - **149-01-05**: a multicenter, open-label study to evaluate the feasibility of switching to treatment with a GnRH agonist following treatment with abarelix
- *Two studies of abarelix immunologic characteristics*
  - **149-01-06**, an in vivo skin-test study to test for reactivity to the components of the abarelix formulation in patients who had had an allergic reaction while being treated with IM abarelix
  - **PPI-02-02-401**, an in vitro study for determining (1) the presence and titers of antibodies to abarelix and carboxymethylcellulose and (2) total IgG/IgE levels in retained serum and plasma samples from patients previously treated with abarelix, Lupron Depot, or Lupron plus Casodex

The 3 controlled, randomized Phase 3 studies (Studies 149-98-02, 149-98-03, and 149-99-03) were identified by the Sponsor as the "primary safety studies." Each of these Phase 3 studies required that patients undergo at least 6 months of treatment (through Study Day 169). These 3 studies and Study 149-98-04 (the only study to enroll patients with advanced symptomatic prostate cancer [the proposed indicated patient population]) were the focus of this safety review and were reviewed in detail. In the 3 controlled studies, patients randomized to the abarelix groups received a 100-mg IM injection on Days 1, 15, 29, and every 28 days thereafter. Patients enrolled in Study 149-98-02 and Study 149 98 03 had the option to continue treatment for up to 1 year. After 1 year, those patients receiving abarelix could continue treatment in rollover Study 149-99-04. Patients receiving treatment with abarelix in Study 149-99-03 (a study of only 6 months duration) and Study 149-98-04 could continue treatment with abarelix in rollover Study 149-99-04.

The 6 supportive clinical studies listed above that enrolled men with prostate cancer were reviewed primarily for safety issues of particular concern that included one or more of the following areas: (1) immediate systemic allergic reactions, deaths, hepatic toxicity, and serious/severe treatment-related adverse events (all studies); (2) premature terminations due to adverse events (all studies conducted under U.S. IND), and effects of treatment on the QT interval (ABACAS 1).

7.2.1 Cumulative Exposure to Abarelix Depot

A total of 1397 prostate cancer patients were exposed to the depot formulation of abarelix. Of these 1397 patients, 1154 patients received the registration dose (100 mg for both induction and maintenance of castration) and 243 patients received nonregistration doses.

Patients treated with abarelix in studies 149-97-04, 149-98-02, 149-98-03, 149-98-04, and 149-99-03 were given the opportunity to continue treatment with abarelix in study 149-99-04. Patients treated in

ABACAS 1 also were given the opportunity to participate in an extension study (ABACAS 1 Extension). Table 35 summarizes the cumulative exposure to the registration dose of abarelix based on the duration of treatment in both the original study and extension studies. Including cumulative exposure in the safety extension studies (Studies 1149-99-04 and ABACAS 1 Extension), 829 patients were exposed to the registration dose for 6 months, 327 were exposed for at least 1 year, and 113 were exposed for at least 2 years. In addition, 26 patients were exposed for at least 3 years (per Sponsor's narrative).

Table 35. Cumulative Exposure to the Registration Dose of Abarelix (100 mg) Including Exposure in Safety Extension Studies 149-99-04 and ABACAS 1 Extension

	Abarelix Depot IM (100 mg dose)			
Initial Enrollment Study	Any Exposure n	6 Months of Exposure n	1 Year of Exposure n	2 Years of Exposure n
Study in the Indicated Prostate Cancer Population				
149-98-04	81	70	30	15
Subtotal	**81**	**70**	**30**	**15**
Pivotal Safety Studies				
149-98-02	180	169	94	34
149-98-03	168	157	90	31
149-99-03	387	345	53	1
Subtotal	**735**	**671**	**237**	**66**
Supportive Safety Studies				
149-97-04	20	10	8	6
ABACAS 1	87	78	52	26
149-01-03	55	0	0	0
149-01-05	176	0	0	0
Subtotal	**338**	**88**	**60**	**32**
Primary and Supportive studies				
Total	**1154**	**829**	**327**	**113**

Source: ISS Update (8 May 03, Table 5-2, Amendment 47).

Medical Officer's Comment.

- *Studies 149-98-02, 149-98-03, and 149-99-03 were the most valuable studies for assessing the overall safety of abarelix relative to that of presently used hormonal therapy for the management of prostate cancer (i.e., GnRH agonists). These studies were considered to be the primary safety studies, both by the Sponsor and by this reviewer, and along with Study 149-98-04 (the indicated patient population), were the studies most thoroughly reviewed for safety.*

7.3 Protocol Defined Safety Assessments in Primary Safety Studies

Important safety assessments included treatment-emergent adverse events, laboratory abnormalities, and development of anti-abarelix antibodies. Table 5 and Table 21 list the schedule of protocol-required safety assessments for Study 149-98-04 (indicated population) and the primary controlled clinical safety trials (studies 149-98-02, 149-98-03, and 149-99-03).