7.3.1 Adverse Events

Adverse events were recorded and monitored throughout the clinical trials. The World Health Organization (WHO) Toxicity Scale was used, whenever possible, to rate the severity of adverse events. An endocrine questionnaire was used to record reports of adverse events likely to be a result of decreased androgen levels. Although signs and symptoms recorded on the endocrine questionnaire were considered to be adverse events, as were abnormal hematology and clinical chemistry test results, neither the endocrine questionnaire symptoms nor the laboratory abnormalities were normally recorded as adverse events on the adverse event case report form (CRF).

Because disease progression was assessed as an efficacy endpoint, it was not considered an adverse event. Any preplanned hospitalization for elective procedures, or hospitalization for prostatectomy, was not considered a serious adverse event.

7.3.2 Clinical Laboratory Tests

Laboratory evaluations were performed at screening, at baseline, at 4-week intervals during treatment, at the end-of-treatment, and at the 4-week posttreatment follow-up visit. The following hematology and clinical chemistry assessments were performed:

Hematology	Complete blood count: red blood cell (RBC) count, hemoglobin, hematocrit, platelet count, reticulocyte count, white blood cell (WBC) count
	Differential: Neutrophils, lymphocytes, atypical lymphocytes, monocytes, eosinophils, basophils
Clinical chemistry	Electrolytes and other constituents: sodium, potassium, chloride, bicarbonate, calcium, phosphorus, magnesium
	Liver function tests: alkaline phosphatase, ALT, AST, total bilirubin
	Renal function and other tests: glucose, hemoglobin A_{1c}, blood urea nitrogen (BUN), creatinine, total protein, albumin, creatine kinase
	Lipids: triglycerides, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL). Fasting samples were to be collected at study visits on Days 1, 85, 169, 253, and 337.

If a patient in the abarelix or Lupron treatment groups experienced an elevated ALT or AST value ≥ 5.1 x ULN (grade 3 toxicity, WHO toxicity scale), a repeat blood draw was to be performed 3, 7, and 12 days after the date of the abnormality. If there was not a significant improvement in laboratory values during this period, the patient was to be withdrawn. In the Lupron plus Casodex group, ALT or AST values > 2 x ULN were the reference level used to determine if a patient should be withdrawn from treatment.

Clinically notable laboratory values. To assist in identifying abnormal laboratory test results of particular concern, the sponsor presented in summary tables "clinically notable laboratory values." The limits for these values are listed in Table 36.

Table 36 Limits for Clinically Notable Laboratory Values

Hemoglobin < 8.0 g/dL < 9.5 g/dL > 19.0 g/dL	Bicarbonate < 15.1 mEq/L > 34.9 mEq/L	Total bilirubin > 2.5 x ULN
Hematocrit < 24% > 55%	Calcium < 7.0 mg/dL > 11.0 mg/dL	Glucose < 45 mg/dL > 300 mg/dL
Platelet count < 75 x 10^3/mm^3	Magnesium < 0.5 mEq/L > 3.0 mEq/L	BUN > 35 mg/dL > 2.5 x ULN
WBC count < 2.0 x 10^3/mm^3 > 15.0 x 10^3/mm^3	Alkaline phosphatase > 200 U/L > 5.0 x ULN	Creatinine > 2.0 mg/dL > 2.5 x ULN
Sodium < 125 mEq/L > 155 mEq/L	ALT > 2.5 x ULN > 200 U/L	Creatine kinase > 1000 U/L
Potassium < 3.0 mEq/L > 5.8 mEq/L	AST > 2.5 x ULN > 200 U/L	

WHO Toxicity Grades. In addition to standard shift analyses (e.g., shifts from normal to above the normal range), the Sponsor also provided shift analyses based on WHO toxicity grades for laboratory values of particular importance (e. g., ALT, AST, alkaline phosphatase, and triglycerides). WHO Toxicity Grades are defined in Table 37.

Table 37. WHO Toxicity Grading Scale

	Grade 0 x ULN	Grade 1 x ULN	Grade 2 x ULN	Grade 3 x ULN	Grade 4 x ULN
AST	≤ 1.25	1.26 - 2.59	2.60 - 5.09	5.10 - 10.00	> 10.00
ALT	≤ 1.25	1.26 - 2.59	2.60 - 5.09	5.10 - 10.00	> 10.00
Alkaline Phosphatase	≤ 1.25	1.26 - 2.59	2.60 - 5.09	5.10 - 10.00	> 10.00
BUN	≤ 1.25	1.26 - 2.59	2.60 - 5.09	5.10 - 10.00	> 10.00
Triglycerides	≤ 1.0	1.1 - 1.5	1.6 - 2.0	2.1 - 2.6	> 2.6
Cholesterol	≤ 1.0	1.1 - 1.5	1.6 - 2.0	2.1 - 2.6	> 2.6

7.3.3 Anti-abarelix Antibodies

Plasma samples were collected at screening, at Days 85, 169, 253, and 337, and at the follow up visit for testing for anti-abarelix antibodies. Testing was based on an enzyme-linked immunosorbent assay (ELISA) for determination of the titer of anti-abarelix IgG antibodies.

PART A. Clinical Trial in Indicated Patient Population

- **Clinical Trial 149-98-04** – "A Multi-Center Study of Abarelix-Depot in Patients with Prostate Cancer in Whom GnRH Agonists are Contraindicated"

7.4 Enrollment and Patient Disposition (Study 149-98-04)

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 38). A total of 69 patients (83%) completed 169 days of treatment. Of the 14 patients who withdrew before Day 169, 2 withdrew because of an adverse event (immediate onset 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 because of an adverse event [immediate onset allergic reaction], 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 38 Patient Enrollment and Disposition (Safety Population - Study 149-98-04)

Disposition	N (%) of Patients
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.

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

7.5 Extent of Exposure to Abarelix in Indicated Patient Population (Study 149-08-04 and Extension Study 149-99-04)

7.5.1 Study 149-98-04

Table 39 summarizes patient exposure to abarelix in Study 149-98-04. Duration of exposure was defined as the time from the first dose of abarelix depot to 28 days (4 weeks) after the day of the last dose of abarelix. The median duration of exposure was 28 weeks (range, 4 to 52 weeks). Seventy (70) of the 81 patients (86 %) were exposed to abarelix for at least 24 weeks.

Table 39 Patient Exposure to Abarelix in Study 149-98-04 (Safety Population)

Duration of Treatment (Weeks)	Number of Patients Exposed to Abarelix [1] N =81
4	81
8	79
12	75
16	74
20	74
24	70
28	43
32	34
36	29
40	18
44	9
48	3
52	2

1 Includes the 9 patients from Site 499 in Mexico that was disqualified because of inadequate documentation.
Source: Final Report for Study 149-98-04, Table 10-3.

7.5.2 Cumulative Exposure to Abarelix (Studies 149-98-04 and 149-99-04)

Forty (40) of the 72 ITT patients in study 149-98-04 entered the rollover study (Study 149-99-04) to continue treatment with abarelix. (The ITT population does not include 9 patients from Site 499 in Mexico that was disqualified by the Sponsor because of inadequate documentation). Summaries of the cumulative duration of exposure to abarelix, combined over both studies for the ITT population, are provided in Table 40 and Table 41. Sixty-one (61) of the 72 ITT patients (85%) and 33 of the 72 patients (46%) received at least 24 weeks and 48 weeks of treatment with abarelix, respectively. The median duration of treatment for these 72 patients was 40 weeks.

Table 40 Cumulative Exposure to Abarelix in ITT Patients (Study 149-98-04 and extension Study 149-99-04)

Duration of Exposure (Weeks)	Number (%) of Patients Exposed to Abarelix N	(%)
At least 1 injection	72	(100)
≥12 weeks	66	(92)
≥24 weeks	61	(85)
≥36 weeks	41	(57)
≥48 weeks	33	(46)
≥60 weeks	27	(38)
≥72 weeks	23	(32)
≥84 weeks	18	(25)
≥96 weeks	15	(21)
≥108 weeks	13	(18)
≥120 weeks	6	(8)
≥132 weeks	5	(7)
≥144 weeks	4	(6)

Source: Table 6-1, Addendum to Report for Study 149-98-04, Vol. 18.

Table 41 Cumulative Exposure to Abarelix in ITT Patients (Study 149-98-04 and extension Study 149-99-04)

Parameter	Weeks of Exposure
Minimum	4
Q1	24
Median	40
Q3	82
Maximum	149

Source: Table 6-2, Addendum to Report for Study 149-98-04, Vol. 18.

7.6 Adverse Events (Study 149-98-04)

7.6.1 Overview of Adverse Events

All treatment-emergent adverse events (events not seen at baseline or events that worsened after baseline) were collected through the last day of the final treatment cycle. Only adverse events considered to be treatment-related were collected during the follow-up period (more than 28 to 35 days after the last day of the final treatment cycle).

Unless otherwise indicated, adverse events described in this section of the review, pertain only to those reported during the patient's participation in Study 149-98-04 and do not include those treatment-emergent adverse events reported during the patient's participation in the rollover extension study (Study 149-99-04).

An overall summary of the number of patients experiencing one or more adverse events in Study 149 98-04 is presented in Table 42. Seventy-seven of the 81 patients (77/81, 95%) experienced an adverse event. Treatment related adverse events were reported for 33 of 81 patients (41%). Of the treatment related adverse events, 6 and 3 were classified as severe and serious, respectively.

Table 42 Overview of number of Patients Experiencing Adverse Events (Study 149-98-04)

Type of Adverse Event	Abarelix (N = 81) n (%)
Any adverse event	**77 (95)**
• Severe or life-threatening	34 (42)
• Serious	17 (21)
Any treatment-related adverse events	**33 (41)**
• Severe	6 (7)
• Serious	3 (4)
Withdrawal due to adverse event (excluding disease progression and/or death)	**3 (4)**
Death on study	**6 (7)**

Source: Table 10-4, pg 158, Final Report for Study 149-98-04.

7.6.2 Most Common Adverse Events (All Relationships and Severity)

Adverse events (all relationships and all degrees of severity) were reported by 77 of 81 patients (95%). Those that occurred in at least 5 patients are listed by preferred term in decreasing order of frequency in Table 43. Adverse events reported in > 10% of patients (and percentage of patients reporting each of them) were hot flashes (79%), Sleep disturbances (44%), pain (31%), breast enlargement (30%), breast pain (20%), back pain (17%), constipation (15%), peripheral edema (15%), dizziness (12%), upper respiratory infection (12%), and diarrhea (11%).

Table 43 Most Common Adverse Events (All Relationships) (Study 149-98-04)

Preferred Term [1]	Abarelix N = 81 n (%) [2]
Any adverse event	77 (95)
Hot flashes	64 (79)
Sleep disturbance due to hot flashes	36 (44)
Pain	25 (31)
Breast enlargement	24 (30)
Breast pain or nipple tenderness	16 (20)
Back pain	14 (17)
Constipation	12 (15)
Peripheral edema	12 (15)
Dizziness	10 (12)
Headache	10 (12)
Upper respiratory tract infection	10 (12)
Diarrhea	9 (11)
Dysuria	8 (10)
Fatigue	8 (10)
Micturition frequency	8 (10)
Nausea	8 (10)
Urinary retention	8 (10)
Urinary tract infection	8 (10)
Anxiety	6 (7)
Hematuria	6 (7)
Leg pain	6 (7)
Coughing	5 (6)
Myalgia	5 (6)
Urinary incontinence	5 (6)
Vomiting	5 (6)

[1] Adverse events that occurred in at least 5 patients.
[2] Number (%) of patients reporting the adverse event.

Source: Table 10-5, pg 159, Final Report for Study 149-98-04.

7.6.3 Treatment Related Adverse Events

Adverse events considered to be related to treatment (other than those reported on the Endocrine Questionnaire) were reported in 33 of 81 patients (41%). Treatment related adverse events (other than those reported on the Endocrine Questionnaire) that occurred in at least 2 patients are listed in Table 44. Treatment-related adverse event that occurred in >2% of patients (and the percentage of patients reporting each of them) were constipation (5%), diarrhea (5%), headache (5%), myalgia (5%), back pain (4%), and fatigue (4%).

Table 44 Most Common Treatment-Related Adverse Events (Study 148-98-04)

Preferred Term [1]	Abarelix N = 81 n (%) [2]
Any treatment-related adverse event	33 (41)
Constipation	4 (5)
Diarrhea	4 (5)
Headache	4 (5)
Myalgia	4 (5)
Back pain	3 (4)
Fatigue	3 (4)
Allergic reaction	2 (2)
Decreased urine flow	2 (2)
Dizziness	2 (2)
Micturition frequency	2 (2)
Nocturia	2 (2)
Pain	2 (2)
Rash	2 (2)
Skin nodule	2 (2)

[1] Treatment-related adverse events that occurred in at least 2 patients. Includes events with a reported relationship of definite, possible, and unknown. . Does not include adverse events reported on the Endocrine Questionnaire (See Table 45).

[2] Number (%) of patients reporting the adverse event.

Source: Table 10-6, pg 106, Final Report for Study 149-98-04.

7.6.4 Adverse Events Reported on the Endocrine Questionnaire

Adverse events reported on the endocrine questionnaire are summarized in Table 45.

Table 45 Adverse Events Reported on the Endocrine Questionnaire (Study 149-98-04)

Event	Abarelix N = 81 n (%) [1]
Hot flashes	64 (79)
Sleep disturbance due to hot flashes	36 (44)
Breast enlargement	24 (30)
Breast pain or nipple tenderness	16 (20)

[1] Number (%) of patients reporting the adverse event.
Source: Table 10-11, pg 168, Final Report for Study 149-98-04.

Medical Officer's Comments

- *Events reported on the Endocrine Questionnaire were those that are commonly associated with reduced serum testosterone concentrations (medical castration) and are to be expected.*

7.6.5 Adverse Events Associated with Patient Withdrawals

Excluding progression of disease (n = 10) and death (n = 6, see Table 48), 3 patients (Nos. 401-4001, 409-4057, and 416-4067) were withdrawn from Study 149-98-04 because of an adverse event. All 3 were withdrawn because of a systemic allergic reaction (see Section 7.9.1).

7.6.6 Severe or Life-Threatening Adverse Events

All Treatment Relationships

Adverse events were assessed as severe or life-threatening by the investigator in 34 of 81 patients (42%). Severe or life-threatening adverse events occurring in at least 2 patients are listed in Table 46. Six events leading to death were reported as life-threatening: 3 events of progressive metastatic prostate cancer, 1 event of multiple organ failure secondary to progressive prostate cancer, 1 event of renal failure secondary to progressive prostate cancer, and 1 event of respiratory failure secondary to pulmonary embolus (Table 48).

Table 46 Severe or Life-Threatening Adverse Events (All Relationships, Study 149-98-04)

Preferred Term [1]	Abarelix N = 81 n (%) [2]
Any severe or life-threatening adverse event	34 (42%)
Back pain	5 (6)
Urinary retention	5 (6)
Pain	4 (5)
Metastases	3 (4)
Abnormal gait	2 (2)
Abnormal renal function	2 (2)
Anemia	2 (2)
Cachexia	2 (2)
Dehydration	2 (2)
Headache	2 (2)
Hematuria	2 (2)
Nausea	2 (2)
Peripheral edema	2 (2)

[1] Events that occurred in at least 2 patients.
[2] Number (%) of patients reporting the adverse event.

Source: Table 10-7, pg 161, Final Report for Study 149-98-04.

Treatment-Related

Nine (9) adverse events in 6 of 81 patients were reported as severe treatment-related (relationships to treatment of unknown, possible, probable, or definite, see Table 47). None of these events was reported as life-threatening. All 3 of the patients with pain reported as possibly related to treatment (Patient Nos. 471-4008 [onset Day 1, possibly related], 473-4019 [onset Day 50, unknown relationship], and 499-4106 [onset Day 32, unknown relationship]) had castrate levels of testosterone (≤ 50 ng/dL) on Study Day 8 or 9. Both Patient Nos. 473-4019 and 499-4106, according to the Sponsor, had castrate levels of testosterone prior to and following the report of severe back pain.

Medical Officer's Comments

- *In Patient No. 471-4008, serum testosterone concentrations at baseline and Days 5 and 9 were 237 ng/dL, 68 ng/dL, and 13 ng/dL, respectively. Based on these values it is unlikely, but*

possible (as assessed by the Investigator), that the severe bone pain at the onset of treatment with abarelix was due to a brief (< 5 day) increase in serum testosterone. The adverse event was treated with Tylenol and resolved 2 weeks later.

Table 47 Patients With Severe, Treatment-Related Adverse Events (Study 149-98-04)

Patient No.	Age (yr)	Race[1]	Preferred Term (Verbatim Description)	Onset (day)	Duration (days)	Relationship to Treatment
401-4001	85	C	Allergic reaction (allergic reaction with mild anaphylactic-type symptoms)	141	1	Probable
473-4003	77	C	Rash (skin rash)	312	35	Possible
471-4008	77	AA	Abnormal gait (inability to ambulate due to increased bone pain)	1	15	Possible
			Skeletal pain (worsening bone pain)	1	15	Possible
473-4019	62	C	Nausea (nausea)	11	2	Unknown
			Back pain (exacerbation of lumbar spine L4, L5 pain)	50	59	Unknown
416-4067	64	H	Urticaria (urticaria)	15	1	Definite
499-4106	67	H	Back pain (dorsolumbar pain)	32	74	Unknown
			Pain (left intercostal pain)	32	74	Unknown

[1] Race: C = Caucasian, AA = African American, H = Hispanic
Source: Table 10-8, pg 162, Final Report for Study 149-98-04.

7.6.7 Non-fatal, Serious Adverse Events

All Relationships

Seventeen (17) serious adverse events (excluding deaths) were reported in 13 patients. Urinary retention was reported in 3 patients and allergic reaction was reported in 2 patients. The following events were each reported in 1 patient: abnormal renal function, abscess, aggravated angina pectoris, deep thrombophlebitis, dehydration, fever, gastritis, hematuria, hyponatremia, hypovolemia, pulmonary embolism, and urticaria.

Medical Officer's Comments

- *This reviewer concurs with the Investigators and the Sponsor that these events, with the exception of the 2 allergic reactions and the single instance of urticaria (see below), were most likely the sequelae of co-morbid disorders in this elderly population of men with advanced symptomatic prostate cancer.*

Treatment-Related

Two instances of immediate allergic reaction and 1 instance of urticaria within 1 hour of dosing were reported to be related to treatment with abarelix and are described further in Section 7.9.1.

7.7 Deaths (Study 149-98-04)

In Study 149-98-04, 6 deaths were reported: 4 deaths occurred before day 169 and 2 deaths occurred after day 169 (Table 48). Patient No. 441-4050 died secondary to a pulmonary embolism. In the

remaining 5 patients, death was attributed to causes associated with progressive prostate cancer. All deaths were reported by the Investigators as not related to treatment with abarelix.

Four (4) patients who continued treatment in Study 149-99-04 also died (Table 48).

Table 48 Summary of Patient Deaths (Study 149-98-04 and Rollover Study 149-99-04)

Patient	Age (yr)	Race[1]	Cause of Death	Last Dose (Day)	Day of Death	Days From Last Dose
Death in Study 149-98-04						
402-4030	71	C	Progression of prostate cancer	85	118	33
477-4043	79	C	Progression of prostate cancer	168	188	20
409-4044	94	C	Progression of prostate cancer	29	45	16
441-4050	89	C	Respiratory failure secondary to pulmonary embolism	29	61	32
477-4064	77	C	Metastatic prostate cancer with renal failure	142	149	7
499-4101	55	H	Multiple organ failure secondary to progressive prostate cancer	197	216	19
Death in Rollover Study 149-99-04						
422-4037	69	C	Myocardial infarction	1	26 (200)[2]	25
428-4005	77	C	Pneumonia	1	30 (339)[2]	29
438-4028	71	C	Cardiac arrest	308	331 (612)[2]	23
441-4036	94	C	Metastases NOS	85	106 (274)[2]	21

[1] Race: C = Caucasian; H = Hispanic

2 First value reflects number of days in rollover Study 149-99-04. Value in ( ) reflects cumulative days in Studies 149-98-04 and 149-99-04.

Source: Table 10-9, Final Report for Study 149-98-04 and Table 10-7, Final Report for Study 149-99-04.

Medical Officer's Comments

- *Six of the 10 deaths were directly attributed to progression of the patient's prostate cancer. The other 4 deaths were attributed to concomitant conditions that are common causes of death in the elderly.*
- *According to the Sponsor, serum testosterone levels were ≤ 50 ng/dL at their last on-study assessment for all patients who died of disease progression and for whom testosterone value were available.*

7.8 Laboratory Assessments (Study 149-98-04)

7.8.1 Hematology Assessments

Approximately 40% of patients with a high, normal or unknown baseline hemoglobin value (n = 55) had a shift to low (< LLN). A similar percentage of patients with a high, normal or unknown baseline hematocrit value had a shift to < LLN. The decreases, relative to baseline, for mean and median hemoglobin and hematocrit values, however, were small. No trends in mean or median values for platelets or WBCs were observed.

Medical Officer's Comments

- *A small decrease in hemoglobin and hematocrit values is to be expected following suppression of serum testosterone concentrations.*

7.8.2 Chemistry Assessments

7.8.2.1 Electrolytes

Increases and decreases (shifts outside of the limits of normal) in electrolytes, calcium and phosphorus were generally isolated instances or of short duration. Clinically notable values were infrequent.

7.8.2.2 Renal Function Tests

A significant percentage of patients had elevated creatinine and BUN values at baseline. Shifts to > ULN from a low, normal, or unknown value at baseline in BUN creatinine and occurred in 27 patients (42%) and 10 patients (18%), respectively. Clinically notable renal function test values are summarized in Table 49.

Table 49 Clinically Notable Renal Function Test Results (Study 149-98-04)

		Abarelix Depot N = 81	
Laboratory Test	Cutoff Value	Evaluable[1] n	Experienced n (%)
Blood Urea Nitrogen	> 35 mg/dL	79	14 (18)
	> 2.5 x ULN	79	9 (11)
Creatinine	> 2.0 mg/dL	76	9 (12)
	> 2.5 x ULN	76	6 (8)

[1] Patients whose baseline value was not in the clinically notable range or whose post-baseline value was worse than their clinically notable baseline value.
Source: Table 10-14, pg 172, Final Report for Study 149-98-04.

Medical Officer's Comments

- *Increases in BUN and creatinine levels are not unexpected in this patient population with advanced symptomatic prostate cancer.*

7.8.2.3 Liver Function Tests

Laboratory assessments of liver function are summarized in Section 7.9.2.

7.9 Safety Issues of Special Concern (Study 149-98-04)

7.9.1 Immediate Systemic Allergic Reactions

Immediate systemic allergic reactions were reported in 3 patient during their participation in Study 149-98-04 (Table 50). All 3 reactions were considered as related to treatment with abarelix; the 3 patients received no further doses of abarelix and all were withdrawn from the trial.

The most severe of the allergic reactions occurred in Patient No. 401-4001. This event occurred within moments of his Day 141 injection and was associated with loss of consciousness, a generalized erythematous rash, a drop in blood pressure, and edema of his wrists and ankles as well as around his eyes, lips, and ears. The patient was treated with Benadryl, epinephrine, and Solu-Medrol.

All reported systemic allergic reactions that occurred within 24 hours of dosing with Study Drug or that led to a patient withdrawal are presented and reviewed in Section 7.16.2.

Table 50 Immediate Serious Systemic Allergic Reactions (Study 149-98-04)

Patient	Event Onset	Signs/Symptoms	Severity	Relationship [1]	Treatment and Outcome
401-4001	Immediately after seventh injection **(Day 141)**	"Burning all over"; obtunded; generalized erythematous rash; hypotension; erythema and edema of eyes, lips, and ears; "relatively" short of breath	Severe	Probable	Oxygen, IV Benadryl, SC epinephrine, IV Solu-Medrol, albuterol breathing treatment. Discharged from ER same evening
409-4057	Immediately after third injection **(Day 29)**	Warm neck; urticaria and pruritus of the upper back, neck, and chest	Moderate	Definite	No treatment. Resolved same day
416-4067	5 minutes after second injection **(Day 15)**	Urticaria	Severe	Definite	Oral and intramuscular Benadryl. Resolved same day

1 Investigator's assessment.
Source: modified form Table 10-10, pg 167, Final Report for Study 149-98-04.

7.9.2 Hepatic Toxicity

7.9.2.1 Mean and Median Values for Liver Function Tests

Mean and median values for alkaline phosphatase, ALT, AST, and bilirubin at baseline and on Study Days 85 and 169 are listed in Table 51.

Medical Officer's Comments

- *There was a small increase of 3-4 U/L in mean and median ALT values over time.*

Table 51 Mean and Median Values for Liver Function Tests (Study 149-98-04)

Test	Study Day	Number of Patients	Mean (U/L or mg/dL)	Median (U/L or mg/dL)
Alkaline Phosphatase	Baseline	79	279	116
	85	74	193	102
	169	67	160	86
ALT	Baseline	80	20	18
	85	72	24	21
	169	65	23	21
AST	Baseline	80	25	22
	85	72	25	23
	169	65	25	22
Bilirubin	Baseline	80	0.5	0.4
	85	72	0.4	0.4
	169	65	0.4	0.4

Source: Table 12.7.6.1, Vol. 20, Final report for Study 149-98-04.

7.9.2.2 Shifts to Values Above the Normal Range

Forty-nine percent (49%) of patients had elevated alkaline phosphatase values at baseline. Of the remaining 51% of patients with normal, low, or unknown values at baseline, 8 (20%) had a shift to

> ULN during treatment with abarelix (Table 52). ALT and AST shifts from not elevated at baseline to > ULN while on treatment occurred in 33% and 28% of patients, respectively. One isolated increase in bilirubin to 1.7 mg/dL and ALT to 49 U/L occurred in Patient No. 477-4021 on Day 253, 6 days after a hip fracture according to the Sponsor.

Table 52 Liver Function Tests: Shifts to High (>ULN) From Baseline (Study 149-98-04)

	Abarelix Depot (N = 81)	
Laboratory Test	Evaluable[1] n	Experienced[2] n (%)
Alkaline Phosphatase	41	8 (20)
ALT	75	25 (33)
AST	74	21 (28)
Total Bilirubin	79	1 (1)[3]

[1] Patients whose baseline value was not high and who had at least 1 post baseline value
[2] Shifts to high (>ULN) include normal to high, low to high, and unknown to high.
[3]. Isolated value of 1.7 mg/dL in Pt. No. 477-4021.

Source: Table 12.7.6.2, Vol. 20, Final report for Study 149-98-04

7.9.2.3 Clinically Notable Values for Liver Function Tests

According to the sponsor, screening or baseline alkaline phosphatase levels were elevated in 31 of the 33 patients with on-treatment clinically notable alkaline phosphatase values. Of these 31 patients, 23 had clinically notable values at baseline (14 patients > 200 U/L; 9 patients > 5 x ULN). Clinically notable alkaline phosphatase values of > 5.0 x ULN were observed in 16 patients (20%) during treatment (Table 53). Clinically notable ALT and AST values were reported for 2 and 3 patients, respectively, during treatment with abarelix; no clinically notable total bilirubin values were reported.

Table 53 Incidence of Clinically Notable Liver Function Test Results (Study 149-98-04)

		Abarelix Depot N = 81	
Laboratory Test	Cutoff Value	Evaluable[1] n	Experienced n (%)
Alkaline Phosphatase	> 200 U/L	79	33 (42)
	> 5.0 x ULN	79	16 (20)
ALT	> 2.5 x ULN	80	2 (3)
	> 200 U/L	80	1 (1)
AST	> 2.5 x ULN	78	3 (4)
	> 200 U/L	78	0
Total Bilirubin	> 2.5 x ULN	80	0

[1] Patients whose baseline value was not in the clinically notable range or whose post-baseline value was worse than their clinically notable baseline value.

Source: Table 10-13, pg 171, Final Report for Study 149-98-04.

Medical Officer's Comments

- *These observed increases in alkaline phosphatase are not unexpected in patients with a high incidence of bone metastases.*
- *Thirty three percent (33%) and 28% of patients with normal ALT and AST values at baseline had increases above the ULN on one or more on-treatment assessments. However, only 2 and 3 patients had on-treatment ALT and AST values greater than 2.5 x ULN. The number of patients*

with clinically notable ALT and AST values reported in Study 149-98-04 would not preclude the use of abarelix for the treatment of men with advanced symptomatic prostate cancer.

- *Changes in liver function test values in the controlled clinical trials, that included a larger number of abarelix-treated patients and which compared changes in abarelix-treated patients to changes in patients treated with Lupron or Lupron plus Casodex, are described in Section 7.16.3.*

7.10 Overall Assessment of the Safety of Abarelix in the Indicated Patient Population

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) reported a clinically significant adverse event 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. 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. In summary, 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.

Medical Officer's Comments

- *Based on the reported adverse events in Study 149-98-04, abarelix appears to have a safety profile that is acceptable for the treatment of those men with symptomatic advanced prostate cancer as indicated in the to be approved label. Since 3 of 81 patients (3.7%) experienced an immediate systemic allergic reaction (one of which included syncope and hypotension), abarelix should be administered only by a physician capable of managing a severe systemic allergic reaction and patients must be observed for at least 15 minutes following each administration as per boxed warning in the package label.*

Part B. Controlled 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"

7.11 Patient Disposition (Primary Controlled Safety Studies)

Of the 1,102 patients enrolled in Studies 149-98-02, 149-98-03, and 149-99-03, 284 patients were treated with Lupron, 83 patients were treated with Lupron plus Casodex, and 735 patients were treated with abarelix (Table 54). Ninety percent (90%) of the Lupron group, 84% of the Lupron plus Casodex group, and 91% of the abarelix group completed participation in their respective studies through Study Day 169. Four percent (4%) of the Lupron group, 10% of the Lupron plus Casodex group, and 3% of the abarelix group were withdrawn from treatment before Day 169 because of adverse events.

Of the 358 patients who continued treatment beyond Day 169, 62 continued treatment with Lupron, 48 continued treatment with Lupron plus Casodex, and 248 continued treatment with abarelix. Of the patients who continued treatment, 3 of 62 (5%) of the Lupron group, 1 of 48 (2%) of the Lupron plus Casodex group, and 5 of 248 (2%) of the abarelix group were withdrawn from treatment after Day 169 and before Day 365 because of adverse events.

Table 54. Patient Enrollment and Disposition (Pooled Data from Studies 149-98-02, 149-98-03, and 149-99-03)

	Treatment Group		
	Lupron N = 284 n (%)	Lupron Plus Casodex N = 83 n (%)	Abarelix N = 735 (n (%)
Received Study Drug	*284 (100)*	*83 (100)*	*735 (100)*
Terminated Study Before Day 169	28 (10)	13 (16)	69 (9)
Death	0	0	4 (1)
Adverse event [1]	12 (4)	8 (10)	23 (3)
Patient decision [2]	4 (1)	3 (4)	16 (2)
Protocol violation	8 (3)	2 (2)	7 (1)
Lost to follow-up	1 (1)	0	3 (1)
Other	3 (1)	0	16 (2)
Completed Study Through Day 169	256 (90)	70 (84)	666 (91)
Continued Treatment After Day 169 [3]	*62 (100)*	*48 (100)*	*248 (100)*
Withdrawn from treatment before Day 365	12 (19)	12 (25)	43 (17)
Death	1 (2)	0	2 (1)
Adverse event	3 (5)	1 (2)	5 (2)
Patient decision	3 (5)	5 (10)	15 (6)
Protocol violation	0	3 (6)	3 (1)
Other	5 (8)	3 (6)	18 (7)
Completed treatment before Day 365 (physician's decision)	3 (5)	4 (8)	23 (9)
Completed treatment through Day 365	47 (76)	32 (67)	182 (73)

[1] Includes clinical and laboratory adverse events (e.g., transaminase elevations).
[2] Includes voluntary withdrawal and refusal to receive study drug as randomized.
[3] Only includes patients in studies 149-98-02 and 149-98-03 since Study 149-99-03 was of 6-months duration.
Source: Table 4-a, ISS, Submission of December 2000.

Medical Officer's Comment

- *The percentage of patients who were prematurely withdrawn from the abarelix group for an adverse event was numerically lower or comparable to those for the Lupron or Lupron plus Casodex groups. The overall percentage of patients who terminated prematurely because of*

death was higher in the abarelix group (0.83%, 6 of 735 patients) compared to the combined Lupron and Lupron plus Casodex groups (0.27%, 1 of 367 patients). None of the deaths was attributed to treatment with Study Drugs (see Section 7.14)

7.12 Demographics and Baseline Characteristics (Primary Controlled Safety Studies)

Pooled demographic and other baseline characteristics for the patients in the 3 primary safety studies are listed in Table 55. Similar data for each of the 3 primary safety studies, presented separately by study, are listed in Table 22 and Table 23. In general, the treatment groups were similar with respect to age (median 72 to 74 yr.), race (predominantly Caucasian), and body weight (69% to 73% of patients < 200 pounds).

Table 55. Demographics and Other Baseline Characteristics (Pooled Results from Studies 149-98-02, 149-98-03, and 149-99-03)

	Treatment Group		
Characteristic	Lupron N = 284 n (%)	Lupron Plus Casodex N = 83 n (%)	Abarelix N = 735 n (%)
Age (yr)			
Median (range)	73 (49 - 89)	74 (49 - 93)	72 (46 – 97)
Race/Ethnicity			
Caucasian	233 (82)	69 (83)	619 (84)
African American	28 (10)	10 (12)	71 (10)
Hispanic	16 (6)	2 (2)	23 (3)
Asian	5 (2)	2 (2)	13 (2)
Other	2 (1)	0	9 (1)
Body Weight (lb)			
< 200	195 (69)	61 (73)	507 (69)
≥ 200	89 (31)	22 (27)	228 (31)
Cancer Stage			
T1	56 (20)	13 (16)	140 (19)
T2	117 (41)	27 (33)	257 (35)
T3	27 (10)	4 (5)	83 (11)
T4	4 (1)	1 (1)	2 (< 1)
D0	4 (1)	0	6 (1)
D1.5	56 (20)	33 (40)	176 (24)
D1	7 (2)	1 (1)	36 (5)
D2	13 (5)	4 (5)	35 (5)
Reason for Treatment in the Study			
D1/D2 disease stage[1]	20 (7)	4 (5)	67 (9)
Rising PSA	80 (28)	36 (43)	208 (28)
Neoadjuvant hormonal therapy	134 (47)	33 (40)	338 (46)
Intermittent hormonal therapy	50 (18)	10 (12)	119 (16)
None of the above	0	0	3 (< 1)

[1] The number of patients enrolled for treatment of D1/D2 stage disease may be less than the sum of patients with a baseline diagnosis of D1/D2 stage disease because another reason (e.g., rising PSA, neoadjuvant hormonal therapy, or intermittent hormonal therapy) may have been given on the case report form.

Source: Table 4-B, pg 144, ISS, Submission of December 2000.

Medical Officer's Comments

- *Overall, the 3 treatment groups appeared to be reasonably well balanced.*
- *A higher percentage of patients in the Lupron plus Casodex group (46%) had Stage D prostate cancer compared to the other groups (Lupron: 28%, abarelix 34%).*

7.13 Adverse Events (Primary Controlled Safety Studies)

In this review, adverse events for the primary safety studies (Studies 149-98-02, 149-98-03, and 149-99-03) are presented and discussed in the following manner. An overview of reported adverse events, based on the numbers of patients reporting adverse events summarized into broad categories, is presented (Section 7.13.1). This is followed by a summary and discussion of (a) the most commonly reported adverse events (all degrees of severity and all relationships to Study Drugs, Section 7.13.2), (b) the most commonly reported adverse events possibly related to treatment with Study Drugs (Section 7.13.3), (c) treatment-related adverse events that resulted in withdrawal of patients from the clinical trials (Section 7.13.4), (d) severe or life-threatening treatment-related adverse events (Section 7.13.5), and (e) nonfatal, serious treatment-related adverse events (Section 7.13.6). Within each of the first 3 broad classifications (i.e., Sections 7.13.2-7.13.4), adverse events are summarized by (a) those that occurred during the first 169 days following the onset of treatment (based on pooled data from the 3 primary safety studies) and (b) those that occurred in patients with up to 1 year of exposure to Study Drug (limited to Studies 149-98-02 and 149-98-03 since Study 149-99-03 was only of 6-months duration).

Adverse events associated with allergic reactions and transaminase elevations are reviewed separately in Sections 7.16.2 and 7.16.3, respectively.

7.13.1 Overview of Adverse Events (Primary Safety Studies)

Table 56 summarizes the number and type of adverse events reported from Study Day 1 through Day 169 in the 3 primary safety studies. Most patients reported one or more adverse events during this period. For most adverse event categories, the highest percentage of patients reporting an adverse event was in the Lupron plus Casodex group. Withdrawals due to adverse events were highest in the Lupron plus Casodex group (10% of patients). The reported incidences of adverse events in the Lupron and abarelix groups were similar for most categories of adverse events. Four deaths (4 of 735, <1% of patients) were reported in the abarelix group.

Table 56. Number of Patients Reporting Adverse Events Through Study Day 169 (Pooled Results from Studies 149-98-02, 149-98-03, and 149-99-03)

	Lupron N = 284 n (%)[1]	Lupron Plus Casodex N = 83 n (%)	Abarelix N = 735 n (%)
All adverse events	249 (88)	79 (95)	662 (90)
Severe or life-threatening	51 (18)	15 (18)	105 (14)
Nonfatal serious	26 (9)	12 (14)	67 (9)
Treatment-related adverse events	137 (48)	47 (57)	374 (51)
Severe or life-threatening	15 (5)	2 (2)	22 (3)
Nonfatal serious	2 (1)	2 (2)	10 (1)
Withdrawals due to adverse events	12 (4)	8 (10)	23 (3)
Deaths on study	0	0	4 (1)

Categories are not mutually exclusive.

[1] Number (%) of patients experiencing one or more adverse events in the respective category.

Source: Table 6-A ISS and Table 6-A Safety Update, Submissions of December 2000 and March 2001.

Patients in Study 149-98-02 and Study 149-98-03 were allowed to continue treatment for up to 1 year. Adverse events from these studies from Study Day 1 through Day 365 are summarized in Table 57. In general, the percentages of patients reporting at least one adverse event in each of the adverse event categories were comparable across the 3 treatment groups. However, a higher percentage of patients in the Lupron plus Casodex group (61%) and the abarelix group (52%) reported treatment-

related adverse events than in the Lupron group (42%). A higher percentage of patients in the Lupron plus Casodex group (12%) and the Lupron group (9%) were withdrawn from treatment because of an adverse event.

Table 57. Number of Patients Reporting Adverse Events with Up to 1 Year of Exposure to Study Drug (Pooled Results from Studies 149-98-02 and 149-98-03)

	Lupron N = 89 n (%) [1]	Lupron Plus Casodex N = 83 n (%)	Abarelix N = 348 n (%)
All adverse events	83 (93)	79 (95)	335 (96)
Severe or life-threatening	22 (25)	21 (25)	73 (21)
Nonfatal serious	17 (19)	15 (18)	55 (16)
Treatment-related adverse events	37 (42)	51 (61)	181 (52)
Severe or life-threatening	3 (3)	2 (2)	11 (3)
Nonfatal serious	1 (1)	2 (2)	7 (2)
Withdrawals due to adverse events	8 (9)	10 (12)	15 (4)
Deaths on study	1 (1)	0	6 (2)

Categories are not mutually exclusive.
[1] Number (%) of patients experiencing one or more adverse events in the respective category.
Source: Safety Update, Table 6-I, pg 56, Submission of March 2001.

Medical Officer's Comments

- *The percentages of patients represented in Table 56 and Table 57 who reported adverse in each of the categories were comparable, for the most part, in the Lupron alone and abarelix groups. Exceptions included a higher percentage of patients who experienced treated-related adverse events in the abarelix group (Table 56) and a slightly higher percentage of deaths, also in the abarelix group (Table 56 and Table 57).*

7.13.2 Adverse Events (All Intensities and All Relationships to Study Drug)

All adverse events (regardless of intensity or likely relationship to Study Drug) that occurred through Day 169 in at least 5% of patients treated with abarelix are pooled across studies and listed in Table 58. Adverse events were reported for 249 of 284 (88%) patients in the Lupron group, 79 of 83 (95%) patients in the Lupron plus Casodex group and 662 of 735 (90%) patients in the abarelix group. A similar listing for adverse events that occurred in patients treated for up to 1 year (Studies 149-98-02 and 149-98-03) is presented in Table 59. In patients treated for up to 1 year, adverse events were reported for 83 of 89 (93%) patients in the Lupron group, 79 of 83 (95%) patients in the Lupron plus Casodex group and 335 of 348 (96%) patients in the abarelix group.

Table 58. Adverse Events (All Treatment Relationships) Occurring Through Day 169 in 5% or More of Patients in the Abarelix Group (Studies 149-98-02, 149-98-03, and 149-99-03)

Preferred Term	Lupron N = 284 n (%)	Lupron Plus Casodex N = 83 n (%)	Abarelix N = 735 n (%)
Any Adverse Event	*249 (88)*	*79 (95)*	*662 (90)*
Pain	53 (19)	16 (19)	144 (20)
Upper resp tract infection	45 (16)	15 (18)	139 (19)
Fatigue	43 (15)	17 (20)	131 (18)
Micturition frequency	32 (11)	4 (5)	101 (14)
Headache	33 (12)	14 (17)	99 (13)
Diarrhea	32 (11)	10 (12)	95 (13)
Back pain	23 (8)	13 (16)	66 (9)
Constipation	19 (7)	9 (11)	62 (8)
Dizziness	19 (7)	9 (11)	61 (8)
Coughing	17 (6)	1 (1)	54 (7)
Nausea	19 (7)	6 (7)	53 (7)
Dysuria	23 (8)	2 (2)	50 (7)
Rash[1]	14 (5)	11 (13)	49 (7)
Rhinitis	11 (4)	8 (10)	45 (6)
Abdominal pain	13 (5)	10 (12)	43 (6)
Influenza-like symptoms	14 (5)	3 (4)	43 (6)
Myalgia	21 (7)	6 (7)	43 (6)
Peripheral edema	20 (7)	9 (11)	39 (5)
Testis disorder	13 (5)	3 (4)	38 (5)
Nocturia	12 (4)	3 (4)	36 (5)
Impotence	16 (6)	2 (2)	35 (5)

Based on descending order of frequency in the abarelix group through Day 169
[1] Includes rash, erythematous rash, maculopapular rash
Source: Table 6-E, ISS, pg 163, Vol. 1.108, Submission of December 2000.

Table 59. Adverse Events (All Treatment Relationships) Occurring in 5% or More of Patients With Up to 1 Year of Exposure to Study Drug (Studies 149-98-02 and 149-98-03)

	Treatment Group		
Preferred Term	Lupron N = 89 n (%)	Lupron Plus Casodex N = 83 n (%)	Abarelix N = 348 n (%)
Any Adverse Event	*83 (93)*	*79 (95)*	*335 (96)*
Upper resp tract infection	23 (26)	22 (27)	87 (25)
Pain	22 (25)	21 (25)	85 (24)
Fatigue	15 (17)	19 (23)	63 (18)
Diarrhea	15 (17)	11 (13)	59 (17)
Micturition frequency	10 (11)	7 (8)	52 (15)
Headache	10 (11)	14 (17)	51 (15)
Back pain	12 (13)	14 (17)	48 (14)
Dizziness	10 (11)	10 (12)	45 (13)
Constipation	6 (7)	9 (11)	32 (9)
Dysuria	7 (8)	4 (5)	32 (9)
Myalgia	10 (11)	7 (8)	32 (9)
Peripheral edema	19 (21)	12 (14)	32 (9)
Rash[1]	11 (12)	14 (17)	32 (9)
Influenza-like symptoms	8 (9)	6 (7)	31 (9)
Nausea	7 (8)	6 (7)	30 (9)
Accidental injury	3 (3)	4 (5)	29 (8)
Abdominal pain	5 (6)	10 (12)	27 (8)
Rhinitis	6 (7)	9 (11)	27 (8)
Surgical intervention	7 (8)	8 (10)	27 (8)
Coughing	10 (11)	2 (2)	25 (7)
Nocturia	3 (3)	4 (5)	25 (7)
Testis disorder	2 (2)	4 (5)	23 (7)
Urinary tract infection	4 (4)	7 (8)	23 (7)
Pruritus	8 (9)	2 (2)	21 (6)
Purpura	3 (3)	6 (7)	20 (6)
Sinusitis	7 (8)	4 (5)	19 (5)
Hematuria	5 (6)	3 (4)	18 (5)
Leg pain	2 (2)	4 (5)	18 (5)
Micturition urgency	1 (1)	0	18 (5)
Anemia	6 (7)	8 (10)	17 (5)
Chest pain	4 (4)	6 (7)	17 (5)
Dyspnea	6 (7)	3 (4)	17 (5)
Infection	5 (6)	4 (5)	17 (5)
Skin disorder	4 (4)	4 (5)	17 (5)

Events occurring in at least 5% of the abarelix depot group

[1] Includes rash, erythematous rash, or maculopapular rash

Source: Safety Update, Table 6-P, pg 61, Submission of March 2001.

Medical Officer's Comments

- *The types and incidences of reported adverse events are compatible with the study population (men with carcinoma of the prostate with a median age of > 70 yr.). For most categories, the reported incidence of adverse events was similar in the abarelix and Lupron groups.*
- *Categories of adverse events in which the percentage of patients reporting an event through Day 169 in the abarelix group exceeded that in the in the Lupron group by ≥ 3% (Table 58) were upper respiratory tract infection, fatigue, and micturition frequency (all 3% higher).*

- *In patients treated for up to 1 year, adverse event categories for which the percentage of patients reporting an event in the abarelix group exceeded that in the Lupron group by ≥ 3% (Table 59) were micturition frequency, headache, accidental injury, nocturia, testis disorder, urinary tract infection, purpura, leg pain, and micturition urgency.*

7.13.3 Treatment-Related Adverse Events

All treatment-related adverse events that occurred through Day 169 in the 3 primary safety studies in at least 2% of patients treated with abarelix are pooled across studies and listed in Table 60. Treatment-related adverse events were reported for 136 of 284 (48%) patients in the Lupron group, 48 of 83 (58%) patients in the Lupron plus Casodex group and 373 of 735 (51%) patients in the abarelix group. A similar listing for adverse events that occurred in patients treated for up to 1 year (Studies 149-98-02 and 149-98-03) is presented in Table 61. In patients treated for up to 1 year, adverse events were reported for 37 of 89 (42%) patients in the Lupron group, 51 of 83 (61%) patients in the Lupron plus Casodex group and 181 of 348 (52%) patients in the abarelix group.

Table 60. Treatment-Related Adverse Events Occurring Through Day 169 in 2% or More of Patients in the Abarelix Group (Studies 149-98-02, 149-98-03, and 149-99-03)

Preferred Term	Lupron N = 284 n (%)	Lupron Plus Casodex N = 83 n (%)	Abarelix N = 735 n (%)
Any Treatment-Related AE	*136 (48)*	*48 (58)*	*373 (51)*
Fatigue	34 (12)	12 (14)	106 (14)
Headache	19 (7)	7 (8)	61 (8)
Testis disorder	12 (4)	2 (2)	35 (5)
Pain	10 (4)	2 (2)	30 (4)
Impotence	16 (6)	2 (2)	29 (4)
Micturition frequency	9 (3)	1 (1)	27 (4)
Diarrhea	12 (4)	3 (4)	23 (3)
Dizziness	8 (3)	2 (2)	20 (3)
Libido decreased	21 (7)	2 (2)	19 (3)
Rash[1]	3 (1)	3 (4)	19 (3)
Weight increase	2 (1)	0	16 (2)
Flatulence	5 (2)	3 (4)	15 (2)
Muscle weakness	4 (1)	2 (2)	15 (2)
Pruritus	5 (2)	1 (1)	15 (2)
Insomnia	10 (4)	2 (2)	13 (2)
Nausea	11 (4)	1 (1)	13 (2)
Nocturia	3 (1)	2 (2)	13 (2)
Myalgia	11 (4)	2 (2)	12 (2)

Based on descending order of frequency in the abarelix depot group through Day 169.

[1] Rash, erythematous rash, maculopapular rash.

Source: Table 6-G, pg 166, ISS Vol. 1.108, Submission of December 2000.

Table 61. Treatment-Related Adverse Events Occurring in 1% or More of Patients in the Abarelix Group With Up to 1 Year of Exposure to Study Drug (Studies 149-98-02 and 149-98-03)

	Treatment Group		
Preferred Term	Lupron N = 89 n (%)	Lupron Plus Casodex N = 83 n (%)	Abarelix N = 348 n (%)
Any Treatment-Related AE	*37 (42)*	*51 (61)*	*181 (52)*
Fatigue	8 (9)	15 (18)	50 (14)
Headache	6 (7)	7 (8)	31 (9)
Testis disorder (atrophy)	1 (1)	3 (4)	20 (6)
Pain	3 (3)	4 (5)	18 (5)
Micturition frequency	1 (1)	2 (2)	17 (5)
Dizziness	2 (2)	2 (2)	12 (3)
Pruritus	4 (4)	1 (1)	11 (3)
Diarrhea	1 (1)	3 (4)	10 (3)
Paraesthesia	0	0	9 (3)
Myalgia	3 (3)	2 (2)	8 (2)
Nocturia	0	3 (4)	8 (2)
Rash [1]	1 (1)	3 (4)	8 (2)
Testicular pain	1 (1)	4 (5)	8 (2)
Anorexia	1 (1)	1 (1)	7 (2)
Impotence	2 (2)	2 (2)	7 (2)
Muscle weakness	1 (1)	3 (4)	7 (2)
Injection site pain	3 (3)	0	6 (2)
Nausea	3 (3)	1 (1)	6 (2)
Somnolence	1 (1)	1 (1)	6 (2)
Anemia	0	5 (6)	5 (1)
Depression	0	3 (4)	5 (1)
Flatulence	2 (2)	3 (4)	5 (1)
Rhinitis	0	3 (4)	5 (1)
Abdominal pain	1 (1)	5 (6)	4 (1)
Alopecia	2 (2)	0	4 (1)
Constipation	0	6 (7)	4 (1)
Libido decreased	2 (2)	2 (2)	4 (1)
Peripheral edema	7 (8)	1 (1)	4 (1)
Arthralgia	0	3 (4)	2 (1)
Dry Skin	0	2 (2)	2 (1)
Malaise	0	2 (2)	2 (1)

Events occurring in at least 2% of patients in any treatment group.

[1] Includes rash, erythematous rash, or maculopapular rash.

Source: Table 6-Q, pg 63, Safety Update, Submission of March 2001.

Medical Officer's Comments

- *Adverse event categories for which the percentage of patients reporting an event in the abarelix group exceeded that in the Lupron group by ≥ 2% through Day 169 (Table 60) were fatigue and rash (both by 2%).*
- *In patients treated for up to 1 year, adverse event categories for which the percentage of patients reporting an event in the abarelix group exceeded that in the Lupron group by ≥ 2% (Table 61) were fatigue, headache, testis disorder (atrophy), pain, micturition frequency, diarrhea, paraesthesia, and nocturia.*

- *The percentages of patients experiencing a treatment-related adverse event in the abarelix group were greater than those in the Lupron group (51% vs 48% through Day 169; 52% vs 42% for up to 1 year of treatment). However, the percentages of patients experiencing a treatment-related adverse events in the abarelix group were lower than those in the Lupron plus Casodex group (51% vs 58% through Day 169; 52% vs 61% for up to 1 year of treatment).*
- *The number of adverse categories, for which the percentage of patients was higher in the abarelix group relative to the Lupron group, appeared to increase with increasing duration of treatment (see preceding comments). This apparent relative increase may be misleading and should be accepted with reservation for the following reason. The overall incidence of treatment-related adverse events in patients treated with Lupron for up to 1 year (Study 149-98-02) was reported to be lower than that for the pooled data for patients treated with Lupron for only 6 months in Studies 149-98-02 and 149-99-03.*

7.13.4 Adverse Events Resulting in Patient Withdrawal

The treatment-related adverse events that led to withdrawal of patients from the 3 primary safety studies are summarized and listed by preferred terms in Table 62. Overall, 5 of 284 (1.8%) patients in the Lupron group, 6 of 83 (7.2%) patients in the Lupron plus Casodex group and 19 of 735 (2.6%) patients in the abarelix group were withdrawn because of a treatment related adverse event. (A treatment related adverse event was defined as an adverse event considered to have an unknown, possible, probable, or definite relationship to Study Drug.)

Medical Officer's Comments

- *None of the adverse events resulting in a patient's withdrawal occurred with an incidence of > 2%. The most frequent adverse events (based on percentage of affected patients) were (a) increased hepatic enzymes (2.4%) and fatigue (2.4.%) in the Lupron plus Casodex group, (b) hot flashes (1.1%) in the Lupron group, and (c) increased hepatic enzymes (0.7%) and allergic events (0.8%, includes allergic reactions, urticaria, and rash) in the abarelix group.*
- *Hepatotoxicity is a known complication of treatment with Casodex and other antiandrogens. Hot flashes are an expected consequence of medical castration and are to be expected.*
- *The percentages of patients withdrawn for hepatotoxicity and allergic reactions in the abarelix group, based on this reviewer's assessment of the data, are slightly higher than those represented in Table 62, which are based on the sponsor's assessment. Systemic allergic reactions and hepatotoxicity are reviewed in detail in Sections 7.16.2 and 7.16.3, respectively.*

Table 62. Withdrawals Due to Treatment-Related Adverse Events (Studies 149-98-02, 149-98-03, 149-99-03)

	Lupron			Lupron Plus Casodex®			Abarelix		
	Through Day 169	Beyond Day 169	Overall	Through Day 169	Beyond Day 169	Overall	Through Day 169	Beyond Day 169	Overall
Evaluable Patients [A]	N = 284 n (%)	N = 79 n (%)	N = 284 n (%)	N = 83 n (%)	N = 71 n (%)	N = 83 n (%)	N = 735 n (%)	N = 325 n (%)	N = 735 n (%)
Number of adverse events	6	1	7	6	2	8	16	3	19
Withdrawals due to adverse events	4 (1)	1 (< 1)	5 (2)	4 (5)	2 (3)	6 (7)	16 (2)	3 (1)	19 (3)
Preferred Term									
Hepatic enzymes increased [1]	0	0	0	2 (2)	0	2 (2)	5 (1)[2]	0	5 (1)
Allergic reaction	0	0	0	0	0	0	4 (1)[3]	0	4 (1)
Depression	0	0	0	1 (1)	0	1 (1)	2 (< 1)	0	2 (< 1)
Hot flushes	2 (1)	1 (< 1)	3 (1)	1 (1)	0	1 (1)	1 (< 1)	1 (< 1)	2 (< 1)
Anemia	0	0	0	0	0	0	1 (< 1)	0	1 (< 1)
Chest pain	0	0	0	0	0	0	0	1 (< 1)	1 (< 1)
Fatigue	1 (< 1)	0	1 (< 1)	1 (1)	1 (1)	2 (2)	1 (< 1)	0	1 (< 1)
Rash	0	0	0	0	0	0	1 (< 1)	0	1 (< 1)
Syncope	0	0	0	0	0	0	1 (< 1)	0	1 (< 1)
Urticaria	1 (< 1)	0	1 (< 1)	0	0	0	0	1 (< 1)	1 (< 1)
Headache	1 (< 1)	0	1 (< 1)	0	0	0	0	0	0
Insomnia	1 (< 1)	0	1 (< 1)	0	0	0	0	0	0
Libido decreased	0	0	0	1 (1)	0	1 (1)	0	0	0
Myalgia	0	0	0	0	1 (1)	1 (1)	0	0	0

[A] Sponsor's Analyses; Listed in descending order of frequency in the abarelix depot group (overall).
[1] Includes events of hepatic enzymes increased, SGPT increased, and hepatic function abnormal
[2] One patient with elevated liver enzymes (Patient 50-3085 in Study 149-98-03) elected to withdraw for "personal reasons" and is not included in this listing. Inclusion of this patient would increase the total to 6 patients as in Table 92.
[3] The sponsor's assignment of patients to the category of "allergic reaction" as represented in this listing differs somewhat from that used by this reviewer. See Section 7.16.2.1 for more information about patient withdrawals due to allergic reactions.
Source: Table 6-C, pg 158, ISS Vol. 1.108, Submission of December 2000.

7.13.5 Severe or Life-Threatening Adverse Events

Across the 3 controlled studies (Studies 149-98-02, 149-98-03, and 149-99-03), severe or life-threatening adverse events were reported for 60 of 284 patients (21%) in the Lupron group, 21 of 83 patients (25%) in the Lupron plus Casodex group, and 125 of 735 patients (17%) in the abarelix group. Across these same studies, *treatment-related*, severe or life-threatening adverse events were reported for 15 of 284 patients (5%) in the Lupron group, 2 of 83 patients (2%) in the Lupron plus Casodex group, and 23 of 735 patients (3%) in the abarelix group. The treatment-related, severe or life-threatening adverse events experienced by patients treated with abarelix are listed by patient in Table 63.

Medical Officer's Comments

- *Many of these severe or life threatening adverse events are not unexpected in a population of elderly men with prostate cancer. Others would be expected as a consequence of decreased testosterone levels resulting from treatment with abarelix.*
- *Three of the patients experienced severe increases in transaminases (Patient Nos. 37-2160, 50-3018, and 50-3085) and 5 of the patients (Patient Nos. 11-2218, 16-3028, 09-3246, 313-3087, and 333-3336) experienced allergic reactions. (The adverse event in Pt. No. 333-3336 was called a vasovagal reaction by the Investigator but the signs and symptoms were indistinguishable from those of an allergic reaction and the patient was withdrawn from the study.) Allergic reactions and hepatotoxicity are reviewed in detail in Sections 7.16.2 and 7.16.3, respectively.*

Table 63. Severe or Life-Threatening Treatment-Related Adverse Events in Abarelix Treatment Groups (Studies 149-98-02, 149-98-03, and 149-99-03)

Study No.	Patient No.	Age (yr)	Race[1]	Preferred Term	Verbatim Description	Onset Day	Event Duration (days)	Relationship
149-98-02	37-2085	63	C	Libido decreased	Decreased Libido	24	NR [2]	Definite
	13-2149	75	C	Aggravated depression	Worsening depression	110	19	Possible
				Neurosis	Suicidal ideations	114	15	Possible
	37-2160	50	H	Hepatic enzymes increased	Elevated transaminases	29	164	Definite
	13-2178	54	C	Headache	Headache	21	3	Possible
	11-2218	71	C	Allergic reaction	Drug reaction	15	1	Definite
149-98-03	50-3018	75	C	Hepatic enzymes increased	Elevated liver enzymes	169	13	Possible
	16-3028	75	A	Flushing	Whole body warmth	169	1	Probable
				Erythematous rash	Whole body redness	169	1	Probable
	50-3085	62	C	Elevated AST	Elevated AST	253	NR	Possible
	71-3108	71	AA	Depression	Depression	107	NR	Possible
	50-3175	79	C	Pain	Pain lower arms and bottom rib cage	15	1	Unknown
	09-3246	81	C	Allergic reaction	Allergic reaction	85	1	Definite
149-99-03	310-1032	58	AA	Micturition frequency	Exacerbation of urinary frequency	74	NR	Unknown
				Micturition urgency	Exacerbation of urinary urgency	74	NR	Unknown
	390-1206	71	C	Urinary tract infection	Urinary tract irritation	28	17	Possible
	350-1357	63	C	Impotence	Impotence	54	NR	Definite
	314-1385	78	C	Hot flushes	Intolerable hot flashes	140	NR	Definitely
	357-1448	83	C	Pain	Pain right shoulder	13	NR	Unknown
	306-1544	87	C	Fatigue	Fatigue	30	51	Possible

[1] Race: C = Caucasian, AA = African American, H= Hispanic, A = Asian.
[2] NR = Not Resolved.

(Continued)

Table 63. Severe or Life-Threatening Treatment-Related Adverse Events In Abarelix Treatment Groups (Studies 149-98-02, 149-98-03, and 149-99-03) (Continued)

Study No.	Patient No.	Age (yr)	Race[1]	Preferred Term	Verbatim Description	Onset Day	Event Duration (days)	Relationship
149-99-03	337-2016	57	AA	Headache	Worsening headaches	18	52	Possible
(Continued)	377-2060	63	C	Back pain	Flank pain	125	18	Unknown
	391-2358	70	C	Fatigue	Fatigue	40	NR	Probable
				Somnolence	Lethargy	40	NR	Probable
	391-2522	63	C	Depression	Depression	12	158	Probable
	313-3087	74	A	Allergic reaction	Systemic allergic response	56	1	Probable
	333-3336	72	C	Syncope	Vasovagal reaction	15	1	Unknown

[1] Race: C = Caucasian, AA = African American, H= Hispanic, A = Asian.
[2] NR = Not Resolved
Source: Table 6-H, ISS (Submission of December 2000) and Table 6-S, pg 66, Safety Update (Submission of March 2001).

7.13.6 Nonfatal, Serious Treatment-Related Adverse Events

Across the 3 controlled studies (Studies 149-98-02, 149-98-03, and 149-99-03), nonfatal serious adverse events were reported for 35 of 284 patients (12%) in the Lupron group, 15 of 83 patients (18%) in the Lupron plus Casodex group, and 89 of 735 patients (12%) in the abarelix group. Across these same studies, treatment-related nonfatal serious adverse events were reported for 3 of 284 patients (1%) in the Lupron group, 2 of 83 patients (2%) in the Lupron plus Casodex group, and 12 of 735 patients (2%) in the abarelix group. The treatment-related nonfatal serious adverse events in the controlled studies are listed by treatment group and patient in Table 64.

Medical Officer's Comments

- *Of the 12 nonfatal serious adverse events in the abarelix-treated patients, 6 were systemic allergic reactions (listed as a cutaneous reaction[urticaria, n = 1 or rash, n = 1] or allergic reaction[n = 4] and 4 were related to hepatic toxicity. One reaction (Patient No. 333-3336) was listed as a vasovagal reaction but may have been a systemic allergic reaction as discussed in the Medical Officer's Comments in Section 7.13.5. Allergic reactions and hepatotoxicity in abarelix-treated patients are reviewed in detail in Sections 7.16.2 and 7.16.3, respectively.*
- *Two patients in the Lupron plus Casodex group experienced serious adverse events related to elevations in transaminases. Increased transaminases are an expected adverse effect in patients treated with antiandrogens such as Casodex.*

Table 64. Nonfatal, Serious Treatment-Related Adverse Events (Studies 149-98-02, 149-98-03, 149-99-03)

Study	Patient No.	Preferred Term (verbatim description)	Onset (day)	Severity	Relationship to Treatment
Lupron Treatment Group (N = 284)					
149-98-02	46-2065	Fall (collapse without syncope)	286	Moderate	Possible
149-99-03	301-1295	Urticaria acute (acute urticaria)	67	Severe	Definite
	328-3084	Ketosis (diabetic ketoacidosis)	80	Severe	Probable
Lupron Casodex Treatment Group (N = 83)					
149-98-03	27-3049	Hepatic enzymes increased (elevated transaminases)	43	Moderate	Definite
	01-3144	SGPT increased (elevated SGPT)	57	Moderate	Possible
Abarelix Depot Treatment Group (N = 735)					
149-98-02	37-2160	Hepatic enzymes increased (elevated transaminases)	29	Severe	Definite
	11-2218	Allergic reaction (drug reaction)	15	Severe	Definite
149-98-03	09-3036	Hepatic enzymes increased (elevated liver function tests)	29	Moderate	Definite
	50-3085	Hepatitis (chemical hepatitis)	253	Moderate	Probable
	27-3200	Urticaria (urticaria)	197	Mild	Definite
	76-3224	Allergic reaction (allergic reaction)	29	Mild	Probable
	09-3246	Allergic reaction (allergic reaction)	85	Severe	Definite
149-99-03	313-1063	Migraine aggravated (exacerbation of migraine HA)	21	Moderate	Possible
	338-1259	Hepatic enzymes increased (elevated transaminases)	29	Moderate	Possible
	357-2226	Rash (rash)	85	Moderate	Definite
	313-3087	Allergic reaction (systemic allergic response)	56	Life-threatening	Probable
	333-3336	Syncope (vasovagal reaction)	15	Severe	Unknown

Source: Safety Update - Table 6-D and Table 6-O, Submission of March 2001.

7.14 Deaths (All Abarelix Clinical Trials)

7.14.1 Studies Sponsored by Praecis

In the 3 primary, controlled safety studies, a total of 12 patients died (1 in the Lupron group and 11 in the abarelix group), either during the treatment period (within 28 days of the last dose of Study Drug) or during the posttreatment follow up period (Table 65). In the uncontrolled studies conducted in North America (Studies 149-97-04, 149-98-04, 149-99-04, and 149-01-05), a total 19 patients died, 18 patients during or following treatment with abarelix and 1 patient during treatment with Lupron in cross-over Study 149-01-05 (Table 66). None of the deaths, according to the Sponsor, was attributed to treatment with abarelix. The Sponsor also reported that progression of prostate cancer was either

the underlying or immediate cause of death in 11 of the 29 patients treated with abarelix who were reported to have died (Table 65 and Table 66).

Table 65. Listing of Patients Who Died During or Following Treatment with Abarelix or Lupron (Controlled Studies 149-98-02, 149-98-03, and 149-99-03)

Study	Patient Number	Age (yr)	Race[1]	Cause of Death	Last Dose (day)	Day of Death	Days From Last Dose
Lupron (N = 284)							
149-98-02	22-2119	80	C	Myocardial infarction	308	338	30
Lupron Plus Casodex (N= 83)							
				No Deaths			
Abarelix Depot (N = 735)							
149-98-02	22-2031	73	C	Pulmonary carcinoma	309	349	40
149-98-02	41-2075	72	C	Cardiac failure	253	305	52
149-98-02	41-2120	85	C	Pulmonary carcinoma	253	290	37
149-98-02	41-2137	77	C	Intracranial hemorrhage	197	214	17
149-98-02	42-2254	68	C	Myocardial infarction	179	187	8
149-98-03	71-3189	51	C	Metastatic prostate cancer	86	123	37
149-99-03	317-1216	67	C	Pancreatic carcinoma	29	115	86
149-99-03	392-1399	79	C	Chr obstruct. lung disease	113	185	72
149-99-03	341-1540	89	C	Empyema right lung	85	101	16
149-99-03	308-2093	80	C	Pneumonia	113	134	21
149-99-03	330-3443	61	AA	Metastatic prostate cancer	149	165	16

[1] Race: C = Caucasian, AA = African American
Source: Data Listing 2.1 (ISS, Vol. 1.110), Submission of December 2000.

Table 66. Listing of Patients Who Died During or Following Treatment with Abarelix (Uncontrolled Studies 149-97-04, 149-98-04, 149-99-04, and 149-01-05)

Patient Number	Age	Race[1]	Cause of death	Last Dose (Day)	Day of Death	Days From Last Dose
Study 149-97-04 (n = 263)						
37-4766	54	C	Acute myocardial infarction	309	321	12
38-4775	63	C	Metastatic prostate carcinoma	454	466	12
02-4760	82	C	Bronchial aspiration	252	291	39
22-4763	81	C	Metastatic prostate carcinoma	85	154	69
Study 149-98-04 (n = 81)						
402-4030	71	C	Progression of prostate cancer	85	118	33
477-4043	79	C	Progression of prostate cancer	168	188	20
409-4044	94	C	Progression of prostate cancer	29	45	16
441-4050	89	C	Pulmonary embolus	29	61	32
477-4064	77	C	Renal failure 2nd to prostate cancer	142	149	7
499-4101	55	H	Progression of prostate cancer	197	216	19
Study 149-99-04 (n = 278)						
001-2601	81	C	Cardiac arrest 2nd to prostate cancer	1179[2]	1190[2]	11
012-3027	84	C	Massive stroke	400	422	22
038-3179	72	C	Pneumonia	393	406	13
383-1366	82	C	Subendocardial infarction	282	301	19
442-4037	69	C	Myocardial infarction	174	200	26
428-4005	77	C	Pneumonia	310	339	29
438-4028	71	C	Cardiac arrest	589	612	23
441-4036	94	C	Metastatic prostate cancer	253	274	21
Study 149-01-05 (n = 176)						
06-1004[3]	86	C	"Ventricular fibrillation" 2nd CAD	113	116	3

[1] Race: C = Caucasian, H = Hispanic
[2] For all patients in Study 149-99-04, number represents cumulative dosing from prior study and study 149-99-04.
[3] Patient died 3 days after his second dose of Lupron and 56 days after his third (and last) dose of abarelix.
Source: Table 10-7, Vol. 91 (Study 97-04); Table 10-9, Vol. 1 (Final Report for Study 149-98-04); Table 8-K, Final Report for Study 149-99-04, Table 10-7); and Final Report for Study 149-01-05. Submissions of December 2000, February 2003, and April 2003.

Medical Officer's Comments

- *Of the 29 deaths in abarelix-treated patients in the 3 primary controlled studies and the uncontrolled North American studies, 11 were attributed to progression of prostate cancer as either the underlying or the immediate cause of death. According to the Sponsor, end-of-treatment testosterone data were available for 9 of these patients. All were suppressed to ≤50 ng/dL at the time of their last assessment.*
- *Of the remaining 18 deaths, 6 were a result of a cardiac adverse event (myocardial infarction [n = 4], cardiac arrest/cardiac failure [n = 2]), 2 were a result of a stroke, 1 was secondary to a pulmonary embolus, 5 were attributed to respiratory/infectious causes (pneumonia [n = 3], empyema right lung [n = 1], or chronic obstructive lung disease [n = 1]), 3 were attributed to coexisting carcinomas (pulmonary [n = 2] or pancreatic [n = 1]), and 1 was due to aspiration.*
- *In the active controlled, primary safety studies, the percentage of abarelix-treated patients reported to have died (11 of 735, 1.50%) was numerically greater than that of the active control-treated patients (1 of 367, 0.27%). The basis for this imbalance is unclear. Of the 11 deaths in*

the abarelix-treated patients 3 cases (2 cases of pulmonary carcinoma and 1 case of pancreatic carcinoma) were very unlikely to have been related to treatment with abarelix, and 2 cases were related to progression of prostate cancer. Of the remaining 6 deaths, 2 occurred > 50 days after the patient's last dose of abarelix. The remaining 4 deaths all occurred on-treatment (i.e., within 28 days of the last dose of abarelix. These 4 deaths were attributed to an intracranial hemorrhage, a myocardial infarction, an empyema of the right lung, and chronic obstructive lung disease, respectively. In summary, the causes of death in the abarelix-treated patients appear to be compatible with those that would be expected in a population of elderly men with carcinoma of the prostate. The findings from the primary controlled safety regarding patients who died do not significantly alter the risk/benefit ratio for abarelix for the palliative treatment of those men with advanced, symptomatic prostate cancer that are described in labeling (see Section 10.2) and do not preclude approval for its use in such patients.

7.14.2 Studies Sponsored By Sanofi-Synthelabo

Two studies, ABACAS 1 and ABACAS 1 Extension, were conducted in Europe by Sanofi-Synthelabo. ABACAS 1 was a randomized, active controlled study of 1 year duration in which men with prostate cancer were randomized to treatment with either abarelix (n = 87) or Zoladex plus Casodex (n =90). ABACAS 1 Extension was a rollover study in which patients who had successfully completed treatment with abarelix in ABACAS 1 could continue abarelix treatment (n = 51 patients). In ABACAS 1, a total of 5 patients were reported to have died (1 patient in the Zoladex plus Casodex group and 4 patients in the abarelix group), either during treatment or during the posttreatment period (Table 67). Three patients were reported to have died in the ABACAS 1 Extension Study while receiving treatment with abarelix.

Table 67 Listing of Patients Who Died During or Following Treatment with Abarelix or Zoladex plus Casodex in ABACAS 1 and ABACAS 1 Extension.

Study Patient Number	Age	Race[1]	Cause of death	Last Dose (Day)	Day of Death	Days From Last Dose
ABACAS 1 (Controlled Study)						
Zoladex plus Casodex Treatment Group (n = 90)						
27790104	?	?	Progression of prostate cancer	1	-A-	-A-
Abarelix Treatment Group (n = 87)						
5280005	77	C	Pulmonary embolus	28	64	36
21540221	69	C	Cerebral hemorrhage &/or Parkinson's Disease	56	76	20
27790103	72	?	Progression of prostate cancer	281	-B-	-B-
38270143	62	?	Progression of prostate cancer	257	-D-	-D-
ABACAS 1 Extension (Uncontrolled Study, n = 51, all patients treated with abarelix)						
7450274	82	C	Cardiac arrest	597	628	31
21540062	76	C	Rupture of thoracic aneurysm	336	356	20
26700223	62	C	Auto accident	336	342	6

A: Date of death and relationship to last dose of study drug not clearly reported
B: Reported as several months post study.
D: Reported as about 1 year post study.
Source: Final Report for ABACAS 1 Extension (Table 10-7), Submission of April 2003; Final Report for ABACAS 1 (Data Listing 16.2.7.2.2), Submission of February 2003.

Medical Officer's Comments

- *In ABACAS 1, 2 deaths were reported to have occurred during treatment with abarelix and 2 were reported to have occurred either several months or 1 year, respectively, after the last dose of abarelix. For the 2 patients who died during treatment, the causes of death were reported as "suspicion of cerebrovascular disorder and/or with aggravated Parkinson's Disease" and "pulmonary embolism," respectively. The Study Investigators did not exclude a possible relationship between the deaths and treatment with abarelix. The Sponsor, however, excluded a possible relationship between the deaths and treatment with abarelix. Based on the known safety profile of abarelix to date, there is no basis at this time for attributing either of these on-treatment deaths to treatment with abarelix.*
- *Although there is a small numeric imbalance in the number of on-treatment deaths in the abarelix treatment group (2 deaths) compared to the number in the comparator group (either 1 or 0), this imbalance does not affect the risk/benefit assessment for the use of abarelix for the palliative treatment of those men with advanced, symptomatic prostate cancer that are described in labeling (see Section 10.2).*

7.15 Laboratory Assessments (Primary Controlled Safety Studies)

Medical Officer's Comments

Laboratory data for the 3 primary safety studies were reviewed in the following manner:

- Mean values, median values, and mean changes from baseline values for each laboratory test at protocol-designated assessment times were reviewed for differences across treatment groups.
- Percentages of patients with laboratory values that shifted to outside of the normal range on one more or more occasions during treatment were reviewed for differences across treatment groups. Shift tables containing selected test values are provided in this review.
- Notable laboratory values (abnormal values that were considered to be of particular concern based on the Sponsor's criteria) were reviewed.

7.15.1 Hematology Assessments

7.15.1.1 Mean Changes From Baseline Values

Medical Officer's Comment

- *There were no remarkable or consistent differences in mean changes from baseline values in the pooled hematology values from the 3 primary safety studies. Isolated or intermittent changes for some measurements at some assessment times were noted but no consistent patterns suggestive of increased toxicity in the abarelix groups were observed.*

7.15.1.2 Shifts to Outside of the Normal Range

Percentages of patients with selected hematology values that shifted to outside of the normal range on one more or more occasions during treatment are presented in Table 68. For each measurement, the percentage of patients with a shift to low (i.e., normal to low, high to low, and unknown to low) or a shift to high (i.e., normal to high, low to high, and unknown to high) is listed. Data are also presented separately for changes that were observed between Study Days 1-169 (pooled data from Studies 149-98-02, 149-98-03, and 149-99-03) and between Study Days 1-365 (pooled data from only Studies 149-98-02 and 149-98-03).

Medical Officer's Comments

- *For the pooled data for the period from Day 1-169, all differences between the abarelix group and the Lupron group or the Lupron plus Casodex group were ≤ 3% with the following*

exceptions. Differences of >3% in shifts from normal to low included: a greater percentage of Lupron or Lupron plus Casodex patients shifting to low for the categories of hematocrit, WBC, and neutrophils. The percentages of patients who shifted from normal to high for eosinophils was higher in the Lupron group (14%) and the Lupron plus Casodex group (17%) than in the abarelix group (10%).

- *For the period from Day 1-365, in which data from only Studies 149-98-02 and 149-98-03 were assessed, there were no remarkable differences between the abarelix and Lupron groups. Differences of >4% in shifts from normal to low or high included: (a) a greater percentage of Lupron patients shifting to low for the categories of hemoglobin and hematocrit, (b) a greater percentage of abarelix patients shifting to low for the category of white blood cells, and (3) a greater percentage of Lupron patients shifting to high for the category of eosinophils (23% vs 15%). It is not known it these differences between the Day 1-169 and Day 1-365 comparisons are a result of chance and the smaller sample size in the Day 1-365 comparison (more likely in this reviewer's opinion) or the longer treatment period.*

7.15.1.3 Clinically Notable Hematology Values

The sponsor defined upper and lower limits for selected hematology values (clinically notable hematology values, Table 36) that represented changes of particular clinical significance. Table 69 summarizes the number and percentage of subjects in the 3 primary safety studies that exhibited clinically notable hematology values. Overall, the number of such patients was low, although the highest percentages of such changes in virtually each category were observed in the pooled abarelix group.

Medical Officer's Comment

- *The greatest differences between the abarelix and the Lupron groups were observed for decreases in hemoglobin and increases in WBC values. Nineteen of 735 (2.6%) patients in the abarelix group, compared to 4 of 283 (1.4%) patients in the Lupron group, had hemoglobin values below 9.5 g/dL. Of these 23 subjects, only one, a patient in the abarelix group, had a hemoglobin value below 8.0 g/dL. In the abarelix group, a 2-fold higher percentage of patients (1.8% of the abarelix group vs 0.7% of the Lupron group) had WBC values of greater than 15,000/μL.*
- *Considering the study populations, namely elderly men with prostate cancer and other serious medical problems, the absolute number of clinically notable hematology values and the differences across groups are not worrisome.*

Table 68. Hematology Value Shifts to Outside the Normal Range (Studies 149-98-02, 149-98-03, 149-99-03)

	Lupron (N=284)				Lupron +Casodex (N=83)				Abarelix (N=735)			
	Shift to Low[1]		Shift to High[2]		Shift to Low		Shift to High		Shift to Low		Shift to High	
	Eval[3]	Shift	Eval[3]	Shift	Eval	Shift	Eval	Shift	Eval	Shift	Eval	Shift
Test	N	(%)	N	(%)	N	(%)	n	(%)	N	(%)	n	(%)
Hemoglobin												
Days 1-169[4]	264	(27)	279	(1)	77	(23)	79	(1)	690	(25)	716	(1)
Days 1-365[5]	80	(48)	89	(1)	77	(31)	79	(1)	335	(36)	338	(1)
Hematocrit												
Days 1-169	271	(32)	280	(1)	80	(28)	80	(0)	687	(28)	721	(1)
Days 1-365	85	(47)	89	(2)	08	(49)	80	(0)	334	(42)	342	(1)
White Blood Cell												
Days 1-169	273	(8)	277	(4)	79	(14)	77	(5)	693	(10)	710	(5)
Days 1-365	87	(11)	88	(5)	79	(15)	77	(6)	328	(18)	343	(6)
Platelet												
Days 1-169	276	(1)	279	(4)	79	(3)	81	(5)	713	(3)	724	(6)
Days 1-365	87	(2)	88	(6)	79	(5)	81	(7)	342	(4)	346	(9)
Neutrophils												
Days 1-169	283	(5)	264	(17)	78	(6)	78	(14)	723	(2)	678	(17)
Days 1-365	89	(6)	82	(26)	78	(8)	78	(22)	344	(4)	325	(23)
Lymphocytes												
Days 1-169	264	(17)	280	(5)	78	(15)	78	(4)	682	(16)	722	(2)
Days 1-365	82	(27)	88	(5)	78	(19)	78	(5)	328	(23)	344	(5)
Eosinophils												
Days 1-169	283	(0)	277	(14)	81	(0)	77	(17)	729	(0)	706	(10)
Days 1-365	89	(0)	87	(23)	81	(0)	77	(17)	348	(0)	337	(15)

[1] Shifts to low include normal to low, high to low, and unknown to low.
[2] Shifts to high include normal to high, low to high, and unknown to high.
[3] Patients whose baseline value was not low (shift to low) or not high (shift to high) and who had a least 1 lab result in the specified period.
[4] Includes Studies 149-98-02, 149-98-03, and 149-99-03.
[5] Includes only Studies 149-98-02 and 149-98-03.
Source: Modified from Tables 5.1.2 & 5.2.2 from ISS (Submission of December 2000) and Table 4.1.1 of Safety Update (Submission of March 2001).

Table 69. Clinically Notable Hematology Values (Studies 149-98-02, 149-98-03, 149-99-03)

	Treatment Group								
	Lupron (N=284)			Lupron + Casodex (N=83)			Abarelix (N=735)		
	Eval n	Experienced[1] n	(%)	Eval n	Experienced n	(%)	Eval n	Experienced n	(%)
Hemoglobin									
<8.0 g/dL	283	0		82	0		734	1	(0.1)
<9.5 g/dL	283	4	(1.4)	82	2	(2.4)	733	19	(2.6)
>19.0 g/dL	283	0		82	0		733	0	
Hematocrit									
<24%	283	0		82	0		733	1	(0.1)
>55%	283	0		82	0		733	1	(0.1)
Platelet count									
<75,000/µL	282	2	(0.7)	83	0		733	4	(0.5)
White blood cell count									
<2,000/µL	282	0		83	0		733	1	(0.1)
>15,000/µL	282	2	(0.7)	83	0		733	13	(1.8)

[1] Number and percent of patients who developed a clinically notable value in the respective category.
Source: Modified from Tables 4.2 and 12.8.10 of Safety Update, Submission of March 2001.

7.15.2 Chemistry Assessments

Laboratory data for tests of liver function (e.g., bilirubin) or of liver injury (e.g., transaminases) are presented and reviewed separately in Section 7.16.3.

7.15.2.1 Mean Changes from Baseline Values

Medical Officer's Comment

- *There were no remarkable or consistent differences (with one exception) in mean changes from baseline values in the pooled chemistry values from the 3 primary safety studies. Isolated or intermittent changes for some measurements at some assessment times were noted but no consistent patterns suggestive of increased toxicity in the abarelix groups were observed.*
- *The exception was serum triglyceride levels that tended to be higher in the abarelix group (see Table 70). Mean fasting serum triglyceride levels were numerically higher by 10-15 mg/dL in the abarelix group compared to the Lupron group in the controlled safety studies. This difference was more apparent when the absolute changes from baseline within each treatment group were reviewed, with the increases from baseline for fasting triglycerides ranging from 10.5 to 21.9 mg/dL in the abarelix group. The differences across treatment groups were even greater when the abarelix group was compared to the Lupron plus Casodex group.*
- *These increases in mean fasting serum triglyceride levels, although not desirable, are not a significant safety concern in the population to be treated with abarelix.*

Table 70. Mean Fasting Serum Triglycerides (mg/dL) and Mean Changes from Baseline during Treatment (Controlled Studies 149-98-02, 149-98-03, and 149-99-03)

Statistic	Mean Fasting Triglycerides (mg/dL)		
	Lupron (N = 284)	Lupron +Casodex (N= 83)	Abarelix (N = 735)
Baseline			
Mean	177	190	178
Day 85			
Mean	188	190	201
Mean change	9.1	-2.9	21.9
N	(272)	(80)	(704)
Day 169			
Mean	190	180	200
Mean change	13.1	-17.6	19.7
N	(251)	(69)	(660)
Day 253			
Mean	183	171	199
Mean change	-6.0	-28.2	10.5
N	(52)	(40)	(209)
Day 337			
Mean	185	185	200
Mean change	-9.0	-20.6	11.5
N	(51)	(35)	(185)

Source: Submission of March 27, 2001 Supplemental Chemistry Analyses, Table: 5.6.1.1.

7.15.2.2 Shifts to Outside of the Normal Range

Percentages of patients with selected chemistry values that shifted to outside of the normal range on one more or more occasions during treatment are presented in Table 71. Data are presented separately for changes that were observed between Study Days 1-169 (pooled data from Studies 149-98-02, 149-98-03, and 149-99-03) and between Study Days 1-365 (pooled data from only Studies 149-98-02 and 149-98-03).

Medical Officer's Comments

- *Differences of ≥ 5 in the percentage of patients who shifted to high in the abarelix group compared to the Lupron group were observed for potassium (both treatment periods), BUN (Days 1-169 only), and triglycerides (both treatment periods). The difference in the percentage of patient that shifted to high for triglycerides was even greater when the abarelix group was compared to the Lupron plus Casodex group. A difference of ≥ 5 in the percentage of patients who shifted to high in the Lupron group compared to the abarelix group was observed only for creatinine (Days 1-365).*
- *Differences of ≥ 5 in the percentage of patients who shifted to low in the abarelix group compared to the Lupron group were observed for total protein (Days 1-365 only) and HDL cholesterol (Days 1-365 only). However, a numerically greater percentage of patients in the Lupron plus Casodex group shifted to low for HDL cholesterol than in the abarelix group. The reported high percentage of patients in all treatment groups that shifted to low for total cholesterol is surprising and of unknown significance.*
- *The higher percentage of abarelix-treated patients who showed shifts to high in their serum triglyceride levels is in agreement with the observations reported in Section 7.15.2.1. Of note,*

there were no significant differences between the Lupron and abarelix groups in terms of the percentage of patients who had a shift to high for total cholesterol.

- *The pattern of increases in serum triglyceride levels is shown in greater detail in Table 72 in which the magnitude of the increases, based on WHO Toxicity Grades, is represented. The largest relative increase was observed in Toxicity Grade 1.*
-

7.15.2.3 Clinically Notable Chemistry Values

The sponsor defined upper and lower limits for selected chemistry values (clinically notable hematology values) that represented changes of particular clinical significance. Table 73 summarizes the number and percentage of subjects in the 3 primary safety studies that exhibited clinically notable chemistry values. For most laboratory assessments, the number of such patients exhibiting notable chemistry values was low.

Medical Officer's Comments

- *In general, the percentages of patients exhibiting notable chemistry values were similar across the treatment groups. Categories showing the highest percentages of these notable values included BUN and creatinine as would be expected in elderly men with prostate cancer.*

Table 71. Chemistry Value Shifts to Outside the Normal Range (Studies 149-98-02, 149-98-03, 149-99-03) [A]

	Lupron (N=284)				Lupron +Casodex (N=83)				Abarelix (N=735)			
	Shift to Low[1]		Shift to High[2]		Shift to Low		Shift to High		Shift to Low		Shift to High	
	Eval[3]	Shift	Eval[3]	Shift	Eval	Shift	Eval	Shift	Eval	Shift	Eval	Shift
Test	N	(%)	n	(%)	N	(%)	n	(%)	N	(%)	n	(%)
Potassium												
Days 1-169 [4]	280	(1)	278	(2)	81	(2)	76	(5)	727	(2)	716	(7)
Days 1-365 [5]	86	(1)	87	(3)	81	(4)	76	(7)	347	(3)	341	(9)
BUN												
Days 1-169	283	(0)	251	(24)	81	(0)	67	(16)	730	(0)	649	(30)
Days 1-365	89	(0)	81	(33)	81	(0)	67	(21)	348	(0)	314	(36)
Creatinine												
Days 1-169	283	(0)	250	(11)	81	(0)	67	(7)	730	(<1)	657	(12)
Days 1-365	89	(0)	81	(23)	81	(0)	67	(15)	348	(1)	309	(16)
Total Protein												
Days 1-169	281	(2)	271	(8)	81	(1)	80	(13)	729	(3)	705	(7)
Days 1-365	88	(1)	84	(7)	81	(2)	80	(14)	347	(6)	345	(8)
Cholesterol												
Days 1-169	204	(23)	279	(4)	55	(20)	81	(2)	530	(19)	718	(5)
Days 1-365	57	(37)	88	(3)	55	(25)	81	(4)	236	(32)	344	(5)
Triglycerides												
Days 1-169	279	(3)	239	(29)	81	(6)	64	(14)	722	(2)	625	(38)
Days 1-365	87	(2)	75	(31)	81	(11)	64	(20)	345	(3)	283	(45)
HDL												
Days 1-169	252	(4)	274	(5)	73	(11)	81	(7)	648	(6)	721	(6)
Days 1-365	79	(3)	88	(7)	73	(15)	81	(9)	308	(11)	344	(7)

[A] Liver function test are presented separately in Table 84 to Table 88.
[1] Shifts to low include normal to low, high to low, and unknown to low.
[2] Shifts to high include normal to high, low to high, and unknown to high.
[3] Patients whose baseline value was not low (shift to low) or not high (shift to high) and who had a least 1 lab result in the specified period.
[4] Includes Studies 149-98-02, 149-98-03, and 149-99-03.
[5] Includes only Studies 149-98-02 and 149-98-03.
Source: Modified from Table 5.4.2.1, supplemental safety submission, March 27, 2001.

Table 72. Triglyceride Shifts in Toxicity Grade - Baseline to Most Extreme On-Study Value on Study Days 85 and 169 (Pooled Data from Controlled Studies 149-98-02, 149-98-03, and 149-99-03)

		Baseline																	
		Lupron Depot [n, (%)]						Lupron Depot + Casodex [n, (%)]						Abarelix Depot [n, (%)]					
	Grade	0	1	2	3	4	Total	0	1	2	3	4	Total	0	1	2	3	4	Total
Highest On Study Grade	N/A	10	1	0	0	0	11	3	0	0	0	0	3	1	0	0	0	0	25
	0	197 (72)	12 (4)	1 (<1)	0	0	210	58 (73)	4 (5)	1 (1)	0	0	63	475 (67)	18 (3)	2 (<1)	1 (<1)	0	496
	1	25 (9)	15 (5)	1 (<1)	0	0	41	4 (5)	4 (5)	1 (1)	0	0	9	106 (15)	39 (5)	7 (1)	1 (<1)	0	153
	2	5 (2)	5 (2)	4 (1)	1 (<1)	0	15	1 (1)	2 (3)	1 (1)	0	0	4	21 (3)	14 (2)	5 (1)	0	0	40
	3	2 (1)	0	0	0	0	2	0	1 (1)	2 (3)	0	0	3	3 (<1)	8 (1)	4 (1)	0	2 (<2)	17
	4	1 (<1)	1 (<1	1 (<1	0	2 (1)	5	0	1 (1)	0	0	0	1	1 (<1)	0	1 (<1)	2 (<2)	0	4
	Total	240	34	7	1	2	284	66	12	5	0	0	83	630	80	19	4	2	735

[1] Toxicity Grade: 0 = ≤1.25 x ULN; 1 = 1.26 -< 2.6 x ULN; 2 = 2.6 - < 5.1 x ULN; 3 = 5.1 – 10 x ULN; 4 = > 10 x ULN
Source: Table 5.6.3, pg 188, Vol. 1.110, Submission of December 2000.

Table 73. Clinically Notable Chemistry Values (Studies 149-98-02, 149-98-03, 149-99-03) [1]

	Treatment Group								
	Lupron (N=284)			Lupron + Casodex (N=83)			Abarelix (N=735)		
	Eval n	Experienced[2] n	(%)	Eval n	Experienced n	(%)	Eval n	Experienced n	(%)
Serum sodium									
<125 mEq/L	281	1	(0.3)	83	0		732	0	
>155 mEq/L	281	6	(2.1)	83	1	(1.2)	732	12	(1.6)
Serum potassium									
<3.0 mEq/L	281	1	(0.3)	81	0		731	1	(0.1)
>5.8 mEq/L	281	3	(1.1)	81	0		731	14	(1.9)
Serum bicarbonate									
<15.1 mEq/L	283	2	(0.7)	83	0		734	0	
>34.9 mEq/L	283	1	(0.3)	83	2	(2.4)	734	2	(0.3)
Calcium									
<7.0 mEq/L	283	0		81	0		733	0	
>11.0 mEq/L	283	0		81	1	(1.2)	733	3	(0.4)
Glucose									
<45 mg/dL	282	2	(0.7)	83	0		733	4	(0.5)
>300 mg/dL	282	11	(3.9)	83	6	(7.2)	733	37	(5.0)
Blood urea nitrogen									
>35 mg/dL	283	20	(7.1)	83	9	(10.8)	730	50	(6.8)
>2.5 x ULN	283	0		83	0		730	4	(0.5)
Creatinine									
>2.0 mg/dL	283	8	(2.8)	83	3	(3.6)	733	9	(1.2)
>2.5 x ULN	283	1	(0.4)	83	0		733	4	(0.5)
Creatine kinase									
>1000 U/L	283	4	(1.4)	83	0		734	5	(0.7)

[1] Notable liver function values are presented in Section 9.9.2.

[2] Number and percent of patients who developed a clinically notable value in the respective category.

Source: Modified from Tables 4.2 and 12.8.10 of Safety Update, Submission of March 2001.

7.16 Safety Issues of Special Concern

7.16.1 Cutaneous Allergic Reactions

Allergic-type skin disorders occurring through Day 169 and reported to have an unknown, possible, probable, or definite relationship to Study Drugs are summarized in Table 74.