5) fulfilled other criteria where treatment with LHRH superagonists were contraindicated

Exclusion criteria included: 1) prior hormonal therapy for metastatic prostate cancer other than neoadjuvant hormonal therapy 2) neoadjuvant hormonal therapy for prostate cancer within the previous 6 months before enrollment 3) known androgen independent (hormone refractory) prostate cancer 4) currently taking or planning to take PC SPES, a herbal therapy for prostate cancer and 5) recent history of drug sensitivity to an LHRH superagonist.

A.5. Endpoints:

Primary efficacy endpoints: The primary efficacy endpoints were the avoidance of orchiectomy within the first 4 weeks of treatment (through day 29) and within the first 12 weeks of treatment (through day 85). (According to the entry criteria, it is assumed that all patients are at risk to undergo bilateral orchiectomy at the time of study entry.)

Secondary efficacy endpoints: 1) percentage change from baseline in PSA levels 2) serum levels of testosterone, dihydrotestosterone (DHT), luteinizing hormone (LH), and follicle stimulating hormone (FSH).

Tertiary efficacy endpoints: 1) change in intensity of pain as measured by the visual analogue scale for pain 2) disease response (National Prostate Cancer Project criteria) 3) acid phosphatase kinetics and 4) quality of life as measured by the Southwest Oncology Group 9039 assessment.

A.6. Withdrawals, compliance, and protocol violations: Three of the 48 patients terminated the study after Day 29 and before Day 85. One patient died of progressive prostate cancer, 1 patient withdrew voluntarily, and 1 patient was withdrawn by the investigator because his veins were not accessible.

A.7. Efficacy Analysis: The primary efficacy endpoints were the prevention of bilateral orchiectomy at Days 29 and 85. Failure to prevent bilateral orchiectomy must be associated with therapeutic failure of abarelix-depot. Requirement for orchiectomy due to worsening symptoms or the progression of disease in the presence of castrate testosterone levels (<50 ng/dL) was not counted as a failure to prevent surgery.

All 48 patients in the ITT population avoided bilateral orchiectomy through Day 29 and through Day 85. Three patients terminated the study after Day 29 and before Day 85 (1 patient died of progressive prostate cancer, 1 patient withdrew voluntarily, and 1 patient was withdrawn by the investigator because his veins were not accessible). Since none had undergone an orchiectomy or had been scheduled for an orchiectomy at the time of study termination, and since none were withdrawn from the study because of an adverse event, all 3 patients were considered to have avoided an orchiectomy based on LOCF as defined in the statistical analysis plan. A 100% avoidance of orchiectomy was therefore achieved at Day 29 and at Day 85 (Table 3).

Table 3. Percentage of patients who avoided bilateral orchiectomy through Day 29 and Day 85. (N = 48).

	Avoided orchiectomy N (%)	95% confidence interval
Through day 29	48 (100%)	(92.6, 100)
Through day 85	48 (100%)	(92.6, 100)

Supportive secondary endpoints:

1) Achievement of medical castration: One patient had castrate levels of testosterone at baseline. One patient did not achieve castrate T levels during the study. The percentage of patients castrate by planned visit day is shown in Table 4.

Table 4. Percentage of patients with T levels <50 ng/dL by visit day. (N = 48)

	Evaluated (N)	Castrate N (%)
Baseline	48	1 (2%)
Day 2	46	14 (30%)
Day 8	47	41 (87%)
Day 15	47	42 (89%)
Day 29	48	47 (98%)
Day 85	45	43 (96%)
Day 169	25	25 (100%)

Reviewer's comments: Review of the patient who did not achieve castrate levels of T does not reveal a reason why castrate levels were not attained. Thirty per-cent of patients at Day 2 and 87% of patients at Day 8 had castrate levels of serum testosterone. On Days 29, 85, and 169, 98%, 96%, and 100% of patients had castrate levels of serum T. This trial was not designed to evaluate longer term maintenance of castrate levels of serum T.

Achievement and maintenance of castration through day 85 was defined as castrate levels of T on Days 29, 57, and 85. By this definition and using LOCF, 46 of the 48 ITT patients (95.8%) achieved and maintained castrate T levels.

2) Serum androgen levels: Median testosterone levels in the ITT population are shown in Table 5.

Table 5. Median serum testosterone levels.

	N	Median (ng/dL)
Baseline	48	362
Day 2	46	74
Day 8	47	22
Day 15	47	14
Day 29	48	8
Day 57	45	9
Day 85	45	8
Day 113	38	9
Day 141	31	10
Day 169	25	9

Median and mean testosterone levels remained below 20 ng/dL on days 197, 225, 253, and 281.

3) Serum gonadotrophin levels: Median LH levels are shown in Table 6 and median FSH levels in Table 7.

Table 6. Median LH levels.

	Evaluated (N)	Median (IU/L)
Baseline	48	8
Day 2	46	1
Day 8	47	1
Day 15	46	1
Day 29	48	1
Day 57	45	1
Day 85	45	1
Day 113	38	1
Day 141	31	1
Day 169	25	1

Values below the detection limit of 1 IU/L are reported as 1 IU/L.

Table 7. Median FSH levels

	Evaluated (N)	Median (IU/L)
Baseline	48	8
Day 2	46	6
Day 8	47	2
Day 15	46	1
Day 29	48	1
Day 57	45	1
Day 85	45	1
Day 113	38	1
Day 141	31	1
Day 169	25	1

Values below the detection limit of 1.0 IU/L are reported as 1 IU/L.

4) Serum PSA levels: In nearly all patients, PSA levels decreased sharply from baseline to Day 29. PSA levels then remained suppressed in all but 1 patient through day 169. Median serum PSA levels are shown in Table 8.

Table 8. Median PSA levels.

	N	Median (ng/mL)
Baseline	48	84.7
Day 15	47	20.7
Day 29	48	6.4
Day 57	45	3.0
Day 85	45	3.2
Day 113	38	2.4
Day 141	31	2.6
Day 169	25	1.8

The percentage of patients with a >50% reduction in PSA is shown in Table 9.

Table 9. Percentage of patients with a >50% reduction in PSA.

	N	N (%) with >50% reduction in PSA
Overall	48	48 (100)
Day 15	47	41 (87)
Day 29	48	47 (98)
Day 57	45	44 (98)
Day 85	45	44 (98)
Day 113	38	37 (97)
Day 141	31	30 (97)
Day 169	25	25 (100)

5) Visual analogue scale pain score in patients with cancer-related pain or bone pain at baseline: Twenty-four of 48 patients (50%) had a 24-hour VAS pain assessment at

baseline. VAS score was measured on a continuous scale of 0 to 10 where 0 represents no pain and 10 represents the worst pain imaginable. The VAS scores in these patients are shown in Table 10.

Table 10. Median VAS pain score.

	Evaluated (N)	Median score
Baseline	24	4.3
Day 2	21	4.0
Day 8	21	4.1
Day 15	24	3.9
Day 29	23	1.8
Day 57	21	1.4
Day 85	20	1.6
Day 113	18	1.1
Day 141	16	0.9
Day 169	14	1.2

A.8. Safety Analysis:

A.8.1. Extent of exposure: Fifty-seven patients are included in the interim safety analysis. These include the 48 patients in the ITT and an additional 9 patients from site 499 in Mexico. The symptomatic condition for study entry of these 57 patients is summarized in Table 11.

Table 11. Symptomatic condition for study entry.

	N (%)
Bone pain from skeletal metastases	28 (49%)
Impending neurological compromise	4 (7%)
Ureteral obstruction	9 (16%)
Bladder outlet obstruction	16 (28%)

In this trial, eligible patients for study entry had 1 of the 4 following conditions secondary to prostate cancer: 1) bone pain from skeletal metastases 2) bilateral retroperitoneal adenopathy causing ureteral obstruction 3) impending neurological compromise and/or 4) the presence of an enlarged prostate gland or pelvic mass causing bladder outlet obstruction. In these patients, the sponsor believes that therapy with a GNRH agonist is "contraindicated." These 4 groups of patients (total number of 48 from the ITT group) were reviewed.

Patients with impending neurological compromise

Four of the 48 patients (8%) were thought by the investigator to have "impending neurological compromise." These patients are listed in Table 12.

Table 12. Patients with "impending neurological compromise"

Patient #	Symptoms	Fracture Risk at Day 1 (Site)	Impending Neurologic Compromise At Day 1	Neurologic Examination At Day 1	Day Castrate Level of T Reached
428-4005	Severe low Back pain	Yes (T10)	Yes	No neuro exam submitted in narrative or Table 15.17.2	8
416-4001	Pain in upper back and pelvis	Yes (L1 and rib)	Yes	Normal	15
409-4015	Not reported	Not specified (spine mets by CT and bone scan)	Yes	Normal	29
416-4016	Mid-back pain	Yes (T11)	Yes	Normal	2

Reviewer's comments: It is not clear whether these 4 patients had vertebral or epidural metastases. In the opinion of the investigator, all had impending neurologic compromise. Three of the 4 patients had a normal neurologic examination (no neurologic examination is reported in the fourth patient). In patients with impending neurologic compromise and a normal neurologic examination, abarelix has at least theoretical advantages over lhRH agonist therapy because no testosterone "surge" is seen with abarelix. The reviewer is aware of no clinical data which compares GnRH antagonists with the combination of a LHRH agonist and an androgen receptor blocking agent. In patients with acute neurological deficits, the use of abarelix alone would not be as efficacious as orchiectomy because only 30% of patients receiving abarelix achieved castrate levels of serum testosterone by Day 2.

Patients with bilateral retroperitoneal adenopathy causing ureteral obstruction

Seven of the 48 patients (15%) had retroperitoneal adenopathy and ureteral obstruction. These patients are listed in Table 13.

Table 13. Patients with retroperitoneal adenopathy and ureteral obstruction

Patient #	Hydonephrosis At Baseline	Urethral catheter and/or ureteral stent at baseline	Serum creatinine at baseline	Day Castrate level of T Reached
473-4003	Yes (left)	Yes (L stent)	1.7	8
401-4009	Yes (left)	No	1.7	8
402-4020	None reported	No	1.2	8
402-4022	Yes (left)	No	1.5	2
438-4028	Yes (? Side)	Yes (urethral catheter)	1.8	8
409-4045	Yes (bilateral)	Yes (urethral catheter)	0.8	2
477-4046	Yes (bilateral)	Yes (bilateral stents)	4.9	8

Reviewer's comments: Of the 7 patients with ureteral obstruction, only 1 had a significantly elevated serum creatinine and this patient underwent the placement of bilateral ureteral stents prior to receiving abarelix.

Enlarged prostate or pelvic mass

Thirteen of the 48 patients (27%) had an enlarged prostate or pelvic mass. These patients are listed in Table 14.

Table 14. Patients with an enlarged prostate or pelvic mass.

Patient #	Catheter at baseline	Creatinine at baseline	Day castrate level of T reached
471-4007	No	1.5	8
412-4013	Yes (removed on Day 29)	1.0	8
439-4014	Yes (removed on Day 169)	1.0	8
438-4023	No	4.4	At Baseline
472-4024	Suprapubic catheter (remained in place through Day 169)	3.6	2
438-4025	No	0.9	8
438-4029	No	1.3	15
441-4032	No	1.1	8
427-4038	Yes (removed on Day 85)	1.3	8
441-4040	Yes (removed on Day 85)	0.8	8
438-4041	No	0.9	Never castrate
441-4042	No	1.5	8
409-4047	No	1.6	8

Reviewer's comments: Five of the thirteen patients had a urethral or suprapubic catheter in place at baseline. In the opinion of this reviewer, these patients exhibited no "contraindication" to LHRH agonist therapy. It is not clear how many of the other 8 patients would have experienced increasing voiding symptoms or urinary retention if they would have received LHRH agonist or LHRH agonist plus anti-androgen therapy.

Bone pain from skeletal metastasis

Twenty-four of 48 patients (50%) had bone pain from skeletal metastases. These patients are listed in Table 15.

Table 15. Patients with bone pain from skeletal metastases

Patient #	Risk of fracture	Site
427-4002	Yes	Left hemipelvis – mid-sacrum
477-4004	Yes	Right and left femur
473-4006	No	Bilateral hips and left clavicle
471-4008	No	Not reported
412-4010	No	Not reported
422-4012	Yes	Ribs
422-4017	Yes	T1, L1-4, T10,11, and 12, right acetabulum
402-4018	Yes	Right humerus
473-4019	No	Not specified
477-4021	No	Right hip, left ribs
402-4026	Yes	Thoracic spine, left femur
402-4027	Yes	Bilateral femurs
402-4030	Yes	Spine
473-4031	Yes	Multiple sites
447-4033	No	Not specified
447-4034	No	Not specified
438-4035	No	Back and hips
441-4036	No	Generalized pain
422-4037	Yes	Vertebrae
447-4039	No	Thigh
477-4043	Yes	Arms, legs
409-4044	No	Back
422-4048	Yes	Multiple sites

Reviewer's comments: The investigator judged that the risk for a pathologic fracture existed in 12 of the 24 patients. In the patients at risk for fracture (particularly in the spine, hip, and femur), avoiding a testosterone "surge" by treatment with abarelix has theoretic advantage over treatment with a LHRH agonist alone. This trial was not designed to compare efficacy and safety of GnRH antagonists and LHRH agonists (with or without androgen blockade).

Total exposure in these 57 patients is shown in Table 16. Because of the interim cutoff, each patient's total adverse event experience for the entire duration of treatment may not have been reported and will be presented in the final study report.

Table 16. Patient exposure to Abarelix

Duration (weeks)	Abarelix N=57
4	0
8	2
12	1
16	7
20	8
24	9
28	8
32	11
36	5
40	3
44	3

A.8.2. Serious adverse events:

Deaths: Three patients (#'s 402-4030,404-4044, and 499-4101) died during the study. In the investigator's opinion, all 3 deaths were caused by progressive metastatic prostate cancer.

Reviewer's comment: After reviewing these cases, the reviewer agrees that all 3 of these deaths were caused by progressive prostate cancer.

Seven serious adverse events (excluding deaths) occurred in 6 (11%) of patients. With the exception of 1 allergic event, serious adverse events were thought by the investigator to be the sequelae of comorbid disorders in the elderly or underlying malignancy. The following events occurred in 1 patient each: abnormal renal function, angina pectoris, allergic reaction, fever, gastritis, hypovolemia, and urinary retention. The allergic event is discussed under A.8.3.

Reviewer's comment: The reviewer agrees that the only serious adverse event probably related to study medication is the allergic event discussed below.

A.8.3. Discontinuation due to adverse event:

One patient (# 401-4001) withdrew from the study because of an adverse event. This 85 year-old man had a Gleason 9, Stage D2 prostate cancer with bladder outlet obstuction. Baseline PSA was 25.5 ng/mL. Medical castration was achieved on day 8 and was maintained during the study period. Immediately after his Day 141 dose, he experienced loss of consciousness, a generalized erythematous rash, drop in blood pressure, and edema of wrists, ankles, and around the eyes, lips, and ears. He was treated with Benadryl, epinephrine, and steroid. Within 4 hours the patient's condition returned to baseline. No further abarelix was administered.

Reviewer's comment: In the opinion of the reviewer, this patient had a severe anaphylactic/anaphylactoid reaction to abarelix.

Four other patients experienced potential allergic symptoms and allergic reactions reported as adverse events. Patient # 412-4025 developed pruritis which was reported as "moderate." The pruritis occurred on day 77, was not treated, and continued at the time of data cutoff. Abarelix was continued without worsening of the pruritis. Three other patients (one with itchy knees, one with a left groin rash, and one with bilateral groin rash) developed possible allergic symptoms; these resolved.

A.8.4. Frequent adverse events: Most adverse events were the sequelae of comorbid disorders in the elderly, underlying malignancy, and/or the effects of medical castration. A summary of adverse events is presented in Table 17.

Table 17. Summary of adverse events.

	N=57 N (%)
All adverse events	54 (95)
Severe or life-threatening	19 (33)
Serious	9 (16)
Treatment-related adverse events	22 (39)
Severe	4 (7)
Serious	1 (2)
Withdrawal due to adverse event (excluding disease progression and/or death)	1 (2)
Deaths on study	3 (5)

Adverse events occurring in at least 5 patients are listed in Table 18.

Table 18. Most common adverse events.

	N=57 N (%)
Pain	15 (26)
Back pain	9 (16)
Diarrhea	8 (14)
Nausea	8 (14)
Peripheral edema	8 (14)
Dizziness	7 (12)
Headache	7 (12)
Constipation	6 (11)
Urinary frequency	6 (11)
Upper respiratory infection	6 (11)
Anxiety	5 (9)

Adverse events which were considered by the investigator to be treatment related and occurred in at least 2 patients are listed in Table 19.

Table 19. Most common treatment-related adverse events.

	N (%)
Constipation	4 (7)
Fatigue	4 (7)
Diarrhea	3 (5)
Headache	3 (5)
Back pain	2 (4)
Dizziness	2 (4)
Urinary frequency	2 (4)
Myalgia	2 (4)
Pain	2 (4)
Skin nodule	2 (4)

Adverse events reported on the endocrine questionnaire are listed in Table 20.

Table 20. Incidence of adverse events reported on the endocrine questionnaire.

	N = 57 N (%)
Breast enlargement	15 (26)
Breast pain or nipple tenderness	10 (18)
Hot flashes	48 (84)
Sleep disturbance from hot flashes	23 (40)

A.8.5. Changes in laboratory values:

Hematology: Slight decreases in mean and median values of hemoglobin and hematocrit were observed to day 85 with a slight increase in reticulocytes. Forty percent of patients with a high, normal, or unknown baseline value (N=40) had a shift to low in hematocrit. The mean hematocrit at baseline was 38.3 and at day 85 the mean hematocrit was 37.4. No clinically meaningful trends in WBC's, platelets, or differential counts were observed.

Electrolytes: No clinically meaningful changes were observed in electrolytes, calcium, phosphorous, or magnesium.

Liver function tests: Elevation of alkaline phosphatase was commonly observed. Fifty-one percent of patients had an elevated alkaline phosphatase at baseline. Of the remaining 49% of patients with normal, low, or unknown values at baseline, 5 (18%) had a shift to high (>ULN) during the study.

Transaminase elevations occurred in one-third of the patients (Table 21). Elevations were without clinical sequelae and generally mild, transient, and reversible with continued dosing.

Table 21. Shifts to high (>ULN) from baseline: Liver function tests

	Evaluable (N)	Elevated (N) (%)
Alkaline phosphatase	28	5 (18)
ALT	53	18 (34)
AST	52	16 (31)
Total bilirubin	57	0

The incidence of "clinically notable" liver function test results are shown in Table 22.

Table 22. Incidence of clinically notable liver function tests

Test	Cutoff value	Evaluable (N)	Elevated (N) (%)
Alkaline phosphatase	>200 U/L	57	25 (44)
	>5XULN	57	12 (21)
ALT	>2.5XULN	57	2 (4)
	>200 U/L	57	1 (2)
AST	>2.5XULN	55	3 (5)
	>200 U/L	55	0
Total bilirubin	>2.5XULN	57	0

Reviewer's comment: The significance of the elevated transaminases is difficult to determine in this group of patients with advanced prostate cancer.

Renal function tests: Minor elevations in BUN and creatinine occurred in 7 patients (19%) and 17 patients (37%) respectively.

Lipids: Forty-two percent of patients had shifts to high (>ULN) in triglycerides. As fasting blood samples were not required, the sponsor believes that these changes are difficult to assess.

A.9. Reviewer's assessment of safety and efficacy in Trial 149-98-04:

An opinion concerning whether Trial 149-98-04 supports the approval of abarelix depot for the treatment of advanced prostate cancer will be rendered following review of the final study report which will include an additional 26 patients.

/S/

George S. Benson, MD
Medical Officer
Division of Reproductive and Urologic Drugs

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

/s/

George Benson
6/21/01 08:44:33 AM
MEDICAL OFFICER

Mark S. Hirsch
7/2/01 10:53:22 AM
MEDICAL OFFICER

Addendum to Appendix A – Final Study Report for Clinical Trial 149-98-04 ("A Multi-Center Study of Abarelix-Depot in Patients with Prostate Cancer in Whom GnRH Agonists are Contradicated") Study initiation date: February 24, 1999, Study completion date: September 25, 2000. An interim study report was submitted with NDA 21320. The final study report for Trial 149-98-04 was received on March 16, 2001, with the safety update.

A.1 (Addendum) Study population: Eighty-three patients were enrolled in the study and 81 (98%) received at least 1 dose of abarelix-depot. Eighteen centers in the United States and 1 center in Mexico enrolled at least 1 patient. All patients (N=9) treated at a single center in Mexico were excluded from the efficacy analyses because of "regulatory noncompliance" at that site resulting in an ITT population of 72 patients. The results of 48 ITT patients were submitted in the interim analysis and an additional 26 ITT patients are included in the final study report. The safety population is the 81 patients who received at least 1 dose of abarelix-depot (Table 1.).

Table 1. Analysis populations

	Abarelix N (%)
Enrolled	83
Safety population	81 (98%)
Intent-to-treat population	72 (87%)

A summary of baseline demographic data is shown in Table 2.

Table 2. Baseline demographic data (ITT population).

	Abarelix N=72
Race/ethnicity	N (%)
Caucasian	62 (87%)
African American	6 (8%)
Hispanic	4 (5%)
Age	Years
Median (range)	73 (40-94)

Patient disposition is shown in Table 3.

Table 3. Patient disposition.

	Abarelix-](%)
Enrolled	83
Received at least one dose of study drug	81 (98%)
Terminated before day 169 Intolerable adverse event Voluntary withdrawal Death Other	14 (17%) 2 (2%) 4 (5%) 4 (5%) 4 (5%)
Completed through day 169 * One patient discontinued after day 169 because of an intolerable adverse event	69 (83%)

The Gleason grade, baseline PSA, and symptomatic condition for study entry are shown in Table 4.

Table 4. Gleason grade, baseline PSA, and symptomatic condition for study entry.

	Abarelix- N=72 N (%)
Gleason grade 2-4 5-6 7 8-10 unknown	 6 (8%) 8 (11%) 15 (21%) 34 (47%) 9 (13%)
PSA (ng/ml) <20 >20 and <100 >100 and <1000 >1000	 14 (19%) 24 (33%) 25 (35%) 9 (13)
Symptomatic condition for study entry Bone pain from skeletal metastases Impending neurological compromise Ureteral obstruction Enlarged prostate or pelvic mass Other	 31 (43%) 6 (8%) 9 (13%) 25 (35%) 1 (1%)

Reviewer's comments: When the final study report is compared with the interim analysis, there are 7 additional patients with bone pain, 2 additional patients with impending neurological compromise, 2 additional patients with ureteral obstruction, and 12 additional patients with an enlarged prostate or pelvic mass. The patient listed as "other" was found to not have one of the conditions required for study entry (a bone lesion which was not prostate cancer).

A.2 (Addendum) Efficacy: The primary efficacy endpoints were the avoidance of orchiectomy through day 29 and through day 85. Seventy patients (97%) in the ITT population avoided bilateral orchiectomy through day 29 and through day 85 (Table 5).

Table 5. Percentage of patients who avoided orchiectomy through day 29 and through day 85 (N=72).

	Avoided orchiectomy N (%)	95% confidence interval
Through day 29	70 (97%)	(90.3, 99.7)
Through day 85	70 (97%)	(90.3, 99.7)

Two patients who withdrew for treatment related adverse events (patient 416-4067 on day 15 for urticaria and patient 409-4057 on day 29 for allergic reaction) were considered failures to avoid orchiectomy on days 29 and 85 as specified in the statistical analysis plan although neither actually underwent orchiectomy. Five other patients withdrew from the study after day 29 and before day 85 (2 patients died of prostate cancer, 1 patient withdrew voluntarily, 1 patient was withdrawn by the investigator because the patient's veins were not accessible, and 1 patient was withdrawn by the investigator because he did not meet the inclusion criteria). Since none of these 5 patients were withdrawn from the study because of a treatment related adverse event, all 5 patients were considered to have avoided orchiectomy based on LOCF as defined in the statistical analysis plan.

Supportive secondary endpoints:

1) Achievement of medical castration: One patient (438-4041) did not achieve castrate levels of serum testosterone during any time point during the study. Two patients (438-4023 and 416-4067) were already castrate at baseline. The percentage of patients castrate by planned visit day is shown in Table 6.

Table 6. Percentage of patients with T levels < 50 ng/dL by visit day (N=72)

	Evaluated (N)	Castrate (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%)

Achievement and maintenance of castration through day 85 was defined as castrate levels of testosterone on days 29, 57, and 85. By this definition and using LOCF, 65 of the 72 ITT patients (90.3%) achieved and maintained castrate levels of serum testosterone.

2) Serum androgen levels: Median testosterone levels in the ITT population are shown in Table 7.

Table 7. Median serum testosterone levels (ITT population)

	N	Median (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

Median decreases in DHT, LH, FSH, and PSA levels at each of the study time points were essentially unchanged from the interim study report.

A.3 (Addendum) Safety analysis: Eighty-one patients received at least 1 dose of study drug and compromise the safety population. These patients include 72 in the ITT population and another 9 patients from site 499 in Mexico. The symptomatic condition for study entry of these 81 patients is shown in Table 8.

Table 8. Symptomatic condition for study entry.

	N (%)
Bone pain from skeletal metastases	35 (43%)
Impending neurological compromise	6 (7%)
Ureteral obstruction	11 (14%)
Bladder outlet obstruction	28 (35%)
None of the above (Patient had a bone lesion which was found to not be prostate cancer)	1 (1%)

Of the 81 patients, 57 were discussed in the interim analysis. Of the additional 24 cases in the final study report, 7 had bone pain from skeletal metastases, 2 had impending neurological compromise, 2 had ureteral obstruction, 12 had bladder outlet obstruction, and one did not meet the inclusion criteria.

Patients with impending neurological compromise

The 2 additional patients with impending neurological compromise are described in Table 9.

Table 9. Patients with impending neurological compromise.

Patient #	Symptoms	Fracture risk at Day 1 (site)	Impending neurological compromise at Day 1	Neurologic examination at Day 1	Day castrate level of T reached
428-4059	Back pain	Not reported	present	Pin and thermal sensation abnormal on left	15
443-4062	Mild "bone pain"	Yes –T12	present	Normal	8

A total of 6 patients with "impending neurologic compromise" were enrolled in the trial. In the opinion of the investigator, based primarily on x-ray findings, all of these patients had impending neurologic compromise. Four of the 6 patients had a normal neurologic examination, 1 had decreased pin and thermal sensation on the left, and in 1 patient no neurologic examination is reported.

Reviewer's comment: It is not clear whether these 6 patients had vertebral or epidural metastases. No exacerbation of impending neurologic compromise or overt neurologic signs or symptoms developed in these patients after the administration of abarelix-depot. In patients with impending neurologic compromise, no neurologic symptoms and a normal neurologic examination, abarelix has theoretical advantages over LHRH agonist therapy because no testosterone "flare" is seen following abarelix-depot injection. The reviewer is aware of no clinical data which compares GnRH antagonists with the combination of a LHRH agonist and an androgen receptor blocking agent. In patients with acute neurologic deficits (eg paraplegia), the reviewer believes that abarelix-depot would not be appropriate as monotherapy. The use of abarelix-depot would not be expected to be as efficacious as orchiectomy because only 30% of patients receiving abarelix-depot achieved castrate levels of testosterone by Day 2.

Patients with bilateral retroperitoneal adenopathy causing ureteral obstruction

The 2 additional patients (total of 9) with bilateral retroperitoneal adenopathy and ureteral obstruction are listed in Table 10.

Table 10. Patients with retroperitoneal adenopathy and ureteral obstruction

Patient #	Hydronephrosis at baseline	Urethral catheter and/or ureteral stent at baseline	Serum creatinine at baseline (mg/dL)	Day castrate level of T reached
473-4074	Yes (right)	no	1.1	8
416-4067	Yes	no	0.9	Castrate at baseline

Patient 416-4067 had hydronephrosis and bladder outlet obstruction with an AUA symptom score of 26. He was discontinued from the study on Day 15 after experiencing severe urticaria following the injection of abarelix.

Patient 473-4074 had right hydronephrosis and bladder outlet obstruction at baseline (post-void residual of 390 cc and AUA symptom score of 28). On day 29, his AUA symptom score was 14 and his post void residual 176 cc. On day 85 his post void residual was 498 cc, he was azotemic, and he had left hydronephrosis on CT scan. On day 91 the patient withdrew from the study and underwent bilateral orchiectomy.

Reviewer's comment: It is difficult to determine whether the hydronephrosis in these patients is secondary to retroperitoneal adenopathy, locally invasive prostate cancer, or bladder outlet obstruction. In addition, 8 of the 9 patients had normal or mildly elevated serum creatinine levels (the other patient had a creatinine of 4.9 and bilateral ureteral stents in place). In patients with retroperitoneal adenopathy and a normal serum creatinine (particularly in the presence of unilateral hydronephrosis), the reviewer believes that LHRH agonist therapy is not "contraindicated."

Enlarged prostate or pelvic mass

Twelve additional patients (total of 25) with an enlarged prostate or pelvic mass are shown in Table 11.

Table 11. Patients with an enlarged prostate or a pelvic mass

Patient #	Urethral catheter at baseline	Creatinine at baseline	Day castrate level of T reached
441-4050 (died of respiratory failure on day 57)	No	1.5	8
439-4051	Yes (removed on day 85)	0.8	2
412-4054	No	0.8	2 (maintained through day 85, but non-castrate T levels on days 113,141, and 169)
412-4058	No	1.0	29
438-4061	No	0.9	2
402-4063	Yes (removed on day 29)	3.8 (remained elevated – 7.0 on day 169)	2
477-4064 (died of renal failure on day 149)	Yes (removed on day 29)	1.9 (7.4 on day 141)	8
473-4065	No	0.8	15
416-4066	Yes (never removed)	1.0	8
401-4069	Yes (removed on day 85)	1.5	8
473-4071	No	1.2	15
402-4072	No	0.9	8

Reviewer's comments: Ten of the 25 patients with an "enlarged prostate or pelvic mass" had a urethral or suprapubic catheter in place at baseline. These patients exhibited no "contraindication" to LHRH agonist therapy. In eight of the 10 patients, the catheter was removed during the trial (3 by Day 29, 4 by Day 85, and 1 by Day 169). No patient experienced urinary retention as a result of abarelix-depot therapy. It is not clear how many of the other 15 patients would have experienced urinary retention if they would have been treated with LHRH agonist therapy.

Bone pain from skeletal metastases

Seven additional patients (total of 31) with bone pain from skeletal metastases are listed in Table 12.

Table 12. Patients with bone pain from skeletal metastases.

Patient #	Risk of fracture	Site
409-4049	No	Multiple sites
477-4052	No	Multiple sites
427-4055	No	Multiple sites
409-4056	No	Multiple sites
409-4057	No	Multiple sites
409-4060	No	Multiple sites
409-4068	No	Multiple sites

Reviewer's comments: The investigator judged that the risk of pathologic fracture was present in 12 of the 31 patients. In patients at risk for fracture (particularly in the spine, hip, and femur), avoiding a testosterone "surge" by treatment with abarelix-depot has theoretical advantages over treatment with a LHRH agonist alone. This trial was not designed to compare efficacy and safety of abarelix and LHRH agonists with or without androgen blockade.

Adverse events:

The most common adverse events and most common treatment-related adverse events are nearly identical to those reported in the interim analysis (Tables 18 and 19). The only exception is the incidence of "allergic reactions" which is discussed below.

Treatment related severe adverse events: Nine events in 6 patients (7%) were judged by the investigator to be severe and treatment related. These patients are listed in Table 13.

Table 13. Patients with severe, treatment-related adverse events

Patient #	Age	Description	Onset (day)	Relationship to treatment
401-4001	85	Allergic reaction with mild anaphylactic symptoms	141	Probable
473-4003	77	Skin rash	312	Possible
471-4008	77	Worsening bone pain and abnormal gait	1	Possible
473-4019	62	Back pain and nausea	50	Unknown
416-4067	64	Urticaria	15	Definite
499-4106	67	Back pain and intercostal pain	32	Unknown

Deaths: Six deaths occurred during the study.

Reviewer's comment: The reviewer agrees with the investigators that 5 of these deaths were caused by progressive prostate cancer and 1 was due to a pulmonary embolus.

Other significant adverse reactions:

Allergic reactions: No allergic reactions were reported following the first injection of study drug. Three patients (401-4001, 409-4057, and 416-4067) were withdrawn from study drug due to signs and/or symptoms of allergy. Patients with allergic signs/symptoms are shown in Table 14.

Table 14. Patients with allergic signs/symptoms

Patient #	Event onset	Signs/symptom	Severity	Relationship
401-4001	Immediately after 7th injection	Obtunded, generalized skin rash, hypotension, edema eyes, lips and ears, peripheral edema	Severe	Probable
473-4003	2 days after 13th injection	Skin rash	Severe	Possible
438-4025	20 days after 4th injection	Pruritis	Moderate	Unknown
438-4028	13 days after 8th injection	Dry itchy skin	Mild	Unknown
427-4005	8 days after 1st injection	Rash	Moderate	Unknown
409-4057	Immediately after 3rd injection	Warm neck,urticaria and pruritis of back, neck, and chest	Moderate	Definite
416-4067	5 minutes after 2nd injection	Urticaria	Severe	definite

The most severe allergic reaction occurred in patient 401-4001. This reaction with "mild anaphylactic-type symptoms" occurred within moments of his day 141 injection. This event consisted of a momentary loss of consciousness, a generalized erythematous rash, a drop in blood pressure, shortness of breath, and edema of his wrists and ankles as well as around his eyes, lips, and ears. He was treated with intravenous saline, Benadryl, epinephrine, Solu-Medrol, and albuterol. The emergency 911 number was called and he was taken to the emergency room. His blood pressure prior to the injection was 100/62. Within minutes after the injection, his BP was 80 mmHg by Doppler and his pulse was 56. Three minutes later his BP was 169/79. Within 4 hours his condition slowly improved

to baseline. He was discharged from the emergency room 4 hours after the abarelix injection.

Two other patients discontinued because of an adverse event. Patient 416-4067 experienced severe urticaria shortly after receiving abarelix depot on day 15. He was treated with diphenhydramine in the clinic and he was discharged to home 1 hour after the start of the adverse event. Patient 409-4057 experienced urticaria of the upper back, neck, and chest immediately after his third injection on day 29. He received no treatment and his symptoms resolved the same day.

Reviewer's comments: One patient experienced a severe systemic allergic reaction and 2 additional patients withdrew from the trial because of allergic reactions. The incidence of study withdrawal due to an "allergic" event was 4%. One other patient (# 473-4003) experienced a "severe" skin rash.

Elevated transaminases: In compliance with the protocol, study drug was to be discontinued if any transaminase was elevated to >5 X ULN. No patient was withdrawn from the study for elevated transaminases. ALT and AST elevations (>ULN) occurred in 33% and 28% of patients respectively. Elevations were generally mild, transient, and reversible with continued dosing. One patient had an increase in bilirubin to 1.7 mg/dL which occurred 6 days after a hip fracture. The incidence of clinically important liver function test results is shown in Table 15.

Table 15. Incidence of clinically important liver function test results with abarelix-depot (N=81)

Test	Cutoff value	Evaluable (N)	Experienced (N,%)
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

Reviewer's comment: The significance of the elevated transaminases is difficult to determine in this group of patients with advanced prostate cancer.

The incidence of adverse events reported on the endocrine questionnaire is shown in Table 16.

Table 16. Incidence of adverse events reported on the endocrine questionnaire (N=81).

Event	N (%)
Breast enlargement	24 (30%)
Breast pain or nipple tenderness	16 (20%)
Hot flashes	64 (79%)
Sleep disturbance due to hot flashes	36 (44%)

A. 4 (Addendum) - Reviewer's assessment of safety and efficacy in Trial 149-98-04

LHRH agonists are not "contraindicated" in the 4 conditions (bone pain from skeletal metastases, retroperitoneal adenopathy causing ureteral obstruction, impending neurological compromise, and the presence of an enlarged prostate gland or pelvic mass causing bladder outlet obstruction) required for study entry. Because of the testosterone "surge" seen with LHRH agonists, product labels state that patients with any of the 4 conditions listed should be "closely observed" during LHRH therapy.

The primary efficacy endpoint in this trial was the percentage of patients who avoided bilateral orchiectomy at days 29 and 85. Seventy of the 72 patients (97%) achieved this endpoint at each of the time intervals. Achievement of medical castration following abarelix-depot was reached by 30% of patients by Day 2, 79% by Day 8, 88% by Day 15, 96% by Day 29, 97% by Day 85, and 93% by Day 169. This trial was not designed to evaluate longer term maintenance of castrate levels of serum testosterone.

Four groups of patients with advanced prostate cancer were evaluated:

1) Impending neurologic compromise:

It is not clear whether these 6 patients had vertebral or epidural metastases. No exacerbation of impending neurologic compromise or overt neurologic signs or symptoms developed in these patients after the administration of abarelix-depot. In patients with impending neurologic compromise, no neurologic symptoms and a normal neurologic examination, abarelix has potential advantages over LHRH therapy because no testosterone "surge" is seen following abarelix-depot injection. The reviewer is aware of no clinical data which compares GnRH antagonists with the combination of a LHRH agonist and an androgen receptor blocking agent. In patients with acute neurologic deficits (eg paraplegia), the reviewer believes that abarelix-depot would not be appropriate as monotherapy. The use of abarelix-depot would not be expected to be as efficacious as orchiectomy because only 30% of patients receiving abarelix-depot achieved castrate levels of testosterone by Day 2.

2) Bilateral retroperitoneal adenopathy causing ureteral obstruction:

It is difficult to determine whether the hydronephrosis in these patients is secondary to retroperitoneal adenopathy, locally invasive prostate cancer, or bladder outlet obstruction. In addition, 8 of the 9 patients had normal or mildly elevated serum creatinine levels (the other patient had a creatinine of 4.9 and bilateral ureteral stents in place). In patients with retroperitoneal adenopathy and a normal serum creatinine (particularly in the presence of unilateral hydronephrosis), the reviewer believes that LHRH agonist therapy is not "contraindicated."

3) Enlarged prostate or pelvic mass:

Ten of the 25 patients with an "enlarged prostate or pelvic mass" had a urethral or suprapubic catheter in place at baseline. In the opinion of the reviewer, these patients exhibited no contraindication to LHRH agonist therapy. In eight of the 10 patients, the catheter was removed during the trial (3 by Day 29, 4 by Day 85, and 1 by Day 169). No patient experienced urinary retention as a result of abarelix-depot therapy. It is not clear how many of the other 15 patients would have experienced urinary retention if they would have been treated with LHRH agonist therapy.

4) Bone pain from skeletal metastases:

The investigator judged that the risk of pathologic fracture was present in 12 of the 31 patients. In patients at risk for fracture (particularly in the spine, hip, and femur), avoiding a testosterone "flare" by treatment with abarelix-depot has potential advantages over treatment with a LHRH agonist alone. This trial was not designed to compare efficacy and safety of GnRH antagonists and LHRH agonists with or without androgen blockade.

None of the patients experienced disease exacerbation caused by abarelix–depot. In the opinion of this reviewer, because of the lack of a testosterone "surge," abarelix-depot would be appropriate initial therapy for patients with epidural metastases (and no neurologic findings) and patients who are at risk for spine, hip, or long bone fractures. In addition, patients who are at risk for acute urinary retention may benefit more from abarelix-depot than from LHRH agonist therapy.

From a safety perspective, 1 patient experienced a severe systemic allergic reaction and 2 other patients withdrew from the study because of allergic symptoms (both had urticaria). The incidence of study withdrawal because of an allergic adverse event was 4%. The significance of the elevated transaminases is difficult to determine in this group of patients with advanced prostate cancer.

The occurrence of allergic reactions (particularly severe, systemic allergic reactions) is concerning. Three of the 81 patients withdrew from this trial because of allergic reactions. In the combined trials submitted in this NDA, the incidence of anaphylactic/anaphylactoid reactions is 0.5%. In the opinion of this reviewer, abarelix is superior to LHRH agonists with regard to eliminating the testosterone "surge" and more rapidly decreasing serum testosterone levels. In a small subset of patients with prostate cancer, abarelix would provide a medical alternative to bilateral orchiectomy. In the opinion of this reviewer, the incidence of anaphylactic/anaphylactoid reactions precludes approval of abarelix for the general indication of advanced prostate cancer. This reviewer believes that abarelix should be approved for limited use only in those patients with advanced prostate cancer who are at significant risk for clinical "flare" secondary to testosterone "surge." These patients would include those with impending spinal cord compression, azotemia secondary to hydronephrosis, impending urinary retention, and impending long bone or spine fracture. A boxed warning concerning anaphylactic/anaphylactoid reactions should be included in the label. In addition, patients should be closely observed for 1 hour after injection.

/s/

George S. Benson, MD
Medical Officer
Division of Reproductive and Urologic Drugs

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

/s/

George Benson
6/21/01 08:46:45 AM
MEDICAL OFFICER

Mark S. Hirsch
7/2/01 11:53:52 AM
MEDICAL OFFICER

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-320 (abarelix; Plenaxis for advanced prostate carcinoma)

Sponsor: Praecis Pharmaceuticals

Submission: Resubmission of NDA after initial NA action.

Review date: July 3, 2003

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Concur: D.C. Throckmorton, M.D., Division Director, HFD-110

Distribution: NDA 21-320
HFD-580/Shames
HFD-580/Monroe
HFD-580/Crisostomo

Background

Abarelix is a decapeptide containing some amino acids not found in nature. It is a selective antagonist of gonadotropin releasing hormone. After expedited review, the original NDA was not approved based on concerns regarding durability of effect and the risk of anaphylaxis. Among the materials provided in the resubmission is the study report for ABACAS 1, which indicates some degree of QT prolongation. The Division of Cardio-Renal Drug Products is asked if the data are adequate for interpretation, whether the effect is cause for concern, what other studies should be performed, and whether the findings are adequately described in the proposed label.

Response

Materials provided for review included the ABACAS-1 study protocol, report and datasets.

The best indicators of arrhythmogenic risk are documented torsade events, unexplained sudden deaths, and unexplained syncope.

There are, apparently, no documented arrhythmias.

There have been 27 deaths among 1166 subjects exposed to study drug (834 on the proposed dosing regimen). Of these deaths, most were attributed to disease progression, and none appear to be sudden and unexplained.

Anaphylaxis was reported in about 0.5% of subjects exposed to drug, a risk of about 0.03% per treatment. Some cases of syncope were reported in association with anaphylaxis, but not notably outside this context. Cases of anaphylaxis occurred within 8 minutes of drug administration; this is long before peak plasma levels are achieved, so it is unlikely that syncope in the first few minutes after drug administration could signify an arrhythmic event.

The proposed dosing regimen is 100 mg IM on days 1, 15, and 29, and then event 28 days. After a single IM administration, peak plasma levels of the parent are achieved after several days and then decline with a half-life of about 2 weeks. Abarelix is excreted

unchanged in the urine and as products of hydrolysis in the feces. It is not metabolized by P450. Factors affecting plasma levels are not described in materials available for review (including the proposed label), so perhaps there are none.

There is no mention of preclinical assessment of parent drug or products of hydrolysis on HERG. Studies in piglet purkinje fibers showed action potential shortening at a concentration of 30 μM. No electrophysiological effects were identified in intact mammals of 3 species.

The consult request background document seems to suggest that the only available QT data are from the ABACAS-1 study. A quick inspection of the datasets supporting the ISS for the original submission is consistent with that.

ABACAS-1, entitled "Comparison of the efficacy and safety of abarelix versus goserelin plus bicalutamide in patients with advanced or metastatic prostatic cancer: a one year, randomized, open-label, multicentre, phase III trial", was conducted in 5 western European countries between 1999 and 2001. There were two treatment groups and a variety of end points. The protocol called for 12-lead ECGs to be recorded on day -14, month 3, and month 12. It appears that the on-treatment ECGs were obtained just prior to a dose (trough). ECGs were to be centrally read.

Eighty-seven subjects were randomized to abarelix and 90 to comparator. All were males, and all but one was Caucasian. The supplied ECG dataset contains 621 records with 177 distinct subject IDs, of whom 87 belong to treatment group 1, thus identified as abarelix.

Based on these data, neither treatment appears to have a systematic effect on heart rate at trough, as shown in Table 1.

Table 1. Heart rate changes

	Abarelix		Comparitor	
	N	mean±SD	N	mean±SD
Baseline	87	67±13	90	68±12
Day 84	80	67±12	81	66±12
Change	80	0.2±11	81	-1.4±12

The baseline uncorrected QT as a function of heart rate (all subjects) is shown in Figure 1.

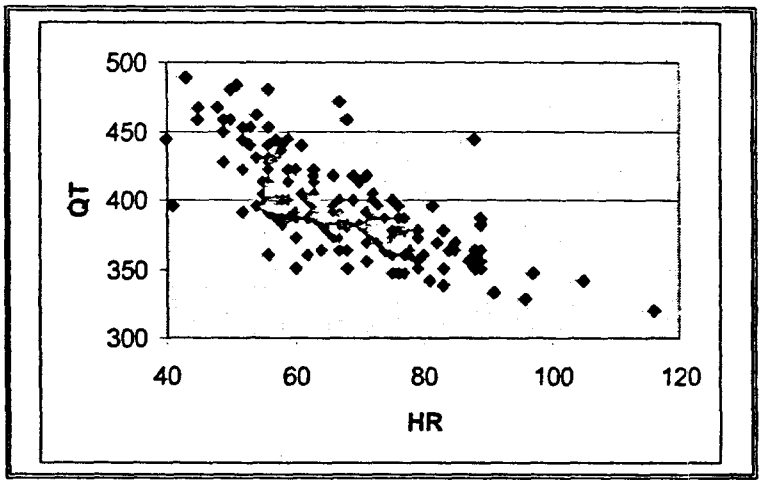

Figure 1

Fridericia-corrected baseline QT data are shown in Figure 2.

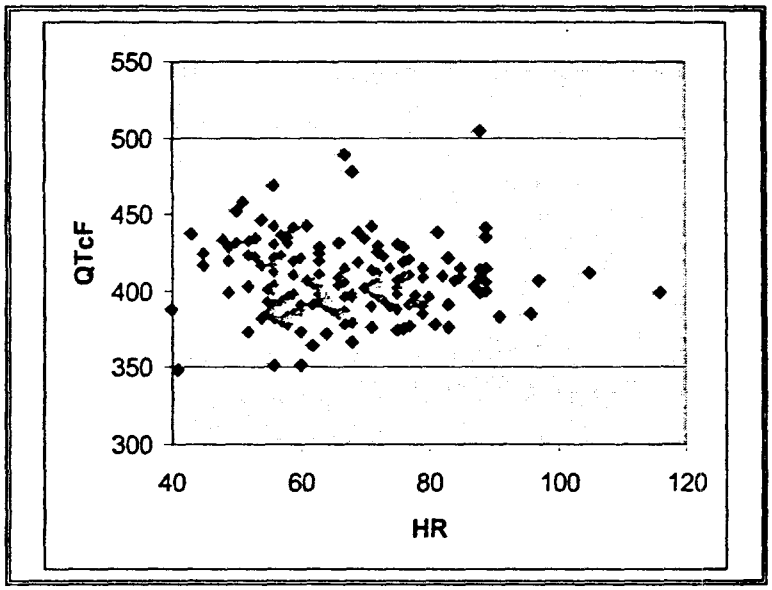

Figure 2

The change from baseline in QTcF is shown as a function of time in study in Figure 3.

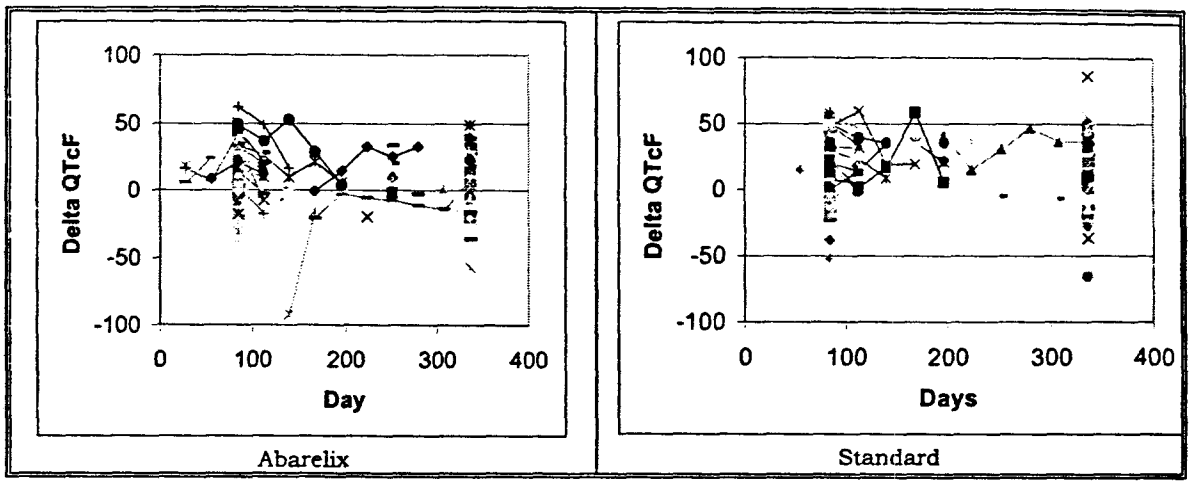

Figure 3. Change from baseline in QTcF.

Both treatments clearly prolong repolarization, and the amount of prolongation is similar at 3 and 12 months.

No attempt was made to reproduce the sponsor's calculation of a mean effect on QTcF. The reported values of 12 ms or abarelix and 18 ms on standard therapy appear to be consistent with Figure 3.

There has not been a large or long experience with abarelix, so available clinical experience is not particularly helpful, but the experience to date does not reveal overt proarrhythmia or events likely to represent proarrhythmic risk.These data are sufficient to rule out perhaps a true risk of one event in a few hundred patient-years.

Standard preclinical evaluation of parent drug and metabolites should be performed, if they have not already been.

A review of these data by Dr. Craig Pratt suggests that these data mean that abarelix poses no more, and possibly less, proarrhythmic risk than standard therapy. Such a conclusion is patently unwarranted, for several reasons. First, risk across drugs is poorly correlated with the effect on QT, and estimated relative risk across drugs that share nothing in terms of structure or function is particularly difficult to defend. Second, the only QT data available were obtained at the interdosing interval. Effects at peak plasma levels of parent drugs or metabolites cannot be inferred; the integral risk may be much higher than is suggested by QT data at trough. Information on the time course of QT effects after a dose should be obtained.

At the end of the day, if a case can be made that abarelix confers a substantial clinical benefit in its target population, some proarrhythmic risk should be acceptable. However, if the clinical benefit is short of mortality, it would appear that a more complete characterization should be obtained, specifically with respect to changes in QTcF as a function of time, and, given the difficulty with enforcing phase IV commitments, such information should be obtained and reviewed prior to approval.

Even if post-marketing safety data are reassuring, some attempt should be made to obtain similar clarification of the QT effects with standard therapy. What are the preclinical effects? What is the time course of QT effects after a dose? Which agent is responsible?

The Division of Cardio-Renal Drug Products appreciates the opportunity to consult on this drug. DRUDP is welcome to contact DCRDP for further clarification or follow-up.

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

/s/

Norman Stockbridge
7/3/03 10:58:52 AM
MEDICAL OFFICER

Doug Throckmorton
7/3/03 01:30:29 PM
MEDICAL OFFICER

MEMORANDUM

Date: July 2, 2003

To: Scott Monroe, M.D.
Medical Team Leader
HFD-580, Division of Reproductive and Urologic Drug Products

Mark Hirsch, M.D.
Medical Team Leader
HFD-580, Division of Reproductive and Urologic Drug Products

From: Charles E. Lee, M.D.
Medical Officer
HFD-570, Division of Pulmonary and Allergy Drug Products

Through: Lydia Gilbert-McClain, M.D.
Acting Medical Team Leader
HFD-570, Division of Pulmonary and Allergy Drug Products

Badrul A. Chowdhury, M.D., Ph.D.
Director
HFD-570, Division of Pulmonary and Allergy Drug Products

Subject: Medical Officer Consultation regarding allergic reactions noted in development program for Plenaxis™ (abarelix for injection suspension)

Materials: Sponsor submissions:
NDA 21-320, N000 AZ, 2/25/03
NDA 21-320, N000 BS, 5/8/03
NDA 21-320, N000 BM, 5/16/03

1. EXECUTIVE SUMMARY

The sponsor, Praecis, has resubmitted their application for Plenaxis™ (abarelix for injection suspension). The product is a GnRH inhibitor proposed for use in patients with advanced carcinoma of the prostate. The original NDA previously received a Not Approvable action on June 11, 2001, because of insufficient clinical information to support the safe and effective use of the product in the intended population. Serious allergic reactions were noted in the pivotal clinical trials; some of these reactions involved hypotension and syncope.

In this submission, the sponsor has provided results of skin tests and in vitro tests for anti-abarelix IgE antibody and anti-CMC IgE and IgG antibodies in patients who had allergic reactions to abarelix and in appropriate control patients. The sponsor has also provided a risk management program to address these reactions.

The sponsor's skin testing data do not provide sufficient information to assess the potential for predicting patients who may be at risk for immediate allergic reactions. The skin tests indirectly support the conclusion that the immediate onset reactions noted during the abarelix clinical development program were of an anaphylactoid or non-immune etiology.

The in vitro tests revealed no meaningful differences in abarelix-specific IgE, CMC-specific IgE or IgG, total IgE, or total IgG levels between abarelix-treated patients and active control-treated patients or between patients who had allergic reactions and those who did not. These data suggest that the reactions noted in the clinical development program in abarelix-treated patients do not have an IgE or IgG-mediated etiology, and also provide indirect evidence that the reactions are anaphylactoid in nature.

An updated estimate of the frequency of immediate onset allergic reactions in abarelix-treated patients in the sponsor's clinical development program was 1.1%. There were no such reactions noted in patients treated with active control. The frequency of immediate onset allergic reactions with hypotension or syncope was 0.5% in abarelix-treated patients. There were no immediate onset allergic reactions with hypotension or syncope in patients treated with active control. Updated estimates of the rates of immediate allergic reactions and immediate allergic reactions associated with hypotension or syncope after various periods of exposure may be found in the statistics review of this submission [NDA 21-320, N000 AZ, 2/25/03, Kate Meaker, M.S.].

The sponsor's risk management plan appears to be acceptable from the clinical standpoint. The sponsor has narrowed the proposed indication to patients with advanced symptomatic carcinoma of the prostate who have impending neurologic compromise, urinary tract obstruction, and/or bone pain from prostate cancer skeletal metastases requiring narcotic analgesia. The new narrowed proposed indication focuses on a population in which the risk of immediate allergic reactions may be acceptable. The sponsor's plan to communicate appropriate risk and benefit information to healthcare providers and patients is comprehensive. The sponsor's plan to monitor the success of

their risk management plan is appropriate from the clinical perspective. In order to further characterize the etiology of these of immediate onset allergic reactions, and as part of the risk management plan, consideration should be given to requesting the sponsor make a Phase 4 commitment to perform skin testing and in vitro testing of a defined number of patients who have such reactions to abarelix in the post-approval period.

2. BACKGROUND

Abarelix suppresses gonadotropin secretion by directly and competitively blocking GnRH receptors at the pituitary gland. The sponsor, Praecis, is developing the product for the treatment of prostate cancer. The abarelix drug substance is a synthetic decapeptide with a molecular weight of 1,416.06. The abarelix drug product is a depot suspension intended for intramuscular injection. It is initially manufactured as an abarelix-acetate water complex and converted to an abarelix-carboxymethylcellulose water complex during manufacture of the drug product. There may be small amounts of free carboxymethylcellulose (CMC) in addition to the abarelix-CMC in the product. The only other excipient in the drug product is 0.9% NaCl.

NDA 21-320, for abarelix for injection suspension, was submitted to the Agency on December 11, 2000, and received a Not Approvable action on June 11, 2001, because of insufficient clinical information to support the safe and effective use of the product in the intended population. In particular, and in regards to this consultation, serious allergic reactions were noted in the pivotal clinical trials. Some of these reactions involved hypotension and syncope. Systemic allergic reactions with hypotension were noted in 0.5% of patients treated with abarelix and in no patients treated with leuprolide or goserelin. Immediate allergic reactions, including erythema, itching, and urticaria without hypotension were noted in 1.2% of patients treated with abarelix, compared with no patients treated with leuprolide or goserelin. These data are described in greater detail in Medical Officer consultation, Charles E. Lee, M.D., NDA 21-320, 4/20/01.

A meeting was held with the sponsor on September 10, 2001, to review and discuss the deficiencies that led to the Not Approvable action. This meeting addressed the sponsor's data regarding the avoidance of testosterone surge in patients with prostate cancer, the proposed format of the Safety Update, CMC issues, and the sponsor's proposed risk management plan for the allergic reactions. The risk management plan included labeling, physician education, patient education, measurement of effectiveness of the safety education, and proposed Phase 4 studies to characterize the mechanism of the allergic reactions. The Division of Pulmonary and Allergy Drug Products (DPADP) provided comments on the sponsor's risk management plan. DPADP commented that the sponsor's risk management plan was not suitable for the broad proposed indication, but might be more acceptable in a much smaller population of prostate cancer patients with advanced disease or those with impending neurologic sequelae. DPADP recommended that the sponsor conduct investigations prior to approval to better clarify the nature of the allergic reactions, and that these investigations should examine both the abarelix peptide and the CMC excipient. The sponsor has completed such investigations, which include skin tests and in vitro tests for anti-abarelix IgE antibody and anti-CMC IgE and IgG antibodies in patients who had allergic reactions to abarelix and in appropriate control patients.

The sponsor has resubmitted their application and has provided a response that includes results of these investigations. This document reviews the following:

- Results of Study 149-01-06, skin testing for allergic type reactions to components of Plenaxis™ (abarelix for injection suspension)
- Results of Study PPI-02-02-401, in vitro testing of IgG/IgE levels in retained serum and plasma samples

This document also reviews the following information included in this submission:

- Sections of the Integrated Summary of Safety Update pertinent to the allergic reactions noted in abarelix clinical studies, including a revised incidence of these reactions
- Sections of proposed labeling that address allergic reactions
- Proposed risk management plan for allergic reactions

3. STUDY 149-01-06: SKIN TESTING FOR ALLERGIC-TYPE REACTIONS TO THE COMPONENTS OF PLENAXIS™

3.1. Summary and conclusions

The sponsor performed skin tests in normal subjects and in one subject with a history of an allergic reaction to Plenaxis™. Skin tests were positive to abarelix at concentrations of 0.001 mg/mL and 0.01 mg/mL in normal subjects. Skin tests were positive to abarelix at a concentration of 0.01 mg/mL in one patient with a history of a delayed allergic reaction to Plenaxis™. There were no patients skin tested who had an immediate reaction to abarelix. Skin tests were negative to sodium carboxymethylcellulose (NaCMC) at concentrations of 0.001 to 0.1 mg/mL in normal subjects and in the patient with the history of the allergic reaction.

These results suggest that abarelix drug substance may provoke non-immune mast cell degranulation. Skin tests suggest that NaCMC does not provoke non-immune mast cell degranulation at any of the concentrations tested. There were no patients skin tested whose reactions were suggestive of an immediate onset allergic reaction. These data do not provide information to assess the potential value of skin testing in predicting patients who may be at risk for immediate allergic reactions. The skin tests indirectly support the conclusion that the immediate onset reactions noted during the abarelix clinical development program were of an anaphylactoid or non-immune etiology and came from non-specific mast cell degranulation. The sponsor's skin testing study is described in more detail below.

3.2. Procedure

The sponsor planned to perform an open-label, three-part study in which skin testing of the components of Plenaxis™ was performed in normal subjects and patients who had been exposed to Plenaxis™ or active control in the sponsor's Phase 2 or 3 clinical studies. The components tested in this study were abarelix acetate drug substance and sodium carboxymethylcellulose (NaCMC), an excipient present in both Plenaxis™ and

the active control drug Lupron® Depot [NDA 21-320, N000 AZ, 2/25/03, Volume 26, page 11].

Patients received intradermal skin tests to histamine positive skin test control and saline negative control. If control tests were valid, patients then received intradermal skin tests with 6 successive dilutions of abarelix acetate (0.000001, 0.00001, 0.0001, 0.001, 0.01, and 0.1 mg/mL) and 3 successive dilutions of NaCMC (0.001, 0.01, and 0.1 mg/mL). Abarelix acetate was diluted with sterile albumin-saline with phenol. NaCMC was diluted with 0.9% sodium chloride injection, USP. The average diameters of wheal and erythema surrounding the injected area were measured 15 minutes after placement of the skin test. A skin test was considered positive if the wheal size for the abarelix or NaCMC dilution was ≥2 mm larger than the saline negative control. Any dilution that produced a positive test was retested in duplicate. No testing of higher dilutions of abarelix or NaCMC were performed in any individual if the duplicate tests were positive [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 12, 17].

3.3. Results of skin testing

Part One of the study was conducted in 15 healthy male subjects, ≥18 years of age, who had never received Plenaxis™, had no known allergies, and who had positive skin test responses to the histamine positive control. Patients were excluded if they had dermatographism, if they had beta blockers within 24 hours of testing, histamine-blocking medication within 7 days of testing, or hydroxyzine within 4 weeks of testing [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 12, 15, 17]. Results of skin tests in Part One of the study are displayed in Table 1.

Table 1. Intradermal skin test results in healthy male subjects [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 28, 31, 116-127].

Skin test	Positive skin test N = 15 n (%)
Histamine positive control	15 (100)
Saline negative control	0 (0)
Abarelix acetate, mg/mL	
0.000001	0 (0)
0.00001	0 (0)
0.0001	0 (0)
0.001	8 (53)
0.01	7 (47)
0.1	Not tested
NaCMC, mg/mL	
0.001	0 (0)
0.01	0 (0)
0.1	0 (0)

Skin tests were positive for histamine positive control and negative for saline negative control in all 15 patients, indicating tests were valid. Skin tests were positive for 0.001 mg/mL abarelix in 8/15 (53%) and positive for 0.01 mg/mL abarelix in 7/15 (47%) of healthy male subjects. No healthy male subject had a positive skin test for any of the NaCMC dilutions tested [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 28, 31, 116-127].

Reviewer comment:
These results suggest that abarelix drug substance can cause non-specific mast cell degranulation, and that positive skin results at abarelix concentrations of 0.001 mg/mL and higher are not related to IgE-mediated hypersensitivity. These data indirectly suggest that the abarelix reactions are of an anaphylactoid or non-immune etiology. NaCMC does not appear to cause mast cell degranulation at any of the concentrations tested.

Part Two of the study was to be conducted in up to 19 of the male patients treated with either Plenaxis™ or Lupron® Depot active control who experienced allergic reactions that resulted in a discontinuation from a Phase 2 or 3 clinical study. Only patients in the US were contacted to participate. Unfortunately, only one eligible patient participated in this part of the study. The other 18 eligible patients either were unable to be contacted (4 patients, refused to participate (5 patients), were not from the US (5 patients), or were deceased (4 patients). [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 11, 12].

The patient that was tested was patient number 038-4776 from the sponsor's Phase 3 study 149-97-04. In study 149-97-04 he had pruritus and a raised, red rash on his chin from 3 to 48 hours after injections of Plenaxis™ on multiple occasions. The rash was at the site of a pre-existing folliculitis. The patient did not have associated generalized pruritus, urticaria, angioedema, respiratory symptoms, or syncope. His symptoms resolved within 24 hours with treatment with hydrocortisone cream. He eventually was withdrawn from Phase 3 study 149-97-04 because of these symptoms [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 1-34]. Results of skin tests for this patient are displayed in Table 2.

Table 2. Intradermal skin test results for a patient with a history of delayed allergic reactions to Plenaxis™ in the sponsor's clinical trials [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 28, 116-127].

Skin test	Positive skin test N = 1 n (%)
Histamine positive control	1 (100)
Saline negative control	0 (0)
Abarelix acetate, mg/mL	
0.000001	0 (0)
0.00001	0 (0)
0.0001	0 (0)
0.001	0 (0)
0.01	1 (1)
0.1	Not tested
NaCMC, mg/mL	
0.001	0 (0)
0.01	0 (0)
0.1	0 (0)

Skin tests were positive for histamine positive control and negative for saline negative control in this patient, indicating tests were valid. For abarelix, skin tests were positive only at the 0.01 mg/mL dilution, a dilution that produced positive skin tests in healthy individuals. The patient did not have a positive skin test to any of the NaCMC dilutions tested. The patient had mild pruritus and erythema of the chin after placement of the 0.001 mg/mL concentration of abarelix. The skin test was negative at this concentration. Skin testing was continued with the 0.01 mg/mL concentration of abarelix, which was

positive. The patient's symptoms decreased during the period when 0.01 mg/mL concentration was tested, and resolved within 30 minutes of onset. The sponsor notes that the symptoms began after placement of a skin testing dose that was negative and that the symptoms resolved despite placement of skin tests for a higher dose. The skin test was positive at a concentration that was positive for subjects who never received the medication. The sponsor concluded that the patient's skin testing results were not suggestive of IgE-mediated sensitivity to abarelix [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 28, 31-34, 124, 127].

Reviewer comment:
This patient's adverse event was not suggestive of an IgE-mediated reaction. This reviewer concurs with the sponsor that the patient's pruritus and erythema of the chin that were noted during skin testing are not suggestive of an IgE-mediated reaction because the skin test was negative at the time of onset and because the symptoms resolved with continued testing with a higher dilution of abarelix.

As this patient's original adverse event in study 149-97-04 was not suggestive of IgE-mediated reaction, these skin test results do not provide evidence for or against an IgE-mediated etiology of abarelix-associated allergic reactions. Skin tests to abarelix at 0.01 mg/mL were positive in healthy controls, and this patient's positive skin test is also likely to be due to non-specific mast cell degranulation. It is unfortunate that the sponsor was not able to skin test any of the other patients who experienced allergic reactions during Phase 2 or 3 studies.

Part Three of the study was to be conducted in 5 male patients who had received Plenaxis™ in a previous clinical trial, but did not have allergic reactions. Part Three of the study was to be conducted only if patients in Part Two of the study were sensitive to lower concentrations of abarelix or NaCMC than patients in Part One of the study. Part Three of the study was not conducted because these conditions were not met [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 11, 28].

4. STUDY PPI-02-02-401: IN VITRO TESTING OF IgG AND IgE LEVELS IN RETAINED SERUM AND PLASMA SAMPLES

4.1. Summary and conclusions

The sponsor's in vitro testing results reveal no meaningful differences in abarelix-specific IgE, CMC-specific IgE or IgG, total IgE, or total IgG levels between abarelix-treated patients or leuprolide or goserelin-treated patients or between patients who had allergic reactions and those who did not. These data suggest that the reactions noted in abarelix-treated patients during the clinical development program do not have an IgE or IgG-mediated etiology, and provide indirect evidence that the reactions are anaphylactoid in nature. The sponsor's in vitro testing is described below.

4.2. Procedure

The sponsor developed a set of assays to measure the levels of immunoglobulins against abarelix peptide and CMC in samples of serum or plasma as part of an ongoing safety risk management program and to further investigate the immediate-onset allergic reactions noted in clinical studies.

Samples were assayed from patients who experienced allergic reactions. For each patient, samples collected prior to administration of the first dose and closest to the date of the allergic reaction were assayed. There were samples from 56 patients who had reactions that included immediate onset hypotension/syncope, bronchoconstriction, angioedema, flushing, rash, urticaria, pruritus, dermatitis, and eczema. These 56 patients included 45 treated with abarelix, 10 treated with leuprolide, and one treated with goserelin. Of these 56 patients, 19 patients (16 abarelix and 3 leuprolide) had a reaction that resulted from withdrawal from the study. Samples included those from five patients who had immediate allergic reactions associated with hypotension or syncope after exposure to abarelix.

Samples were also assayed from patients exposed to abarelix or leuprolide active control in clinical studies. The sample collected prior to administration of the first dose and the last available post-dose sample were assayed. These samples were from 30 abarelix-treated and 30 leuprolide active control patients who did not demonstrate any evidence of an allergic reaction [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 152-155].

The individual assays are described below.

4.2.1. Radioimmunoassay (RIA) for detection of IgE antibodies to abarelix

The sponsor notes that this assay was developed to allow the most sensitive detection of IgE immunoglobulin against abarelix. Patient samples were diluted 1:10 and IgE antibodies in the sample were captured by an antibody specific for human IgE. The presence of IgE antibodies specific for abarelix and abarelix-like peptides were determined by measuring the binding of ^{125}I-labeled abarelix to the captured IgE antibodies. A rabbit antiserum containing IgG against abarelix was used as a positive control because a human polyclonal antiserum containing IgE specific to abarelix was not available. The sponsor notes that a $1:10^6$ dilution of the positive control could be detected with a signal three times that of the negative control. A $1:10^5$ dilution could be detected with a signal at least ten times that of the negative control [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 156-157].

4.2.2. Enzyme-linked immunosorbent assay (ELISA) for detection of IgE antibodies to abarelix

Each patient sample, diluted 1:10, was measured for direct binding of IgE bound to a solid surface coated with abarelix. An alkaline phosphatase-conjugated secondary antibody specific for human IgE and paranitrophenyl phosphate (PNPP) color agent was used to detect IgE bound to the abarelix — [NDA 21-320, N000 AZ, 2/25/03, Volume 26, page 157].