CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-320

Medical Review(s)

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review of NDA

NDA	21-320
Sponsor	Praecis Pharmaceuticals Inc One Hampshire Street Cambridge, MA 02139
Submission Type	Complete response to "Not Approvable" action
Drug	
Established name	Abarelix for injectable suspension
Trade name	Plenaxis™
Chemical class	Synthetic decapeptide
Drug Class	Gonadotropin releasing hormone (GnRH) antagonist
Indication (Approved)	Palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia.
Route of Administration	Intramuscular injection
Dosage Form	Suspension
Dosing Regimen	Administered on Day 1, Day 15, Day 29 and once every 28 days thereafter
Dose	100 mg per dosing
Dates	
Submitted	February 25, 2003
CDER stamp date	February 27, 2003
PDUFA dates	August 27, 2003 (original date) November 27, 2003 (revised date because of submission of significant new clinical data on July 14, 2003).
Related NDAs	None
Related INDs	IND 51-710 (Prostate cancer) IND [redacted]
Medical Reviewer	Scott Monroe MD
Date Review Completed	November 25, 2003

FINAL

November 25, 2003

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EXECUTIVE SUMMARY

1 RECOMMENDATIONS

1.1 Recommendation Regarding Approval

1.1.1 Approvability

It is recommended that abarelix for injectable suspension (Plenaxis™) be approved for the palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH (GnRH) agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: 1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia. It is further recommended that (1) abarelix suspension be available only through a restricted distribution program and (2) only physicians who have enrolled in the Plenaxis™ PLUS Program (Plenaxis™ User Safety Program), based on their attestation of qualifications and acceptance of prescribing responsibilities, may prescribe abarelix.

1.1.2 Basis for Recommendation regarding Approvability (Risk/Benefit Analysis)

No hormonal therapy for the management of advanced prostate cancer is more effective than surgical orchiectomy. The goal of medical hormonal therapy is to reduce serum testosterone concentrations to ≤ 0.5 ng/dL (i.e., testosterone concentrations comparable to those observed following orchiectomy). Treatment of prostate cancer with a GnRH agonist (e.g., leuprolide) initially increases serum testosterone concentrations for 1–2 weeks before reducing testosterone to castrate levels. The initial rise in testosterone may cause a worsening of the signs or symptoms of prostate cancer. Most commonly, the immediate consequence of this initial increase in circulating testosterone is an increase in bone pain in those patients with bone metastases. Less frequently, more serious adverse events can occur, including ureteral obstruction, bladder neck outlet obstruction, spinal cord compression and paralysis, and rarely, death.

Abarelix for injectable suspension (hereafter referred to as abarelix), in contrast to GnRH agonists, is a true GnRH antagonist that is devoid of LH and FSH releasing activity. Consequently, abarelix is able to reduce serum testosterone to castrate levels without an initial antecedent surge. Abarelix could therefore provide significant clinical benefit, compared to a GnRH agonist, for the hormonal management of advanced symptomatic prostate cancer in those men described above in Section 1.1.1. In the clinical trials conducted by the Sponsor, abarelix has been shown to be safe and effective for the palliative treatment of men with advanced symptomatic prostate cancer who have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia. For men with less severe prostate cancer, the potential benefits of treatment with abarelix *do not* outweigh the risks of treatment.

1.2 Recommendations on Phase 4 Studies and Risk Management Steps

Risk Management Program. It is recommended that approval of abarelix be contingent upon the Sponsor's implementing and maintaining a comprehensive Risk Management Program that includes at least the following components: (1) a restricted distribution program for abarelix; (2) limiting prescribers of abarelix to those physicians who have enrolled in the Plenaxis™ User Safety Program, based on their attestation of medical qualifications and acceptance of prescribing responsibilities; (3) a Patient Information Sheet that requires the patient to acknowledge by signature that he has read, understands, and agrees with all the statements contained in the Information Sheet; (4) expedited reporting of specific adverse events (e.g., immediate allergic reactions) that would not otherwise require expedited reporting because they are listed in labeling; (5) measures to actively monitor and evaluate the Risk Management Program; and (6) a physician/ healthcare provider education program.

Phase 4 Studies. It is recommended that the following Phase 4 studies be conducted: (1) one or more use studies (a) to assess physician knowledge and understanding of risks and benefits of abarelix and (b) to evaluate appropriate use of abarelix by physicians and adherence to label recommendations regarding patient safety monitoring; (2) a study to estimate the incidence of immediate-onset allergic systemic reactions; (3) a study to characterize abarelix-induced immediate-onset systemic reactions by evaluating skin test reactivity to abarelix and determining anti-abarelix IgE and IgG antibody levels in patients experiencing immediate onset systemic allergic reactions; and (4) a study to assess the effectiveness of pretreatment with an oral anti-histamine with and without oral steroids in patients who experience abarelix-induced urticaria and/or pruritus.

2 SUMMARY OF CLINICAL FINDINGS

2.1 Brief Overview of Clinical Program

2.1.1 Drug

Abarelix is a synthetic decapeptide with potent antagonistic activity against naturally occurring GnRH. It directly inhibits gonadotropin (LH and FSH) secretion by competitively blocking GnRH receptors in the pituitary and, as consequence, the secretion of testicular androgens.

2.1.2 Design of the Clinical Program

Data from 10 clinical studies in men with prostate cancer were submitted by the Sponsor to support the safety and efficacy of abarelix. Four studies (a single uncontrolled study in the indicated population and 3 randomized, active controlled studies in men with less advanced prostate cancer) were considered to be the primary studies in support of the efficacy and safety of abarelix. In all studies, patients assigned to treatment with abarelix received 100 mg by IM injections on Days 1, 15, 29, and every 28 days thereafter for up to either 24 weeks or one year, depending on the study protocol. Active comparator (Lupron or Lupron plus antiandrogen [Casodex, 50 mg/day]) was administered in standard fashion. All of these studies were conducted in North America.

Indicated patient population (advanced symptomatic prostate cancer). Study 149-98-04 was an open label, single arm (abarelix only), multicenter, 24-week study that enrolled and treated 81 men with advanced, symptomatic prostate cancer. Patients had the option to continue treatment in a safety extension study. Of the 81 patients who enrolled, 9 patients from one site were excluded from the efficacy analysis due to inadequate documentation by the Investigator. The specific reasons given for enrollment of the remaining 72 patients were: bone pain from prostate cancer skeletal metastases (n = 31); an enlarged prostate gland or pelvic mass causing bladder neck outlet obstruction (n = 25); bilateral retroperitoneal adenopathy with ureteral obstruction (n = 9); impending neurological compromise from spinal, spinal cord, or epidural metastases (n = 6); or other (n = 1). The median age was 73 years, range 40 to 94 years. There were 62 Caucasians, 6 African Americans, and 4 Hispanics. Sixty (60) patients were treated for at least 24 weeks; in the extension phase, 33 and 15 patients were treated for at least 48 and 96 weeks, respectively.

Controlled clinical studies (prostate cancer patients without advanced symptomatic disease). Three randomized, open label, active comparator controlled, multicenter studies were conducted to assess pharmacodynamic effectiveness (i.e., suppression of serum testosterone to ≤ 50 ng/dL without initially inducing a testosterone surge) and safety in prostate cancer patients who did not have advanced symptomatic disease. Patients were randomized 2:1 to treatment with abarelix or active comparator (Lupron in Studies 149-98-02 and 149-99-03 and Lupron plus Casodex in Study 149-98-03). Treatment periods were 6 months (Study 149-99-03) or 12 months (Studies 149-98-02 and 149-98-03) with all abarelix patients having the option to continue treatment in an extension safety study. Across the 3 studies, 284, 83, and 735 patients received Lupron, Lupron plus Casodex, and abarelix, respectively.

2.2 Efficacy

2.2.1 Study 149-98-04 (Indicated Patient Population)

The primary objective of this trial was to demonstrate that patients with advanced symptomatic prostate cancer could avoid orchiectomy through 12 weeks of treatment. This is the period when signs or symptoms of a clinical flare due to a GnRH-induced testosterone surge would occur and which, depending upon severity, might require surgical orchiectomy for management.

None (0%) of the 72 patients required orchiectomy while being treated with abarelix, including the extension phase (median combined duration of therapy was 40 weeks). However, 2 patients were withdrawn before Week 12 for treatment-related adverse events (immediate-onset systemic allergic reactions consisting of urticaria, and urticaria and pruritus, respectively) and received alternate therapy. In this trial, medical castration (serum testosterone ≤ 50 ng/dL) was achieved in 57 of the 72 patients (79%) on Day 8, 68 of 71 patients (96%) on Day 29, 63 of 65 patients (97%) on Day 85, and 55 of 59 patients (93%) on Day 169. Although the study was not designed or powered to assess specific clinical outcomes, the following were observed: (1) none of 8 patients with vertebral or epidural metastases and without neurological symptoms at entry developed neurological symptoms, (2) ten of 13 patients with bladder outlet obstruction and a bladder drainage catheter had the catheter removed by 12 weeks, and (3) eleven of 15 patients with pain due to skeletal metastases were able to reduce the potency, dose and/or frequency of narcotic analgesia by Week 12

2.2.2 Controlled Clinical Studies

2.2.2.1 Primary Pharmacodynamic Efficacy Assessment and Efficacy Endpoints

The goal of hormonal therapy in prostate cancer is to suppress serum androgen concentrations to those observed following surgical castration. Based on these considerations, the Division has accepted attainment of castration concentrations of testosterone by Day 29 and maintenance of these levels through at least 3 dosing cycles as a surrogate efficacy endpoint for GnRH agonists. In these abarelix clinical trials, there were 3 primary pharmacodynamic efficacy endpoints.

1. **Achievement and maintenance of serum testosterone concentrations of ≤ 50 ng/dL from Study Day 29 through Study Day 85.** A patient was classified as a failure for this efficacy endpoint if (a) his serum testosterone was > 50 ng/dL on Study Day 29 or (b) his serum testosterone was > 50 ng/dL on 2 consecutive measurements obtained 2 weeks apart on Study Days 29, 43, 57, 71, or 85.
2. **Avoidance of a testosterone surge.** A patient was considered to have experienced a testosterone surge if 2 of his serum testosterone measurements between Study Days 2 and 8 (inclusive) exceeded his study baseline measurement by 10% or greater.
3. **Rapidity of medical castration.** Success was defined as the patient's serum testosterone reaching a level of ≤50 ng/dL on Study Day 8.

A successful outcome in each clinical trial required that (1) abarelix was not inferior to treatment with the active control for Endpoint No. 1 and (2) abarelix was superior to treatment with the active control for Endpoint Nos. 2 and 3.

2.2.2.2 Pharmacodynamic Efficacy Results

Proportion of patients who achieved and maintained testosterone levels ≤ 50 ng/dL. Serum testosterone concentrations ≤ 50 ng/dL were achieved and maintained by 91.7%, 92.9%, and 89.6% of the abarelix patients and by 95.5%, 95.2%, and 97.4% of the active control patients, respectively, in the 3 controlled clinical studies (see Table A). Based on an agreement with the Division, abarelix treatment was to be declared non-inferior to the comparator treatment if the lower bound of the 95% CI for the difference between the treatment groups was not less than –10%. By these criteria (i.e., no 2 consecutive testosterone values > 50 ng/dL between Days 29-85) abarelix treatment was considered

to be non-inferior, although the lower bound for the difference in Study 149-99-03 was slightly below the limit of –10% (i.e., -11.5%).

Table A. Percentages of Patients Who Achieved Testosterone Suppression by Day 29 and Maintained Suppression through Day 85 (No 2 Consecutive Testosterone Values > 50 ng/dL)

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

Avoidance of a testosterone surge. Across Studies 149-98-02 and 149-98-03 combined, no patients (0 of 348) in the abarelix treatment groups experienced a testosterone surge while 84% of patients (144 of 172) in the active control groups experienced a surge ($p < 0.001$).

More rapid attainment of medical castration. Across Studies 149-98-02 and 149-98-03 combined, 24%, 56%, 70%, 73%, and 94% of patients had serum testosterone concentrations ≤ 50 ng/dL on treatment Days 2, 4, 8, 15, and 29, respectively. No patients in the active control groups were medically castrate on Day 8, the protocol defined efficacy endpoint.

2.2.2.3 Unresolved Efficacy Issues

When failure to maintain suppression was defined by more rigorous criteria that included (a) any observed serum testosterone > 50 ng/dL just prior to dosing beginning on Day 29 and every 28 days thereafter and (b) lack of suppression through Days 169 and 365, the effectiveness of abarelix, in terms of testosterone suppression, decreased over time. These findings are summarized in Table B.

Table B. Percentages of Patients Who Achieved Testosterone Suppression by Day 29 and Maintained Suppression Though Days 169 and 365 (No Serum T > 50 ng/dL, LOCF Analysis)

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

This issue of decreased effectiveness in some patients with on-going treatment is addressed in labeling. Physicians are advised to measure serum testosterone concentrations at Day 29 and every 8 weeks thereafter just prior to dosing to assess the effectiveness of treatment.

2.3 Safety

2.3.1 Exposure to Study Drug

A total of 1397 prostate cancer patients were exposed to abarelix. Of theses, 1154 patients were exposed to the registration dosing regimen (100 mg for induction and maintenance of testosterone suppression). Including cumulative exposure in the safety extension studies, 829, 327, 113, and 26 patients were exposed to the registration dose for at least 6, 12, 24, and 36 months, respectively.

2.3.2 General Safety Findings

2.3.2.1 Study 149-98-04

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. No patient (with one possible exception who reported

severe bone pain) had a clinically significant adverse event suggestive of a testosterone-induced clinical flare following the onset of treatment. In these patients with advanced symptomatic disease, 6 of 81 patients died (5 due to progression of disease) 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 on each patient 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.

2.3.2.2 Controlled Clinical Studies

The types of the reported adverse events and the proportion of patients reporting them in the controlled clinical trials were compatible with the study population (men with carcinoma of the prostate with a median age of > 70 years). For most categories of adverse events, the reported frequencies were similar in the abarelix and active control groups. The percentages of patients that were withdrawn because of treatment-related adverse events were similar in the Lupron and abarelix treatment groups and higher in the Lupron plus Casodex group. 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.

Changes in safety laboratory values also were generally similar across the treatment groups with the exception of increases in transaminases (described in Section 2.3.3) and triglycerides. 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. Other than these exceptions, there were no remarkable or consistent differences in mean changes from baseline values in the pooled hematology and chemistry values from the 3 primary safety studies. Isolated, intermittent, and or extreme changes for some measurements at some assessment times were noted, but no consistent patterns suggestive of increased toxicity in the abarelix groups were observed.

In the 3 primary, controlled safety studies, 12 patients died (1 in the Lupron group and 11 in the abarelix group). Of the 11 deaths in the abarelix-treated patients, 5 a were result of disease progression (n = 2) or coexisting carcinomas (n = 3). Two deaths occurred > 50 days after the patient's last dose of abarelix. The remaining 4 deaths were attributed to an intracranial hemorrhage, a myocardial infarction, an empyema of the right lung, and chronic obstructive lung disease. None were attributed to treatment with abarelix. The deaths appear to be compatible with causes that would be expected in a population of elderly men with carcinoma of the prostate.

2.3.3 Safety Issues of Particular Concern

During clinical trials with abarelix, 3 safety issues of concern were identified: immediate systemic allergic reactions, hepatic toxicity, and prolongation of the QT interval.

Immediate-onset systemic allergic reactions. Immediate-onset systemic allergic reactions (occurring within 30 minutes of dosing), were observed in 1.1% (15/1397) of patients dosed with abarelix across all non-investigator-initiated clinical trials. In 14/15 patients who experienced an allergic reaction, each developed symptoms within 8 minutes of injection. The cumulative rates for an allergic reaction on Days 56, 141, 365, and 676 were 0.51%, 0.80% 1.24% and 2.91%, respectively. Seven (7) patients experienced hypotension or syncope as part of their allergic reaction, representing 0.5% of all patients. The cumulative rates for these types of reactions on Days 56, 141,

365, and 617 were 0.22%, 0.32%, 0.61%, and 1.67%, respectively. No immediate-onset systemic allergic reactions occurred in the active comparator groups. Patients should be observed for at least 30 minutes after each injection of abarelix by a physician capable of treating a severe systemic allergic reaction.

- **Hepatic toxicity**. A greater proportion of patients treated with abarelix in the controlled safety trials had an increase in serum transaminase levels (particularly ALT levels) than patients treated with Lupron alone or Lupron plus Casodex. A small percentage of these increases were of clinical significance in both groups. The percentages of abarelix-treated patients reporting serum ALT values >2.5 times upper limit of normal or >200 U/L were 8.2% and 1.8%, respectively. In the active comparator groups combined, the percentages of patients reporting serum ALT values >2.5 times upper limit of normal or >200 U/L were 6.6% and 1.1%, respectively. The percentages of patients reporting serum AST >2.5 times upper limit of normal or >200 U/L were similar in the abarelix and active comparator groups. The effects of abarelix on the liver should be addressed in labeling and will require periodic monitoring of serum transaminase levels.

Prolongation of the QT interval. Treatment with either abarelix or active comparator (Lupron, Lupron plus Casodex, or Zoladex plus Casodex) prolonged the mean Fridericia-corrected QT interval by > 10 msec from baseline. In approximately 20 to 40% of patients in the abarelix and active comparator treatment groups, there were either changes from baseline QTc of >30 msec or end-of-treatment QTc values exceeding 450 msec. It is unclear whether these changes were directly related to Study Drugs, to androgen deprivation therapy, or to other variables. Because abarelix may prolong the QT interval, physicians should carefully consider whether the risks of abarelix treatment outweigh the benefits in patients with baseline QTc values >450 msec.

2.4 Dosing

The recommended dose of abarelix is 100 mg by IM injection on Days 1, 15, 29, and every 28 days thereafter. This dose was effective in suppressing serum concentrations of testosterone to ≤ 50 ng/dL by treatment Day 29 and maintaining serum testosterone at these concentrations through treatment Day 85 in approximately 90% of men. However, with continued dosing the effectiveness of abarelix, in terms of maintenance of suppression of serum testosterone, decreases (see Section 2.2.2.3 above). This decrease is most noticeable at the end of each 28-day dosing cycle (i.e., just before the next dose of abarelix) and in men who weigh more than 225 pounds. This issue is addressed in labeling and physicians are advised to measure serum testosterone at Day 29 and every 8 weeks thereafter just prior to dosing.

2.5 Special Populations

Abarelix is to be used only for the palliative treatment of men with advanced symptomatic prostate cancer. This will limit its use primarily to elderly men. The Sponsor performed standard subset safety and efficacy (pharmacodynamic) analyses on pooled data from the 3 controlled studies based on race (African American and non-African American) and age (< 65 yr. and ≥ 65 yr., safety analyses only). No obvious differences across these groups were identified. However, the total numbers of patients less than 65 years of age and patients who were African American were small. The pharmacokinetics of abarelix was not evaluated in patients with renal or hepatic impairment. Abarelix has not been studied in pediatric patients, and it is not indicated (per labeling) for use in women or pediatric patients.

CLINICAL REVIEW

1 INTRODUCTION AND BACKGROUND

1.1 Drug

Established Name	Abarelix for injectable suspension (abarelix carboxymethylcellulose)
Proposed Trade Name	Plenaxis™
Drug Class	Gonadotropin releasing hormone (GnRH) antagonist
Chemical Class	Synthetic decapeptide
Indication (Approved)	Palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia
Dose	100 mg administered by intramuscular injection
Dosing Regimen	Intramuscular dosing on Day 1, Day 15, Day 29 and once every 28 days thereafter

1.2 State of Armamentarium for Indication

1.2.1 Carcinoma of the Prostate

Cancer of the prostate is the most frequent noncutaneous malignancy and the second most frequent cause of death from cancer in men over 50 years of age. When localized, prostate cancer can be cured by radical prostatectomy or radiation therapy. However, in some men, it is discovered only in advanced stages with metastatic lesions. Although progress has been made in the diagnosis and treatment of prostate cancer, survival of patients with metastatic disease is usually less than 3 to 4 years.

Prostate cancer is an androgen-dependent tumor in most men at the time of initial presentation. Growth of prostate glandular tissue is regulated by a complex of growth factors of which androgens play a pivotal role. GnRH (also known as luteinizing hormone-releasing hormone or LHRH) is secreted by the hypothalamus and stimulates the pituitary gland to release the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH stimulates the secretion of testicular testosterone, which accounts for approximately 95% of circulating testosterone.

1.2.2 Medical Treatment of Advanced Prostate Cancer

Surgical castration or treatment with high doses of estrogenic compounds (generally diethylstilbestrol [DES]) to suppress testicular androgen production were the mainstay of treatment for advanced prostate cancer for decades. However, the reluctance of many men to accept surgical castration for therapy and the adverse effects of estrogen therapy (particularly cardiovascular adverse events) encouraged investigators to develop alternative methods of medical castration. Today, agonists of GnRH, such as Lupron Depot (leuprolide, approved by the FDA for the treatment of prostate cancer in 1985) and Zoladex (goserelin), have almost totally replaced estrogenic compounds as a medical treatment choice.

The therapeutic action of GnRH agonists in the management of prostate cancer is via a reduction in circulating levels of testicular androgens. GnRH agonists down-regulate their own receptors on the

pituitary gonadotropes, resulting in complete, or near complete, cessation of LH secretion, and secondarily, a marked reduction in the secretion of testosterone from the testes. Achievement of castration levels of serum testosterone (considered to be a serum testosterone value of ≤ 50 ng/dL) is generally obtained by 1 month after the start of therapy. In contrast to surgical castration, however, treatment with a GnRH agonist initially results in a significant, albeit temporary (1 to 2 weeks), increase in testicular androgen secretion, commonly referred to as a "testosterone surge." The initial rise in serum testosterone may cause a worsening of prostate cancer symptoms referred to as a "clinical flare." Most commonly, the immediate consequence of this initial increase in circulating testosterone levels in men with metastatic disease is an increase in bone pain. Less frequently, more serious adverse events can occur, including ureteral obstruction, bladder neck outlet obstruction, spinal cord compression and paralysis, and rarely, death. For these reasons, concomitant antiandrogen therapy (e.g., Casodex) is generally administered for at least the first month of therapy when GnRH agonists are used to treat men with advanced symptomatic prostate cancer. Even with concomitant antiandrogen therapy, GnRH agonists must be used with caution in patients presenting with large local lesions, impending ureteral or bladder neck outlet obstruction, and severe skeletal pain requiring the use of narcotic analgesics. Antiandrogens, however, have their own spectrum of adverse effects, and they may not completely block the adverse consequences of a testosterone surge. Consequently, GnRH agonists, even if administered with concomitant antiandrogen therapy, are generally considered inappropriate therapy for men with vertebral or epidural metastases or neurologic symptoms of spinal cord compression.

Abarelix, in contrast to GnRH agonists such as Lupron Depot (also called "Lupron" throughout this review), is a true GnRH antagonist that is devoid of any LH and FSH releasing activity. Consequently, administration of abarelix and other compounds in this class, more rapidly inhibit the secretion of LH and testicular testosterone, without initially producing an increase in serum testosterone concentrations. It is likely that the use of a true GnRH antagonist for the medical treatment of men with advanced carcinoma of the prostate will not cause an increase in prostate cancer-related symptoms, as is often observed following the onset of treatment with a GnRH agonist.

1.3 Important Milestones in Product Development

1.3.1 Significant Regulatory Interactions and Decisions

IND 51-710 for drug PPI-149 (subsequently referred to as abarelix acetate) was filed by Pharmaceutical Peptides, Inc. (presently known as Praecis Pharmaceuticals, Inc) in October 1996. An issue of ongoing discussion (and apparent disagreement) between the Sponsor and the Division of Reproductive and Urologic Drug Products (DRUDP) was the definition of the primary efficacy endpoint for the Phase III clinical program (namely, the "attainment and maintenance of testosterone suppression"). Communications from DRUDP to the Sponsor on March 26, 1999 and June 18, 1999 stated that a single testosterone measurement of > 50 ng/dL between Study-Days 29-85 would constitute a "treatment failure" in either the abarelix or comparator treatment arms. However, during a teleconference on March 30, 2000, DRUDP agreed to the Sponsor's proposal that the primary analysis for successful testosterone suppression would be based on Definition 2 below and that Definition 1 (DRUDP's preference until that time) would be utilized for secondary analyses.

Definition 1 Requires patients to achieve and maintain castration levels of testosterone on all days that testosterone is measured between Days 29 and 85, inclusive.

Definition 2 Requires that patients not have 2 consecutive non-castrate testosterone values 2 weeks apart between Days 29 and 85, inclusive.

In December 2000, the Sponsor filed original NDA 21-320 for the indication —

The Application was given a priority review. On June 11, 2001, The Office of Drug Evaluation III

issued a Not Approvable Letter. The letter cited clinical, chemistry, microbiology, and facilities deficiencies.

The specific *clinical deficiencies* and the steps that would be required to resolve them that were cited in the Not Approvable Letter were the following:

1. Sufficient information to support the safety of abarelix for use in the proposed population was not provided in the current application.
2. Abarelix is intended for chronic use and the data contained in the current application have not demonstrated sustained efficacy as assessed by serum testosterone levels. Moreover, in Study 149-99-03, abarelix was marginally inferior to Lupron Depot® in the percentage of patients who achieved and maintained castration from Day 29 through Day 85. This is worrisome given that more patients in this study were randomized to abarelix than in Studies 149-98-02 and 149-98-03 combined.

To address the above deficiencies, the Sponsor was informed that the following would be required:

1. Conduct investigations to better clarify the nature of the severe systemic allergic reactions (e.g., reactions resulting in hypotension or syncope) that were reported in at least 0.4% of the population treated with abarelix. The ultimate objectives of these investigations should be either to decrease the actual incidence of systemic allergic reactions or to mitigate their consequences.
2. Provide additional data that demonstrate sustained efficacy of abarelix and that abarelix is not inferior to Lupron Depot in the percentage of patients who achieve and maintain castration from Day 29 and beyond.
3. Propose a postmarketing risk management plan for abarelix that includes specific goals and methods to evaluate whether these goals are being met. This risk management plan should be developed after further data regarding the allergic reactions and lack of sustained efficacy over time have been obtained. This plan could include proposed labeling, physician and/or patient education, distribution options, or any additional proposals that would improve the risk-benefit profile of abarelix."

Subsequent to the issuance of the Not Approvable Letter, the Sponsor (1) met with DRUDP on September 10, 2001 and July 18, 2002 and (2) had several teleconferences with DRUDP in an effort to agree upon the specific information and course of action by which the clinical deficiencies could be resolved. Meeting minutes from July 2002 state the following:

> "DRUDP believes that there may be an unmet medical need for those metastatic prostate cancer patients such as those with ureteral obstruction or impending neurological compromise from spinal cord compression who need castration yet are not candidates for surgical orchiectomy or GnRH therapy. ... The Division noted possible approval of abarelix for this specific population if the following items were provided by the sponsor:

- black box warning in the product insert labeling discussing severe systemic allergic reactions
- risk management plan that assures use in only the designated sub-population
- results of ongoing investigations assessing the etiology of severe systemic allergic reactions
- clear labeling describing the indicated population and instructing prescribers to monitor testosterone periodically beyond six months due to the potential for waning efficacy
- safety update with specific emphasis on patients in Study 149-98-04

Medical Officer's Comments Regarding Present Submission

- *In the present submission, the sponsor has addressed the 5 items identified in the minutes of the July 2002 meeting. Specifically, the following has been provided in the present submission:*
  - *a black box warning regarding immediate onset systemic allergic reactions has been added to the Package Inset*
  - *the Sponsor has proposed a risk management plan*
  - *Final Reports for 2 studies (PPI-02-401 and 149-01-06) that investigated the possible etiology of the immediate onset systemic allergic reactions have been submitted*
  - *revised labeling that identifies the indicated population as men with advanced symptomatic prostate cancer who have one or more of the following (1) impending neurological compromise, (2) urinary tract obstruction, and/or (3) bone pain necessitating narcotic analgesia*
  - *additional follow-up information (primarily safety information) for patients with advanced symptomatic prostate cancer initially enrolled in Study 149-98-04 who continued treatment with abarelix in rollover Study 149-99-04*
- *DRUDP withheld agreeing with the Sponsor at the July 2002 meeting that prostate cancer patients who have bone pain necessitating narcotic analgesia would be candidates (per labeling) for treatment with abarelix. The inclusion of this subset in the label indication is a review issue.*
- *The Sponsor's recommendations for ensuring that serum testosterone levels are suppressed to ≤50 ng/dL in proposed labeling are not adequate.*
- *The wording of the proposed black box warning will need to be modified (See proposed labeling changes later in this review).*
- *The Sponsor's risk management program will need to be modified as described later in this review.*

1.4 Other Relevant Information

1.4.1 Related Submissions

Studies included in NDA 21-320 were conducted primarily under IND 51-710

1.4.2 Foreign Marketing Status

Abarelix is not marketed in any foreign country nor has it been approved for marketing in any foreign country. Since submission of the present NDA, the Sponsor has filed an application for marketing of abarelix in Germany.

1.5 Important Issues with Pharmacologically Related Agents

No other GnRH antagonists are presently under review for the indication of palliative management of advanced symptomatic prostate cancer. The clinical development of GnRH antagonists for chronic treatment (e.g., treatment of prostate cancer has be difficult primarily because these compounds have exhibited a propensity to release histamine and have relatively low bioactivity compared to GnRH agonists. Two GnRH antagonists (Cetrotide [Serono] and Antagon

[Organon]) have been approved for short-term use, in conjunction with pituitary gonadotropins, in women undergoing ovarian hyperstimulation for treatment of infertility.

2 CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS

2.1 Chemistry

The primary Chemistry Reviewer stated the following in his review of November 12, 2003 (revised): "The sponsor has provided adequate data to demonstrate product quality. Therefore, from a CMC point of view, the data support approval of the NDA."

2.2 Toxicology Review

No significant new toxicology information was included with the present submission. In the original submission of December 2000, there were no preclinical toxicology findings, per se, that would preclude approval of abarelix for the proposed indication of treatment of prostate cancer. In his review of the present submission, the primary toxicology reviewer (Dr. Krishan Raheja) made the following concluding statement: "The toxicity studies data confirm the safety of abarelix for clinical use."

2.3 Clinical Pharmacology and Biopharmaceutics Review

No data that would provide significant new information about the pharmacology (other than QT interval data) or the pharmacokinetics of abarelix were included in the present submission. In his review of the Sponsor's original submission of December 2000, the primary clinical pharmacology reviewer (Dr. Dhruba Chatterjee) stated (as did the medical reviewer) that patients on abarelix therapy for more than 3 months might experience a reduction in overall efficacy. The biopharmaceutical reviewer stated that the sponsor should consider collecting exposure-response information (for both safety and efficacy) for abarelix from doses higher than that presented in the present NDA. He also stated that "a higher dose of abarelix (provided that this is supported by safety data) may lead to a higher serum level of the drug ... resulting in a higher suppression of testosterone and less variability in serum testosterone levels."

Medical Officer's Comments

- *The Medical Reviewer continues to concur with the above recommendations.*
- *The Sponsor has not directly addressed the issue of a decrease in efficacy over time. Rather, the Sponsor has added the recommendation to the proposed label that . This recommendation is not adequate.*

Re-analyses by Dr. Chatterjee of the Sponsor's data concerning the effect of treatment with abarelix, Lupron, Lupron plus Casodex, and Zoladex plus Casodex on the QT interval in study patients is presented in Section 7.16.4.2.

2.4 Statistics

There were no new statistical issues regarding efficacy or safety in the present submission. The present statistical review focused on delineating further the cumulative rate of immediate systemic allergic reactions as a function of duration of dosing (see Section 7.16.2.2).

2.5 Consultations

Three Divisions/Offices were consulted regarding safety-related issues. These were (1) Division of Pulmonary and Allergy Drug Products (DPADP) regarding systemic allergic reactions; (2) Division of Cardio-Renal Drug Products (DCRDP) regarding changes in the QT interval; and (3) Office of

Drug Safety/Division of Drug Risk Evaluation (DDRE) regarding the Risk-Management Program (RMP). The specific recommendations from each of these consultations are provided in the relevant sections of this review in the Integrated Review of Safety.

3 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

3.1 Pharmacokinetics

Pharmacokinetic parameters for a single IM dose of 100 mg of abarelix for injectable suspension (the to-be-marketed drug) and 15µg/kg of abarelix peptide in an aqueous solution (not to-be-marketed formulation) are listed in Table 1.

Table 1. Mean ± SD Pharmacokinetic Parameters Following a Single Injection of Abarelix Depot Suspension or Abarelix Aqueous Solution (n = 14 per group)

	C_{max} (ng/mL)	T_{max} (days or hrs)	$AUC_{0-\infty}$ (ng • day/mL)	CL/F (L/day)	$t_{1/2}$ (days)
Abarelix injectable suspension [1]	43.4 ± 32.3	3.0 ± 2.9 (d)	500.4 ± 95.7	208.1 ± 47.8	13.2 ± 3.2
Abarelix aqueous solution [2]	57.8 ± 15.3	1.0 ± 0.3 (h)	12.0 ± 1.9	104.8 ± 14.1	1.0 ± 0.3 (h)

[1] 100 mg abarelix IM; [2] 15 µg/kg IM.
Source: Study 149-99-01, Annual Report for IND 51,710, pg. 22, Serial 183.

3.2 Pharmacodynamics

The pharmacodynamic effects of abarelix on serum concentrations of pituitary gonadotropins, testosterone and dihydrotestosterone are presented and discussed in detail in the efficacy section of this review (Sections 6.12.2 and 6.12.3).

4 DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1 Clinical Data Submitted in Support of NDA 21-320

4.1.1 IND Clinical Trials

The sponsor has submitted either complete or preliminary clinical reports from 17 studies conducted under IND 51-710 (treatment of prostate cancer - 15 studies)

4.1.2 NonIND Clinical Trials

Study Reports for 2 studies (ABACAS 1 and ABACAS 1 Extension), both conducted in Europe and originally sponsored by Sanofi-Synthelabo, were submitted. Neither was conducted under the US IND.

4.1.3 Secondary Sources of Clinical Data

Since abarelix is not marketed in any country, no postmarketing data were submitted. Several publication and abstracts, based on the studies for which Final Study Reports were provided, were submitted. These publications or abstracts did not contain any significant information that was not included in the actual study reports.

4.2 Overview of Clinical Studies Included in the NDA

Data from 19 clinical studies (either complete clinical reports or limited data) were submitted by the Sponsor. Four of the 19 studies were conducted with an injectable solution formulation of abarelix (that is not

to be marketed) administered by continuous subcutaneous (SC) infusion (Studies 149-96-01 and 149-97-03). Three of the 19 studies (Studies 149-99-01, 149-00-03, and 149-02-01) were pharmacokinetic studies that were conducted in normal male volunteers. Two of the 19 studies were designed to evaluate the immunologic characteristics of abarelix and were conducted primarily in normal men volunteers (Study 149-01-06) or with blood specimens obtained from other clinical trials (Study PPI-02-02-401). The remaining 10 clinical studies were conducted in men with prostate cancer using the to be marketed formulation of abarelix. Two of these 10 studies (ABACAS 1 and ABACAS 1 Extension) were conducted in Europe and originally sponsored by Sanofi-Synthelabo and not Praecis. Neither was conducted under the U.S. IND. A listing of the 19 studies (study identifier and title) from which data were provided (either in this submission or cross referenced back to the original NDA submission of December 2000) is provided below.

Studies from which clinical data in NDA 21-320 were obtained are the following:

- *One uncontrolled study of abarelix in the Sponsor's indicated prostate cancer population:*
  - **149-98-04**: a multicenter study of abarelix 100 mg IM in 81 patients with advanced symptomatic prostate cancer in whom the use of a GnRH agonist, without concomitant use of an antiandrogen, was likely to induce a "clinical flare" (i.e., an increase in the patient's prostate cancer-related signs and symptoms)
- *Three active comparator, controlled studies of abarelix in men with prostate cancer (these studies provided a data set of 735 patients treated with abarelix 100 mg and 321 patients treated with Lupron or Lupron plus Casodex*
  - **149-98-02**: a phase 3, multicenter, open-label, randomized study of abarelix 100 mg versus Lupron Depot 7.5 mg in prostate cancer patients
  - **149-98-03**: a phase 3, multicenter, open-label, randomized study of abarelix 100 mg versus Lupron Depot 7.5 mg plus daily Casodex 50 mg in prostate cancer patients
  - **149-99-03**: a phase 3, multicenter, open-label, randomized study of abarelix 100 mg versus Lupron Depot 7.5 mg in prostate cancer patients
- *Six supportive studies of abarelix in men with prostate cancer*
  - **149-97-04**: a Phase 1/2, multicenter, dose-escalation study of abarelix 10 to 150 mg administered by SC or IM injection
  - **149-99-04**: a rollover study that enabled continued treatment of patients who had received abarelix in Studies 149-97-04, 149-98-02, 149-98-03, 149-98-04, or 149-99-03
  - **ABACAS 1** (a European study originally sponsored by Sanofi-Synthelabo): a Phase 3, multicenter, open-label, randomized study of abarelix 100 mg IM versus Zoladex 3.6 mg plus Casodex 50 mg
  - **ABACAS 1 Extension** (a European study sponsored by Sanofi-Synthelabo): a rollover study that enabled continued treatment of patients who had received abarelix in Study ABACAS 1
  - **149-01-03**: a multicenter, open-label study of abarelix 100 mg IM vs. Lupron Depot 7.5 mg in patients with prostate cancer who planned to undergo brachytherapy or external-beam radiation therapy
  - **149-01-05**: a multicenter, open-label study to evaluate the feasibility of switching to treatment with a GnRH agonist following treatment with abarelix

- *Two studies of abarelix immunologic characteristics*
  - **149-01-06**: an in vivo skin-test study to test for reactivity to the components of the abarelix depot formulation in patients who had had an allergic reaction while being treated with IM abarelix
  - **PPI-02-02-401**: an in vitro study for determining (1) the presence and titers of antibodies to abarelix and carboxymethylcellulose and (2) total IgG/IgE levels in retained serum and plasma samples from patients previously treated with abarelix, Lupron Depot, or Lupron plus Casodex
- *Two studies of abarelix injectable solution administered by continuous SC infusion in patients with prostate cancer*
  - **149-96-01**: a Phase 1/2, multicenter, uncontrolled study of abarelix injectable solution 30 to 50 µg/kg/day
  - **149-97-03**: a Phase 2, multicenter, uncontrolled study of abarelix injectable solution 50 µg/kg/day in patients requiring prostate gland volume reduction before undergoing radiation therapy for prostate cancer
- [redacted]
- *Three pharmacokinetics studies in healthy men*
  - **149-99-01**: an open-label, relative bioavailability, pharmacokinetic, and pharmacodynamic study of abarelix in healthy men, 50 to 75 years of age
  - **149-00-03**: an open-label, randomized, single-dose study to assess the bioequivalence of 0.01% Polysorbate 80 saline to saline for reconstitution of abarelix in healthy men
  - **149-02-01**: an open-label, randomized, single dose pharmacokinetic and pharmacodynamic study to assess the bioequivalence of 0.1% Polysorbate 80 saline to saline for reconstitution of abarelix in healthy men

Table 2 provides a more detailed overview for 18 of these studies. (ABACAS 1 Extension is not listed in the Table). For each study listed in Table 2 is information regarding (a) study design, (b) number of patients enrolled, and (c) study treatments.

Table 2. Tabular Listing of Worldwide Clinical Investigations of Abarelix

Study No. Study Title	Study Design Status	No. Sites/Country	No. Patients/Sex Age Range Race	No. Patients Treatment Dose/Route/Regimen
Primary Efficacy and Safety Studies of Abarelix Depot in Prostate Cancer (Controlled and Randomized Studies)				
149-98-02 A phase III, multi-center, open-label, randomized study of Abarelix Depot vs. Lupron Depot 1-Month in patients with prostate cancer who are candidates for initial hormonal therapy	Phase 3 Multicenter Open-label Randomized Controlled Complete	26 sites/USA	269 male patients 49 - 89 yr. 232 Caucasian 18 African American 12 Hispanic 7 Asian	180 patients Abarelix depot 100 mg IM every 4 weeks (plus day 15) for up to 1 year --- 89 patients Lupron Depot 7.5 mg IM every 4 weeks for up to 1 year
149-98-03 A phase III, multi-center, open-label, randomized study of Abarelix-Depot vs. Lupron Depot 1-Month plus daily Casodex in patients with prostate cancer who are candidates for initial hormonal therapy	Phase 3 Multicenter Open-label Randomized Controlled Complete	22 sites/USA	251 male patients 49 - 97 yr 203 Caucasian 31 African American 10 Hispanic 5 Asian 2 Other	168 patients Abarelix depot 100 mg IM every 4 weeks (plus day 15) for up to 1 year --- 83 patients Lupron Depot 7.5 mg IM every 4 weeks for up to 1 year plus Casodex 50 mg PO daily for up to 1 year
149-99-03 [1] A phase 3 multicenter, open-label, randomized study of Abarelix-Depot 100 mg IM vs Lupron Depot 7.5 mg IM in patients with prostate cancer who are candidates for initial hormonal therapy	Phase 3 Multicenter Open-label Randomized Controlled Complete	49 sites/USA 7 sites/Canada	582 male patients 46 - 89 yr 486 Caucasian 60 African American 19 Hispanic 8 Asian 9 Other	387 patients Abarelix depot 100 mg IM every 4 weeks (plus day 15) for 24 weeks --- 195 patients Lupron Depot 7.5 mg IM every 4 weeks for 24 weeks

[1] Primary objective of this Study was to obtain additional safety data for Abarelix. Efficacy data were considered supportive by the Sponsor.

Source: Table 3.1, pg 31-37, Vol. 17, Submission of February 25, 2003.

(continued)

Table 2 Tabular Listing of Worldwide Clinical Investigations of Abarelix (Continuation)

Study No. Study Title	Study Design Status	No. Sites/Country	No. Patients/Sex Age Range Race	No. Patients Treatment Dose/Route/Regimen
Study of Abarelix in the Indicated Prostate Cancer Population				
149-98-04 A multi-center study of Abarelix-Depot in patients with prostate cancer in whom GnRH agonists are contraindicated	Multicenter Open-label Uncontrolled Complete	16 sites/USA 1 site/Mexico	81 male patients 40 - 94 yr 62 Caucasian 6 African American 13 Hispanic	81 patients Abarelix depot 100 mg IM every 4 weeks (plus day 15) for up to 1 year
Supportive Efficacy and/or Safety Studies of Abarelix Depot in Prostate Cancer				
149-97-04 A multi-center, open-label, dose-escalation study of the safety and therapeutic effects of PPI-149 depot, administered as an intramuscular or subcutaneous injection in prostate cancer patients who are candidates for initial hormonal therapy	Phase 1/2 Multicenter Open-label Dose-ranging Nonrandomized "Controlled" [1] Complete	29 sites/USA 1 site/Canada	296 male patients 49 - 93 yr 221 Caucasian 52 African American 5 Asian 17 Hispanic 1 Other	54 patients Abarelix depot, phase 1: 10-150 mg IM or SC every 4 weeks (plus or minus day 15) for an open-ended time period 209 patients Abarelix depot, phase 2: 100 mg IM for 4 weeks (plus day 15), then 50 or 100 mg every 4 weeks for an open-ended time period 33 patients Prospective concurrent control [1]
149-99-04 A rollover, multicenter, open-label maintenance study of patients with prostate cancer who were previously treated with abarelix-depot 50 mg or 100 mg IM	Phase 3 Multicenter Open-label Uncontrolled Ongoing	55 sites/USA	292 male patients 41 - 94 yr 263 Caucasian 15 African American 1 Asian 12 Hispanic 1 Other	14 patients Abarelix depot 50 mg IM every 4 weeks for an open-ended time period 278 patients Abarelix depot 100 mg IM every 4 weeks for an open-ended time period

[1] Patients who declined treatment with Abarelix were enrolled in a "prospective concurrent control group" (Sponsor's terminology) and received a commercially available GnRH agonist (Lupron Depot or Zoladex) with or without an antiandrogen (e.g., Casodex).

(Continued)

Table 2 Tabular Listing of Worldwide Clinical Investigations of Abarelix (Continuation)

Study No. Study Title	Study Design Status	No. Sites/Country	No. Patients/Sex Age Range Race	No. Patients Treatment Dose/Route/Regimen
Supportive Efficacy and/or Safety Studies of Abarelix Depot in Prostate Cancer (continued)				
149-01-03 An open-label comparison of neoadjuvant hormonal therapy (NHT) with abarelix depot 100 mg IM or Lupron Depot 7.5 mg IM in patients with prostate cancer planned to undergo brachytherapy or external-beam radiation therapy	Phase 2 Multicenter Open-label Randomized Controlled Complete	25 sites/USA	82 male patients 51-83 yr 58 Caucasian 19 African American 3 Hispanic 2 Other	55 patients Abarelix 100 mg IM every 4 weeks (plus day 15) for up to 8 weeks (patients were allowed to receive an additional injection while waiting for brachytherapy or external beam radiation therapy) --- 27 patients Lupron Depot 7.5 mg IM every 4 weeks for up to 8 weeks (patients were allowed to receive an additional injection while waiting for brachytherapy or external beam radiation therapy)
149-01-05 An open-label study to evaluate the feasibility of switching to treatment with an LHRH agonist following 12 weeks of treatment with abarelix in patients with prostate cancer	Phase 2/3 Multicenter Open-label Uncontrolled Abarelix portion complete	22 sites/USA	176 male patients 43 – 89 yr 139 Caucasian 24 African American 9 Hispanic 3 Asian 1 Other	176 patients Abarelix 100 mg IM every 4 weeks (plus day 15) for 12 weeks Lupron Depot 7.5 mg IM every 4 weeks for 8 weeks following the treatment with abarelix, or Zoladex 3.6 mg SC every 4 weeks for 8 weeks following the treatment with abarelix
Supportive Efficacy and/or Safety Study of Abarelix Depot in Prostate Cancer (Conducted by Sanofi-Synthelabo)				
ABACAS 1 Comparison of the efficacy and safety of abarelix versus goserelin plus bicalutamide in patients with advanced or metastatic prostate cancer: a one-year, randomized, open-label multicenter phase III trial	Phase 3 Multicenter Open-label Randomized Controlled Complete	9 sites/France 6 sites/Germany 6 sites/The Netherlands 3 sites/Belgium 3 sites/Italy	177 male patients 48 - 89 yr 175 Caucasian 1 Black 1 Asian	87 patients Abarelix depot 100 mg IM every 4 weeks (plus day 15) for 1 year --- 90 patients Zoladex 3.6 mg SC every 4 weeks for 1 year plus Casodex 50 mg daily PO for 1 year

(Continued)

Table 2. Tabular Listing of Worldwide Clinical Investigations of Abarelix (Continuation)

Study No. Study Title	Study Design Status	No. Sites/Country	No. Patients/Sex Age Range Race	No. Patients Treatment Dose/Route/Regimen
Immunologic Studies				
149-01-06 Skin testing for allergic-type reactions to the components of Plenaxis™	Phase I Multicenter Open-label Uncontrolled Complete	2 sites/USA	15 male subjects 23 – 56 yr 6 Caucasian 6 African American 1 Hispanic 1 Asian 1 Other 1 male patient 81 yr 1 Caucasian	15 subjects 1 patient Histamine control Saline control NaCMC dilutions 0.001 mg/mL 0.01 mg/mL 0.1 mg/mL Abarelix acetate dilutions 0.000001 mg/mL 0.00001 mg/mL 0.0001 mg/mL 0.001 mg/mL 0.01 mg/mL 0.1 mg/mL
PPI-02-02-401 In vitro testing of IgG/IgE levels in retained serum and plasma samples	Tested stored serum and plasma samples from studies 149-97-04, 149-98-02, 149-98-03, 149-98-04, 149-99-03, 149-99-04, ABACAS 1, and ABACAS 1 Extension			

(Continued

Table 2. Tabular Listing of Worldwide Clinical Investigations of Abarelix (Continuation)

Study No. Study Title	Study Design Status	No. Sites/Country	No. Patients/Sex Age Range Race	No. Patients Treatment Dose/Route/Regimen
Other Studies: Abarelix Injectable Solution in Prostate Cancer				
149-96-01 A multi-center, open-label, dose-escalation study of the safety and therapeutic effects of PPI-149, administered as a subcutaneous, continuous infusion in patients with stage D1 or D2 metastatic prostate cancer or patients with a rising PSA level after radiation therapy, radical prostatectomy, or other local therapy who are candidates for initial hormonal therapy	Phase 1/2 Multicenter Open-label Uncontrolled Complete	5 sites/USA	26 male patients 48 - 82 yr 22 Caucasian 1 African American 1 Hispanic 2 Other	26 patients Abarelix injectable solution 30-50 µg/kg/day by continuous SC infusion for 14 to 28 days
149-97-03 Phase II, multicenter, open-label study of PPI-149, administered as a subcutaneous, continuous infusion for 57 to 85 days (8 to 12 weeks) in patients undergoing radiation therapy, interstitial seed implantation or other radiation therapy	Phase 2 Multicenter Open-label Uncontrolled Complete	10 sites/USA	36 male patients 55 - 81 yr 26 Caucasian 7 African American 2 Asian 1 Hispanic	36 patients Abarelix injectable solution 50 µg/kg/day by continuous SC infusion for up to 84 days
Other Studies:				

(Continued)

Table 2. Tabular Listing of Worldwide Clinical Investigations of Abarelix (Continuation)

Study No. Study Title	Study Design Status	No. Sites/Country	No. Patients/Sex Age Range Race	No. Patients Treatment Dose/Route/Regimen
Other Studies: Pharmacokinetics of Abarelix				
149-99-01 Open-label, relative bioavailability, pharmacokinetic and pharmacodynamic study of Abarelix-Depot in healthy men ages 50 to 75	Single center Open-label Sequential dosing Controlled Complete	1 site/USA	16 male subjects 52 - 75 yr 6 Caucasian 10 Hispanic	16 subjects Abarelix injectable solution 10-15 µg/kg single IM dose 3-week washout Abarelix depot 100 mg single IM dose
149-00-03 An open-label, randomized, single-dose, parallel group study to assess the bioequivalence of NV2 to saline for reconstitution of Abarelix Depot 100 mg in healthy males, ages 50 to 75 years	Phase I Single center Open-label Parallel group Controlled Complete	1 site/USA	35 male subjects 50 – 74 yr 12 Caucasian 20 Hispanic 3 African American	17 healthy subjects Abarelix reconstituted with NV2 100 mg single IM --- 18 healthy subjects Abarelix reconstituted with saline 100 mg single IM
149-02-01 An open-label, randomized, single-dose, parallel group study to assess the bioequivalence of Polysorbate Saline Vehicle (PSV) to 0.9% Sodium Chloride Inj., USP for Reconstitution of Plenaxis™ 100 mg in healthy males, ages 45 to 75 years	Phase I Single center Open-label Parallel group Controlled Complete	1 site/USA	65 male subjects 45 – 75 yr 10 Caucasian 50 Hispanic 5 African American	33 healthy subjects Abarelix reconstituted with PSV 100 mg single IM --- 32 healthy subjects Abarelix reconstituted with saline 100 mg single IM

4.3 Exposure to Abarelix in Prostate Cancer Patients

A total of 1397 prostate cancer patients were exposed to abarelix for injectable suspension. Of those 1397 patients, 1154 patients received the registration dose (abarelix 100 mg for both induction and maintenance of castration) and 243 patients received non-registration doses.

4.3.1 Patient Exposure to Abarelix in Primary (non-Extension) Clinical Studies

Table 3 lists the initial or primary studies in which the 1154 patients received the registration dose of abarelix (100 mg). These studies were: (1) the indicated prostate cancer population: 149-98-04; (2) the 3 primary controlled studies: 149-98-02, 149-98-03 and 149-99-03; and (3) the supportive studies 149-97-04, ABACAS 1, 149-01-03, and 149-01-05. Also shown are the total and by-study numbers of patients exposed to the registration dose for at least 6 months (based on receiving the Day 141 injection) and 1 year (based on receiving the Day 337 injection). Across the 8 studies, 829 patients were exposed to the registration dose for 6 months and 191 patients were exposed for 1 year.

Table 3. Patient Exposure to 100 mg Dose of Abarelix Depot [1]

	Abarelix (100 mg dose)		
Study	Any Exposure n	6 Months of Exposure (received Day 141 dose) n	1 Year of Exposure (received Day 337 dose) n
Study in Indicated Prostate Cancer Population			
149-98-04	81	70	2
Subtotal	**81**	**70**	**2**
Primary Controlled Studies			
149-98-02	180	169	94
149-98-03	168	157	89
149-99-03	387	345	0
Subtotal	**735**	**671**	**183**
Supportive Studies			
149-97-04	20	10	5
ABACAS 1	87	78	1
149-01-03	55	0	0
149-01-05	176	0	0
Subtotal	**338**	**88**	**6**
Primary and Supportive Studies			
Total	**1154**	**829**	**191**

1 Does not include exposure in rollover studies 149-99-04 or ABACAS 1 Extension.
Source: ISS Update (8 May 03, Table 5-1, Amendment 47).

4.3.2 Cumulative Exposure to Abarelix including Exposure in Extension Studies

Patients treated with abarelix in studies 149-97-04, 149-98-02, 149-98-03, 149-98-04, and 149-99-03 were given the opportunity to continue treatment with abarelix in study 149-99-04. Patients treated in Study ABACAS 1 were given the opportunity to participate in an extension study (ABACAS 1 Extension). Table 4 summarizes the cumulative patient exposure to the registration dose of abarelix based on the duration of treatment in both the original and extension study. Including cumulative exposure in the extension studies, 327 patients were exposed to abarelix for at least 1 year, and

113 patients were exposed for at least 2 years. In addition, 26 patients were exposed for at least 3 years (per Sponsor's narrative).

Table 4. Cumulative Exposure to the Registration Dose of Abarelix (100 mg) Including Exposure in Safety Extension Studies 149-99-04 and ABACAS 1 Extension

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

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

4.4 Postmarketing Experience

Abarelix is not approved for marketing in any country. No GnRH antagonists are presently approved for long-term therapy in any markets.

4.5 Literature Review

Several publications based on Praecis sponsored studies were provided. These publications did not contain any substantive information that was not included in the Sponsor's final study reports. The Sponsor also provided several publications regarding the possible influence of androgens and sex steroids on the QT interval. Information from these latter publications is considered in Section 7.16.4.

5 CLINICAL REVIEW METHODS

5.1 How Review was Conducted

The review conducted by this Medical Officer focused on (1) the clinical study in the indicated target population (Study 149-98-04, advanced symptomatic prostate cancer), (2) the controlled and randomized primary efficacy studies (Studies 149-98-02, 149-09-03), and (3) the controlled and randomized primary safety studies (Studies 149-98-02, 149-98-03, and 149-99-03). All materials

submitted for these studies were considered during the conduct of this review. Review of safety extension study 149-99-04 focused on major safety issues, namely, drug-related serious adverse events, adverse events leading to patient withdrawal, acute systemic allergic reactions, potential liver toxicity, and deaths. Pharmacodynamic data from Study 149-97-04 supporting dose selection for the pivotal efficacy studies also were reviewed. Supportive IND studies conducted with the solution formulation of abarelix, ——— and studies 149-01-03, 149-01-05, ABACAS 1, and ABACAS 1 Extension were reviewed primarily for the safety issues of acute systemic allergic reactions and deaths.

Study 149-98-04 also was reviewed independently by G. Benson MD, Medical Officer, DRUDP during the review of original NDA 21-320. In the Executive Summary (dated June 21, 2001), Dr. Benson states the following: "This reviewer believes that Trial 149-98-04 supports the approval of abarelix for limited use only in those patients with far advanced prostate cancer (not currently on hormonal therapy) 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."

5.2 Overview of Materials Consulted in Review

The following materials were reviewed during the conduct of the review of original NDA 21-320. Selected materials were reviewed again during the present review cycle:

- Original NDA 21-320; Submission Date of December 11, 2000
  - Volumes 1, 44-110
  - Selected electronic case report forms (CRFs) and SAS transport datasets
- Safety Update (submitted March 13, 2001)
- Submission of March 27, 2001 (requested supplemental safety listings and analyses for laboratory data)
- Submission of April 6, 2001 (requested supplemental safety data for allergic reactions)
- Submission of April 9, 2001 (requested supplemental efficacy analyses)
- Submissions of April 26 and April 27, 2001 (requests for additional safety data from Study 149-99-04)
- Submission of May 4, 2001 (requested supplemental safety listings)
- Submission of May 8, 2001 (errata for submission of April 27, 2001)

The following materials were submitted as part of the resubmission of NDA 21-302 (Complete Response to a Not Approvable Action)

- Resubmission of NDA 21-320; Submission Date of February 25, 2003
  - Volumes 1, 16-54
  - Selected electronic case report forms (CRFs) and SAS transport datasets
- Final Report for Study 149-01-05 (Submitted April 25, 2003)
- Final Report for ABACUS 1 Extension (Submitted April 25, 2003)
- Submission of May 8, 2003 (ISS Update and errata)
- Submissions of June 19, 2003, June 25, 2003, and June 30, 2003 (Datasets for ABACAS 1 and ABACAS 1 Extension)

- Submission of July 9, 2003 (Additional QT data from US studies)
- Submission of July 18, 2003 (Requested safety analyses [cardiac AEs and liver enzymes])
- Annual Report for IND 51,710 (Submitted July 18, 2003)
- Submission of September 29, 2003 (Requested additional safety information, primarily Study 149-01-05)
- Submission of October 30, 2003 (Requested additional efficacy analyses for Studies 149-01-05, 149-98-02, 149-98-03, and ABACAS 1)
- Submission of November 18, 2003 (Requested efficacy subset analyses for race)
- Numerous revisions to the Package Insert, Patient Information Sheet, and Risk Management Plan

5.2.1 Safety Update

A formal Safety Update was not submitted during the review. However, the Submissions of April 25, 2003 for Study 149-01-05 (cross-over component) and ABACAS 1 Extension should be considered to be Safety Updates as they provided information on the only clinical trials for which data had not been previously submitted.

5.3 Overview of Methods Used to Evaluate Data Quality and Integrity

5.3.1 Independent FDA Analyses of Safety and Efficacy and FDA Requests for Additional Data and Analyses

During the original review cycle for NDA 21-320, the accuracy of the Sponsor's primary efficacy analyses (based on the data listings provided by the Sponsor) was confirmed by K. Meaker, MS, FDA statistician (See separate statistical review dated June 12, 2001). In addition, the Medical Reviewer prepared separate supplemental efficacy tabulations based on the Sponsor's submitted data. The Sponsor also submitted, at the request of the Medical Reviewer, supplemental efficacy analyses based on long-term (up to one year) pharmacodynamic data.

During the present review cycle, analyses and summary tables relating to systemic allergic reactions were updated and confirmed using the data listings provided by the Sponsor. Additional tabulations and statistical analyses pertaining to immediate systemic allergic reactions also were performed by the FDA statistician (Ms. Meaker, see review dated July 25, 2003), Charles Lee MD (Medical Officer, Division of Pulmonary and Allergy Drug Products, see review dated July 2, 2003) and the primary Medical Reviewer. At the request of the Medical Reviewer, the sponsor also provided additional safety analyses pertaining to (1) laboratory safety assessments (particularly liver enzyme changes) and adverse events for Study 149-99-04 (rollover safety study) and (2) QT interval changes and cardiac adverse events possibly related to QT interval changes. Additional analyses for changes in serum testosterone concentrations (efficacy analyses) for Studies 149-01-05 and ABACAS 1 were provided by the Sponsor at the request of the Medical Reviewer. QT interval data provided by the Sponsor were independently reanalyzed by the FDA Clinical Pharmacology Reviewer (Dr. Chatterjee).

5.3.2 Division of Scientific Investigation Site Inspections

During the original review cycle, 4 study centers (2 each that participated in Studies 149-98-02 and 149-99-03) were inspected by the Division of Scientific Investigation (DSI). The summary report issued by DSI (dated June 5, 2001) stated the following: "The data submitted in support of this NDA by Drs. Zinner, Gleason, Friedel, and Barzell appeared to be adequate and in compliance with U.S. Federal regulations and/or good clinical investigational practices."

During the present review cycle, 3 centers from Study 149-98-04 (the only study that enrolled the indicated patient population) were inspected by DSI. A Form 483 was issued for 2 of the 3 sites, primarily for administrative infractions and protocol deviations that had no impact on the primary efficacy assessment and the safety assessments. In their summary report, DSI stated the follow: "The data submitted in support of this NDA by Drs. Centeno, Gange, and Friedel appear acceptable."

5.3.3 Laboratory Assessments of Safety and Efficacy

Hormone measurements (e.g., testosterone), measurements of tumor biomarkers (e.g., PSA), and general safety measurements (serum chemistries and complete blood counts) for the primary studies conducted in North America were performed at a Central Laboratory

5.3.4 Site Monitoring

For the primary clinical trials conducted in North America,

was responsible for initiating and monitoring sites, handling serious adverse event reports, maintaining the clinical trial database, and performing statistical analyses according to their standard operating procedures. According to the Sponsor

performed site monitoring visits on a regular basis. During these visits, information recorded on the case report forms was verified against source documents. The sponsor conducted site audits to monitor both the regulatory and protocol compliance of selected clinical investigators and the overall performance of the contract research organization

Medical Officer's Comments

- *are a well known, qualified clinical laboratory and a Contract Research Organization, respectively. Both are widely used by the pharmaceutical industry to conduct and/or monitor drug clinical trials.*
- *Assay validation procedures and quality control are addressed and reviewed in the original Biopharmaceutical Review. No areas of concern were identified by the Biopharmaceutical Reviewer.*

5.4 Ethical Standards by which Studies were Conducted

Studies sponsored by Praecis in North America appeared to be conducted in accordance with acceptable ethical standards.

5.5 Financial Disclosure Statements

During the original review cycle, financial disclosure statements from the study in the indicated patient population (149-98-04), the 3 primary controlled efficacy and/or safety studies (149-98-02, 149-98-03, and 149-99-03) and supportive study 149-97-04 were reviewed by J. Best, MSN, R.N., Regulatory Project Manager, DRUDP. According to the Sponsor's submission, all investigators who responded certified that "none of the financial arrangements of concern to the FDA existed during the period covering the dates of their participation in the studies." In her Memo of May 2, 2001, Ms. Best stated that across these 5 studies financial statement responses were obtained from all principal investigators and that none had any disclosable information. The Sponsor was not able to obtain financial disclosure statements from 1 or more subinvestigators at each of 1 or 2 sites from 4 of these 5 studies. The principal reason for not obtaining financial disclosure information according to the Sponsor was that "the individuals in question had left the practice and could not be contacted." Ms. Best made the following conclusion in her Memo of May 2, 2001: "Adequate documentation was submitted to comply with 21 CFR 54. While the sponsor could have used other means to obtain documentation from non-compliant investigators, the rate of return is acceptable. There was no disclosure of financial interests that could bias the outcome of the trials."

During the present review cycle, financial disclosure information was submitted for investigators from Praecis sponsored Studies 149-99-04, 149-01-03, 149-01-05, 149-01-06, and ABACAS 1 (non-U.S. study originally sponsored by ——). Financial disclosure information was obtained from all principal investigators and all subinvestigators (with 2 exceptions) for all Praecis sponsored studies. The 2 exceptions were a single subinvestigator at each of 2 sites in Study 149-99-04). According to the Sponsor, "All investigators who responded certified that none of the financial arrangements of concern to FDA existed during the period covering the dates of their participation in the studies." For Study ABACAS 1, financial disclosure information was not obtained from 9 of 29 principal investigators.

Medical Officer's Comment

- *Failure to obtain financial disclosure statements from subinvestigators at 1 (n=3) or 2 (n=2) centers among all the North American Centers for the studies listed above will not jeopardize the integrity of the data or the safety and efficacy conclusions derived from the primary North American clinical trials. Each of the 3 controlled primary studies and the study in the indicated population was multicenter, and each was conducted at ≥ 19 sites.*
- *No conclusion can be made as to potential significant financial conflicts of investigator's in Study ABACAS 1 because of the high nonresponder rate (9 of 29 investigators did not respond). Data from this study, however, were not consider to be of material importance to the review of NDA 21-320 with 2 exception, the effect of treatment on the QTc interval and the occurrence of immediate systemic allergic reactions. Data concerning the effect of treatment on the QTc interval also were obtained from Studies 149-98-02 and 149-98-03. QTc data from all of the studies showed similar trends. The incidence of immediate allergic reactions in ABACAS 1 and ABACAS 1 Extension was comparable to that observed across all other study centers.*

6 INTEGRATED REVIEW OF EFFICACY (PRIMARY CLINICAL STUDIES)

6.1 Brief Summary of Efficacy Findings

Indicated Patient Population. Abarelix, without concomitant antiandrogen therapy, can be administered to men with advanced symptomatic androgen dependent prostate cancer (the indicated patient population) with little risk of a testosterone-induced clinical flare. All patients treated with abarelix (n = 72 in the efficacy evaluable population) in Study 149-98-04, avoided orchiectomy through study Day 85, the protocol defined primary efficacy endpoint. No patient (with one possible exception) reported adverse events during the initial treatment period suggestive of a testosterone-induced clinical flare.

Controlled Clinical Trials. In the primary controlled clinical trials, in which serum testosterone concentrations were closely monitored for up to 1 year, no patient experienced an increase in testosterone values after the initial administration of abarelix. In these trials, approximately 25% and 70% of abarelix-treated patients were medically castrate (serum testosterone ≤ 50 ng/dL) by Days 2 and 8, respectively. By the Sponsor's protocol defined definition of maintenance of medical castration (i.e., no 2 consecutive serum testosterone values > 50 ng/dL), approximately 90% (point estimate) of abarelix-treated men in the controlled clinical trials were medically castrate by treatment Day 29 and maintained medical castration through Day 85. During this period, abarelix treatment was not statistically inferior to that of Lupron or Lupron plus Casodex. However, if maintenance of medical castration was assessed by more rigorous criteria (i.e., no serum testosterone values >50 ng/dL after Study day 29), abarelix was not shown to be non-inferior to Lupron over the period from Days 29-85 and was slightly inferior to Lupron over the period from Days 29-169. After treatment Day 169, the effectiveness of abarelix, relative to that of Lupron or Lupron plus Casodex, in terms of maintaining medical castration, was further reduced (i.e., abarelix was less effective). This decrease in the effectiveness of abarelix will require the monitoring of serum testosterone concentrations in patients receiving long term treatment under the dosing regimen employed in the controlled clinical trials. The differences between abarelix and Lupron, in terms of maintaining long term and reliable suppression of serum testosterone, also will need to be addressed in labeling.

6.2 Format and Content of the Integrated Review of Efficacy

In the Integrated Review of Efficacy, efficacy findings from the single clinical trial in the indicated patient population (patients with advanced symptomatic prostate cancer, Study 149-98-04) are first presented. Efficacy findings from the 3 primary controlled clinical trials conducted in North America (Studies 149-98-02, 149-98-03, and 149-99-03) are then presented and reviewed.

Although only 81 patients were treated with abarelix in Study 149-98-04 and only 72 of these patients were included in the efficacy analyses (there was inadequate documentation at one center in Mexico), this study provides substantial information about the short-term effects of abarelix treatment on the signs and symptoms of prostate cancer in the indicated patient population. Most importantly, this study provided information as to whether treatment with abarelix would produce a "clinical flare" in the signs or symptoms of advanced prostate cancer in patients with advanced symptomatic prostate cancer.

In the primary controlled clinical trials, the primary endpoints were based on the effect of abarelix on serum testosterone concentrations (a surrogate endpoint). Few, if any, patients in the controlled studies had advanced symptomatic prostate cancer. However, it is reasonable to conclude that the effect of abarelix on serum testosterone concentrations in these studies would be indicative of that which would occur in patients with advanced symptomatic cancer. In addition, these studies provide information about (1) the efficacy of abarelix, assessed in terms of the surrogate endpoint of

suppression of serum testosterone concentrations in a much large number of men with prostate cancer and (2) the efficacy of abarelix compared to a the most widely used GnRH agonist (Lupron).

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"

6.3 Study Objective (Study 148-98-04)

The primary objective of this study was the prevention of orchiectomy in symptomatic patients with advanced prostate cancer treated with abarelix. The secondary objectives were to determine (1) the safety of treatment with abarelix in this population, (2) the effects of treatment on PSA kinetics, and (3) the pharmacodynamic efficacy of abarelix treatment (e.g., suppression of serum testosterone levels) in these patients.

6.4 Overview of Study (Study 148-98-04)

This was a multicenter, open-label, noncomparative clinical trial that enrolled patients with advanced symptomatic prostate cancer. The study was conducted at 18 centers in the United States and 1 center in Mexico. Eligible patients at entry had 1 or more of the following 4 conditions secondary to prostate cancer: (1) bone pain from skeletal metastases, (2) bilateral retroperitoneal adenopathy causing ureteral obstruction, (3) the presence of an enlarged prostate gland or pelvic mass causing bladder outlet obstruction, and/or (4) impending neurological compromise. According to the Sponsor, treatment with a GnRH agonist was contraindicated in these patients. Patients were to receive abarelix (100 mg per dose) by IM injection on Study Days 1, 15, 29, 57, 85, 113, and 141 for a treatment duration of 24 weeks (i.e., 28 days past the final scheduled dose of abarelix). Study assessments were to be performed throughout the treatment period, at the completion of treatment (Day 168), and at a follow-up visit 8 to 9 weeks after the last injection. At the investigator's discretion, patients were permitted to continue to receive additional doses of abarelix starting on Day 169 and continuing every 28 days thereafter. After initiation of the rollover study (Study 149-99-04), patients who successfully completed at least 24 weeks of treatment in Study 149-98-04, were allowed to continue treatment with abarelix in Study 149-99-04.

Medical Officer's Comments

- *GnRH agonists are not actually "contraindicated" in at least 3 of the 4 conditions listed above (i.e., bone pain from skeletal metastases, retroperitoneal adenopathy causing ureteral obstruction, and the presence of an enlarged prostate gland or pelvic mass causing bladder outlet obstruction). Because of the testosterone "surge" seen at the onset of treatment with a GnRH agonist, product labels for GnRH agonists state that patients with any of the conditions listed above should be "closely observed" at the onset of GnRH therapy.*

6.5 Study Design (Study 148-98-04)

6.5.1 Enrollment Criteria

The patient population in this study represented a group at high risk for developing a worsening of their signs or symptoms of prostate cancer or a neurologic and/or urologic emergency from exacerbation of their prostate cancer secondary to a GnRH analog-induced surge of testosterone. Risks included one or more of the following: spinal cord compression, urinary obstruction of both the upper or lower tracts, and continued significant bone pain in the presence of narcotic analgesic treatment.

6.5.1.1 Inclusion Criteria

Inclusion criteria included the following:

- Male patient > 18 years old
- Diagnosed with advanced, life-threatening, symptomatic prostate adenocarcinoma based on histological evidence or on clinical suspicion with an elevated PSA or acid phosphatase measurement; advanced, life-threatening, symptomatic prostate cancer was defined as 1 or more of the following:
  - bone pain from prostate cancer skeletal metastases that was expected to be exacerbated by administration of a GnRH agonist
  - impending neurological compromise from spinal, spinal cord, or epidural metastases that could have worsened or advanced to spinal cord compression upon administration of a GnRH agonist
  - bilateral retroperitoneal adenopathy with ureteral obstruction (with or without azotemia) that could have progressed to hydronephrosis, azotemia, or worsening obstruction upon administration of a GnRH agonist
  - presence of an enlarged prostate gland or pelvic mass caused by prostate cancer that had caused bladder neck outlet obstruction that could have worsened or resulted in urinary retention upon administration of a GnRH agonist
- Had symptomatic prostate cancer and GnRH agonist therapy was otherwise contraindicated
- Bilateral orchiectomy was the only treatment option and was unacceptable to the patient

Medical Officer's Comment

- *As stated previously, many clinicians would not consider GnRH therapy with concomitant antiandrogen treatment to be absolutely contraindicated in at least 3 of the 4 conditions listed above.*

6.5.1.2 Exclusion Criteria

A patient was excluded from participation if he met any of the following criteria:

- Prior hormonal therapy for metastatic prostate cancer, other than neoadjuvant hormonal therapy
- Neoadjuvant hormonal therapy for prostate cancer within the previous 6 months before enrollment
- Known androgen-independent (hormone-refractory) prostate cancer
- Currently taking or planning to take PC SPES® (Botaniclab, Inc.), an herbal therapy for the treatment of prostate cancer
- Recent history of drug sensitivity to a GnRH agonist
- Treatment with any investigational drug within 30 days before enrollment

6.5.2 Treatment Administered

This was an open label, non-comparative clinical trial. All participants received abarelix 100 mg by IM injection on Days 1, 15, 29, 57, 85, 113, and 141. The duration of treatment in this study was planned as a minimum of 24 weeks (28 days beyond the Day 141 dose) with an option to continue. For patients continuing the study after the successful completion of 24 weeks, abarelix 100 mg was

administered by IM injection on day 169 and 28 days thereafter at the investigator's discretion. Patients who were continuing to receive abarelix on or after Day 169 were enrolled in rollover Study 149-99-04 when it became available at each study site.

6.5.3 Schedule of Assessments

The Schedule of Assessments is presented in Table 5. During the screening period (Day –14 to Day 1), the patient's eligibility for the study was determined according to the inclusion and exclusion criteria. After their first injection of study medication on Day 1, all patients were to return to the clinic for study assessments on Days 2, 8, 15, 29, 57, 85, 113, 141, and 169. The posttreatment period began 28 days after the last injection. Patients also were to return to the clinic for assessments 28 days after the last injection (end of treatment), and 4 to 5 weeks posttreatment (8 to 9 weeks after the last injection).

At the investigator's discretion, patients were permitted to continue to receive injections of study medication on Day 169 and every 28 days thereafter for up to 1 year.

Table 5 Schedule of Assessments (Study 149-98-04)

	Study Day													
Procedure	**-14 to 1**	**1**	**2**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**365**	**End of Tx[1]**	**FU[2]**
Informed consent	x													
General medical history	x													
Prostate cancer history[3]	x													
Cancer staging/response	x[4]							x[4]			x[4]			
Symptomatic assessment[5]	x		x	x	x	x	x	x			x[6]		x	x
Physical examination[7]	x				x	x	x	x			x		x	x
Vital signs	x	x			x	x	x	x			x		x	x
Hematology		x				x	x	x	x	x	x[6]		x	x
Clinical chemistry		x				x	x	x	x	x	x[6]		x	x
Acid phosphatase[8]		x		x		x	x	x	x	x	x[6]		x	x
Special chemistry panel[9]	x	x	x	x	x	x	x	x	x	x	x[6]		x	x
Urinalysis	x							x			x			
Baseline signs/symptoms	x	x												
EQ-5D (EuroQoL)		x			x		x	x			x	x[10]		x
SWOG 9039		x			x		x	x			x	x[10]		x
Endocrine questionnaire		x		x		x	x	x	x	x	x[7]		x	x
Avoidance of orchiectomy						x		x						
Abarelix depot dosing		x			x	x	x	x	x	x	x[11]			
Adverse events, concomitant Rx	Recorded and monitored throughout the study													

[1] End of treatment: 28 days after the last injection.
[2] Follow-up: 28 to 35 days after treatment end.
[3] Included date of diagnosis, tumor, nodes, and metastases (TNM) staging, Gleason Grading System.
[4] Method at discretion of investigator; same method repeated on day 85 and every 12 weeks for patients continuing the study on or after day 169.
[5] As applicable to the patient, scans and ultrasounds were to be performed only every 12 weeks.
[6] Repeated every 28 days at the time of dosing for patients continuing the study on or after day 169.
[7] Included height and weight measurements and Eastern Cooperative Oncology Group (ECOG) Performance Scale.
[8] Total and prostatic fraction.
[9] Serum levels of testosterone, DHT, LH, FSH, and PSA.
[10] Patients continuing the study on or after day 169.
[11] Patients continuing the study received abarelix depot on day 169 and every 28 days thereafter at the investigator's discretion; patients with testosterone. > 50 ng/dL on day 169 were to receive an extra injection on day 183, 2 weeks before their next regularly scheduled injection.

Source: Final Report for Study 149-98-04, Table 7-1, pg 30, Vol. 19, Submission of February 25, 2003.

6.5.4 Efficacy Endpoints

6.5.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint was

- Rate of avoidance of bilateral orchiectomy within the first 4 weeks of treatment (through Day 29) and within the first 12 weeks of treatment (through Day 85).

A patient was considered a treatment failure when the decision to perform a bilateral orchiectomy was made (not when the surgery was actually performed). Patients requiring orchiectomy because of worsening of symptoms or progression of disease in the presence of medically castrate levels of testosterone (≤ 50 ng/dL) were not considered treatment failures. Patients who did not complete 84 days of abarelix treatment because of adverse events or laboratory abnormalities considered related to study medication were considered treatment failures. Otherwise, patients who withdrew from the study without requiring an orchiectomy were considered treatment successes under last observation carried forward (LOCF) guidelines.

Medical Officer's Comment

- *It is not clear if this endpoint was discussed with DRUDP since this study was not a pivotal study in the original abarelix development program.*
- *Although avoidance of orchiectomy for 85 days is not a clinically significant long-term outcome, per se, it is a reasonable and meaningful endpoint in assessing the clinical potential of abarelix in this population. Avoidance of orchiectomy is indirect evidence that treatment with abarelix (1) did not induce a clinically serious "flare" in the patient's symptoms of prostate cancer and (2) was associated with some degree of diminution in the patient's signs and symptoms of prostate cancer.*

6.5.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints were:

- Percentage change from baseline PSA levels
- Serum levels of testosterone, dihydrotestosterone (DHT), luteinizing hormone (LH), and follicle-stimulating hormone (FSH)

6.5.4.3 Tertiary Efficacy Endpoints

Tertiary efficacy endpoints included:

- Change in intensity of pain as measured by the visual analog scale (VAS) for pain
- Disease response (National Prostate Cancer Project [NPCP] criteria)
- Acid phosphatase kinetics (both total and prostatic fraction)
- Quality of life as measured by the Southwest Oncology Group (SWOG) 9039 assessment

Other efficacy assessments included the following:

  - Castration rates by visit day
  - Achievement and maintenance of medical castration
  - In patients with bladder neck outlet obstruction: urine flow rate, postvoid residual volume, American Urological Association (AUA) symptom score, presence of urinary catheter