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, 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 10.3.1. 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.

10.3.3 Recommendations on Phase 4 Studies and Risk Management Program

10.3.3.1 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 only 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 will 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.

10.3.3.2 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.

NDA 21-320
Plenaxis™ (abarelix for injectable suspension)
Praecis Pharmaceuticals, Inc.

Medical Officer Review for Original NDA.

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

/s/

Scott Monroe
11/25/03 02:12:22 PM
MEDICAL OFFICER

Mark S. Hirsch
11/25/03 02:41:58 PM
MEDICAL OFFICER
I concur.

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review of Original NDA

NDA	21-320
Sponsor	Praecis Pharmaceuticals Inc One Hampshire Street Cambridge, MA 02139
Submission Type	Original NDA
Drug	
Established name	Abarelix suspension (abarelix carboxymethylcellulose)
Trade name	Plenaxis™
Chemical class	Synthetic decapeptide
Drug Class	Gonadotropin releasing hormone (GnRH) antagonist
Proposed Indication	
Route of Administration	Intramuscular injection
Dosage Form	Suspension
Dosing Regimen	Administered on Day 1, Day 15, and Day 29 and once every 28 days thereafter
Dose	100 mg per dosing
Dates	
Submitted	December 11, 2000
CDER stamp date	December 12, 2000
PDUFA date	June 12, 2001
Related NDAs	None
Related INDs	IND 51-710 (Prostate cancer)
Medical Reviewer	Scott Monroe MD
Date Review Completed	May 11, 2001

(23 May 2001 FINAL)

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

EXECUTIVE SUMMARY

1 RECOMMENDATIONS

1.1 Recommendation Regarding Approval

1.1.1 Approvability

It is recommended that abarelix . suspension (NDA 21-320) receive an approvable action. Based on the demonstrated safety profile of abarelix and the incidence (0.4-0.5%) of serious, anaphylactic-like reactions observed in clinical trials to date and the available alternative of orchiectomy for therapy in high risk patients, approval cannot be recommended at this time. The use of abarelix (when and if approved) should be limited to men with advanced prostate cancer in whom (1) orchiectomy is not an acceptable treatment option and (2) treatment with a superactive gonadotropin releasing hormone (GnRH) agonist, such as leuprolide or goserelin, is likely to produce a serious exacerbation of the patient's disease. Such patients would include men with vertebral or epidural metastatic lesions and those with partial ureteral obstruction due to their prostate cancer.

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 orchiectomy. The goal of medical hormonal therapy is to reduce serum testosterone concentrations to ≤ 0.5 ng/dL (i.e., testosterone levels comparable to those observed following orchiectomy). Treatment of prostate cancer with a superactive GnRH agonist initially increases serum testosterone concentrations for 1–2 weeks before reducing testosterone to castrate levels. The initial rise in serum testosterone may cause a temporary worsening of symptoms. Most commonly, the immediate consequence of this initial increase in circulating androgen levels 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. The long-term consequences of the initial transient increase in testosterone secretion on disease progression, if any, are not known.

Abarelix, in contrast to superactive GnRH agonists, is a true GnRH antagonist that is devoid of LH and FSH releasing activity. Consequently, abarelix is able to more rapidity reduce serum testosterone to castrate levels without an initial antecedent surge. Abarelix could therefore provide some potential clinical benefits (not rigorously proven in this NDA) over a superactive GnRH agonist for the hormonal management of advanced prostate cancer, particularly in men with impending spinal cord compression or ureteral obstruction. However, abarelix offers no proven benefit over conventional superactive GnRH agonist therapy for men with less advanced prostate cancer. In its present formulation and with the Sponsor's recommended dosing regimen, abarelix may actually be somewhat less effective than once-monthly Lupron (and perhaps other GnRH agonists) in reliably suppressing serum testosterone to levels ≤ 50 ng/dL during long term treatment.

During the clinical development program for abarelix, immediate postdosing systemic reactions, accompanied by hypotension and/or loss of consciousness (anaphylactic or anaphylactoid reactions), were reported in 5 or 6 of 1166 (0.4-0.5%) patients treated with abarelix. Similar reactions were not reported for any patients treated with active comparator (i.e., Lupron or goserelin). Because of the reported incidence of these serious systemic reactions, the risk-benefit ratio for abarelix does not warrant its use for the treatment of prostate cancer in most men. Approval for use in those men at high risk for developing a serious complication following initiation of treatment with a superactive GnRH agonist may be warranted after the Sponsor (1) conducts additional investigations to elucidate the mechanism(s) responsible for the immediate postdosing serious systemic reactions and (2) is able to reduce, or has made all reasonable efforts to reduce, the incidence of these reactions.

1.2 Specific Recommendations to the Sponsor

Prior to approval of abarelix for use in the limited population described in Section 1.1.1, the sponsor will need to:

1. Conduct additional clinical investigations to elucidate the mechanism(s) responsible for the reported serious anaphylactic-like reactions.
2. Reduce the incidence of these reactions based on information obtained from Item No. 1 above or make all reasonable efforts to reduce their incidence.
3. Agree to implement risk management procedures and education programs for medical care providers and patients to ensure that:
   a) The use of abarelix is limited to the high risk population described above.
   b) Physicians and patients are informed of the additional risk associated with the use of abarelix, namely, potentially life-threatening anaphylactic-like reactions.
   c) Physicians are prepared to treat an anaphylactic-like reaction should it occur.
   d) Patients are observed for 1 hour after each dosing.
4. Provide appropriate drug labeling regarding
   a) The occurrence of anaphylactic or anaphylactoid reactions in 0.4%-0.5% of patients treated with abarelix in clinical trials. Labeling will require a boxed warning concerning this risk.
   b) The possibility of hepatotoxicity and the need for monitoring of serum transaminase levels.
   c) The possibility that up to 20% of patients treated with abarelix may not maintain serum testosterone levels ≤ 50 ng/dL when treated for up to 1 year.
   d) Provide guidance for appropriate monitoring of serum testosterone levels to identify patients with inadequate suppression.
5. Commit to conducting Phase IV dose optimization studies to reduce the proportion of subjects who do not have adequate long-term suppression of serum testosterone. Such studies might investigate (a) a shorter interval between each dosing with abarelix, (b) a modification of the formulation to delay the early release of abarelix, and (c) increasing the dose or dosing frequency of abarelix for men who weigh more than 200 pounds.

2 SUMMARY OF CLINICAL FINDINGS

2.1 Overview of Clinical Program

2.1.1 Drug

Abarelix for suspension (abarelix carboxymethylcellulose, Plenaxis™) is a gonadotropin releasing hormone (GnRH) antagonist. It is a synthetic decapeptide. The proposed dosing regimen is 100 mg of abarelix administered by intramuscular (IM) injection on Days 1, 15, and 28, and once every 28 days thereafter.

2.1.2 Clinical Program

Data from 12 clinical studies were submitted by the Sponsor to support the safety and efficacy of abarelix depot. Four of these 12 studies were conducted
— or with an injectable solution formulation of abarelix (not the to-be-marketed formulation) administered by continuous subcutaneous (SC) infusion to men with prostate

cancer (2 studies). Of the remaining 8 studies, seven were conducted in men with prostate cancer using the to-be-marketed formulation of abarelix and one was a pharmacokinetic study conducted in normal male volunteers. Three of the 7 studies conducted with the formulation in men with prostate cancer were active controlled, randomized clinical trials. They were designated by the sponsor as the principal safety (all 3 studies) and efficacy (2 of the 3 studies) studies.

2.1.3 Design of the Controlled Studies

Studies 149-98-02, 149-89-03, and 149-99-03 were the principal safety and efficacy studies. Study 149-99-03, however, was considered a supportive and not a primary efficacy study. These studies were adequately controlled, active comparator, randomized, open label, multicenter clinical trials in which patients with prostate cancer that might benefit from hormonal therapy (i.e., reduction in androgen levels) were enrollment. Patients were randomly assigned in a 2:1 ratio to treatment with either abarelix or the active comparator (Lupron [Studies 149-98-02 and 149-99-03] or Lupron + 50 mg oral Casodex [an antiandrogen, Study 149-98-03]). All patients were to receive an injection of abarelix (100 mg) or Lupron (7.5 mg) once every 28 days through Study Day 141. Patients assigned to the abarelix group also received Study Drug on Day 15. Patients, who in the Investigator's opinion had benefited from their initial treatment, were offered the opportunity to continue treatment for an additional 28 weeks (through Study Day 365) in Studies 149-98-02 and 149-98-03. The treatment period was defined as the interval from the patient's first injection of Study Drug through 28 days after his final injection. Patients underwent efficacy and safety assessments at monthly or more frequent intervals in each of the studies.

2.2 Efficacy

2.2.1 Primary Efficacy Assessment and Efficacy Endpoints

Prostate cancer is an androgen-dependent tumor in most men at the time of initial presentation. The goal of hormonal therapy in prostate cancer is to suppress serum androgen levels to those normally observed following surgical castration. Based on these considerations, the FDA has accepted for this application, and prior applications for GnRH agonists, attainment of castration levels of testosterone (i.e. ≤ 50 ng/dL by Day 29) and maintenance of these levels through at least 3 dosing cycles as a surrogate efficacy endpoint in clinical trials of the treatment of advanced prostate cancer. In these abarelix clinical trials, there were 3 primary efficacy endpoints, all based on serum testosterone concentrations. The endpoints were as follows:

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, and 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. Achievement of Endpoint No. 1 was mandatory for marketing approval. Achievement of Endpoint Nos. 2 and 3 was required to support a labeling claim.

2.2.2 Efficacy Results (Primary Endpoints)

The principal efficacy trials achieved the 3 primary efficacy endpoints as described below.

Proportion of patients who achieved and maintained testosterone levels ≤ 50 ng/dL. Serum testosterone levels ≤ 50 ng/dL were achieved and maintained by 95.5% and 95.2% of the active control patients and 91.7% and 92.9% of the abarelix patients, respectively, in Studies 149-98-02 and 149-98-03. Based on a prior agreement with DRUDP, treatment with abarelix was declared as non-inferior to that of Lupron since the lower bound of the 95% CI for the difference between the treatment groups was not less than –10%. The lower bound of the 95% CI for supportive Study 149-99-03, however, was slightly below the limit of –10% (i.e., -11.5%).

	Treatment Group							
	Lupron		Lupron plus Casodex		Abarelix		Percent Difference	
	N [1]	Percent [2]	N	Percent	N	Percent	Value	95% CI [3]
149-98-02	89	95.5	—	—	180	91.7	-3.8	(-9.7, 2.1)
149-98-03	—	—	83	95.2	168	92.9	-2.3	(-8.4, 3.7)
149-99-03	194	97.4	—	—	388	89.6	-7.7	(-11.5, -4.0)

[1] Number of subjects in the ITT population.
[2] Percentage of subjects who achieved and maintained testosterone suppression (i.e., no two consecutive testosterone values > 50 ng/dL)
[3] 95% two-sided confidence intervals for the between-group difference in proportions

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

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

2.2.3 Other Efficacy Issues (Reliability of Long Term Testosterone Suppression)

By more rigorous, secondary definitions of successful maintenance of testosterone suppression (definitions that did not require 2 consecutive testosterone values > 50 ng/dL and which required suppression of testosterone through Study Day 169), abarelix appeared to be inferior to Lupron in one of the 2 primary efficacy studies (Study 149-98-02) and supportive efficacy Study 149-99-03 as shown in the Table below.

Cumulative Probability of Achieving and Maintaining Medical Castration Through Day 169 (No Serum Testosterone Value > 50 ng/dL)

	Treatment Group [1]				
	Lupron	Lupron + Casodex	Abarelix	Difference	
Study	Cumulative Probability (%)			Value	95% CI
149-98-02	85.6		74.7	-11.0	(-21.04, -0.90)
149-98-03		83.0	82.8	-0.3	(-10.59, 10.07)
149-99-03	90.9		75.7	-15.2	(-21.38, -9.03)

[1] Per Protocol population

At the end of one year of treatment, the differences between the proportion of on-treatment patients with castrate levels of testosterone (values ≤ 50 ng/dL) in the abarelix groups and the active control groups ranged from 15-24 %, with better suppression in the active control groups. It is not known, however, if the difference in reliability of suppression of testosterone is clinically important. These differences between abarelix and Lupron, in terms of long term reliability of testosterone suppression, will need to be addressed in labeling.

2.2.4 Proposed Label Claim

The sponsor's label claim that treatment with abarelix (a) is not associated with an initial surge of testosterone and (b) suppresses serum testosterone levels more rapidly than a superactive GnRH agonist (i.e. Lupron) is fully supported by the clinical data. The sponsor's claim that [redacted] will need to be clarified in labeling. The target population for abarelix, unless the sponsor is able to reduce the incidence of serious, systemic reactions, will be restricted to that described in Section 1.1.1.

2.3 Safety

2.3.1 Exposure to Study Drug

A total of 1166 prostate cancer patients were exposed to abarelix depot. Of the 1166 patients, 834 patients were exposed to abarelix in accordance with the proposed registration dosing regimen (100 mg for both induction and maintenance of testosterone suppression. A total of 752 of these patients were exposed to abarelix for at least 6 months, and 190 patients were exposed for at least 1 year. Patients were monitored monthly or more frequently throughout the treatment period. Overall this was a relatively small, but adequate, sample size considering the recommended target population for this new molecular entity.

2.3.2 General Safety Findings

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 a 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 2.3.4) and triglycerides. 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 principal 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. Mean fasting serum triglyceride levels were numerically higher by 10-15 mg/dL in the abarelix group compared to the Lupron group in the controlled safety studies. This increase in triglycerides, although not desirable, is not a significant safety concern in the population of men to be treated with abarelix.

2.3.3 Patient Deaths

In the controlled safety studies, a total of 12 patients died (1 in the Lupron group and 11 in the abarelix group), either during the treatment period (within 28 days of the last dose of Study Drug) or during the posttreatment follow up period. In the uncontrolled studies, a total of 16 patients treated with abarelix died. None of the deaths was attributed to treatment with Study Drug. Ten (10) of the 27 deaths in abarelix-treated patients were attributed to progression of prostate cancer. Of the remaining 17 deaths, 8 were a result of a cardiovascular adverse event (myocardial infarction, stroke, or pulmonary embolus), 5 were attributed to respiratory/infectious causes (pneumonia, empyema, or chronic obstructive lung disease), 3 were attributed to coexisting carcinomas (pulmonary or pancreatic), and 1 was due to aspiration.. Although the proportion of abarelix-treated patients in the controlled studies who died (11 of 735, 1.4%) was greater than that of the active control-treated

patients (1 of 367, 0.3%), it is likely, as reported by the Investigators, that none of these deaths was a result of treatment with abarelix.

2.3.4 Safety Issues of Particular Concern

During clinical trials with abarelix, 2 safety concerns were identified: hepatic toxicity and serious systemic allergic reactions.

Hepatic toxicity. A greater proportion of patients treated 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. These increases were, for the most part, completely reversible, either with continued dosing (generally with mild elevations) or following discontinuation of treatment (with more significant elevations). None of the increases was associated with clinical jaundice and none (with one exception) was associated with an increase in bilirubin to > 2.5 x ULN. (The exception was a patient whose bilirubin increase was attributed to pancreatic cancer). The adverse effects of abarelix on the liver appear to be a manageable risk that (a) can be addressed in labeling and (b) will require the monitoring of serum transaminase levels.

Serious systemic reactions. Allergic reactions that were observed in patients treated with abarelix included those limited to cutaneous manifestations and those with serious systemic manifestations Delayed cutaneous reactions occurred in a similar proportion of patients in both the abarelix and active control treatment groups. Immediate systemic reactions (occurring within one hour of dosing) were observed only in the abarelix groups and were reported for 14 of 1166 patients (1.2%). Immediate systemic reactions that were associated with hypotension and/or loss of consciousness were reported in 5 or 6 of 1166 (0.4%-0.5%) patients treated with abarelix. All of these patients recovered rapidly with medical intervention and without any known sequelae. Although no similar reactions were observed in the Lupron treated patients, serious anaphylactic-like reactions have been reported in patients receiving Lupron and other superactive GnRH agonists. Although the exact incidence of such reactions is not known, they appear to occur with a frequency well below that observed in the abarelix-treated patients.

The sponsor should conduct additional follow up investigations for those patients who previously had an immediate postdosing reaction. Such testing should include (1) screening for the presence of IgE antibodies and (2) appropriate intradermal testing both in patients who had an immediate reaction and a control group of abarelix-treated patients who did not exhibit such reactions. (See Section 12.3.2 for details regarding additional testing).

2.4 Dosing

See Section 1.2, Item Nos. 4 and 5, regarding dosing issues that the Sponsor should address to improve the reliability of testosterone suppression in patients treated with abarelix for longer than 6 months.

2.5 Special Populations

Abarelix is to be used only for the management of advanced prostate cancer. This will limit its target population primarily to elderly men. Based on the present safety profile of abarelix, it should be labeled to specifically exclude its in any group other than men with advanced prostate cancer. The sponsor performed standard subset safety analyses for the data from the controlled safety studies based on race (African American and non-African American) and age. No obvious differences across these groups were identified. However, the total number of African American patients included in these analyses was small (n = 71) and only 152 patients were less than 65 years of age.

CLINICAL REVIEW

3 INTRODUCTION AND BACKGROUND

3.1 Drug

- **Established Name** Abarelix for depot suspension (abarelix carboxymethylcellulose)
- **Proposed Trade Name** Plenaxis™
- **Drug Class** Gonadotropin releasing hormone (GnRH) antagonist
- **Chemical Class** Synthetic decapeptide
- **Proposed Indication**

- **Dose** 100 mg administered by intramuscular injection
- **Dosing Regimen** Intramuscular dosing on Day 1, Day 15, and Day 29 and once every 28 days thereafter

3.2 Overview of Disease and Treatment Options

3.2.1 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 a high percentage of 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 three to four 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.

3.2.2 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, superactive agonists of GnRH, such as Lupron (approved by the FDA for the treatment of prostate cancer in 1985) and goserelin, have totally replaced estrogenic compounds as a medical treatment choice.

The therapeutic action of superactive GnRH agonists in the management of prostate cancer is via a reduction in circulating levels of testicular androgens. Superactive GnRH agonists down-regulate their own receptors on the pituitary gonadotropes, resulting in a suppression of LH secretion, and secondarily, a suppression of testicular androgen production. Achievement of castration levels of serum testosterone 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 week), increase in gonadal androgen production and secretion, commonly referred to a "testosterone surge." The initial rise in serum testosterone may cause a temporary worsening of symptoms referred to as "a flare." Most commonly, the immediate consequence of this initial increase in circulating androgen levels 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, superactive GnRH agonists must be used with caution in patients presenting with large local lesions, and are generally considered inappropriate therapy, unless administered with concomitant antiandrogen therapy (e.g., Casodex), for men with vertebral or epidural metastases or neurologic symptoms of spinal cord compression. Antiandrogens, however, have their own spectrum of adverse events, and it is has not been proven that they completely block the adverse consequences of an androgen surge, particularly in the presence epidural metastases or impending spinal cord compression.

Abarelix, in contrast to superactive GnRH agonists such as Lupron, 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, rapidly reduce the secretion of LH, and secondarily testicular androgens, without initially producing a surge of testosterone. 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 that are often observed following the onset of treatment with a superactive GnRH agonist.

3.3 Important Milestones in the Development of Abarelix Depot Suspension

3.3.1 Significant Regulatory Interactions and Decisions

IND 51-710 for drug PPI-149 (abarelix acetate) was filed by Pharmaceutical Peptides, Inc. (presently known as Praecis Pharmaceuticals, Inc) in October 1996. The first-in-man clinical study investigated the safety and ability of a solution of abarelix, administered by a continuous SC infusion, to reduce serum testosterone concentrations to ≤ 50 ng/dL (levels comparable to those in men after orchiectomy). During the clinical development program that resulted in the filing of the present NDA, the Sponsor has had frequent interactions with the Division of Reproductive and Urologic Drug Products (DRUDP) via both meetings and teleconferences.

An end of Phase II meetings was held with DRUDP on August 4, 1998. Important information conveyed to the Sponsor at that meeting (based on the meeting minutes) included the following:

1. "The indication should be similar to the currently approved labeling for the GnRH agonists for the palliative treatment of advanced prostate cancer. More rigorous clinical trials than the trials proposed are needed to support additional labeling claims. These should be well-controlled studies designed for the intended patient population with such endpoints as time-to-progression and survival."
2. "The Division agrees with the percentage of patients castrate on Day 8 and Day 85 as acceptable endpoints...."

Medical Officer's Comment.

- **It is not clear to this reviewer (based on the meeting minutes) which serum testosterone concentrations on intervening days between Day 8 and Day 85 (e.g., all values or only values on selected days) would be considered in determining the percentage of patients who were treatment successes or failures.**

Protocols for 2 pivotal Phase III studies (Protocol 149-98-02 and Protocol 149-98-03) were submitted to DRUDP for review in September 1998. Comments by the Medical Reviewer (Dr. N. Marks) were conveyed to the Sponsor in a regulatory letter (dated February 9, 1999) and included the following:

1. "Although maintenance of castrate levels is not included as a primary endpoint, approval of the drug will be based on demonstration of maintenance of castrate levels of testosterone over the course of treatment [between study days 29 and 85], as well as achievement of castration by day 29."
2. "Even though these pivotal trials are being performed in a broad population, the indication for this drug will be palliative treatment of advanced prostate cancer in patients for whom medical castration is indicated."

During a teleconference on October 28, 1998, the sponsor was told "the definition of failure in the protocol (a testosterone level greater than 50 ng/dL at any one time) should not be revised."

3.3.2 Issues Arising during Clinical Trials

The definition of "attainment and maintenance of testosterone suppression" remained an issue of ongoing discussion (and apparent disagreement) between the Sponsor and DRUDP until March 30, 2000. Communications to the Sponsor on March 26, 1999 and June 18, 1999 indicated that a single testosterone measurement > 50 ng/mL between Study Days 29-85 would constitute a "treatment failure" in either the abarelix or comparator treatment arms. 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) 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.

3.4 Other Relevant Information

3.4.1 Related Submissions

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

3.4.2 Foreign Marketing Status

Abarelix is not marketed in any foreign country nor has it been approved for marketing in any foreign country

3.4.3 Other Pharmacologically Related Agents Under Study

No other GnRH antagonists are presently under review for the indication of the palliative management of prostate cancer. 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.

4 CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS

4.1 Toxicology Review

There were no preclinical toxicology findings, per se, that would preclude approval of abarelix for the proposed indication of treatment of prostate cancer. Preclinical toxicology findings reported by the primary toxicology reviewer (Dr. Krishan Raheja) that are of particular relevance to this clinical review are (1) possible hepatotoxicity of abarelix, (2) the histamine releasing activity of abarelix, and (3) acute effects of abarelix on the cardiovascular system.

No hepatotoxicity was reported in the 6-month rat and 12-month monkey toxicity studies. Review of the histopathology data for the 2-year mouse and rat carcinogenicity studies also did not reveal any treatment-related liver damage. However, in a 28-day toxicity study, in which monkeys received continuous SC abarelix in doses ranging from 100 to 4650 µg/kg/day, changes in certain enzymes, relative to control animals, were observed. Changes included increases in GGT levels, but no increases in serum transaminase levels and no histologic evidence of liver damage.

The capacity of abarelix to directly stimulate the release of histamine from mast cells was assessed in a rat peritoneal mast cell assay. Based on the results of this assay, the sponsor concluded that abarelix would have minimal histamine releasing activity at pharmacologically relevant human serum concentrations of 48 ng/mL.

Cardiovascular effects were observed in dogs and monkeys after an IV dose of abarelix (10 mg/kg in dogs and 1 mg/kg in monkeys). Findings included signs of decreased cardiac output and decreased blood pressure in dogs and signs of lethargy in monkeys. One of the 3 monkeys also developed tachycardia and rapid breathing, accompanied by pale extremities and slow capillary refill. Following administration of IV fluids, the monkey rapidly recovered. The severity of the cardiovascular findings was significantly reduced when abarelix was administered intramuscularly, and there were no toxic effects when abarelix was administered subcutaneously. No other significant, consistent, dose-related cardiovascular effects were observed across species.

Medical Officer's Comments

- **The sponsor did not report the histamine releasing capacity of abarelix relative to presently approved superactive GnRH agonists or GnRH antagonists.**
- **The adverse cardiovascular effects observed in preclinical studies are likely to be observed only if abarelix were to be inadvertently administered intravenously instead of intramuscularly.**

4.2 Clinical Pharmacology and Biopharmaceutics Review

According the primary reviewer (Dr. Dhruba Chatterjee), there were no biopharmaceutical findings that would preclude the approvability of abarelix for the proposed indication. This reviewer, as well as the medical reviewer, noted that patients on abarelix therapy for more than 3 months might experience a reduction in overall efficacy as the capacity of 100 mg abarelix, administered once monthly, appeared to suppression testosterone less reliably than did the active control comparators in the 3 controlled clinical trials. 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 Comment

- **The medical reviewer concurs with the above recommendations.**

5 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

5.1 Pharmacokinetics

Pharmacokinetic parameters for a single IM dose of 100 mg of abarelix depot suspension (the proposed to-be-marketed drug) or 15µg/kg of abarelix peptide in an aqueous solution 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 Depot [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

5.2 Pharmacodynamics

The pharmacodynamic effects of abarelix on serum concentrations of pituitary gonadotropins, testosterone and dihydrotestosterone are presented and discussed in the efficacy section of this review (Sections 8.4.2 and 8.4.3.4).

6 DESCRIPTION OF CLINICAL DATA AND SOURCES

6.1 Clinical Data Submitted in Support of NDA 21-320

6.1.1 IND Clinical Trials

The sponsor submitted clinical data from 11 studies conducted under either IND 51-710 (treatment of prostate cancer - 9 studies) Additional information regarding these studies is provided in Section 6.2.

6.1.2 NonIND Clinical Trials

Serious adverse event data from 1 ongoing nonIND clinical study (ABACAS 1), conducted in Europe and sponsored by Sanofi-Synthelabo, also were submitted.

6.1.3 Secondary Sources of Clinical Data

Since abarelix depot has not been marketed in any country to date, no postmarketing data were submitted. No published data regarding the findings from the Phase II or Phase III clinical trials were provided by the Sponsor. The sponsor provided published clinical reports supporting the potential clinical benefits of a GnRH antagonist (e.g. abarelix) that would not initially stimulate the secretion of testosterone prior to reducing serum concentrations of testosterone to therapeutic levels for the palliative management of advanced prostate cancer.

6.2 Overview of Clinical Studies Included in the NDA

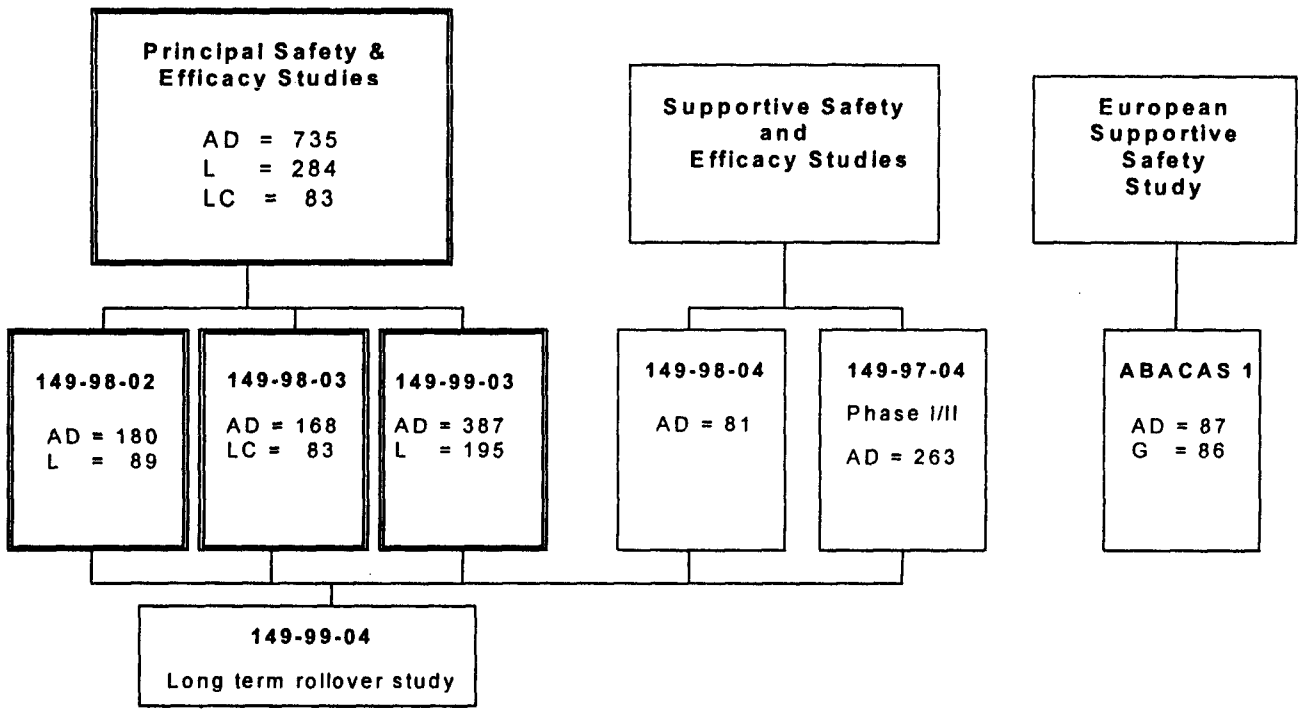
Data from 12 clinical studies were submitted by the Sponsor to support the safety and efficacy of abarelix depot. Figure 1 provides an overview of these studies and includes the study identifier, the number of patients enrolled, and the number of patients assigned to each treatment group. Four of these 12 studies

with an injectable solution formulation of abarelix administered by continuous SC infusion (Studies. 149-96-01 and 149-97-03) and not the to-be-marketed formulation. (In this review the terms "abarelix" and "abarelix depot" both refer to the depot formulation of abarelix unless otherwise stated). Of the remaining 8 studies, one (Study No. 149-99-01) was a pharmacokinetic study that was conducted in normal male volunteers. In this 2 period, crossover pharmacokinetic study, each patient received a single dose of the injectable solution formulation of abarelix and a single dose of the depot suspension formulation. The remaining 7 clinical studies were conducted in men with prostate cancer using the depot formulation of abarelix. A brief description of these studies is provided below.

1. **Study 149-97-04**. This was an open label, partially controlled, Phase I/II dose ranging and tolerability study of the abarelix depot formulation. Data from this study were used to determine the dose of abarelix that was subsequently studied in the Phase III clinical program.
2. **Study 149-98-02**. This was one of the two open-label, randomized, active-comparator controlled (Lupron), Phase III trials that provided primary efficacy and safety data in support of this NDA.
3. **Study 149-98-03**. This was one of the two open-label, randomized, active-comparator controlled (Lupron + Casodex), Phase III trials that provided primary efficacy and safety data in support of this NDA.
4. **Study 149-99-03.** This study was an open-label, randomized, active-comparator controlled, Phase III trial. This study, in conjunction with Studies 149-98-02 and 149-98-03, provided the primary safety data in support of the NDA as well as supportive efficacy data.
5. **Study 149-98-04**. This open label, uncontrolled study investigated the efficacy and safety of abarelix in a subset of men with advanced prostate cancer who might be expected to experience clinically significant adverse events from the testosterone surge that occurs following the initial dose of a GnRH agonist. This study provided supportive efficacy and safety data.
6. **Study 149-99-04.** This was a rollover study for patients who had been treated in one of the 5 clinical trials listed above and who wished to continue treatment with abarelix. It provided additional supportive, long-term safety data.
7. **Study ABACAS 1.** This open labeled, randomized, active-comparator controlled (Zoladex + Casodex), Phase III trial is being conducted in Europe and sponsored by Sanofi-Synthelabo. This study provided limited supportive safety data (serious adverse event data).

Table 2 provides a more detailed overview of each clinical trial represented in the NDA. Included in Table 2 for each study is information regarding (a) study design, (b) number of patients enrolled, and (c) study treatments.

Figure 1. Clinical Trials with Abarelix Depot in Men with Prostate Cancer



Study Drugs: AD = Abarelex Depot; L = Lupron; LC = Lupron + Casodex; G = Goserelin
Numbers refer to numbers of patients treated with respective Study Drug in each clinical trial.

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
Principal 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: Modified from December 2000 submission, Vol. 108 pgs 131-134 and Safety Update (submitted 13 March 2001), pg 101.

(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				
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
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
ABACAS 1 [2] 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 Ongoing	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	86 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

[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).

[2] Only reports of serious adverse events were provided by the sponsor of this NDA (Praecis).

(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 in Healthy Volunteers				
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
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

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6.3 Patient Exposure to Abarelix in Prostate Cancer Studies

6.3.1 Exposure to Abarelix Through 1 Year

A total of 1079 prostate cancer patients were exposed to abarelix depot in studies sponsored by Praecis. Of those 1079 patients, 834 patients received the proposed registration dose (100 mg for both induction [initial 1 or 2 doses] and maintenance of castration levels of testosterone) and 245 patients received nonregistration doses. An additional 87 prostate cancer patients received the proposed 100 mg registration dose of abarelix in Study ABACUS 1 (sponsored by Sanofi-Synthelabo).

Table 3 shows the distribution of the 834 patients who received the proposed registration dose of abarelix in one of the principal safety studies (Studies 149-98-02, 149-98-03, and 149-99-03) and the supportive safety studies (Studies 149-98-04 and 149-97-04). Also shown are the total and by-study numbers of patients exposed to the 100-mg dose for 6 months (based on receiving the Day 141 injection) and 1 year (based on receiving the Day 337 injection). Across the 5 studies, 752 patients were exposed to the proposed registration dose for 6 months and 190 patients were exposed for 1 year.

Table 3. Patient Exposure to the 100 mg Dose of Abarelix Depot (Proposed Registration Dosing Regimen)

	Abarelix Depot IM (100 mg dose)		
		6 Months of Exposure (received day 141 dose)	1 Year of Exposure (received day 337 dose)
Study	n	n	n
Principal Safety Studies			
149-98-02	180	170	94
149-98-03	168	157	89
149-99-03	387	345[1]	0
Subtotal	**735**	**672**	**183**
Supportive Safety Studies			
149-98-04	81	70	2
149-97-04	18	10	5
Subtotal	**99**	**80**	**7**
Principal and Supportive Safety Studies			
Total	**834**	**752**	**190**

[1] Patients had the option to continue treatment beyond 6 months in Study 149-99-04.

Source: Safety Update (submitted 13 March 2001), Table 10 A, pg 122.

6.3.2 Exposure to Abarelix Beyond 1 Year

Safety data from patients treated with either 50 mg or 100 mg doses of abarelix for more than 1 year were obtained in Study 149-99-04 (see Table 4).

Table 4. Study 149-99-04 – Number of Patients Treated with Abarelix for More than One Year

Duration of Exposure in Weeks [1]	Treatment Group	
	Abarelix 50 mg N	Abarelix 100 mg N
76-80	14	111
100-104	14	49
132-136	12	18
154-160	0	2

[1] Includes exposure to abarelix in previous clinical trial.
Source: Safety Update, Table 8-j, pg 111.

7 CLINICAL REVIEW METHODS

7.1 Materials Consulted during Medical Review

The following materials were consulted during the conduct of this review:

- Original NDA 21-320; Submission Date of December 11, 2000
  - Volumes 1, 44-110
  - Electronic case report forms (CRFs) and case report tabulations (CRTs)
- 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)
- Submission of April 13, 2001 (revised label)
- 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 listing)
- Submission of May 8, 2001 (errata for submission of April 27, 2001)
- Annual Reports for IND 51-710 (submitted February 20, 2001)
- Minutes of all regulatory meetings and telephone conferences with Sponsor that were contained in Division files

The Safety Update of March 13, 2001 contained updated information for the 3 controlled clinical trials (Studies 149-98-02, 149-98-03, 149-99-03) and Study 149-98-04. It also contained new information for Study 149-99-04. Information contained in the Safety Update is presented and discussed in the relevant sections of this review.

7.2 Review Processes and Procedures

7.2.1 Materials Reviewed

The review conducted by this medical officer focused on the controlled and randomized primary efficacy studies (Studies 149-98-02, 149-09-03) and the controlled and randomized primary safety studies (Studies 149-98-02, 149-98-03, and 149-99-03). All materials submitted in paper format for

these studies were considered during the conduct of this review. Reviews of supplemental studies 149-97-04, 149-98-04, and 149-99-04 focused on safety issues, namely, drug-related serious adverse events, adverse events leading to patient withdrawal from the clinical trial, allergic reactions, potential liver toxicity, and deaths. Pharmacodynamic data from Study 149-97-04 supporting dose selection for the pivotal efficacy studies were also reviewed. Supportive IND studies conducted with the solution formulation of abarelix were reviewed primarily for the safety issues of allergic reactions and deaths.

Study 149-98-04 was reviewed independently by G. Benson MD, Medical Officer, DRUDP. A copy of the executive summary of his review is provided as Appendix A.

7.2.2 Safety and Efficacy Reviews

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). 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.

Analyses and summary tables relating to systemic allergic reactions were confirmed using the data listings provided by the Sponsor. Additional tabulations and analyses pertaining to systemic allergic reactions also were performed and are included in this review. The sponsor also provided additional safety analyses pertaining to changes in laboratory assessments (serum chemistries, particularly liver enzymes, and hematology measurements) at the request of the medical reviewer.

7.3 Overview of Methods Used to Evaluate Data Quality and Integrity

DSI audits. Four study centers (2 each that participated in Studies 149-98-02 and 149-99-03, respectively) were selected for audit by the Division of Scientific investigation. The audit at 1 study center that participated in Study 149-98-02 and enrolled 25 patients had been completed at the time of this review. No issues that would preclude the use of data from this site to support this NDA application were identified. The other audits are pending.

Financial disclosure statements. The sponsor requested financial disclosure statements for Investigators who participated in abarelix clinical trials. All investigators who responded certified, per the Sponsor, that "none of the financial arrangements of concern to the FDA existed during the period covering the dates of their participation in the studies." The principal reason for not obtaining financial disclosure information was that "the individuals in question had left the practice and could not be contacted." No conflicts of interests were noted. Statements from the remaining Investigators were not obtained.

Medical Officer's Comment

- **Failure to obtain financial disclosure statements from a small number of Investigators, as was the case, should not jeopardize the integrity of the principal clinical trials. Each of the 3 principal trials was multicenter and each involved over 20 sites.**

Central Laboratory. Hormone measurements (e.g., testosterone), measurements of tumor biomarkers (e.g., PSA), and general safety measurements (serum chemistries and complete blood counts) were performed at a Central Laboratory

Site Monitoring.

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 , 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 Biopharmaceutical Review. No areas of concern were identified by the Biopharmaceutical Reviewer.**

8 INTEGRATED REVIEW OF EFFICACY (PRIMARY CLINICAL STUDIES)

8.1 Efficacy Assessments

8.1.1 Primary Efficacy Assessments and Endpoints

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

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

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

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

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

8.1.2 Secondary (Supportive) Efficacy Endpoints and Assessments

8.1.2.1 Alternative Definitions of Maintenance of Testosterone Suppression

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

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

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

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

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

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

8.1.2.2 Secondary (Supportive) Efficacy Assessments

Secondary efficacy assessments included measurements of serum concentrations of dihydrotestosterone (DHT), pituitary gonadotropins (LH and FSH), and prostate specific antigen (PSA). At regular intervals during the study, patients responded to 3 quality-of-life questionnaires: the EuroQoL (EQ-5D Health Questionnaire), the Southwest Oncology Group (SWOG) 9039, and the Visual Analog Scale (VAS) for pain. Disease response also was assessed in patients with a baseline metastatic evaluation of stage D1 or D2. . Quality of life and disease response assessments are not discussed in this review.

8.1.3 Overview of Statistical Analyses for Primary and Secondary Efficacy Endpoints

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

8.1.3.1 Primary Efficacy Endpoints

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

- **Avoidance of a testosterone surge**

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

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

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

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

Primary analysis. Point estimates of the incidence rates based on Definition No. 2 (achievement and maintenance of serum testosterone concentrations of ≤ 50 ng/dL from Study Day 29 through Study Day 85 with no 2 consecutive values > 50 ng/dL) were determined by 2 methods: straightforward proportions and Kaplan-Meier estimates. Missing data were completed using last observation carried forward (LOCF) and straightforward proportions. A noninferiority limit of -10% was applied to the lower bound of the 95% confidence interval (CI) of the difference between the rates in each of the treatment groups. A CI with a lower bound no less than -10% (based on a 2-sided test with $\alpha = 0.05$) was the criterion for success (i.e., noninferiority).

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

8.1.3.2 Supportive Efficacy Endpoints

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

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

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

- **Maintenance of castration once achieved**

Patients who were not castrate on planned visit Day 29 were not considered evaluable for the primary protocol-defined endpoint of maintenance of castration. In this secondary analysis, it was not necessary for patients to have a serum testosterone of ≤ 50 ng/dL by Day 29. Definitions were

modified to determine the proportion of patients who maintained serum testosterone of ≤ 50 ng/dL once suppression was achieved.

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

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

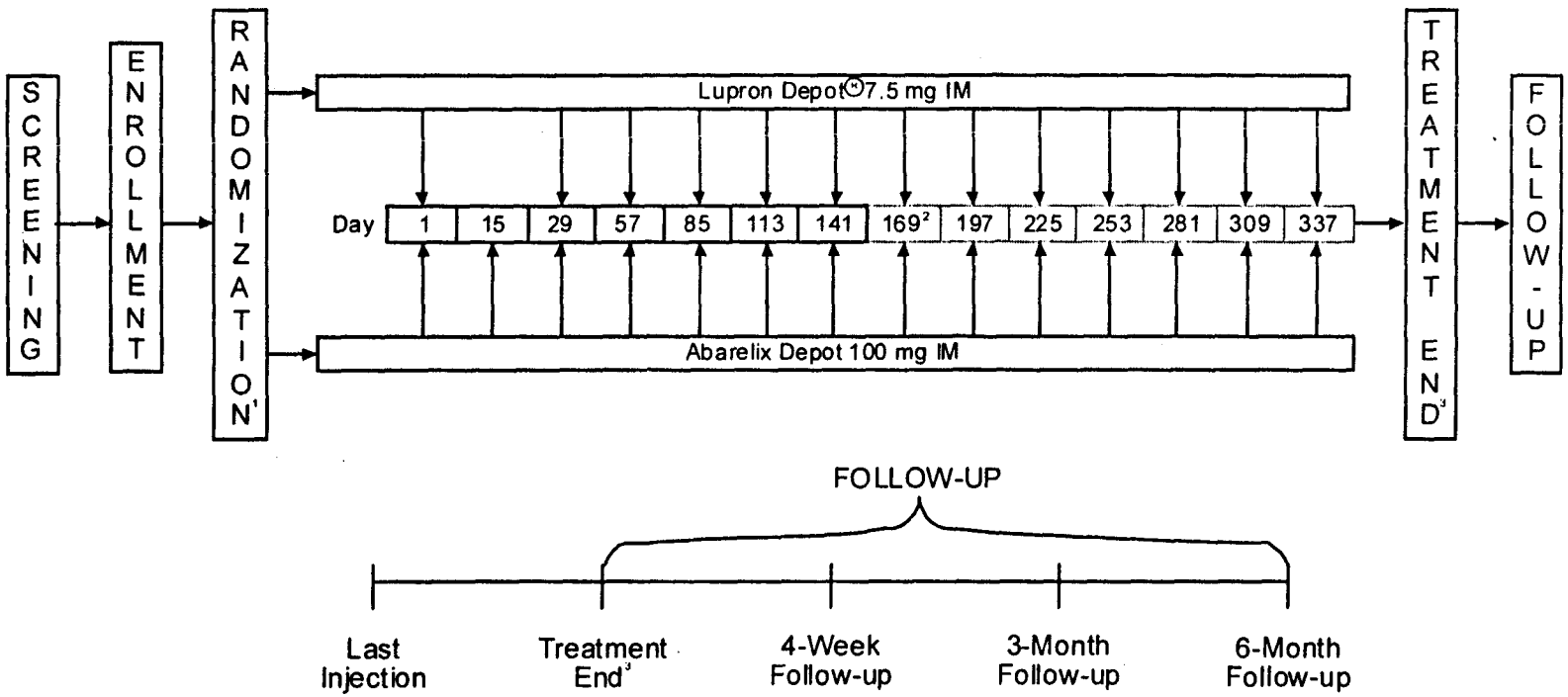
8.2 Primary (Pivotal) Clinical Trials to Support Efficacy Claim

8.2.1 Overall Design

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

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

Figure 2. Overview of Study Design



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

[2] As clinically indicated, patients in Studies 149-98-02 and 149-98-03 could continue treatment with their randomized Study Drug for up to 1 year, including up to 7 additional injections beginning on Day 169 and every 28 days thereafter. If continuing in the study, patients in the abarelix group with testosterone > 50 ng/dL on Day 169 received an extra injection of abarelix on Day 183. Continuing patients in the Lupron group with testosterone > 50 ng/dL on Day 169 were dosed with abarelix on Days 197, 211, 225, and every 28 days thereafter.

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

8.2.2 Patients

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

Inclusion Criteria Included

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

Exclusion Criteria Included

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

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

8.2.3 Study Drugs

8.2.3.1 Dose Selection

In Part 2 of Study 149-97-04 (a Phase I/II pharmacology and safety study of abarelix depot), 209 patients received a 100-mg intramuscular injection of abarelix on Days 1 and 15 followed by 50 or 100 mg on Day 29 and every 4 weeks thereafter for 24 weeks to 2 years. The 100-mg dose was found to be adequate for both induction and maintenance of medical castration (serum testosterone ≤ 50 ng/dL) throughout the assessment period. The 50-mg dose, however, appeared to be suboptimal for maintenance of medical castration after Study Day 85 (per the sponsor). Doses of abarelix higher than 100 mg were not fully evaluated. Based on the findings from Study 149-97-04, the dose and regimen selected for further investigation in Phase III studies (both primary and supportive studies) was 100 mg abarelix administered by IM injection on Study Days 1, 15, 29 and every 4 weeks thereafter for up to 1 year. Patients enrolled in Study 149-99-03 were treated for up to 24 weeks as the duration of this study was only 6 months.

8.2.3.2 Choice of Comparator

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

8.2.3.3 Assignment to Study Drug

Before randomized assignment to treatment group was made, patients were stratified by baseline testosterone level and body weight into 1 of the 4 strata described in Section 8.1.3.1. Within each strata, patient were assigned to abarelix or active control treatment according to a 2:1 randomization scheme (2 abarelix : 1 Lupron or 2 abarelix : 1 Lupron + Casodex).

8.3 Study Procedures and Conduct

8.3.1.1 Schedule of Study Assessments

During the screening period (Days -14 to -1), the patient's eligibility for the study was determined according to the inclusion and exclusion criteria. After their first injection of Study Drug on Day 1, all patients returned to the clinic for study assessments according to the schedule presented in Table 5.

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

8.3.1.2 Key Efficacy Assessments

Key measurements for efficacy assessments included:

- Serum levels of androgens (testosterone and DHT) and gonadotropins (LH and FSH) at screening, baseline (Day 1), each scheduled visit during treatment, end of treatment, 4-week posttreatment follow-up, and if necessary for monitoring of testosterone recovery, 3-months and 6-months posttreatment.
- Serum PSA level at screening, baseline, Day 15, Day 29, every 28 days thereafter during treatment, end of treatment, and 4-weeks posttreatment.

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

8.3.1.3 Pharmacokinetic Assessments

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

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Table 5. Schedule of Study Assessments

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

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

8.4 Results

8.4.1 Demographics and Baseline Disease Characteristics

Twenty-six US sites (Study 149-98-02), 22 US sites (Study 149-98-03), and 49 US/7 Canadian sites (Study 149-99-030 each enrolled 1 or more patients. Baseline demographic characteristics for each of these 3 studies are summarized in Table 6. The majority of patients in each of the trials were Caucasian and ranged from 80% in Study 149-98-03 (abarelix group) to 88% in Study 149-98-02 (abarelix group). The second largest ethnic group was comprised of African Americans, ranging from 6% in Study 149-98-02 (abarelix group) to 13% in Study 149-98-03 (abarelix group) Median treatment group ages ranged from 72 to 74 years while individual ages ranged from 46 to 97 years. Median treatment group weights ranged from 181 to 190 pounds while individual weights ranged from 99 to 365 pounds.

Table 6. Baseline Demographics (Studies 149-98-02, 149-98-03, and 149-99-03)

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

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

Pretreatment testosterone levels and baseline prostate cancer history are shown in Table 7. Median pretreatment testosterone levels ranged from 338 ng/dL (Study 149-98-02, Lupron group) to 389 ng/dL (Study 149-99-03, abarelix group). More than 50% of the patients in each of the 3 studies had early to moderately advanced disease (Disease Stages T1 to T3). The most common reasons for enrollment in each of the studies was neoadjuvant therapy or a rising PSA level. The least common reason for enrollment was for treatment of D1/D2 stage disease.

Table 7. Baseline Disease Characteristics (Studies 149-98-02, 149-98-03, and 149-99-03)

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

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

Medical Officer's Comments

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

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

8.4.2 Primary Efficacy Endpoints

The 3 primary efficacy endpoints are dependent upon changes in serum concentrations of testosterone following administration of Study Drugs. Table 8 lists the median serum testosterone concentrations from baseline through Study Day 169 in Studies 149-98-02 and 149-98-03. Figure 3 shows the median serum testosterone levels during the first 4 weeks of treatment in the Lupron group, the Lupron plus Casodex group, and the abarelix groups combined across both Studies 149-98-02 and 149-99-03. Serum testosterone levels in Study 149-99-03 were similar to those in Study 149-98-02 although measurements were not obtained on Study Days 2 and 4.

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

Medical Officer's Comments

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