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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-320

Statistical Review(s)

Memorandum of Statistical Review

Date: July 25, 2003

NDA #: 21-320

Applicant: Praecis Pharmaceuticals, Inc.

Name of Drug: Plenaxis (abarelix)

Indication: palliative treatment for prostate cancer

Statistical Reviewer: Kate Meaker, M.S. (HFD-715)

Medical Input: Scott Monroe, M.D. (HFD-580)

Background

This NDA was previously reviewed in June, 2001, and received a Not Approvable letter for insufficient clinical information to support the safe and effective use of the product in the intended population. The sponsor then conducted an open-label, uncontrolled, single-arm trial in a new, more restricted, patient population (Study 149-98-04). A revised NDA was submitted February 25, 2003, which included additional safety data along with this single-arm trial.

In the previous review, the Medical Officers identified immediate-onset allergic-type reactions as a potential safety risk for this drug. A life table analysis was presented to quantify the risk.

This statistical review analyzes the updated safety data for this particular risk of concern. Also, the descriptive statistics for the single-arm trial are confirmed.

Safety Analysis – Immediate Onset Allergic-Type Reactions

The safety database includes a total of 1397 patients treated with Plenaxis. These are from the following studies:

Study	# Plenaxis Patients
149-01-03	55
149-01-05	176
149-97-04	221
149-98-02	130
149-98-03	125
149-98-04	41
149-99-03	270
149-99-04	292
ABACAS1	36
ABACAS1 EXT	51

Of a total of 1397 patients treated with Plenaxis, 15 (1.1%) withdrew due to an immediate-onset allergic-type adverse event. The question was raised that this rate might not be constant across time (duration of exposure). To address this question, I performed a life table analysis of the incidence rate of withdrawals due to allergic-type reactions.

The results of the life table analysis are presented in Table 1. The one-year event rate using the life table method is highlighted (Day 365). The estimated event rate is 1.2% at one year, with a 95% two-sided confidence interval of (0.4%, 2.0%). The rate increases after one year, to 2.9% (0.9%, 5.0%) by day 676. The overall event rate of 1.1% is shown at the bottom of Table 1. This is calculated as the number of events as a proportion of the number patients enrolled.

The Medical Officer also requested an analysis of a subset of these adverse events which included only the immediate-onset allergic-type reactions with syncope or hypotension. There were a total of 7 subjects who received treatment with Plenaxis who had this adverse event. These results are shown in Table 2 with the one Year event rate highlighted. The event rate is estimated to be 0.6% at one year, with a 95% two-sided confidence interval of (0.0%, 1.2%). The rate increases after one year, to 1.7% (0.1%, 3.3%) by day 617. The overall event rate is 0.5%.

Table 1: Life Table Analysis of Immediate-Onset Allergic-Type Reactions

Treatment Duration (days)	Number of Patients Withdrawn	Number of Patients Remaining	Allergic-type Reaction Event Rate (%)	95% Confidence Interval on Event Rate (%)	
0	0	1397	0.00	0.00	0.00
1	1	1396	0.07	0.00	0.21
15	3	1394	0.21	0.00	0.46
16	4	1393	0.29	0.01	0.57
29	6	1366	0.43	0.09	0.78
56	7	1317	0.51	0.13	0.88
85	9	1063	0.69	0.24	1.14
141	10	952	0.80	0.30	1.29
196	11	603	0.95	0.37	1.54
365	12	340	1.24	0.43	2.04
589	13	187	1.76	0.46	3.05
617	14	179	2.30	0.63	3.96
676	15	159	2.91	0.87	4.95
Overall Event Rate	15	1397	1.07%	0.60%	1.76%

Source: SAS datasets

Table 2: Life Table Analysis of Immediate-Onset Allergic-Type Reactions with Syncope or Hypotension

Treatment Duration (days)	Number of Patients Withdrawn	Number of Patients Remaining	Allergic-type Reaction Event Rate (%)	95% Confidence Interval on Event Rate (%)	
0	0	1397	0.00	0.00	0.00
1	1	1396	0.07	0.00	0.21
16	2	1395	0.14	0.00	0.34
56	3	1317	0.22	0.00	0.46
141	4	952	0.32	0.00	0.64
365	5	340	0.61	0.00	1.24
589	6	187	1.13	0.00	2.34
617	7	179	1.67	0.07	3.28
Overall Event Rate	7	1397	0.50%	0.20%	1.03%

Source: SAS datasets

Study 149-98-04

This is an open-label, single-arm study of Plenaxis 100mg injection. The patient population was restricted to patients with prostate cancer in whom GnRH agonists are contraindicated. This is the patient population the sponsor focused on after receiving the NA letter for their initial NDA. The primary objective of this study was avoidance of orchiectomy through 4 and 12 weeks of treatment with Plenaxis in symptomatic patients with advanced prostate cancer. This patient population and objective had been discussed with the Division prior to the study.

Patients received injections on Days 1, 15, 29, 57, 85, 113, and 141 for a total treatment duration of 24 weeks. Each injection is considered as treatment duration for 28 days. After completing this protocol, patients were permitted to continue treatment under protocol 149-99-04, an open-label safety extension study.

A total of 83 patients were enrolled, with 81 receiving at least one dose of Plenaxis. Those 81 were included in the safety analyses. There were noncompliance issues at one center in Mexico, with 9 enrolled patients. Those 9 patients were excluded from the ITT population for the efficacy analyses.

The primary objective was the avoidance of orchiectomy at 4 and 12 weeks of treatment. None of the patients required orchiectomy. Based on 72 patients in the ITT population, a 95% two-sided confidence interval on the event rate for orchiectomy in these patients is (0.0%, 5.0%).

Summary

Study 149-98-04 provides information on Plenaxis treatment in patients with prostate cancer in whom GnRH agonists are contraindicated. However, there was no comparator group so the results are only descriptive. The primary efficacy endpoint was the avoidance of orchiectomy, and no patients had an orchiectomy while on treatment. A 95% two-sided confidence interval on the event rate for orchiectomy in these patients is (0.0%, 5.0%).

The life table analysis of the risk for immediate-onset allergic-type reactions indicates that the event rate is 1.24% at 1-year, with a 95% two-sided confidence interval of (0.4%, 2.0%). The rate increases after one year, to 2.9% (0.9%, 5.0%) by day 676.

When the life table analysis is limited to immediate-onset allergic-type reactions which included syncope or hypotension, the event rate is estimated to be 0.6% at 1-year, with a 95% two-sided confidence interval of (0.0%, 1.2%). The rate increases after one year, to 1.7% (0.1%, 3.3%) by day 617.

/S/

Katherine B Meaker, M.S.
Mathematical Statistician

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/s/

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Concur with review

ADDENDUM TO STATISTICAL REVIEW

NDA: 21-320 **Date:** June 8, 2001

Applicant: Praecis Pharmaceuticals, Inc.

Name of Drug: Plenaxis (Abarelix for suspension)

Indication: palliative treatment for prostate cancer

Statistical Reviewers: Kate Meaker, M.S., Mike Welch, Ph.D. (HFD-715)

Medical Officer: Scott Monroe, M.D. (HFD-580)

Background. Percentages of patients who experienced allergic reactions are presented in the Medical Officer's review, Table 42. Of a total of 1166 patients treated with Abarelix, 16 (1.4%) had this type of adverse event and subsequently withdrew from the studies. Of these, 3 patients (0.5%) experienced severe reactions including syncope or hypotension. The question was raised that these rates would not be constant across time and should be reevaluated by taking into account duration of drug exposure.

To address this issue, we performed a life table analysis of the incidence rates of withdrawals due to allergic-type reactions. The 1166 Abarelix patients are from the following studies: 149-97-04 (263); 149-98-02 (180); 149-98-03 (168); 149-98-04 (81); 149-99-03 (387); and the Abacus study (87). From the first four of these studies, 278 patients continued treatment in the follow-on study, 149-99-04. The medical officer's review, Table 41, lists the patient and study number, type of event, and last dosing day for those who experienced an allergic-type reaction. The 16 patients who experienced the adverse events of interest were considered treatment failures at time of event; all other patients were considered as censored observations at time of study withdrawal.

Results. The results of the life table analysis are presented in Table 1. The adverse reaction event rates increase with drug exposure time, with statistically significant (non-zero) event rates within a month of treatment onset. At one year, the rate is about 1.6% with a 95% confidence interval of (0.6%, 2.5%). At approximately two-years, the event rate is 4.1% and the confidence interval indicates that one cannot rule out a rate as high as 7.2%. For the six serious adverse events, the event rate is about 0.7% at one year and 1.1% approaching two years with upper confidence limits of 1.4% and 3.1%, respectively. The one-year event rates are not substantially different from those reported in the clinical review.

It is recommended that the sponsor perform a similar analysis of time to adverse event and discuss the implications of the allergic reaction event rate over time.

Table 1
NDA 21-320 (Plenaxis)
Abarelix Allergic Reaction Withdrawals
Life Table Analysis[1,2]

Treatment Duration (Days)[3]	Number of Patients Withdrawn[4,5]	Number of Patients Remaining[6]	Allergic Reaction Event Rate(%)	95% Confidence Limits Lower	Upper
0	0	1166[7]	0.00	0.00	0.00
1	1	1165	0.09	0.00	0.25
15	3	1163	0.26	0.00	0.55
16	4	1162	0.34	0.01	0.68
29	6	1137	0.52	0.10	0.93
57	7	1114	0.61	0.16	1.06
85	9	1054	0.80	0.28	1.31
141	10	954	0.90	0.34	1.46
197	11	564	1.07	0.42	1.73
229	12	532	1.26	0.51	2.01
365	13	322	1.57	0.61	2.52
617	14	123	2.32	0.57	4.08
650	15	124	3.12	0.79	5.45
676	16	93	4.15	1.09	7.21
Syncope or Hypotension Only[8]					
0	0	1166	0.00	0.00	0.00
1	1	1165	0.09	0.00	0.25
16	2	1162	0.17	0.00	0.41
57	3	1114	0.26	0.00	0.56
141	4	954	0.37	0.01	0.72
365	5	322	0.67	0.00	1.38
617	6	129	1.14	0.00	3.08

NOTES:
1. Sources: Medical officer's review, Tables 41, 42; NDA electronic data sets and listings.
2. SAS LIFETEST Procedure used to compute Product-Limit survival estimates.
3. Days on treatment until adverse event occurred.
4. Patient numbers and event rates are cumulative by treatment duration.
5. Withdrawals shown are due to allergic type reactions. On-treatment days for other subjects are treated as censored observations.
6. Numbers of patients remaining in studies as of time of adverse event.
7. The 1166 Abarelix patients are from following studies: 149-97-04 (263); 149-98-02 (180); 149-98-03 (168); 149-98-04 (81); 149-99-03 (387); Abacus Study (87). An extension study (149-99-04) enrolled 278 patients from earlier studies; the extended time on treatment for these patients are accounted for in the analysis.
8. These 6 cases are a subset of the allergic reaction cases in the top panel.

M. Welch, Ph.D.
Concur: Ed Nevius, Ph.D. Kate Meaker, M.S.

cc:
Archival NDA 21-320
HFD-580/JBest, SMonroe, GBenson, DShames, SAllen; HFD-570/CLee
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/s/

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Concur with review.

Statistical Review and Evaluation
Clinical Studies[1]

Date: June 12, 2001

NDA #: 21-320

Applicant: Praecis Pharmaceuticals, Inc.

Name of Drug: Plenaxis (abarelix)

Indication: palliative treatment for prostate cancer

Documents Reviewed: Vol. 1.116 – 1.188, Amend. 012

Statistical Reviewer: Kate Meaker, M.S. (HFD-715)

Medical Input: Scott Monroe, M.D. (HFD-580)

Introduction

This submission includes two active-controlled clinical trials as the main focus for the efficacy assessment: 149-98-02 and 149-98-03. These are supported by an additional active-control study (149-99-03) and a small study in a high-risk patient population (149-98-04) (See Table 1).

During the protocol development stage, the sponsor and FDA agreed to 3 co-primary efficacy endpoints for studies 149-98-02 and 149-98-03. The first endpoint, achievement and maintenance of medical castration through visit day 85, was required for this indication. A noninferiority comparison, using a 95% 2-sided confidence interval and a delta of 10%, was planned for that endpoint. Success on the first comparison is necessary before further comparisons are done. The other two endpoints, avoidance of testosterone surge and rapidity of reduction in testosterone to castrate levels, were desired by the sponsor for label claims. These were to be compared using superiority tests, each at α=0.025 to adjust for 2 tests. The Medical Officer has requested review of a fourth endpoint, achievement and maintenance of medical castration through visit day 169, for the efficacy assessment.

The primary goal of study 149-99-03 was to collect a large safety database. It has the same patient population as the two studies intended to assess efficacy (149-98-02 and 149-98-03) and enrolled twice as many patients as either of the primary efficacy studies. Study 149-99-03 had a similar study design, but the testosterone levels were not measured as frequently as in the efficacy studies. Only 2 of the 4 efficacy endpoints can be

[1] Keywords: Clinical studies, noninferiority (clinical)

computed for this study. The Medical Officer requested that the efficacy results from study 149-99-03 be assessed with the same criteria as the two main efficacy studies.

In each study, the randomization to the treatment arms is balanced within four strata. The strata are defined by baseline testosterone level (220-500, over 500) and baseline body weight (under 200 lbs., 200 or more lbs.). The applicant selected these two characteristics as potentially influencing the time to medical castration. Not all centers would necessarily enroll subjects in all strata, so the randomization was done across all centers.

Table 1: Summary of Randomized, Controlled Studies

Study Number (Dates Conducted)	Number of Centers (Locations)	Total Sample Size	Type of Control	Design	Duration of Treatment
149-98-02 (12/98 – 9/99)	26 all U.S.	Abarelix Depot 100 mg (n=180) Lupron Depot 7.5 mg (n=91)	Active	Multi-center Open-label Randomized	24 weeks
149-98-03 (12/98 – 10/99)	22 all U.S.	Abarelix Depot 100 mg (n=170) Lupron Depot 7.5 mg + Casodex (n=85)	Active	Multi-center Open-label Randomized	24 weeks
149-99-03 (8/99 – 8/00)	56 49 U.S. 7 Canada	Abarelix Depot 100 mg (n=390) Lupron Depot 7.5 mg (n=194)	Active	Multi-center Open-label Randomized	24 weeks
149-98-04 (2/99 – current)	17 16 U.S. 1 Mexico	Abarelix Depot 100 mg; Interim analysis (n=48)	None Special Population	Multi-center Open-label Single-arm (Descriptive Stats. Only)	24 weeks

STUDY #149-98-02

Background

This is a Phase III, multicenter, open-label, randomized, parallel arm study. The treatment assignment could not be blinded because there was a slight difference in the treatment regimens - one group got one additional injection on Day 15 in the first month. However, all the efficacy assessments were derived from serum testosterone levels, determined by lab analyses at a central lab, which were not susceptible to bias from unblinded patients or clinicians. The testosterone measurements were not provided to the clinic staff, so the efficacy results remained masked. Praecis personnel were blinded to the treatment assignments and lab analysis values until the study was completed.

The patients were at least 18 years old, diagnosed with prostate cancer and determined to be suitable for initial hormone therapy. Patients received abarelix depot 100 mg or Lupron Depot 7.5 mg by intramuscular (IM) injection on days 1, 29, 57, 85, 113, and 141. Patients in the abarelix depot treatment arm received an additional injection on day 15. Patients were followed through day 169 (Week 24) for the efficacy portion of the protocol. Study visits ere planned at a maximum of 2 week intervals (more frequently in first and fourth week), with blood samples drawn to measure testosterone at every visit. A safety extension allowed patients, if clinically appropriate, to continue to receive treatment for up to a total of one year.

After meeting the entry criteria, but before randomization, subjects were assigned to one of 4 strata:

1. Baseline testosterone 220-500 ng/dL and body weight < 200 lbs
2. Baseline testosterone >500 ng/dL and body weight < 200 lbs
3. Baseline testosterone 220-500 ng/dL and body weight ≥ 200 lbs
4. Baseline testosterone >500 ng/dL and body weight ≥ 200 lbs

Randomization to the two treatment arms was balanced within each strata, but was not balanced within centers. Patients were randomized at a 2:1 ratio, with a total of 180 assigned to the abarelix depot treatment arm and 91 assigned to the Lupron Depot arm.

During the protocol development, up to 6 different definitions of endpoints were discussed regarding the achievement and maintenance of medical castration. It was decided that Definition 2 would be the primary efficacy endpoint for approval for this indication. Using this definition, a patient had achieved and maintained medical castration if he was castrate (testosterone ≤ 50 ng/dL) on day 29 and did not have 2 consecutive testosterone measurements > 50 ng/dL two weeks apart (day 29 through day 85). An additional definition, referred to as Definition 5, was considered a secondary endpoint and will also be reviewed here. Definition 5 had the same criteria regarding no 2 consecutive testosterone measurements > 50 ng/dL two weeks apart, but extended through day 169 on treatment.

Two other primary endpoints are also reviewed. A testosterone surge was defined as a patient having 2 (of 3) testosterone measurements between days 2 and 8 exceed his baseline measurement by 10% or greater. The avoidance of a testosterone surge is a clinically important outcome. The rapidity of medical castration was defined as a binary variable indicating a testosterone level $\leq$ 50 ng/dL on day 8. This is also a clinically important outcome.

The agency and the sponsor agreed to three primary variables during the protocol development. The first, which was necessary for approval for this indication, is the achievement and maintenance of medical castration through visit day 85 (referred to as Definition 2). A noninferiority comparison, using a 95% 2-sided confidence interval and a delta of 10%, was planned for this endpoint. Success on the first comparison was to be necessary before further comparisons are done. The other two endpoints, avoidance of testosterone surge and rapidity of reduction in testosterone to castrate levels, were desired by the sponsor for label claims. These were to be compared using superiority tests, each at α=0.025 to adjust for 2 tests. The Medical Officer has requested that I also include a fourth endpoint, achievement and maintenance of medical castration through visit day 169 (referred to as Definition 5), for the efficacy assessment. This was considered a secondary endpoint in the protocol.

A total of 271 patients were randomized to the 2 treatment groups, with 180 assigned to the abarelix treatment arm and 91 assigned to the Lupron Depot arm. Two of the subjects in the Lupron Depot arm dropped before receiving study drug, and were not included in the Intent-to-Treat (ITT) population for the analyses. The applicant presented the descriptive statistics for baseline demographic and disease status variables in Tables 8-8 and 8-9 of the study report (Vol. 1.116). These results show that the groups were similar with regard to these characteristics at baseline.

The disposition of the subjects in the 2 treatment groups is shown in Table 2 below. The groups were similar in terms of both the percentage of dropouts at any stage and the reason for dropouts.

Table 2: Disposition of subjects by group (Study #149-98-02)

	Abarelix Depot N=180	Lupron Depot N=91
	n (%)	n (%)
Randomized to treatment	180 (100%)	91 (100%)
Received Study Drug (ITT)	180 (100%)	89 (98%)
Discontinued before day 85	3 (2%)	5 (5%)
Adverse Event	2 (1%)	2 (2%)
Patient Decision	1 (1%)	3 (3%)
Completed through day 85	177 (98%)	86 (95%)
Discontinued after day 85 but before day 169	8 (4%)	4 (4%)
Adverse Event	1 (1%)	3 (3%)
Patient Decision	4 (2%)	0 (0%)
Other	3 (2%)	1 (1%)
Completed through day 169	169 (94%)	82 (90%)

Source: Vol. 1.116, Table 8-1.

Applicant's Analysis

The first step in the planned analyses was the noninferiority comparison for the achievement and maintenance of medical castration for day 29 through day 85 (Definition 2). This used a 2-sided, 95% confidence interval (CI) on the between-group difference in the percentage of patients who had success on this endpoint. A delta of -10% was predetermined as clinically meaningful. As shown in Table 3, the point estimate for the difference is –3.8% (favoring Lupron Depot) but the lower bound of the CI is greater than -10%. This result supports the conclusion of noninferiority between the treatment groups.

If the results indicated that abarelix was not inferior to Lupron Depot on the first comparison, then two superiority tests were planned, for the avoidance of testosterone surge and the rapidity of medical castration endpoints. A Cochran-Mantel-Haenszel (CMH) test was planned to control for baseline strata. This is appropriate since randomization was done within strata. Each test would use α=0.025 to adjust for two tests. In the study report the applicant made a change from the protocol. For these two superiority tests, the applicant used Fisher's Exact test instead of the CMH test because 1 or more strata would have noninformative cells. The applicant adequately described this in Section 7.11.2. As shown in Table 3, abarelix was significantly different from, and better than, Lupron Depot for each of these two endpoints.

The percent of patients who achieved and maintained medical castration through day 169 (Definition 5) was a secondary endpoint in the protocol. The planned analysis was a 2-sided 95% CI on the between-group difference in the rate, with no prespecified delta. This endpoint is included in this review at the request of the Medical Officer. The results show a point estimate of the difference of –4.9%, favoring Lupron Depot, with a CI which includes zero.

Table 3: Applicant's Results (Study #149-98-02)

N = ITT patient population	Abarelix Depot N=180	Lupron Depot® N=89	Difference (Abarelix – Lupron)
Percent of patients who achieved and maintained medical castration from day 29 through day 85 (Defn. 2)	165 91.7%	85 95.5%	-3.8 (-9.7%, 2.1%) [1]
Avoidance of Testosterone Surge: Percent of patients who experienced testosterone surge during days 2-8	0 0.0%	73 82.0%	p<0.001 [2]
Rapidity: Percent of patients who achieved medical castration by day 8	129 71.7%	0 0.0%	p<0.001 [2]
Percent of patients who achieved and maintained medical castration from day 29 through day 169 (Defn. 5)	157 87.2%	82 92.1%	-4.9 (-12.3%, 2.5%) [3]

[1] Noninferiority comparison: 2-sided 95% confidence interval on difference; delta=10%
[2] Superiority comparison: Fisher's Exact test; 2-sided p-value; adjusted alpha=0.025 per test
[3] No prespecified delta

Source: Vol. 116; Tables 12.4.1.1, 12.4.1.2, 12.4.2.1, 12.4.3.1

Reviewer's Analysis

The efficacy analyses presented by the applicant were the planned methods and were appropriate. I confirmed all the results using the efficacy datasets provided. The only additional analyses I wanted to consider were to show the results by the four strata used for the randomization. The strata were selected because there was potential for some differences in the treatment effect across the categories defined for baseline testosterone level and body weight. The distribution of patients across the 4 strata is shown in Table 4. Because there were only a few patients in strata 4, I summarized the results for each of the two marginal variables.

Table 4: Distribution of subjects by strata (Study #149-98-02)

N = ITT patient population		Abarelix Depot N=180	Lupron Depot N=89
Baseline Testosterone	Body Weight	n (%)	N (%)
220-500 ng/dL	< 200 lbs	87 (48%)	43 (47%)
>500 ng/dL	< 200 lbs	32 (18%)	16 (18%)
220-500 ng/dL	≥ 200 lbs	54 (30%)	27 (30%)
>500 ng/dL	≥ 200 lbs	7 (4%)	3 (3%)
Marginal: Baseline Testosterone			
220-500 ng/dL		119 (66%)	59 (65%)
>500 ng/dL		61 (34%)	30 (33%)
	Marginal: Body Weight		
	< 200 lbs	141 (78%)	70 (77%)
	≥ 200 lbs	39 (22%)	19 (21%)

The by-strata efficacy results are presented only for descriptive purposes, and are not intended to be conclusive. Within each treatment group, the results across the baseline testosterone subgroups were similar for all four of the efficacy variables. Three of the 4 endpoints had similar results across the body weight subgroups as well. The only subgroup comparison with a notable difference was for the rapidity of medical castration endpoint across the body weight subgroups in the abarelix treatment arm. As shown in Table 5 on the next page, patients with higher body weight had a lower rate of success for this endpoint. This was not unexpected to the Medical Officer. Again, this only suggests a potential treatment difference and is not meant to be conclusive.

Table 5: Descriptive statistics by strata (Study #149-98-02)

N = ITT patient population	Abarelix Depot N=180		Lupron Depot N=89	
Marginal: Body Weight	< 200 lbs	≥ 200 lbs	< 200 lbs	≥ 200 lbs
N per strata	119	61	59	30
Rapidity: Percent of patients who achieved medical castration by day 8	97 (82%)	32 (52%)	0 (0%)	0 (0%)

Source: Efficacy datasets

Conclusions - Study #149-98-02

The statistical analyses of Study #149-98-02 support the efficacy of abarelix for this indication. Abarelix was noninferior to the active-control on the primary efficacy endpoint of achievement and maintenance of medical castration for day 29 through day 85. The point estimate for the difference was –3.8% (favoring the active-control arm), but the lower bound of the 2-sided 95% CI was greater than –10%. Additionally, abarelix was superior to the active-control on the two additional desired comparisons, avoidance of testosterone surge and rapidity of medical castration (both p-values <0.001).

STUDY #149-98-03

Background

Study #149-98-03 was a Phase III, multicenter, open-label, randomized, active-control, parallel arm study. The primary objective was compare abarelix to a treatment regimen of Lupron® Depot + Casodex® to assess efficacy. This had the same study design, patient population, and efficacy endpoints as Study # 149-98-02. The only difference was the treatment regimen for the active-control arm. The active-control group in this study received Lupron® 7.5 mg IM injections every 28 days, plus a daily Casodex® tablet.

A total of 255 patients were randomized to the 2 treatment groups, with 170 assigned to the abarelix treatment arm and 85 assigned to the Lupron Depot + Casodex arm. The applicant presented the descriptive statistics for baseline demographic and disease status variables in Tables 8-8 and 8-9 of the study report (Vol. 1.132). These results show that the groups were similar with regard to these characteristics at baseline.

The disposition of the subjects in the 2 treatment groups is shown in Table 6. The groups were similar in terms of dropouts through day 85 on treatment. A total of four subjects, two per arm, dropped prior to receiving any treatment and were not included in the ITT patient population. Between day 85 and day 169, the Lupron+Casodex arm showed a higher rate of dropouts, primarily due to adverse events. The primary efficacy endpoints are all measured prior to day 85, so the unbalanced dropouts after day 85 do not impact the efficacy analyses.

Table 6: Disposition of subjects by group (Study #149-98-03)

	Abarelix Depot N=170	Lupron Depot + Casodex N=85
	n (%)	n (%)
Randomized to treatment	170 (100%)	85 (100%)
Received Study Drug (ITT)	168 (99%)	83 (98%)
Discontinued before day 185	5 (3%)	5 (6%)
Adverse Event	3 (2%)	0 (0%)
Patient Decision	1 (1%)	3 (4%)
Other	1 (1%)	2 (2%)
Completed through day 85	165 (97%)	80 (94%)
Discontinued after day 85 but before day 169	9 (6%)	10 (12%)
Adverse Event	3 (2%)	8 (9%)
Patient Decision	1 (1%)	1 (1%)
Other	5 (3%)	1 (1%)
Completed through day 169	156 (92%)	70 (82%)

Source: Vol. 1.132, Table 8-1.

Applicant's Analysis

The analysis plan for Study #149-98-03 was the same as for study #149-98-02. The first step in the planned analyses was the noninferiority comparison for the achievement and maintenance of medical castration for day 29 through day 85 (Definition 2). This used a 2-sided, 95% confidence interval (CI) on the between-group difference in the percentage of patients who had success on this endpoint. A delta of -10% was predetermined as clinically meaningful. As shown in Table 7, the point estimate of the difference is –2.3% (favoring Lupron Depot + Casodex) but the lower bound of the CI is greater than -10%. This result supports the conclusion of noninferiority between the treatment groups.

If the results indicated that abarelix was not inferior to Lupron Depot + Casodex on the first comparison, then two superiority tests were planned, for the avoidance of testosterone surge and the rapidity of medical castration endpoints. A Cochran-Mantel-Haenszel (CMH) test was planned to control for baseline strata. This is appropriate since randomization was done within strata. Each test would use α=0.025 to adjust for two tests. For these two superiority tests there was a change from the protocol. The applicant used Fisher's Exact test instead of the CMH test because 1 or more strata would have noninformative cells. The applicant adequately described this in Section 7.11.2. As shown in Table 7, abarelix was significantly different from, and better than, Lupron Depot + Casodex for each of these two endpoints.

The percent of patients who achieved and maintained medical castration through day 169 (Definition 5) was a secondary endpoint in the protocol. The planned analysis was a 2-sided 95% CI on the between-group difference in the rate, with no prespecified delta. This endpoint is included in this review at the request of the Medical Officer. The point estimate of the difference is 6.1%, favoring abarelix, with a 95% CI which includes zero.

Table 7: Applicant's Results (Study #149-98-03)

N = ITT patient population	Abarelix Depot N=168	Lupron Depot® N=83	Difference (Abarelix – Lupron/Casodex)
Percent of patients who achieved and maintained medical castration from day 29 through day 85 (Defn. 2)	156 92.9%	79 95.2%	-2.3% (-8.4%, 3.7%) [1]
Avoidance of Testosterone Surge: Percent of patients who experienced testosterone surge during days 2-8	0 0.0%	71 85.5%	p<0.001 [2]
Rapidity: Percent of patients who achieved medical castration by day 8	114 67.9%	0 0.0%	p<0.001 [2]
Percent of patients who achieved and maintained medical castration from day 29 through day 169 (Defn. 5)	152 90.5%	70 84.3%	6.1% (-2.9%, 15.1%) [3]

[1] Noninferiority comparison: 2-sided 95% confidence interval on difference; delta=10%
[2] Superiority comparison: Fisher's Exact test; 2-sided p-value; adjusted alpha=0.025 per test
[3] No prespecified delta

Source: Vol. 132; Tables 12.4.1.1, 12.4.1.2, 12.4.2.1, 12.4.3.1

Reviewer's Analysis

The efficacy analyses presented by the applicant were the planned methods and were appropriate. I confirmed all the results using the efficacy datasets provided. The only additional analyses I wanted to consider were to show the results by the four strata used for the randomization. The strata were selected because there was potential for some differences in the treatment effect across the categories defined for baseline testosterone level and body weight. The distribution of patients across the 4 strata is shown in Table 8. Because there were only a few patients in strata 4, I summarized the results for each of the two marginal variables.

Table 8: Distribution of subjects by strata (Study #149-98-03)

N = ITT patient population		Abarelix Depot N=168	Lupron Depot + Casodex N=83
Baseline Testosterone	Body Weight	n (%)	n (%)
220-500 ng/dL	< 200 lbs	95 (56%)	48 (56%)
>500 ng/dL	< 200 lbs	24 (14%)	13 (15%)
220-500 ng/dL	≥ 200 lbs	45 (26%)	20 (24%)
>500 ng/dL	≥ 200 lbs	4 (2%)	2 (2%)
Marginal: Baseline Testosterone			
220-500 ng/dL		140 (82%)	68 (80%)
>500 ng/dL		28 (16%)	15 (18%)
	Marginal: Body Weight		
	< 200 lbs	119 (70%)	61 (72%)
	≥ 200 lbs	49 (29%)	22 (26%)

The by-strata efficacy results are presented only for descriptive purposes, and are not intended to be conclusive. Within each treatment group, the results across the baseline testosterone subgroups were similar for all four of the efficacy variables. Three of the 4 endpoints had similar results across the body weight subgroups as well. The only subgroup comparison with a notable difference was for the rapidity of medical castration endpoint across the body weight subgroups in the abarelix treatment arm. As shown in Table 9, patients with higher body weight had a lower rate of success for this endpoint. This was not unexpected to the Medical Officer. Again, this only suggests a potential treatment difference and is not meant to be conclusive.

Table 9: Descriptive statistics by strata (Study #149-98-03)

N = ITT patient population	Abarelix Depot N=168		Lupron Depot + Casodex N=83	
Marginal: Body Weight	< 200 lbs	≥ 200 lbs	< 200 lbs	≥ 200 lbs
N per strata	119	49	61	22
Rapidity: Percent of patients who achieved medical castration by day 8	88 (74%)	26(53%)	0 (0%)	0 (0%)

Source: Efficacy datasets

Conclusions - Study #149-98-03

The statistical analyses of Study #149-98-03 support the efficacy of abarelix for the indication of palliative treatment for prostate cancer. Abarelix was noninferior to the active-control on the primary efficacy endpoint of achievement and maintenance of medical castration for day 29 through day 85. The point estimate for the difference was –2.3% (favoring the active-control arm), but the lower bound of the 2-sided 95% CI was greater than –10%. Additionally, abarelix was superior to the active-control on the two additional desired comparisons, avoidance of testosterone surge and rapidity of medical castration (both p-values <0.001).

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STUDY #149-99-03

Background

This was a Phase III, multicenter, open-label, randomized, active-control, parallel arm study. The active-control arm was Lupron Depot 7.5 mg, the same as in Study #149-98-02. The primary objective of this study was to evaluate the safety of abarelix depot through the incidence of adverse events and abnormal laboratory values (see Medical Officer's review of safety). Secondary objectives included two of the desired efficacy endpoints: percent of patients who achieved and maintained medical castration from day 29 through day 85, and percent of patients who were castrate on day 8 (rapidity). The protocol did not plan to assess the percent without a testosterone surge or the percent who achieved and maintained medical castration from day 29 through day 169. It is not possible to derive these endpoints because the testosterone measurements were not taken as often during this study as in the two studies designed to assess efficacy.

Aside from the timing of the testosterone measurements, this study had a similar design as studies #149-98-02 and #149-98-03. It included the same patient population, randomization within strata, and treatment schedule. The statistical analysis plan was different because the efficacy comparisons were not the primary interest, but the planned methods for the comparisons were the same.

A total of 584 patients were randomized to the two treatment groups. I compared descriptive statistics for baseline demographic and disease status variables and found that the groups were similar with regard to these characteristics.

The disposition of the subjects in the two treatment groups was similar in terms of both the percentage of dropouts at any stage and the reason for dropouts (see Table 10).

Table 10: Disposition of subjects by group (Study #149-99-03)

	Abarelix Depot N=390	Lupron Depot N=194
	n (%)	n (%)
Randomized to treatment	390 (100%)	194 (100%)
Received Study Drug (ITT)	388 (99%)	194 (100%)
Discontinued before day 169	49 (13%)	20 (10%)
Adverse Event	14 (4%)	7 (4%)
Patient Decision	10 (3%)	3 (2%)
Other	24 (6%)	10 (5%)
Completed through day 169	341 (87%)	174 (90%)

Source: Vol. 1.149, Table 8-1.

Applicant's Analysis

The efficacy endpoints were planned as secondary endpoints in this study, and only two of the four desired efficacy endpoints could be calculated from the collected measurements. The planned analyses were the same as in the efficacy studies, without the adjustment for multiple tests because these were secondary endpoints. The results are shown in Table 11.

The noninferiority comparison for the achievement and maintenance of medical castration for day 29 through day 85 (Definition 2) used a 2-sided, 95% confidence interval (CI) on the between-group difference in the percentage of patients who had success on this endpoint. A delta of -15% was specified in the protocol as a noninferiority boundary. This is more liberal than the delta of 10% specified in the efficacy studies. As shown in Table 11, the point estimate of the difference is –7.7% (favoring Lupron Depot) and the lower bound of the CI is –11.5%. This lower bound exceeds the –10% delta for the efficacy studies, so this result does not provide strong confirmatory support for efficacy.

In the two studies planned to assess efficacy, the statistical analysis plan would have stopped if the first comparison did not support the noninferiority claim. However, since this study was not primarily designed for efficacy, there was no prespecified plan to protect the overall level of significance for multiple tests. Therefore the additional hypothesis test on the second efficacy endpoint, rapidity of medical castration, was reported. For this endpoint a Cochran-Mantel-Haenszel (CMH) test was planned to control for baseline strata. This is appropriate since randomization was done within strata. In the final analysis a Fisher's Exact test was used because of at least one noninformative cell. As shown in Table 11, abarelix was significantly different from, and better than, Lupron Depot for this endpoint.

Table 11: Applicant's Results (Study #149-99-03)

N = ITT patient population	Abarelix Depot N=388	Lupron Depot® N=194	Difference (Abarelix – Lupron)
Percent of patients who achieved and maintained medical castration from day 29 through day 85 (Defn. 2)	348 89.6%	189 97.4%	-7.7% (-11.5%, -4.0%) [1]
Avoidance of Testosterone Surge: Percent of patients who experienced testosterone surge during days 2-8	NA	NA	NA
Rapidity: Percent of patients who achieved medical castration by day 8	255 65.7%	0 0.0%	$p<0.001$ [2]
Percent of patients who achieved and maintained medical castration from day 29 through day 169 (Defn. 5)	NA	NA	NA

NA – Data was not available to calculate desired endpoint.
[1] Noninferiority comparison: 2-sided 95% confidence interval on difference; delta=15%
[2] Superiority comparison: CMH test; 2-sided p-value; adjusted alpha=0.025 per test

Source: Vol. 149 Tables 12.4.1.1, 12.4.2.1,

Reviewer's Analysis

The efficacy analyses presented by the applicant were the planned methods and were appropriate. I confirmed all the results using the efficacy datasets provided. The only additional analyses I wanted to consider were to show the results by the four strata used for the randomization. The strata were selected because there was potential for some differences in the treatment effect across the categories defined for baseline testosterone level and body weight. The distribution of patients across the 4 strata is shown in Table 12. Because there were only a few patients in strata 4, I summarized the results for each of the two marginal variables.

Table 12: Distribution of subjects by strata (Study #149-99-03)

N = ITT patient population		Abarelix Depot N=388	Lupron Depot N=194
Baseline Testosterone	Body Weight	n (%)	n (%)
220-500 ng/dL	< 200 lbs	200 (51%)	101 (52%)
>500 ng/dL	< 200 lbs	69 (18%)	35 (18%)
220-500 ng/dL	≥ 200 lbs	104 (27%)	52 (27%)
>500 ng/dL	≥ 200 lbs	15 (4%)	6 (3%)
Marginal: Baseline Testosterone			
220-500 ng/dL		304 (78%)	153 (79%)
>500 ng/dL		84 (22%)	41 (21%)
	Marginal: Body Weight		
	< 200 lbs	269 (69%)	136 (70%)
	≥ 200 lbs	119 (31%)	58 (30%)

The by-strata efficacy results are presented only for descriptive purposes, and are not intended to be conclusive. Within each treatment group, the results across the baseline testosterone subgroups were similar for both of the available efficacy variables. However, both of the endpoints showed notable differences across the body weight subgroups in the abarelix treatment arm. As shown in Table 13, patients with higher body weight had a lower rate of success for both endpoints. This was not unexpected to the Medical Officer. Again, this only suggests a potential treatment difference and is not meant to be conclusive.

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Table 13: Descriptive statistics by strata (Study #149-99-03)

N = ITT patient population	Abarelix Depot N=388		Lupron Depot N=194	
Marginal: Body Weight	< 200 lbs	≥ 200 lbs	< 200 lbs	≥ 200 lbs
N per strata	269	119	136	58
Percent of patients who achieved and maintained medical castration from day 29 through day 85 (Defn. 2)	253 (94%)	95 (80%)	131 (96%)	58 (100%)
Rapidity: Percent of patients who achieved medical castration by day 8	200 (74%)	55(46%)	0 (0%)	0 (0%)

Source: Efficacy datasets

Conclusions - Study #149-99-03

The main objective of Study #149-99-03 was to assess the safety of abarelix through the incidence of adverse events and abnormal lab values. Two of the four desired efficacy endpoints were measured in this study as secondary endpoints. The noninferiority comparison on the endpoint of achievement and maintenance of medical castration for day 29 through day 85 did not support the efficacy using the delta of 10% specified in the other studies, but that delta was not prespecified for this study. The point estimate for the difference was –7.7% (favoring the active-control arm), and the lower bound of the 2-sided 95% CI was –11.5%, below –10%. However, on the second endpoint, rapidity of medical castration, abarelix was superior to the active-control (p-value <0.001). The efficacy results of this study are exploratory and do not provide confirmatory, supportive evidence of efficacy.

Conclusions

The two studies which were planned to assess the efficacy of abarelix depot (149-98-02 and 149-98-03) met the prespecified criteria to show efficacy for the indication of palliative treatment for prostate cancer. Specifically, abarelix was noninferior to the active-control treatments on the achievement and maintenance of medical castration for day 29 through day 85 (Definition 2). This was based on a 2-sided, 95% confidence interval (CI) on the between-group difference in the percentage of patients who had success on this endpoint. A delta of -10% was predetermined as clinically meaningful. In each study the lower bound of the CI was greater than –10%, which supports the conclusion of noninferiority of the abarelix treatment arm. In addition to meeting the noninferiority criteria in both studies, abarelix was also shown to be superior to the active-control treatments for the avoidance of testosterone surge and the rapidity of medical castration endpoints.

The objective of Study #149-99-03 was primarily to assess safety, but it was able to contribute evidence for two of the efficacy endpoints. The results for the noninferiority comparison had a lower bound of –11.5%, which was below the specified delta used in the other two studies. This result does not provide clear evidence of efficacy at the level of the primary studies. However, the abarelix group was superior to the active-control for the rapidity of medical castration endpoint. That endpoint supports the conclusion from the other two studies.

Subgroups analyses were done for two variables used to define strata. The strata were used in the randomization of patients to treatment arms. The baseline testosterone subgroup analysis did not show large differences across the two categories. However, there were notable differences across the body weight categories. Specifically, all three studies suggest that patients with body weight of 200 lbs. or more had lower success rates for the rapidity of medical castration, and one study indicated this subgroup might have lower success for the achieve and maintain medical castration for day 29 through day 85 endpoint. These subgroup comparisons are only intended to explore the potential relationship between the baseline characteristic and the efficacy outcomes. These are not appropriate for statistical conclusions.

Comments on the Label

The order in which the clinical efficacy conclusions are presented in the label should match the order in which they were tested. Specifically, the results for the noninferiority comparison for achievement and maintenance of medical castration should be reported first, since that was necessary for getting approval for this indication. The results of the two superiority tests for claims against the active-control groups should follow.

Katherine B Meaker, M.S.
Mathematical Statistician

Concur: Dr. Welch

Dr. Nevius

cc:
Archival NDA 21-320
HFD-580
HFD-580/SMonroe, GBenson, DShames, SAllen
HFD-580/EdeGuia, JBest
HFD-715/ENevius, MWelch, KMeaker, CAnello

Word 7.0\My Documents\NDA21320-Plenaxis\review

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/s/

Katherine Meaker
6/12/01 12:21:56 PM
BIOMETRICS

Mike Welch
6/12/01 12:36:07 PM
BIOMETRICS
Concur with reviewer

S. Edward Nevius
6/13/01 10:42:13 AM
BIOMETRICS
Concur with review.

Screening of New NDA
Division of Biometrics II

Date: 12/19/00

NDA #: 21-320

Priority Classification: Priority Review

Trade Name: Plenaxis

Applicant: Praecis Pharmaceuticals

Generic Name: abarelix

Date of Submission: 12/12/00

Indication: treatment of prostate cancer

No. of Controlled Studies: 3

User Fee Goal Date: 6/12/01

Date of 45-Day Meeting: 1/24/01

Medical Officer: Scott Monroe, M.D. (HFD-580)
George Benson, M.D. (HFD-580)

Project Manager: Eufrecina DeGuia (HFD-580)

Screened by: Kate Meaker, M.S. (HFD-715)

Volume numbers in statistical section: 1.1, 1.116 – 1.187

Anticipated Review Completion Date: 4/30/01

Comments:

1. This application is fileable.

2. SAS datasets and documentation were submitted to the electronic document room.

CHECKLIST

Item	**Check (NA if not applicable)**
Index sufficient to locate necessary reports, tables, etc.	**Yes**
Original protocols & subsequent amendments available in the NDA	**Yes**
Designs utilized appropriate for the indications requested	**Yes**
Endpoints and methods of analysis spelled out in the protocols	**Yes**
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	**NA**
Appropriate references included for novel statistical methodology (if present)	**NA**
Sufficient data listings and intermediate analysis tables to permit statistical review	**Yes**
Data from primary studies on diskettes and/or CANDA submitted	**CDs sent to EDR; Vol. 188**
Intent-to-treat analysis	**Yes**
Effects of dropouts on primary analyses investigated	**OK; low dropouts in all studies**
Safety and efficacy for ~~gender~~, racial, and ~~geriatric~~ subgroups investigated	**Race – No** **Baseline disease status – Yes**

BRIEF SUMMARY OF CLINICAL TRIALS IN ISE

Study Number (Dates Conducted)	Number of Centers (Locations)	Total Sample Size	Type of Control	Design	Duration of Treatment
149-98-02 (12/98 – 9/99)	26 all U.S.	Abarelix Depot 100 mg (n=180) Lupron Depot 7.5 mg (n=91)	Active	Multi-center Open-label Randomized	24 weeks
149-98-03 (12/98 – 10/99)	22 all U.S.	Abarelix Depot 100 mg (n=170) Lupron Depot 7.5 mg + Casodex (n=85)	Active	Multi-center Open-label Randomized	24 weeks
149-99-03 (8/99 – 8/00)	56 49 U.S. 7 Canada	Abarelix Depot 100 mg (n=390) Lupron Depot 7.5 mg (n=194)	Active	Multi-center Open-label Randomized	24 weeks
149-98-04 (2/99 – current)	17 16 U.S. 1 Mexico	Abarelix Depot 100 mg; Interim analysis (n=48)	None Special Population	Multi-center Open-label Single-arm (Descriptive Stats. Only)	24 weeks

/S/

Statistical Reviewer

Concur: Dr. Welch

cc:
Archival NDA #21-320
HFD-580
HFD-580/SMonroe, GBenson, EDeGuia, SAllen
HFD-715/ENevius, MWelch, KMeaker, Chron

/s/

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