CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-088

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies[1]

Date: FEB 7 2000

NDA #: 21-088

Applicant: ALZA Corporation

Name of Drug: Viadur™ Leuprolide Implant

Indication: Palliative treatment of advanced prostate cancer

Documents Reviewed: Vol. 1.3; 1.67 – 1.107; 3.1; 8.5 – 8.6

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

Medical Input: Norman Marks, M.D. (HFD-580)

Summary of Studies

Two clinical studies were submitted to support efficacy in this application (see Table 1). The first study, C-96-011, is an open-label, dose-ranging study with two treatment groups receiving different doses of Viadur™ Leuprolide Implant (1-implant or 2-implants). Only the 1-implant treatment regimen has been submitted in this NDA, so only that treatment group will be considered for efficacy. The second study, C-97-010, was an open-label study with only the 1-implant treatment group. There were no control groups in either clinical study, and no between-group comparisons were planned.

The primary variables of interest to the Medical Officer are:

- the proportion of patients with serum testosterone (T) suppression to castrate level (≤50 ng/dL) by Week 4,
- the proportion of patients with a testosterone escape (two consecutive T values >50 ng/dL) during the 12-month treatment period, and
- the proportion of patients who experience an acute-on-chronic phenomenon (clinically significant increase in serum T) upon removal of the original implant and insertion of a new implant at the end of the 12-month treatment phase.

The first two listed are the efficacy parameters, measuring the ability to achieve and maintain the suppression of serum testosterone (T) below castrate level. The incidence of the acute-on-chronic phenomenon is a safety issue.

[1] Clinical studies; No comparator arms

This review will provide estimates of the three incidence rates, along with 95% confidence intervals, for the two clinical studies separately and combined. There are no comparator treatment groups, so no further statistical analyses are needed. The Medical Officer has also requested input on how the efficacy information is presented in the label.

Table 1: Summary of Clinical Studies

Study Number (Dates Conducted)	# of Centers (Locations)	Treatment Arms (# Randomized)	Indication	Duration of Treatment
C-96-011 (3/97 – 8/98)	9 (US)	n=51 1 implant n=27 2 implants n=24	Palliative trmt of advanced prostate cancer	12-month Treatment Phase; 12-month Safety Extension Phase
C-97-010 (10/97 – 12/98)	19 (US)	1 implant n=80	Palliative trmt of advanced prostate cancer	12-month Treatment Phase; 12-month Safety Extension Phase

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STUDY #C-96-011

Study #C-96-011 was an open-label, multicenter, dose-ranging study which compared a 1-implant Viadur™ treatment group to a 2-implant Viadur™ treatment group. The 1-year Treatment Phase was a stratified, randomized, parallel arm evaluation of efficacy and safety. This was followed by a 1-year Safety Extension Phase using only the 1-implant dose of Viadur™. This study was conducted in 9 centers in the U.S.

All subjects were males with advanced prostate cancer and baseline serum T level ≥ 150 ng/dL. Randomization was based on three strata which were defined by disease status and previous treatment modality. A total of 51 subjects were randomized: 27 to the 1-implant treatment group, 24 to the 2-implant treatment group. Only the 1-implant treatment group results are presented here.

In the applicant's analyses, multiple definitions of the patient population were used in determining the denominator for the calculation of the proportions. In Table 2, this reviewer used the applicable Intent-to-Treat (ITT) patient population for each variable. The ITT group for the Treatment Phase variables is all subjects who received an implant (n=27). For the Safety Extension Phase, the ITT population is all subjects who received a replacement implant after completion of the Treatment Phase (n=25).

Table 2: Efficacy Results (Study #C-96-011)

1-implant treatment group	n	# cases	%	Exact 95% CI (Binomial)
Castrate by Week 4	27	27	100.0%	(89.5, 100.0)
Testosterone Escape	27	0	0.0	(0.0, 10.5)
Acute-on-Chronic Phenomenon	25	0	0.0	(0.0, 11.3)

Source: Vol. 1.68, Final Report, Section 7.4

The applicant concluded that the 1-implant Viadur™ treatment dose effectively suppressed serum T concentrations below the castrate threshold by 4 weeks of treatment and maintained that suppression throughout the remainder of the Treatment Phase. These results support that conclusion. The applicant also reported that none of the patients experienced the acute-on-chronic phenomenon after reimplantation. It is important to note that having zero cases observed in the 25 patients in this study does not necessarily imply that none will be observed in actual clinical use. This will be discussed further in the combined analysis.

Subgroup Analyses

In this study, randomization to the two treatment groups was stratified based on 3 strata defined by disease status and previous treatment modalities. The applicant supplied subgroup analyses by strata for each of the two treatment groups. The results are consistent across all strata, and no between-group comparisons are made. No further statistical analyses are necessary for these subgroups. The by-strata results are not included in the conclusions reported in the label, which is appropriate.

STUDY #C-97-010

Study #C-97-010 was an open-label, multicenter, single-arm study. All subjects received the 1-implant Viadur™ treatment dose during the 1-year Treatment Phase and the 1-year Safety Extension Phase. All subjects were males with advanced prostate cancer and baseline serum T level ≥ 150 ng/dL. A total of 80 subjects were enrolled at 19 centers in the U.S.

Table 3 shows the efficacy results for study #C-97-010. The denominator used in each calculation (n) is the appropriate ITT patient population. Specifically, for the Castrate by Week 4 and Testosterone Escape variables, the ITT population is all patients who received an implant (n=80). For the Acute-on-Chronic variable, the ITT population is all subjects who received a replacement implant after completion of the Treatment Phase (n=70).

Table 3: Efficacy Results (Study #C-97-010)

1-implant treatment group	n	# cases	%	Exact 95% CI (Binomial)
Castrate by Week 4	80	79	98.8%	(93.2, 100.0)
Testosterone Escape	80	0	0.0	(0.0, 3.7)
Acute-on-Chronic Phenomenon	70	0	0.0	(0.0, 4.2)

Source: Vol. 1.84, Final Report, Section 7.4

Only one subject (No. 605) did not achieve serum T concentration below the castrate threshold by Week 4 on treatment. The applicant concluded that, after 4 weeks on treatment, the 1-implant Viadur™ dose effectively suppressed T concentrations below the castrate threshold and maintained that suppression throughout the remainder of the Treatment Phase. These results support that conclusion. As mentioned in the previous section, it is important to note that having zero cases of the acute-on-chronic phenomenon observed in the 70 patients in this study does not necessarily imply that none will be observed in actual clinical use. This will be discussed further in the combined analysis.

Combined Results

The designs of studies C-96-010 and C-97-010 were the same with respect to patient population, treatment regimen, and variable measurement. Therefore it is appropriate to combine the results for an overall estimate of the efficacy and particularly the safety issue (acute-on-chronic phenomenon). Table 4 presents the combined results for the 1-implant treatment groups from the two clinical studies. These indicate that the Viadur™ Leuprolide Implant was effective in suppressing serum testosterone concentration below the castrate threshold by Week 4 and maintaining suppression through the 12-month Treatment Phase (no escapes).

None of the patients experienced the acute-on-chronic phenomenon after insertion of a replacement implant during the Safety Extension Phase. As previously noted, this does not imply that the true incidence rate is zero. The 95% Exact 2-sided Confidence Interval indicates that, with 95% confidence, the true incidence rate may be up to 3.1%.

Table 4: Combined Efficacy Results (Studies #C-96-011 & #C-97-010)

1-implant treatment group	n	# cases	%	Exact 95% CI (Binomial)
Castrate by Week 4	107	106	99.1%	(94.9, 100.0)
Testosterone Escape	107	0	0.0	(0.0, 2.8)
Acute-on-Chronic Phenomenon	95	0	0.0	(0.0, 3.1)

Label Comments

The primary endpoints in both clinical studies were defined by serum testosterone (T) concentration level. Therefore the clinical study results reported in the label should be limited to the serum T results. Other laboratory or clinical measures should not be included in the label.

The applicant has included statements regarding change in serum PSA level in the Clinical Studies section of the proposed label. The wording implies that this is an additional benefit of treatment, along with testosterone changes. The change in serum PSA was not planned as a primary efficacy variable in the protocols. Therefore, information regarding the change in PSA during treatment should not be included in the label unless supported by an additional study planned specifically to investigate the relationship between PSA and the efficacy of Viadur™ Leuprolide Implant for this indication.

Summary

The results indicate that the Viadur™ Leuprolide Implant was effective in suppressing serum testosterone concentration below the castrate threshold by Week 4 and maintaining suppression through the 12-month Treatment Phase (no escapes). None of the patients experienced the acute-on-chronic phenomenon after insertion of a replacement implant during the Safety Extension Phase. However, this does not imply that the true incidence rate is zero. The 95% Exact 2-sided Confidence Interval indicates that, with 95% confidence, the true incidence rate for the acute-on-chronic phenomenon may be up to 3.1%.

The primary endpoints in both clinical studies were defined by serum testosterone (T) concentration level. Therefore the clinical study results reported in the label should be limited to the serum T results. Other laboratory or clinical measures should not be included in the label. Specifically, information regarding the change in PSA during treatment should not be included in the label unless supported by an additional study planned specifically to investigate the relationship between PSA and the efficacy of Viadur™ Leuprolide Implant for this indication.

/S/

Katherine B Meaker, M.S.
Mathematical Statistician

Concur: Dr. Nevius SEN 2/7/00

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cc:
Archival NDA 21-088
HFD-580
HFD-580/NMarks, MMann, LRarick
HFD-580/JBest
HFD-715/ENevius, LKammerman, KMeaker, Division File, Chron

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Clinical Study Designs: DUROS™ Leuprolide Implant Studies in Patients with Prostate Cancer

Study Type	Study No.; Country; Investigators; PI	Study Design	Study Population (Sex; Diagnosis; Age; Race)	Treatment	Nominal Daily Dose (µg)	Mean Treatment Duration (weeks)	No. Of Patients	Final Report Location (Vols)
Dose-ranging, safety and efficacy	C-96-011; USA; 9 Investigators; Fowler	Multicenter, open-label, dose-ranging study of safety and efficacy	Male (n=51) patients with advanced prostate cancer; mean age 72.1 y (range, 55–85 y); Caucasian 70.6%, Black 25.5%, Other 4.0%	DUROS™ Leuprolide Implant, 65 mg			Enrolled: 51 Discontinued: 2 Completed Treatment Phase: 49 No reimplant: 1 Reimplanted: 48	1.68-1.83
				1 implant[a]	120	56.3 (range, 9–61)	1 implant: 27	
				2 implants[a]	240	60.1 (range, 52–62)	2 implants: 24	
Safety and efficacy	C-97-010; USA; 19 Investigators; Fowler	Multicenter, open-label study of safety and efficacy	Male (n=80) patients with prostate cancer; mean age 74.1 y (range, 50–88 y); Caucasian 75%, Black 22.5%, Hispanic 2.5%	DUROS™ Leuprolide Implant, 65 mg	120	49.1 (range, 8–53)	Enrolled: 80 Discontinued: 7 Completed Treatment Phase: 73 No reimplant: 3 Reimplanted: 70	1.84-1.98
				1 implant[b]				

PI=Principal Investigator; No.=number; y=year

[a] The Treatment Phase was a randomized assessment of one and two implants. All patients received one implant in the Safety Extension Phase.

[b] All patients received one implant in the Treatment and Safety Extension Phases.