(Continued)
Carcinogenicity Study: P-values from Trend Test
Sex: Female, Species: Mouse, Dose Levels Included: CTL LOW MED HIGH (0 120 850 6000)
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbol '*': P-value < 0.05

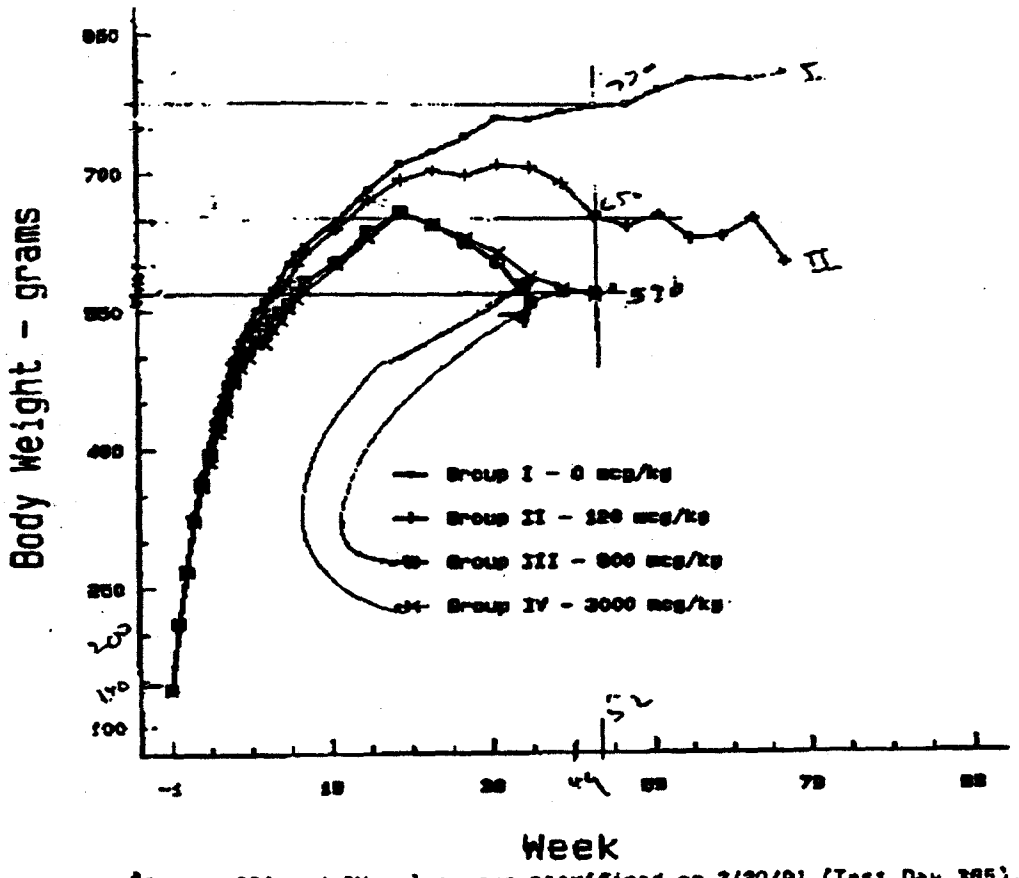
ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
[illegible]	([illegible])	HEMANGIO	(6)	MX	FA 76	1	1 0 0 0	1.0000	0.7631	0.7631
					FA 76	2	32 30 28 33			
					- Total	-	1 0 0 0			
[illegible]	([illegible])	U/ HEMAN	(23)	IN	IN 79-80	1	1 0 0 0	1.0000	0.7664	0.7664
					IN 79-80	2	25 25 26 28			
					- Total	-	1 0 0 0			
[illegible]	[illegible]	PARS DIS	(12)	FA	FA 49	1	0 0 1 0	0.6237	0.7679	0.7679
					FA 49	2	48 47 47 48			
					FA 76	1	0 1 0 0			
					FA 76	2	33 29 28 33			
					- Total	-	0 1 1 0			
[illegible]	[illegible] SK	FIBROSAR	(14)	IN	IN 79-80	1	1 0 0 0	1.0000	0.7664	0.7664
					IN 79-80	2	25 25 26 28			
					- Total	-	1 0 0 0			
UTERUS	(UT)	LEIOMYOM	(24)	IN	IN 0-52	1	1 0 0 0	1.0000	0.7201	0.7201
					IN 0-52	2	2 4 3 2			
					- Total	-	1 0 0 0			
UTERUS	(UT)	STROMAL	(25)	IN	IN 53-78	1	1 0 0 0	1.0000	0.7550	0.7550
					IN 53-78	2	20 21 21 20			
					- Total	-	1 0 0 0			
UTERUS	(UT)	ENDOMETR	(26)	IN	IN 53-78	1	0 1 0 0	0.7470	0.7394	0.7394
					IN 53-78	2	21 20 21 20			
					- Total	-	0 1 0 0			
UTERUS	(UT)	ENDOMETR	(27)	IN	IN 79-80	1	3 1 0 0	0.9969	0.9267	0.9267
					IN 79-80	2	23 24 26 28			
					- Total	-	3 1 0 0			
UTERUS	(UT)	HEMANGIO	(3)	IN	IN 79-80	1	1 1 1 0	0.8439	0.8527	0.8526
					IN 79-80	2	25 24 25 28			
					- Total	-	1 1 1 0			
UTERUS	(UT)	LEIOMYOS	(30)	IN	IN 53-78	1	1 0 0 0	1.0000	0.7550	0.7550
					IN 53-78	2	20 21 21 20			
					- Total	-	1 0 0 0			
UTERUS	(UT)	HEMANGIO	(6)	MX	IN 53-78	1	1 0 0 0	1.0000	0.9457	0.9457
					IN 53-78	2	16 21 21 20			
					FA 54	1	1 0 0 0			
					FA 54	2	46 46 47 48			
					FA 61	1	1 0 0 0			
					FA 61	2	44 43 44 45			
					FA 76	1	1 0 0 0			
					FA 76	2	32 30 28 33			
					FA 77	1	1 0 0 0			
					FA 77	2	29 27 26 32			
					- Total	-	5 0 0 0			

Figure A-5. Body-Weight of Male Rat (p. 38, Vol. 41)

F 1-1 BR-3371

Figure 1
A 24 Month Oncogenicity Study in the Rat
with Decapeptyl Microgranules via Intramuscular Injection

Group Mean Body Weights - Males



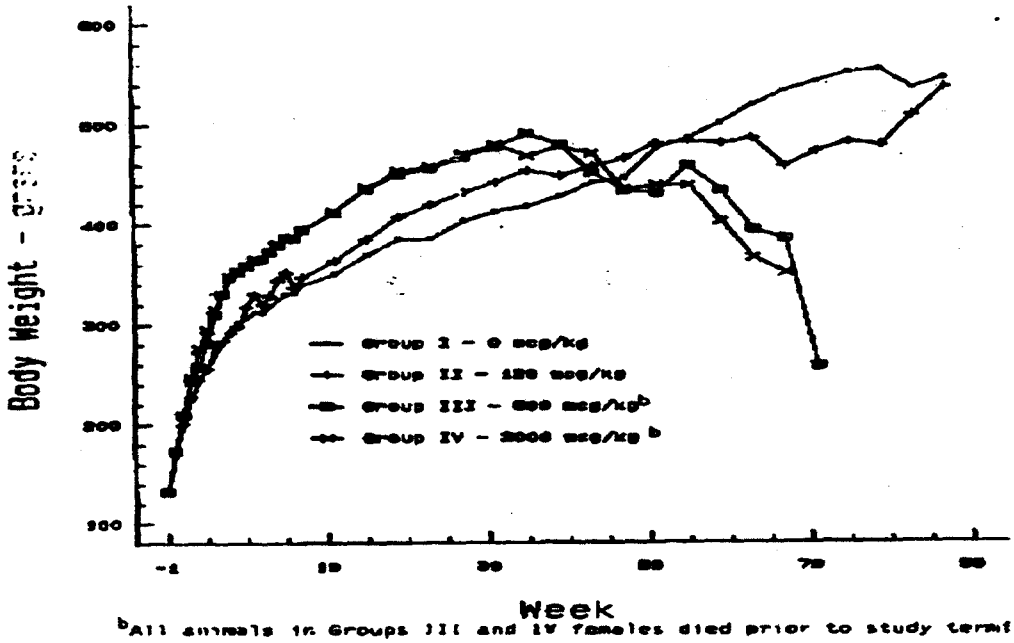
[a]Groups III and IV males were sacrificed on 2/20/91 (Test Day 385).

038

Figure A-6. Body-Weight of Female Rat (p. 39, Vol 41)

F 1-2 88-3371
Figure 1 (cont.)
A 24 Month Oncogenicity Study in the Rat
with Decapeptyl Microgranules via Intramuscular Injection

Group Mean Body Weights - Females



[b]All animals in Groups III and IV females died prior to study termination.

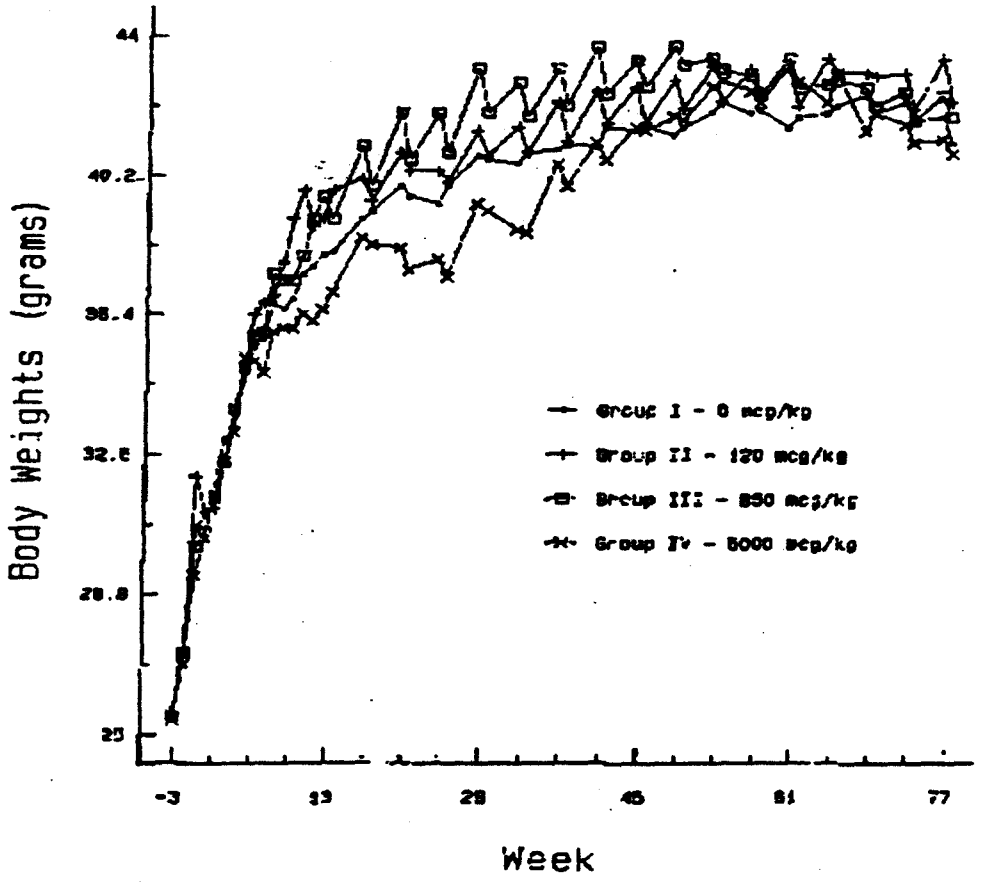
039

APPEARS THIS WAY
ON ORIGINAL

Figure A-7. Body-Weight of Male Mice (p. 29A, Vol 35)

F 1-1 88-3370
Figure 1
An Eighteen Month Oncogenicity Study in Mice
with Decapeptyl Microgranules via Intramuscular Injection

Mean Body Weight Values - Males



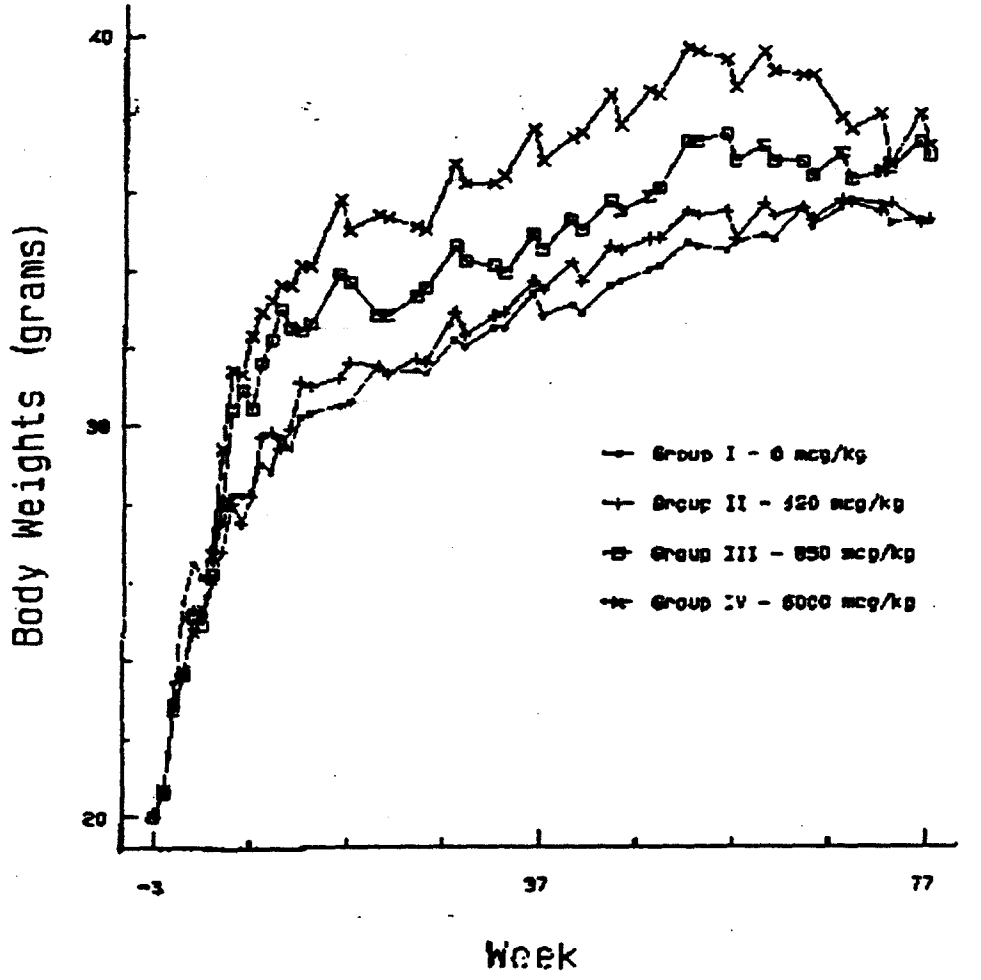
029A

Figure A-8. Body-Weight of Female Mice (p. 29B, Vol 35)

F 1-2 80-3370

Figure 1 (cont.)
An Eighteen Month Oncogenicity Study in Mice
with Decapeptyl Microgranules via Intramuscular Injection

Mean Body Weight Values - Females



References

Lin et al (1994). "Statistical Review and Evaluation of Animal Tumorigenicity Studies." Statistics in the Pharmaceutical Industry. Marcel Dekker, Inc. pp. 19-57.

Thomas et al (1976). "Trend and Homogeneity Analyses of Proportions and Life Table Data. Computers and Biomedical Research. pp. 373-81.

Peto et al (1980). "Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments. In Long-Term and Short-Term Screening Assays for Carcinogens: An Critical Appraisal, International Agency for Research on Cancer, Lyon, France. IARC Monographs Supplement 2. pp. 311-426.

Haseman, J. K. (1983). "A re-examination of false-positive rates for carcinogenesis studies." Fundamental and Applied Toxicology 3, pp. 334-9.

Haseman, J. K. (1984). "Issues in carcinogenicity testing: Dose selection." Fundamental and Applied Toxicology, Vol. 5. pp. 66-78.

Chu, Cueto and Ward (1981). "Factors in the evaluation of 200 national cancer institute carcinogen bioassay." Journal of Toxicology and environmental Health. Vol. 8, pp. 251-80.

D.F.

MAY 9 1994

CAC Executive Committee Final Report

Application: IND [redacted]
Division: HFD-510
Date: May 3, 1994
Reviewer: Krishan Raheja
Chairperson: Taylor 5/5/94
Members: Contrera, Jordan

The committee reviewed the results of the mouse carcinogenicity study on decapeptyl. The study design and dose selection were planned with the concurrence of the review division and based on historical practice for this class of agents. The high dose was 100X the proposed human dose. The study conduct was considered acceptable. The non-neoplastic findings reported in mal and female reproductive tissues are characteristic of the drug class. No tumor were reported. The CAC-EC concurred with the division evaluation that the study findings were acceptable and negative.

cc:
[redacted] IND [redacted]
HFD-510/div file
/Jordan
/Raheja
HFD-502/CAC file

Statistical Review and Evaluation

NDA#: 20-715

MAY 19 2000

Applicant: Debio Recherche Pharmaceutique

Name of Drug: Trelstar (Triptorelin pamoate) for prostate cancer

Documents Reviewed: Volume 2.71

Medical Officer: Norman Marks, M.D., HFD-580

Background

The sponsor has submitted one randomized, controlled, multicenter trial comparing Trelstar (9 injections @3.75 mg) with Lupron (7.5 mg IM every 28 days) for castration in patients with advanced prostatic cancer. Castration was defined as a testosterone level of at most 1.735 nmol/L by month 1 with maintenance below this level from month 2 to month 9. A total of 285 patients were enrolled (N=141 Trelstar, N=144 Lupron). Four (4) patients were excluded from each group's ITT cohort, 7 of these 8 due to lack of testosterone levels at day 29.

Statistical Considerations and Results

The trial was designed as a non-inferiority trial with the object of showing that both the castration incidence and maintenance percentages of the Trelstar group were no more than 10% (absolute) less than those of the Lupron group (power=90% using a one-sided 95% confidence interval). Exact binomial one-sided and two-sided 95% confidence intervals were used to compare the difference in percentages of castration, and standard errors from PROC LIFETEST were used to construct a confidence interval for the difference between the percentages of maintenance of castration using Kaplan-Meier estimates from month 2 to month 9.

Table 1 from the sponsor's submission displays the results for castration at 29 and 57 days. Note that the confidence interval for the difference between castration proportions (Trelstar-Lupron) in the ITT population at 29 days (-15.7%:-1.4%) includes the case in which Trelstar's castration effect would be 10% less than Lupron's.

Table 2 from the sponsor's submission displays the results for maintenance of castration at month 9. The difference between proportions maintaining castration (Trelstar-Lupron= 96.2%-91.2%) is in favor of Trelstar and the confidence interval (-0.7%:10.9%) excludes the case in which Trelstar is 10% worse. Dr. Mann requested a "worst case" analysis in which "missing" observations were taken to be failures in the Trelstar group and successes (through 9 months) in the Lupron group. Using crude percentages, the large-sample confidence interval for the Trelstar-Lupron difference is (-15.5%:0.5%) which includes the case in which Trelstar is 10 % worse than Lupron.

Comments

Dr. Mann has indicated that the lower castration incidence at 29 days on Trelsatr is not crucially important to approval. She is more concerned with the performance in *maintaining* castration once it has occurred. Those figures are favorable to Trelstar, while the worst case scenario does not guarantee a positive evaluation of Trelstar. Both Dr. Mann and Dr. Marks have reviewed patients missing to follow-up and patients designated as treatment failures; they feel that Trelstar is approvable. No further statistical issues were involved in this supplement's evaluation.

/S/

David Hoberman, Ph.D.

Concur: Dr. Kammerman /S/ 5/18/00

Dr. Nevius /S/ 5/17/0

cc:
Arch NDA# 20-715
HFD-580
HFD-580/NMarks, MMann, DShames, JBest
HFD-715/DHoberman, DOB2, Chron

TABLE 1

Achievement of castration - Day 29

Achievement of castration

	Triptorelin pamoate		Leuprolide acetate	
	Day 29	Day 57	Day 29	Day 57
PP population				
Proportion	123/135 (91.1%)	126/129 (97.7)	136/137 (99.3%)	131/135 (97.0%)
Point Estimate			-8.2%	Not applicable
Two-sided 95% CI			(-15.9; -1.4)	Not applicable
One-sided 95% CI			-14.9	Not applicable
ITT population				
Proportion	125/137 (91.2%)	128/131 (97.7%)	139/140 (99.3%)	135/139 (97.1)
Point Estimate			-8.0%	Not applicable
Two-sided 95% CI			(-15.7%; -1.4%)	Not applicable
One-sided 95% CI			-14.8%	Not applicable

Point estimate and CIs for the difference "triptorelin pamoate – leuprolide acetate"

TABLE 2

Cumulative maintenance of castration levels - Survival analysis
ITT Population

reatment group	Assessment	Month 9 (Day 253)
		n
elin pamoate	Failed	5
	Censored	132
	Total	137
Product limit survival estimate at Month 9	Maintenance rate	0.9622 (96.2%)
	Failure rate	0.0378 (3.8%)
	Standard error	0.0166 (1.7%)
euprolide acetate	Failed	12
	Censored	128
	Total	140
Product limit survival estimate at Month 9	Maintenance rate	0.9115 (91.2%)
	Failure rate	0.0885 (8.9%)
	Standard error	0.0244 (2.4%)
fference in maintenance of castration levels		
p-value (Log-Rank test)		0.0923
Point estimate[a]		0.0507 (5.1%)
Standard error for difference in maintenance rates[a]		0.0295 (3.0%)
95% confidence interval (two-sided)		(-0.0071 ; 0.1085) (-0.7% ; 10.9%)
Lower limit of 95% confidence interval (one-sided)		0.0022 (0.2%)

riptorelin pamoate - leuprolide acetate"

STATISTICAL REVIEW AND EVALUATION

MAY 31 1997

NDA #: 20-715/ Drug Class 1S

APPLICANT: Debio R. P., Switzerland

NAME OF DRUG: Decapeptyl Depot 3.75 mg
(triptorelin pamoate for depot suspension)

INDICATION: Palliative Treatment of Advanced Carcinoma of the Prostate

DOCUMENTS REVIEWED: Volumes 1.1, 1.87 thru 1.102

MEDICAL REVIEWER: Daniel Shames, MD (HFD-580).

This review is arranged in five sections. Section I gives a brief introduction of the three studies under this submission. The sponsor's efficacy results and conclusions for individual studies as well as "pooled" studies are briefly described in Section II. Section III contains statistical analyses performed at the request of the medical reviewer. This reviewer's evaluation of these studies is contained in Section IV. Section V contains this reviewer's conclusions that may be conveyed to the sponsor.

I. INTRODUCTION

The sponsor submitted three multicenter long term (24 months) controlled clinical studies:

- o Parmar Study (914CL14P)
- o Botto Study (914CL17E)
- o De Sy Study (914CL7P)

as their core studies in support of their NDA comparing Decapeptyl 3.75 mg (one IM injection every four weeks) to bilateral orchiectomy for the treatment of advanced prostate cancer.

In the Parmar Study, 125 patients (76 in Decapeptyl Group and 49 in the Orchiectomy Group) were enrolled in 6 centers in the United Kingdom. In the Botto Study, 80 patients (40 in Decapeptyl Group and 40 in the Orchiectomy Group) were enrolled in 20 centers in France. In the De Sy Study, 60 patients (44 in Decapeptyl Group and 16 in the Orchiectomy Group) were enrolled in 5 centers in Belgium.

In addition to the results of the individual studies, the data for these three studies were "pooled" through the Integrated Summaries of Effectiveness and Safety. These pooled studies compared the overall response and survival of 256 patients treated by Decapeptyl or orchiectomy.

II. SPONSOR'S EFFICACY RESULTS AND CONCLUSIONS

Parmar Study (914CL14P)

The principal investigator, Dr. Parmar, was responsible for the conduct of the study: The study was initiated on February 4, 1984 and was completed on September 15, 1989.

Study Objective

The objective of the study was to evaluate the efficacy and safety of a sustained release formulation of D-Trp-6-LHRH (Decapeptyl) versus "orchiectomy" in patients with prostate carcinoma.

Study Design

This was an open, comparative, parallel group, multicenter study. The sponsor stated (on page 027, vol. 1.88) that since no randomization codes appeared to be available, this study could not strictly speaking be called "randomized". Patients were assigned to receive either "injection" (Decapeptyl) or "surgery" (orchiectomy). Since the trial involved comparing the benefits of a surgical procedure (orchiectomy) versus hormonal injections with Decapeptyl, it was not possible to introduce any blinding to the treatment groups and both the patients and the investigators were always fully aware of the treatment that was administered.

Efficacy Variables

The following criteria for effectiveness were determined retrospectively. The sponsor stated (on page 036, vol. 1.88) that the choice of the primary and secondary efficacy variables was established at the pre-NDA meeting with the FDA on January 18, 1995 and is based on class labeling for LHRH agonists.

Primary Endpoints:

o Reduction in testosterone to castrate levels

≤ 1.735 nmol/L is the accepted standard testosterone level to achieve castration.

The level of ≤ 3.47 nmol/L was used by Dr. Parmar during the conduct of the trial and was based on the testosterone levels of normal females.

o Relief of Clinical Symptoms

Bone pain and urinary symptoms (obstruction, dysuria, nocturia, urgency, and hematuria).

Secondary Endpoints:

o Prostate-Specific Antigen (PSA)

PSA was not available as a prostate cancer marker at the time of this study. Therefore, prostatic acid phosphatase (PAP), also a marker for prostate cancer, was considered a secondary efficacy variable.

o Survival.

No statistical adjustments of type I error criteria were made for multiple comparisons because of the exploratory type of the analyses.

Disposition of Patients

The *Intent-To-Treat Analysis* included all patients who had the following information recorded on the Patient Identification" section of the Case Report Form at Visit 0: Randomization (Yes or No) - Orchiectomy or Decapeptyl. A total of 125 patients (76 Decapeptyl and 49 orchiectomy) were included in the ITT analysis (#33 was not assigned).

The *Audited Patient Analysis* included all audited patients who had retrievable source documentation and no major protocol violation. A total of 88 patients (51 Decapeptyl and 37 orchiectomy) were included in the analysis.

Table 3 on page 044 in vol. 1.88 provides an accounting of all patients who entered the study and summarizes the number of patients evaluated during each treatment period.

Baseline Comparisons

Baseline values for demographic variables for Intent-to-Treat and Audited Patients are summarized in the Tables 9 and 10 on page 054 in vol. 1.88. Baseline values for primary efficacy variables for Intent-to-Treat and Audited Patients are summarized in the Tables 14 and 15 on pages 064-065 in vol. 1.88.

There were no statistically significant differences between treatment groups in either baseline testosterone levels or in the number of patients with testosterone values above castration levels in either data set (Intent-to-Treat and Audited Patients).

Efficacy Results

Primary Endpoints:

o Reduction in testosterone to castrate levels

A higher percentage of patients in the Decapeptyl Group were at castration level at baseline than in the Orchiectomy Group although the difference was not statistically significant (see Tables 22 and 23 on pages 072-075 in vol. 1.88) for both datasets (Intent-to-Treat and Audited Patients). For intent-to-treat dataset, percentage of patients that were at castration level at baseline were 10.9% for Decapeptyl and 2.5% for Orchiectomy group whereas for audited patients dataset, percentages were 6.4% for Decapeptyl and 3.0% for Orchiectomy.

The reduction in testosterone to castration levels, according to the sponsor's analysis, was similar in both treatment groups (that is, the null hypothesis of equality was not rejected) for various time points except at Month 9. For Intent-To-Treat patients, the percentage of patients at or under the castration level was higher in Decapeptyl Group than in the Orchiectomy Group (Table 22 in Vol. 1.88), but the difference was not statistically significant. Statistically significant difference was achieved at Month 9 ($p=0.043$). For the Audited Patients, the percentage of patients at or under the castration level was higher in Decapeptyl Group than in the Orchiectomy Group (Table 23 in Vol. 1.88) for all months except for Month 6. Statistically significant difference was achieved at Month 9 ($p=0.007$).

o Relief of Clinical Symptoms

The percentage of Intent-To-Treat Patients who experienced a decrease in bone pain severity was higher during the time interval (Month 1 to 24) in the Decapeptyl group than in the Orchiectomy group with the statistical analysis showing significant result at some timepoints (see Table 24 on page 077 in vol. 1.88). The results were similar for Audited Patients at 6 and 24 Months (see Table 25 on page 078 in vol. 1.88).

Fewer than half of the patients in this study experienced obstruction, dysuria, urgency or haematuria at baseline; the most prevalent symptom was nocturia (see Tables 26 and 27 on pages 080 to 089 in vol. 1.88). For most patients in both treatment groups, urinary symptoms remained unchanged during the treatment interval. The percentage of patients in whom nocturia disappeared was higher in Decapeptyl Group than the Orchiectomy Group at most timepoints, but the difference between treatments did not reach statistical significance except in the Audited Patients at two timepoints (see Table 27 in vol. 1.88). The reduction in urinary symptoms, according to the sponsor's analysis, was similar in both treatment groups.

Secondary Endpoints:

o Prostate-Specific Antigen (PSA)

PSA was not available as a prostate cancer marker at the time of this study. Therefore, prostatic acid phosphatase (PAP), also a marker for prostate cancer, was considered a secondary efficacy variable.
None of the between-treatment comparisons of PAP levels during the study were statistically significant (see Tables 28 and 29 on pages 091 and 092 in vol. 1.88)

o Survival

Of the 125 patients (76 in the Decapeptyl Group and 49 in the Orchiectomy Group) considered in the survival analysis during the 24-month period for the Intent-To-Treat population, 60 died (41[53.9%] in the Decapeptyl Group and 19 [38.8%] in the Orchiectomy Group). The Kaplan-Meier estimate of survival (alive at approximately 24 months) was 46.1% in the Decapeptyl Group and 59.0% in the Orchiectomy Group. The difference between the two survival rates was -12.9% in favor of Orchiectomy and the 95% confidence interval was (-31.0%, 5.1%). No statistically significant difference between treatment groups (p=0.2301) was detected by the log-rank test. See pages 446 to 450 in vol. 1.89.

Of the 88 patients (51 in the Decapeptyl Group and 37 in the Orchiectomy Group) considered in the survival analysis during the 24-month period for the Audited population, 33 died (22 [43.1%] in the Decapeptyl Group and 11 [29.7%] in the Orchiectomy Group). The Kaplan-Meier estimate of survival (alive at approximately 24 months) was 56.9% in the Decapeptyl Group and 69.6% in the Orchiectomy Group. The difference between the two survival rates was -12.7% in favor of Orchiectomy and the 95% confidence interval was (-33.0%, 7.5%). No statistically significant difference between treatment groups (p=0.2507) was detected by the log-rank test. See pages 036 to 039D in vol. 1.91.

Sponsor's Conclusions **-- Parmar Study (914CL14P)**

The sponsor stated that monthly intramuscular administration of the slow release preparation of Decapeptyl 3 mg suppressed testosterone secretion to an extent similar to that obtained after surgical orchiectomy. The sponsor further stated that the effectiveness of this suppression in treating advanced prostate cancer was confirmed by a reduction in the clinical symptoms for bone pain and urinary symptoms, which were comparable in both treatment groups. The sponsor finally stated that the monthly intramuscular injection of Decapeptyl was an effective and safe therapy for advanced prostate cancer.

Botto Study (914CL17E)

The principal investigator, Dr. H. Botto, was responsible for the conduct of the study. The study was initiated on September 17, 1983 and was completed on December 30, 1985.

Study Objective

The objective of the study was to compare the effects of treatment with Decapeptyl with Orchiectomy in patients with prostate cancer (stage C and D) who had not been previously treated.

Study Design

This was an open, comparative, parallel group, multicenter (20 centers) study. The sponsor stated (on page 035, vol. 1.93) that since no randomization codes appeared to be available, this study could not strictly speaking be called "randomized". Patients were assigned to receive either "injection" (Decapeptyl) or "surgery" (orchiectomy). Since the trial involved comparing the benefits of a surgical procedure (orchiectomy) versus hormonal injections with Decapeptyl, it was not possible to introduce any blinding to the treatment groups and both the patients and the investigators were always fully aware of the treatment that was administered.

Efficacy Variables

The following criteria for effectiveness were determined retrospectively. The sponsor stated (on page 043, vol. 1.93) that the choice of the primary and secondary efficacy variables was established at the pre-NDA meeting with the FDA on January 18, 1995 and is based on class labeling for LHRH agonists.

<u>Primary Endpoints:</u>

o Reduction in testosterone to castrate levels
($\leq$ 1.735 nmol/L, and also $\leq$ 3.47 nmol/L)

o Relief of Clinical Symptoms
- Bone pain
- Urinary symptoms (obstruction, dysuria, nocturia, urgency, and hematuria).

<u>Secondary Endpoints:</u>

o Reduction in prostatic acid phosphatase (PAP) to normal levels.
o Survival. Each patient was followed until death, to determine overall survival.

Disposition of Patients

Eighty patients were enrolled in the study. They were all considered in the Intent-To-Treat analysis (40 patients in each treatment group). The Audited Patients analysis was performed on 19 patients in the Decapeptyl Group and 30 patients in the Orchiectomy Group. The disposition of patients by visit and by center for both Intent-To-Treat and Audited Patients analysis are described in Tables 1 to 4 on pages 050 to 051 in vol. 1.93. Because the number of patients in each center was too small, no analysis was done for differences among centers.

Baseline Comparisons

Baseline values for demographic variables (age and weight) for Intent-to-Treat and Audited Patients are summarized in the Tables 9 and 10 on page 060 in vol. 1.93. There were no statistically significant differences between the two treatment groups with respect to age and weight.

Baseline values for primary efficacy variables for Intent-to-Treat and Audited Patients are summarized in the Tables 19 and 20 on pages 068-069 in vol. 1.93. There were no statistically significant differences between treatment groups in either baseline testosterone levels or in the number of patient with testosterone values above castration levels in either data set.

Efficacy Results

Primary Endpoints:

o Reduction in testosterone to castrate levels (Intent-To-Treat Analysis)

Castration level of ≤ 1.735 nmol/L:

24 patients (68.6%) in Orchiectomy Group and 5 patients (12.8%) in Decapeptyl Group were below this castration level at Day 15 (p=0.001, Chisquare test), see Table 23 on page 073 in vol. 1.93. At all subsequent timepoints, the differences between the two treatment groups were not significant.

Castration level of ≤ 3.47 nmol/L:

24 patients (72.7%) in Orchiectomy Group and 10 patients (25.6%) in Decapeptyl Group were below this castration level at Day 15 (p=0.001, Chisquare test), see Table 23 on page 074 in vol. 1.93. At all subsequent timepoints, the differences between the two treatment groups were not significant.

o Reduction in testosterone to castrate levels (Audited Patients Analysis)

Castration level of ≤ 1.735 nmol/L:

18 patients (66.7%) in Orchiectomy Group and 3 patients (16.7%) in Decapeptyl Group were below this castration level at Day 15 (p=0.001, Chisquare test), see Table 25 on page 076 in vol. 1.93. At all subsequent timepoints, the differences between the two treatment groups were not significant.

Castration level of ≤ 3.47 nmol/L:

19 patients (70.4%) in Orchiectomy Group and 5 patients (27.8%) in Decapeptyl Group were below this castration level at Day 15 (p=0.005, Chisquare test), see Table 25 on page 077 in vol. 1.93. At all subsequent timepoints, the differences between the two treatment groups were not significant.

o Relief of Clinical Symptoms

In the Intent-To-Treat Analysis, a higher percentage of patients in the Decapeptyl group than in the Orchiectomy group reported a decrease in bone-pain from baseline at all visits, but the differences between the treatment groups were not statistically significant (see Table 27 on page 080 in vol. 1.93). The Audited Patients Analysis showed an almost identical bone-pain profile, with slight, but non-significant, differences at Month 1 and Month 9 (see Table 28 on page 081 in vol. 1.93).

Except for a statistically significant decrease in urinary symptoms at Month 21 (p=0.036) for the Decapeptyl Group of the Intent-To-Treat Analysis, no significant differences between the two treatment groups were observed throughout the entire study period, although the trend was for lower incidence in the Decapeptyl Group than in the Orchiectomy Group (see Tables 29 and 30 on pages 083-084 in vol. 1.93).

Secondary Endpoints:

o Reduction in prostatic acid phosphatase (PAP) to normal levels

For both the Intent-To-Treat Analysis and the Audited Patients Analysis comparison of the average percentage variation from baseline of PAP showed no significant differences between the two treatment groups (see pages 234-235 in vol. 1.93).

o Survival

Of the 80 patients (40 in the Decapeptyl Group and 40 in the Orchiectomy Group) considered in the survival analysis during the 24-month period for the Intent-To-Treat population, 16 died (6 [15.0%] in the Decapeptyl Group and 10 [25.0%] in the Orchiectomy Group). The Kaplan-Meier estimate of survival for approximately 24

months was 69.7% in the Decapeptyl Group and 69.6% in the Orchiectomy Group. The difference between the two survival rates was 0.1% and the 95% confidence interval was (-27.2%, 27.5%). No statistically significant difference between treatment groups (p=0.6293) was detected by the log-rank test. See pages 251 to 258 in vol. 1.93.

Of the 49 patients (19 in the Decapeptyl Group and 30 in the Orchiectomy Group) considered in the overall survival analysis for the Audited population, 11 died (7 [36.8%] in the Decapeptyl Group and 4 [13.3%] in the Orchiectomy Group). The Kaplan-Meier estimate of survival for approximately 24 months was 65.5% in the Decapeptyl Group and 72.3% in the Orchiectomy Group. The difference between the two survival rates was -6.8% and the 95% confidence interval was (-35.7%, 22.0%). No statistically significant difference between treatment groups (p=0.7028) was detected by the log-rank test. See pages 333 to 339 in vol. 1.93.

Sponsor's Conclusions **– Botto Study (914CL17E)**

The sponsor stated that monthly administration of the sustained release formulation of Decapeptyl suppressed testosterone to castration levels to an extent similar to surgical orchiectomy. The sponsor further stated that there was relief of the clinical symptoms of advanced prostate cancer, namely bone pain and urinary symptoms, comparably in both treatment groups. The sponsor finally stated that the results of this study indicated that Decapeptyl was safe and effective in treating patients with advanced prostate cancer.

De Sy Study (914CL7P)

The principal investigator, Dr. De Sy, was responsible for the conduct of the study. The study was initiated on March 2, 1984 and was completed on December 5, 1986.

Study Objective

The main objective of the study was to evaluate the safety and efficacy of a sustained release formulation of D-Trp-6-LHRH (Decapeptyl) compared to bilateral orchiectomy in patients with advanced prostate carcinoma who have not been previously treated.

Study Design

This clinical trial was an open, randomized, comparative, parallel group, multicenter study. Five study centers participated and each of these sites enrolled a minimum of 4 and a maximum of 16 patients during the first six months of the trial. Afterwards, no more patients were admitted into the study. The sponsor stated (on page 012, vol. 1.95) that the randomization scheme and codes were to be found in Appendix V (pages 281-288 in vol. 1.95). The randomization scheme was unbalanced in a ratio of 2:1 for Decapeptyl:Orchiectomy.

Efficacy Variables

The following criteria for effectiveness were determined retrospectively. The sponsor stated (on page 018, vol. 1.95) that the choice of the primary and secondary efficacy variables was established at the pre-NDA meeting with the FDA on January 18, 1995 and is based on class labeling for LHRH agonists.

Primary Endpoints:

o Reduction in testosterone to castrate levels
(≤ 1.735 nmol/L, and also ≤ 3.47 nmol/L)

o Relief of Clinical Symptoms
- Bone pain
- Urinary symptoms (dysuria, pollakiuria, bladder tension, occasional need for catheter, need for permanent catheter, and hematuria).

Secondary Endpoints:

o Reduction in prostatic acid phosphatase (PAP) to normal levels.

o Survival. Each patient was followed until death, to determine overall survival. In case of lost to follow-up, the last available date when the patient was seen was used as a right-censored value.

Disposition of Patients

Sixty patients were enrolled in the study. They were all considered in the Intent-To-Treat analysis (44 patients enrolled in the Decapeptyl Group and 16 in the Orchiectomy Group). Only 8 (13.3%) patients completed the study. The Audited Patients Analysis included all patients for whom source documentation could be retrieved. Fourteen patients (11 in the Decapeptyl Group and 3 in the Orchiectomy Group) were excluded from this analysis for the reasons listed in Table 7 on page 030 in vol. 1.95. Thus, the Audited Patients Analysis was conducted on a total of 46 patients (33 from the Decapeptyl Group and 13 from the Orchiectomy Group). The disposition of patients by visit and by center for both Intent-To-Treat and Audited Patients analysis are described in Tables 1 to 4 on pages 024 to 025 in vol. 1.95.

Baseline Comparisons

All baseline variables related to prostate cancer, including demographic variables (age, weight and height) and disease factors (including disease stage, performance status, bone pain, prior anti-tumor treatment, pain and analgesic intake, urinary symptoms, testosterone level, and normality of prostatic acid phosphatase) are summarized by treatment in Tables 8, 10, 12, 13, 16 for Intent-To-Treat patients and in Tables 9, 11, 14, 15, 17 for the Audited patients on pages 033-042 in vol. 1.95.

Table 8 shows a comparison of the key demographic and baseline characteristics for the Intent-To-Treat population by treatment group. A comparison of Decapeptyl and Orchiectomy groups at baseline showed a statistically significant difference in height only ($p=0.0148$); the Decapeptyl group had a higher mean height. Table 9 shows a comparison of the key demographic and baseline characteristics for the Audited Patients population by treatment group. A comparison of Decapeptyl and Orchiectomy groups at baseline showed no statistically significant differences.

Baseline urinary symptoms, presented in Tables 10 and 11, were not different between treatment groups except for the Audited Patients Analysis in which the rerquirement for occasional catheter was lower in the Decapeptyl Group (4 out of 33, 12.1%) than in the Orchiectomy Group (5 out of 13, 38.5%); but the difference was not statistically significant.

Other clinical and paraclinical evaluations at baseline are found in Tables 12 to 15. None of the between-treatment comparisons showed any statistically significant differences.

Twenty-three (69.7%) patients in the Decapeptyl Group had normal PAP compared to 5 (38.5%) patients in the Orchiectomy Group ($p=0.051$, Table 16). A similar difference is found in the Audited Patients analysis for this parameter: 68.8% (22 out of 32) had normal PAP in the Decapeptyl Group versus 38.5% (5 out of 13) in the Orchiectomy Group, $p=0.060$ (Table 17).

The sponsor stated that the comparison of the main predictive factors did not reveal a significant result; therefore, no adjustment for covariates was done for the main efficacy analysis.

Efficacy Results

Primary Endpoints:

o Reduction in testosterone to castrate levels (Intent-To-Treat Analysis)

Table 18 on pages 045-046 in vol. 1.95 present the data for achievement of castration levels for the Intent-To-Treat population.

Castration level of ≤ 1.735 nmol/L:

10 patients (83.3%) in Orchiectomy Group and 3 patients (7.9%) in Decapeptyl Group were below this castration level at Day 7 ($p<0.001$, Chisquare test). 7 patients (70.0%) in Orchiectomy Group and 9 patients (24.3%) in Decapeptyl Group were below this castration level at Day 14 ($p=0.020$, Chisquare test). At all subsequent timepoints, the differences between the two treatment groups were not significant.

Castration level of ≤ 3.47 nmol/L:

11 patients (91.7%) in Orchiectomy Group and 9 patients (23.7%) in Decapeptyl Group were below this castration level at Day 7 ($p<0.001$, Chisquare test). 8 patients (80.0%) in Orchiectomy Group and 19 patients (52.8%) in Decapeptyl Group were below this castration level at Day 14 ($p=0.160$, Chisquare test). At all subsequent timepoints, the differences between the two treatment groups were not significant.

o Reduction in testosterone to castrate levels (Audited Patients Analysis)

Table 19 on pages 047-048 in vol. 1.95 present the data for achievement of castration levels for the Audited Patients population.

Castration level of ≤ 1.735 nmol/L:

7 patients (77.8%) in Orchiectomy Group and 2 patients (6.7%) in Decapeptyl Group were below this castration level at Day 7 ($p<0.001$, Chisquare test). 4 patients (57.1%) in Orchiectomy Group and 6 patients (20.7%) in Decapeptyl Group were below this castration level at Day 14 ($p=0.076$, Chisquare test). At all

subsequent timepoints, the differences between the two treatment groups were not significant.

Castration level of ≤ 3.47 nmol/L:

8 patients (88.9%) in Orchiectomy Group and 8 patients (26.7%) in Decapeptyl Group were below this castration level at Day 7 (p=0.001, Chisquare test). At all subsequent timepoints, the differences between the two treatment groups were not significant.

o Relief of Clinical Symptoms

The sponsor stated that, except for four borderline cases, for both the Intent-To-Treat and Audited Patients Analyses, there were no significant differences found between the Decapeptyl and Orchiectomy group patients regarding the evolution of pain severity from baseline after any treatment period (see Tables 21 and 22 on pages 051-052 in vol. 1.95).

Of the Intent-To-Treat patients, dysuria decreased at Month 1 in 43.2% of the Decapeptyl Group (16 patients) versus 13.3% in Orchiectomy Group (2 patients), p=0.042 (Table 23 on pages 053-058 in vol. 1.95). Of the Audited patients, dysuria decreased at Month 1 in 51.6% of the Decapeptyl Group (16 patients) versus 16.7% in Orchiectomy Group (2 patients), p=0.039 (Table 24 on pages 059-064 in vol. 1.95). A higher percentage of Orchiectomy patients required occasional use of a catheter at 1 and 2 months (p=0.040 and 0.047 respectively) in Audited patients.

Neither patient population analyses (Intent-To-Treat or Audited Patients) showed any other significant differences in the change from baseline between the two treatment groups at the other time points for any of the six urinary symptoms (dysuria, pollakiuria, bladder tension, occasional need for catheter, need for permanent catheter and hematuria). See Tables 23 and 24 on pages 053-064 in vol. 1.95.

Secondary Endpoints:

o Reduction in prostatic acid phosphatase (PAP) to normal levels

No significant treatment-related differences were found between the Decapeptyl and Orchiectomy Groups after any treatment period with respect to reversion of prostatic acid phosphatase to normality for either efficacy analyses (See Table 25 on pages 066-067 in vol. 1.95).

o Survival

Of the 60 patients (44 in the Decapeptyl Group and 16 in the Orchiectomy Group) considered in the survival analysis during the 24-month period for the Intent-To-Treat

population, 8 died (6 [13.6%] in the Decapeptyl Group and 2 [12.5%] in the Orchiectomy Group). The Kaplan-Meier estimate of survival for approximately 24 months was 81.5% in the Decapeptyl Group and 76.9% in the Orchiectomy Group. The difference between the two survival rates was 4.6% and the 95% confidence interval was (-28.6%, 37.7%). No statistically significant difference between treatment groups (p=0.7687) was detected by the log-rank test. See pages 382 to 382F in vol. 1.96.

Of the 46 patients (33 in the Decapeptyl Group and 13 in the Orchiectomy Group) considered in the survival analysis during the 24-month period for the Audited population, 8 died (6 [18.2%] in the Decapeptyl Group and 2 [15.4%] in the Orchiectomy Group). The Kaplan-Meier estimate of survival for approximately 24 months was 79.2% in the Decapeptyl Group and 75.8% in the Orchiectomy Group. The difference between the two survival rates was 3.5% and the 95% confidence interval was (-30.6%, 37.5%). No statistically significant difference between treatment groups (p=0.8328) was detected by the log-rank test. See pages 337 to 337F in vol. 1.97.

***Sponsor's Conclusions* – De Sy Study (914CL7P)**

The sponsor stated that monthly administration of the sustained release formulation of Decapeptyl suppressed testosterone to castration levels to an extent similar to surgical orchiectomy after 21 days of treatment and onwards. The sponsor further stated that this suppression was accompanied by alleviations of the clinical symptoms of advanced prostate cancer, namely bone pain and urinary symptoms, in a comparable manner in the two treatment groups. The sponsor finally stated that the results of this study indicated that Decapeptyl was safe and effective as Orchiectomy in treating patients with advanced prostate cancer.

Sponsor's Integrated Results of These Studies

The sponsor chose to combine the data by just pooling the patients together from all the three studies as if the patients came from one study. The sponsor stated that (on page 006, vol. 1.100) the integrated results of these studies (based on statistical analysis of the intent-to-treat population) showed that the monthly IM administration of sustained-release Decapeptyl 3.75 mg reduced serum testosterone levels in patients with advanced prostate cancer to an extent similar to that achieved after surgical orchiectomy: 73% of patients in the Decapeptyl group and 74% of patients in the Orchiectomy group were at the castration levels of testosterone at Month 1; 75% of patients in the Decapeptyl group and 80% of patients in the Orchiectomy group were at the castration levels of testosterone at Month 24. The sponsor further stated that the effectiveness of this reduction in testosterone was confirmed by a relief of clinical symptoms which were comparable for Decapeptyl treatment and orchiectomy.

III. STATISTICAL ANALYSES PERFORMED AT THE REQUEST OF THE MEDICAL REVIEWER

In order to evaluate the efficacy of Decapeptyl as compared to Orchiectomy, the medical reviewer requested a failure/success analysis of the intent-to-treat data.

A patient was defined to be a *failure* if one of the following happened:

> *Failure of 1st kind:* At month 1, testosterone level was above the castration level (namely, 1.735 nmol/L);
>
> *Failure of 2nd kind:* At month 1, testosterone level was below the castration level (namely, 1.735 nmol/L) but it went above at least once during the treatment period. The medical reviewer called it an *escape*.

A patient was a *success* if he was not a failure.

Parmar Study (9:14CL14P)

The following Table gives the number and percentage of the patients in the two treatment groups for this study for the three categories: success, failure of 1st kind and failure of 2nd kind.

Treatment	Success	Failure of 1st Kind	Failure of 2nd Kind	Total
Decapeptyl	20 (27.8%)	34 (47.2%)	18 (25.0%)	72 (100%)
Orchiectomy	8 (18.2%)	26 (59.1%)	10 (22.7%)	44 (100%)
Total	28	60	28	116

The following Table is obtained from the above table by combining the two kinds of failures into one category: failure.

Treatment	Success	Failure	Total
Decapeptyl	20 (27.8%)	52 (72.2%)	72 (100%)
Orchiectomy	8 (18.2%)	36 (81.8%)	44 (100%)
Total	28	88	116

The 95% CI for the difference in success rates for the two treatments (Decapeptyl minus Orchiectomy) is (-8.8%, 27.9%). This study favors Decapeptyl over Orchiectomy.

Botto Study (914CL17E)

The following Table gives the number and percentage of the patients in the two treatment groups for this study for the three categories.

Treatment	Success	Failure of 1st Kind	Failure of 2nd Kind	Total
Decapeptyl	19 (47.5%)	13 (32.5%)	8 (20.0%)	40 (100%)
Orchiectomy	29 (74.4%)	4 (10.3%)	6 (15.3%)	39 (100%)
Total	48	17	14	79

The following Table is obtained from the above table by combining the two kinds of failures into one category: failure.

Treatment	Success	Failure	Total
Decapeptyl	19 (47.5%)	21 (52.5%0	40 (100%)
Orchiectomy	29 (74.4%)	10 (25.6%)	39 (100%)
Total	48	31	79

The 95% CI for the difference in success rates for the two treatments (Decapeptyl minus Orchiectomy) is (-50.1%, -5.0%). This study favors Orchiectomy.

De Sy Study (914CL7P)

The following Table gives the number and percentage of the patients in the two treatment groups for this study for the three categories.

Treatment	Success	Failure of 1st Kind	Failure of 2nd Kind	Total
Decapeptyl	22 (52.4%)	9 (21.4%)	11 (26.2%)	42 (100%)
Orchiectomy	10 (66.7%)	2 (13.3%)	3 (20.0%)	15 (100%)
Total	32	11	14	57

The following Table is obtained from the above table by combining the two kinds of failures into one category: failure.

Treatment	Success	Failure	Total
Decapeptyl	22 (52.4%)	20 (47.6%)	42 (100%)
Orchiectomy	10 (66.7%)	5 (33.3%)	15 (100%)
Total	32	25	57

The 95% CI for the difference in success rates for the two treatments (Decapeptyl minus Orchiectomy) is (-48.1%, 16.0%). This study favors Orchiectomy.

IV. STATISTICAL REVIEWER'S EVALUATION

The applicant, Debio R.P.(Switzerland), submitted 3 multicenter long term (24 months) controlled clinical studies: Parmar Study (914CL14P), Botto Study (914CL17E) and De Sy Study (914CL7P) as their core studies in support of their NDA comparing Decapeptyl 3.75 mg (one IM injection every four weeks) to bilateral orchiectomy for the treatment of advanced prostate cancer. These studies were conducted from 1983 to 1986 under the sponsorship of Ipsen Beaufour International, Paris (France) and

Please note that in an active-control trial, one has to be very careful in testing the "correct" hypotheses. The applicant did not test the "correct" interval hypotheses. They tested the null hypothesis of equality.

Evaluation of Patient Discontinuations

The sponsor provided the following Table in a meeting with FDA (February 4, 1997). This Table shows a similar percentage of patient discontinuations in both the treatment groups.

Patient Discontinuations in Intent-to-Treat Analysis

	mo 0	mo 1	mo 3	mo 6	mo 9	mo 12	mo 24
Decapeptyl:							
— Total	160	157	151	140 (87%)	125 (78%)	100 (62%)	42 (26%)
— Died	0	2	6	12 (7%)	16 (10%)	23 (14%)	47 (29%)
Parmar	0	2	6	7	10	15	37
DeSy	0	0	0	3	4	4	5
Botto	0	0	0	2	2	4	5
— Other	0	1	3	8 (5%)	19 (12%)	37 (23%)	71 (44%)
Parmar	0	0	0	1	1	1	3
DeSy	0	1	3	6	10	13	32
Botto	0	0	0	1	8	23	35
Orchiectomy:							
—Total	105	103	94	89 (85%)	81 (77%)	59 (56%)	29 (28%)
—Died	0	2	6	9 (9%)	12 (11%)	16 (15%)	26 (25%)
Parmar	0	2	5	7	9	11	19
DeSy	0	0	0	1	1	1	2
Botto	0	0	1	1	2	4	5
—Other	0	0	5	7 (7%)	12 (11%)	30 (28%)	50 (48%)
Parmar	0	0	0	0	0	0	2
DeSy	0	0	3	5	5	6	13
Botto	0	0	2	2	7	24	35

Although a similar percentage of discontinuations is observed for the two treatment groups, this reviewer is concerned about the effects of large discontinuations on the evaluation of the efficacy of Decapeptyl in these studies. With large discontinuations (for example, in De Sy study, only 8 of the 60 patients completed the study), performing last-observation-carried-forward intent-to-treat analysis may be grossly misleading.

Evaluation of Validity and Accuracy of Data

This reviewer is concerned about the validity and accuracy of the data in these studies. In all three studies, there was no monitoring of investigators or of sites by the sponsor. Further, there were no central laboratories. In the Parmar and Botto studies, codes for randomization were not available. In the De Sy study, some patients in the Decapeptyl group had orchiectomy. A journal article reported 67 patients in the De Sy study whereas in this NDA the De Sy study had only 60 patients. These inadequacies and deficiencies raise serious questions about the quality of the data in this submission. The Division of Scientific Investigations also reported several problems about the quality of these trials.

Evaluation of Poolability of the Studies

In the opinion of this reviewer, these studies cannot be "pooled" together as there are several underlying differences among them. Some of the differences are listed below.

1. *Randomization:* Randomization codes for Parmar and Botto studies are not available. The sponsor stated that these studies could not be called "randomized." For the De Sy study, randomization codes are available and apparently randomization achieved comparability in baseline characteristics between the two treatment groups.
2. *Dosing Schedule:* Decapeptyl was administered according to different schedules during the first month to some or to all patients in these studies. In the Parmar study, it was given on days 1, 8 and 28 and every four weeks thereafter for up to 24 months; in the Botto study, patients received a dose of 100 μg per day for first seven days, 3 mg on day 8, 28 and every four weeks thereafter for up to 24 months; in the De Sy study, it was given on days 1 and 28 and thereafter once each month for up to 24 months.
3. *Measurements of Efficacy Variables:* Efficacy variables of testosterone, bone pain, urinary symptoms and PAP were not measured exactly in a similar fashion in all studies.
4. *Baseline Balance:* The Parmar study had baseline imbalance on five important variables.
5. *Sample Sizes:* Sample sizes are remarkably different for different studies. Large studies may influence overall results if the studies are pooled.
6. *Quality of the Trial:* These trials were conducted very poorly. DSI reported several problems about the quality of these trials.

7. *Homogeneity of Odds-Ratio:* Zelen's exact test of homogeneity of odds-ratio for the three 2x2 tables (Decapeptyl/Orchiectomy vs. Success/Failure) displayed in Section III of this review yields a p-value of 0.0364 indicating that these 2x2 tables should not be pooled.

The sponsor did not identify these facts at the Pre-NDA Meeting of June 16, 1994. Also, FDA did not anticipate these issues at that time either.

Evaluation of the Adequacy of the Active Control

In order to evaluate the adequacy of Orchiectomy as an active control, let us define "success" (see Section III of this review).

Success: A patient on a treatment (Decapeptyl or Orchiectomy) is a *success* if his testosterone level at month 1 is under the castration level of 1.735 nmol/L and stays under this level throughout the duration of the clinical trial, which is 24 months.

When a patient is orchiectomized, his testosterone level should be under the castration level of 1.735 nmol/L. That means, success rate for orchiectomized patients should be ideally 100%.

Let us examine success rates (see Section III of this review) for orchiectomized patients in these trials. In the Parmar Study, 44 patients were orchiectomized and 8 of them were successes. So, the success rate for orchiectomized patients in this study is 18.2%, which is far from the ideal 100%. In the Botto Study, 39 patients were orchiectomized and 29 of them were successes. So, the success rate for orchiectomized patients in this study is 74.4%, which is closer to the ideal 100%. In the De Sy Study, 15 patients were orchiectomized and 10 of them were successes. So, the success rate for orchiectomized patients in this study is 66.7%.

Clearly, based on the observed success rates, Orchiectomy is not an adequate active control in these trials.

Please note that if success rate for orchiectomy was low (that is, far from the ideal 100%), then it would be easier for the sponsor to demonstrate superiority of Decapeptyl over Orchiectomy. But, if success rate for orchiectomy was close to the ideal 100%, then it would be difficult for the sponsor to demonstrate superiority of Decapeptyl over Orchiectomy.

For example, in the Parmar Study, orchiectomy success rate is 18.2% which is closer to zero than the ideal rate of 100%. The 95% CI does not rule out Decapeptyl having a success rate as much as a 27.9% greater than that for Orchiectomy (see Section III of this review) or as much as a 8.8% smaller for orchiectomy.

In contrast, in the De Sy Study, orchiectomy success rate is 66.7% which is much closer to the ideal rate of 100%. The 95% CI does not rule out Decapeptyl having a success rate as much as a 16% greater than that for orchiectomy or as much as 48% worse than that for orchiectomy (see Section III of this review).

Similarly, in the Botto Study, the orchiectomy success rate is 74.4% which, compared with the Parmar study, is much closer to the ideal of 100%. The 95% CI does not rule out Decapeptyl having a success rate as much as a 5% smaller than that for orchiectomy or as much as 50% worse than that for orchiectomy (see Section III of this review).

In summary, the 95% CI for the Parmar Study favors Decapeptyl whereas the 95% CIs for the Botto and De Sy Studies favor Orchiectomy.

Evaluation of Survival through 24 Months

The following Table displays Kaplan-Meier survival estimates at 24 months for the two treatments for each study along with 95% CI for the difference in survival rates.

Study	Decapeptyl	Orchiectomy	95% CI for the difference
Parmar Study	46.1%	59.0%	(-31.0%, 5.1%)
Botto Study	69.7%	69.6%	(-27.2%, 27.5%)
De Sy Study	81.5%	76.9%	(-28.6%, 37.7%)

In the Parmar Study, patients in the Orchiectomy treatment group appeared to have better survival than Decapeptyl. The 95% CI for the difference does not rule out Orchiectomy having as much as 31.0% greater survival than Decapeptyl.

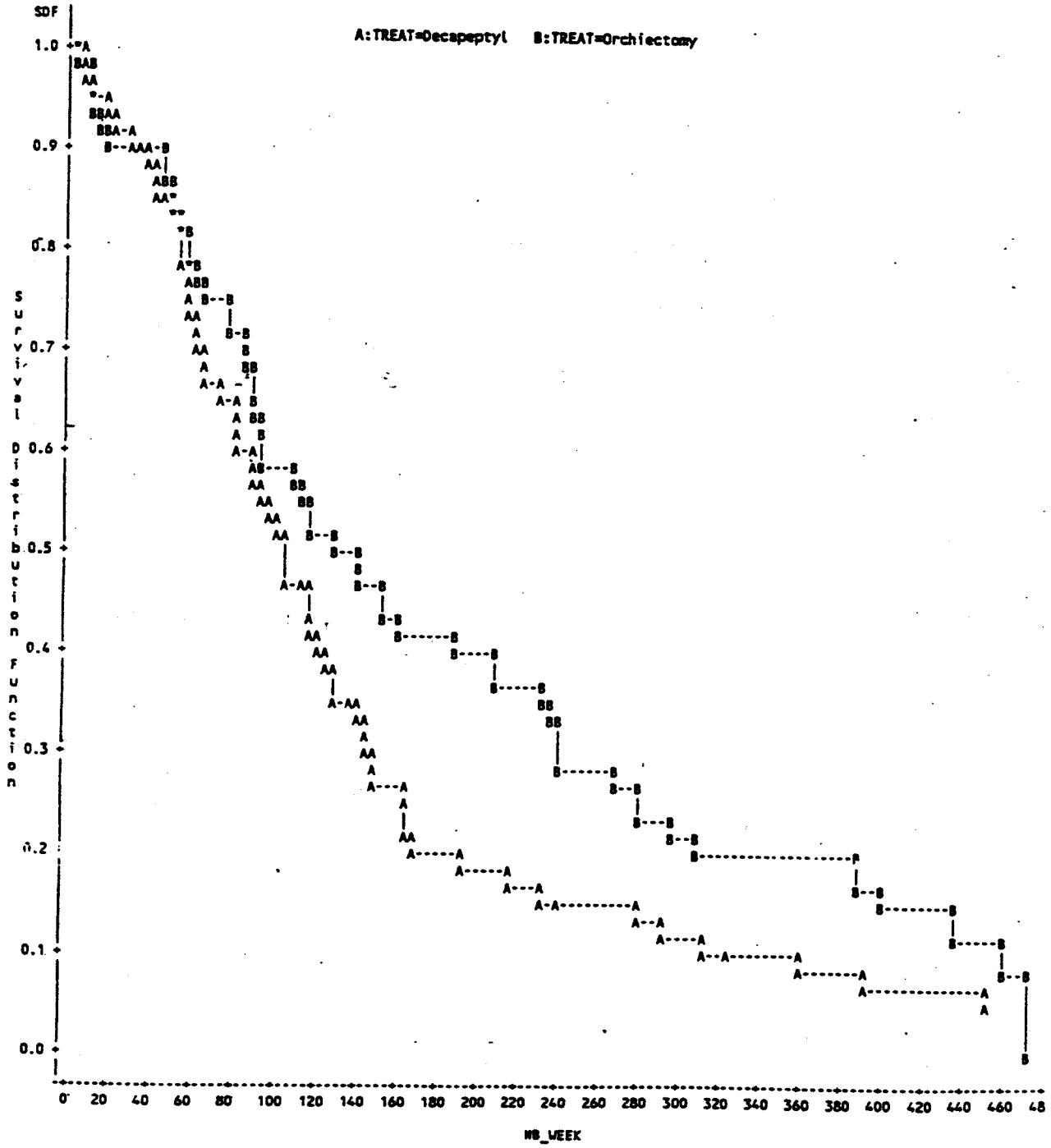
For the Botto Study, Orchiectomy appears to be similar to Decapeptyl in improving survival. The 95% CI for the difference does not rule out Orchiectomy having as much as 27.2% greater survival than Decapeptyl.

In the De Sy Study, patients in the Orchiectomy group appeared to have worse survival than Decapeptyl. But the 95% CI for the difference does not rule out Orchiectomy having as much as 28.6% greater survival than Decapeptyl.

For the Botto and De Sy Studies, 95% CIs are really wide here.

The Kaplan-Meier survival curves for the two treatment groups are displayed in the following figure for a period of approximately 9 years for the Parmar Study. Note that the top curve is for Orchiectomy and the bottom curve is for Decapeptyl. The maximum vertical difference between the two curves suggests that survival is not comparable between the two treatment groups. Orchiectomy is favored in the Parmar Study.

Kaplan-Meier Survival Curves
Survival Through 470 Weeks (Approximately 9 years)
Parmar Study



Evaluation of Individual Studies

Parmar Study (914CL14P)

The sponsor stated (on page 027, vol. 1.88) that since no randomization codes appeared to be available, this study could not strictly speaking be called "randomized." The sponsor provided the following Table in a meeting with FDA (February 4, 1997) and admitted a lack of randomization for this study because of baseline imbalance.

Baseline Variables with Statistically Significant Between-Treatment Comparisons - Parmar Study
(Intent-to-Treat Analysis)

	Decapeptyl	Orchiectomy	p-value
Observed Mets in Prior Prosate Biopsy			
No	55 (87.3%)	22 (68.8%)	0.029
Yes	8 (12.7%)	10 (31.3%)	
N	63	32	
Bone Pain			
No	40 (54.1%)	30 (71.4%)	0.046
Slight	7 (9.5%)	5 (11.9%)	
Moderate	26 (35.1%)	6 (14.3%)	
Severe	1 (1.4%)	1 (2.4%)	
N	74	42	
Urinary Obstruction			
No	65 (89.0%)	30 (75.0%)	0.051
Yes	8 (11.0%)	10 (25.0%)	
N	73	40	
Normal PAP Value			
No	40 (72.7%)	17 (51.5%)	0.044
Yes	15 (27.3%)	16 (48.5%)	
N	55	33	
Gastrointestinal Disease			
No	52 (78.8%)	18 (51.4%)	0.005
Yes	14 (21.2%)	17 (48.6%)	
N	66	35	

In the absence of randomization, statistical results cannot be interpreted. Hence, Parmar study is not interpretable.

Botto Study (914CL17E)

For this study, randomization codes are not available. This study achieved a baseline balance in terms of statistically nonsignificant differences between the two treatment groups for various variables. Usually, by the application of randomization one achieves a baseline balance for various variables among the treatment groups, but achieving baseline balance does not necessarily guarantee that randomization was used. The sponsor stated (on page 035, vol. 1.93) that since no randomization codes appeared to be available, this study could not strictly speaking be called "randomized".

In the absence of randomization, statistical results cannot be interpreted. Hence, the Botto study is not interpretable.

De Sy Study (914CL7P)

For this study, randomization scheme and codes are available. The sponsor stated (on page 012, vol. 1.95) that the randomization scheme and codes were to be found in Appendix V (pages 281-288 in vol. 1.95). The randomization scheme was unbalanced in a ratio of 2:1 for Decapeptyl:Orchiectomy.

There were several inadequacies and deficiencies regarding data quality and the conduct of this study. Some of them are listed below.

1. Some patients in the Decapeptyl group had orchiectomy.
2. Patients randomized to the Orchiectomy group were not informed that they were participating in a clinical trial and that there was an investigative treatment.
3. After the initial three months, testosterone levels were performed every three months only. This may or may not have provided comparable levels of testosterone for Decapeptyl and Orchiectomy patients.
4. A journal article reported the De Sy study had 67 patients whereas in this NDA it had only 60 patients.

Although in a meeting with FDA (February 4, 1997), the sponsor clarified these inadequacies and deficiencies, a major concern that still exists is the presence of a large number of dropouts. Only 8 of the 60 patients (i.e., 13.3%) completed the study. With such a large number of dropouts, performing last-observation-carried-forward intent-to-treat analysis or audited patients analysis may be grossly misleading. Even though a similar percentage of dropouts is observed for the two treatment groups, it is not feasible to do a meaningful statistical analysis for this study.

V. STATISTICAL REVIEWER'S CONCLUSIONS (That may be conveyed to the applicant)

The applicant, Debio R.P.(Switzerland), submitted three multicenter long term (24 months) controlled clinical studies, Parmar Study (914CL14P), Botto Study (914CL17E) and De Sy Study (914CL7P), as their core studies in support of their NDA comparing Decapeptyl 3.75 mg (one IM injection every four weeks) to bilateral orchiectomy for the treatment of advanced prostate cancer. These studies were conducted from 1983 to 1986 under the sponsorship of Ipsen Beaufour International, Paris (France) and —— (Belgium). In addition to the results of the individual studies, the sponsor provided results for the "pooled studies" through the Integrated Summaries of Effectiveness and Safety.

General Conclusions

Adequacy of Active Control: Orchiectomy was not an adequate active control in these trials.

Patient Discontinuations: There was a high rate of losses to follow-up in all three studies, but especially in the De Sy Study where only 8 of the 60 patients (13.3%) completed the study duration of 24 months. With such a large number of patient discontinuations, performing last-observation-carried-forward intent-to-treat analysis would be grossly misleading.

Adequacy of Randomization: There was a lack of randomization in the Parmar study. For the Botto study, no randomization codes appeared to be available. Hence, the Botto study can not be called randomized.

Comparison of Survival Rates: In comparing survival rates at 24 months between the two treatment groups, we found that orchiectomy was favored in the Parmar Study. There were wide confidence intervals for the Botto and De Sy Studies.

Comparison of Success Rates: In comparing success rates between the two treatment groups, we found that Decapeptyl was favored in the Parmar Study and Orchiectomy was favored in the Botto and De Sy studies.

Adequacy of Poolability of Studies: The sponsor chose to combine the data by just pooling the patients together from all the three studies as if the patients came from one study. These studies should not be pooled in this way as these are not combinable. Further, Zelen's exact test of homogeneity of odds-ratio for the three 2x2 tables (Decapeptyl/Orchiectomy vs. Success/Failure) for the three studies yields a p-value of 0.0364 indicating that these three 2x2 tables should not be pooled.

Validity and Accuracy of Data: The Division of Scientific Investigations (DSI) reported several problems about the validity and accuracy of the data in these trials.

Specific Conclusions about Individual Studies

Parmar Study (914CL14P)

The sponsor stated that since no randomization codes appeared to be available, this study could not strictly speaking be called "randomized." In the absence of randomization, statistical results cannot be interpreted. Hence, this study is not interpretable.

Botto Study (914CL17E)

The sponsor stated that since no randomization codes appeared to be available, this study could not strictly speaking be called "randomized." In the absence of randomization, statistical results cannot be interpreted. Hence, this study is not interpretable.

De Sy Study (914CL7P)

This study was poorly designed and poorly conducted. There were several inadequacies and deficiencies regarding data quality and the conduct of this study. With a large number of patient discontinuations, it is not feasible to do a really meaningful statistical analysis for this study. Hence, this study is also uninterpretable.

/S/

Baldeo K. Taneja, Ph.D.
Mathematical Statistician

Concur: Dr. Kammerman 5/30/97

Dr. Nevius 5/31/97

cc:
Arch. NDA 20-715
HFD-580
HFD-580/Dr. Rarick/Dr. Jolson/Dr. Shames/Ms. Pauls/Mr. Dunson
HFD-715/Dr. Nevius/Dr. Kammerman/Dr. Taneja/Division File

This review contains 25 pages of text.