STAT REVIEW

AUG 16 1994

STATISTICAL REVIEW AND EVALUATION

NDA #: 19-943/Drug Class 3S

Applicant: TAP Pharmaceuticals, Inc.

Name of Drug: Lupron Depot 3.75mg (leuprolide acetate for depot suspension)

Indication: Uterine Leiomyomata (Fibroids)

Documents Reviewed: Volumes 1.1, 1.5-1.15 of NDA 19-943 dated March 30, 1994

Medical Reviewer: This review has been discussed with the medical officer, Lisa D. Rarick, M.D., (HFD-510)

Relevant Issues Discussed in this Review

1. The results of Study M90-411 indicate that Lupron 3.75mg and Lupron 7.5mg are statistically associated with an increase in hemoglobin and hematocrit levels and with a reduction in uterine volume. There was no enhancement in the treatment effect by Lupron 7.5mg over that of Lupron 3.75mg.

2. A significantly greater percentage of Lupron 3.75mg and Lupron 7.5mg patients experienced hot flashes and vaginitis than did placebo patients. In addition, a significantly greater percentage of Lupron 7.5mg patients experienced dizziness, depression, arthralgia, and abdominal pain than did placebo patients.

3. Lupron 3.75mg and Lupron 7.5mg patients experienced a significantly greater reduction in bone mineral density levels and a significantly greater increase in total cholesterol and LDL levels than did placebo patients.

Background

Three U.S. double-blind, randomized, placebo-controlled, 24-week studies (M86-034, M86-049, M86-062) which were conducted to evaluate the safety and efficacy of Lupron Depot 3.75mg in the treatment of uterine fibroids were reviewed by this statistical

Key Words: abdominal pain, arthralgia, bone mineral density, cholesterol, depression, dizziness, hematocrit, hematologic, hemoglobin, hot flashes, intramuscular, iron-deficiency anemia, stratification, uterine fibroids, uterine leiomyomata, uterine volume, vaginitis, vasodilation

reviewer in a Statistical Review and Evaluation dated July 28, 1989. It was concluded in this review that the results of the three studies were consistent in that the leuprolide patients in each study experienced a significantly greater mean percent reduction in uterine volume (primary efficacy parameter) than did the corresponding placebo patients.

The sponsor's current submission states that (based on an October 1989 advisory committee recommendation and subsequent discussions with representatives of the Division of Metabolism and Endocrine Drug Products) "it was decided that Lupron Depot might be used most effectively to treat leiomyoma patients with iron-deficiency anemia due to excessive uterine bleeding, who are surgical candidates and who are also receiving iron therapy."

Consequently, the sponsor has submitted the results of Study M90-411 which was designed in accordance with the above recommendations. A statistical review and evaluation of Study M90-411 follows.

Study M90-411

This randomized, double-blind, multicenter (50 centers) placebo-controlled study was conducted "to determine if Lupron Depot plus iron is more effective than iron alone in the preoperative treatment of anemia due to prolonged or excessive bleeding associated with uterine leiomyomata" and to "determine if Lupron Depot 3.75mg or 7.5mg is more effective in this treatment."

Eligible patients were stratified by their pretreatment hematocrit level (less than or equal to 28% versus greater than 28%) and randomized to receive 12 weeks of double-blind treatment with Lupron 7.5mg, Lupron 3.75mg, or placebo. Patients received an intramuscular injection subsequent to randomization and at weeks 4 and 8 of the 12-week double-blind treatment period. All patients received iron and calcium supplementation daily throughout the study.

The primary efficacy endpoint was the change in hematologic status where a response was defined in the study protocol as an increase of 2g/dl in hemoglobin (HGB) and/or 6% in hematocrit (HCT).

The response to treatment was also analyzed using two alternate response definitions "from accepted clinical practice."

The sponsor stated that since it was possible for patients to achieve a protocol defined response and still be anemic, that a more clinically relevant response was the attainment of a HGB level of at least 12g/dl and/or a HCT level of at least 36%. This level of response was considered to be the level that would allow for autologous blood donation prior to surgery and the

level at which there would be a diminished need for any blood transfusion if blood was lost at surgery.

The second alternate response definition was the attainment of a HGB level of at least 12g/dl as proposed by the FDA according to the sponsor.

Analyses were based on data classified as acceptable for efficacy evaluation (evaluable patient analyses) as well as on all available data (all patient analyses).

Analyses were conducted based on 4-, 8-, and 12-week data. Furthermore, in order to adjust for possible bias due to the "worst" patients terminating early or undergoing early surgery, last-observation carried forward analyses were also conducted.

This review will focus on the all patient last observation carried forward-analyses.

Reviewer's Comments on Study M90-411

A total of 309 patients (107 Lupron 7.5mg, 104 Lupron 3.75mg, 98 placebo) were randomized to receive double-blind treatment. Three patients were excluded from the all patient population due to the absence of efficacy data.

A total of 28 patients (3 Lupron 7.5mg, 11 Lupron 3.75mg, 14 placebo) discontinued from the study prematurely. The primary discontinuation reasons were "pre-study criteria not met" (1 Lupron 7.5mg, 4 Lupron 3.75mg, 3 placebo) and adverse events (1 Lupron 7.5mg, 3 Lupron 3.75mg, 1 placebo).

Based on data submitted by the sponsor, I have constructed Table 1 which displays adverse events which were experienced by significantly more Lupron patients than placebo patients. It should be noted that the two most commonly reported Lupron 3.75mg adverse events were vasodilation (hot flashes) and vaginitis which were also the two most commonly reported adverse events reported by the Lupron 3.75mg patients who were enrolled in the three above mentioned previously submitted studies. A significantly greater percentage of Lupron 3.75mg patients experienced vasodilation and vaginitis than did placebo patients in the currently submitted Study M90-411. This was also the case with regard to combined analyses conducted with regard to Studies M86-034, M86-049, and M86-062 (Table 23 in the July 28, 1989 Statistical Review).

Based on data submitted by the sponsor, I conducted statistical analyses regarding the protocol defined responder results. In examining these results which are displayed in Table 2, one notes that patients in each Lupron treatment group experienced a significantly greater responder rate than did the placebo

patients. This was due primarily to the Stratum B results although the Lupron Stratum A responder rates were also numerically greater than the corresponding Stratum A placebo rates. There was no statistical significant difference between the Lupron 7.5mg and 3.5mg treatment group responder rates.

As mentioned above, the sponsor also compared treatment groups utilizing two alternate responder definitions "from accepted clinical practice".

Based on data submitted by the sponsor, I compared treatment groups with regard to their clinically defined response rates. Table 3 displays the results with regard to the attainment of a hemoglobin level of at least 12g/dl and/or a hematocrit level of at least 36%. In examining this table one notes that the responder rates were significantly greater in each Lupron treatment group than in the placebo group. The results in this case were consistent across strata. Once again, there was no significant difference in responder rates between the two Lupron treatment groups.

Similar results were obtained with regard to the second alternate response definition (HGB at least 12g/dl) as the Lupron 7.5mg, Lupron 3.75mg, and placebo response rates were 74.2%, 76.2%, and 51.4% respectively (Lupron 7.5mg versus placebo: $p<.01$, Lupron 3.75mg versus placebo: $p<.001$).

The results of the sponsor's HCT and HGB mean change from baseline to final visit analyses are displayed in Tables 4 and 5. In examining these tables, one notes that the results are consistent with the above mentioned responder results in that the Lupron treatment groups experienced significantly greater mean HCT and HGB increases than did the placebo patients. Once again, there was no significant difference detected with regard to mean increases between the Lupron treatment groups.

As mentioned in the background section of this review, the primary efficacy parameter in the previously submitted three studies was the change in uterine volume over the 24-week double-blind treatment period. In these studies, a patient was considered to be a treatment responder if she experienced a reduction from baseline in uterine volume of at least twenty-five percent. It was noted in the Statistical Review dated July 28, 1989 that the uterine volume responder rate was significantly ($p<.001$)greater in the Lupron 3.75mg group than in the corresponding placebo group in each of these studies.

The corresponding uterine volume responder results in Study M90-411 were consistent with the results of the three previously submitted studies in that there was a significantly ($p<.001$) greater percentage of uterine responders in each Lupron treatment group (Lupron 7.5mg: 62.1%, Lupron 3.75mg: 60.0%) than in the

placebo group (27.5%).

This statistical reviewer in his Statistical Review dated July 28, 1989 concluded that the nonsignificant bone mineral results in Studies M86-034, M86-049, and M86-062 were inconclusive due to small sample sizes, questions regarding the quality of the data and to the different methodologies employed by the individual investigators.

The determination of bone mineral density in Study M90-411 was limited to eleven sites using QDR equipment for dual energy x-ray absorptiometry (DEXA) of whole vertebral body of the spine (L1-L4). In order to standardize the results across the eleven sites where BMD was measured, the original data were read and analyzed by a central reader. Sixty-one patients (18 Lupron Depot 7.5mg, 20 Lupron 3.75mg, 23 placebo) comprised the sponsor's bone mineral density population.

In examining the sponsor's bone mineral density results which are displayed in Table 6, one notes that the Lupron 3.75mg patients experienced a significantly ($p<.01$) greater mean percent reduction in bone mineral density than did placebo patients.

In addition, there were statistical indications that Lupron was associated with an increase in total cholesterol (Lupron 7.5mg: 26.1, Lupron 3.75mg: 28.5, placebo: 16.2, Lupron 7.5 versus placebo: $p<.05$, Lupron 3.5mg versus placebo: $p<.01$) levels as well as with LDL (Lupron 7.5mg: 18.5, Lupron 3.75mg: 21.9, placebo: 10.6, Lupron 7.5 versus placebo: $p<.05$, Lupron 3.75mg versus placebo: $p<.01$) increases.

Reviewer's Concluding Comments on Study M90-411(May be Conveyed to the Sponsor)

The results of Study M90-411 indicate that Lupron 3.75mg and Lupron 7.5mg are statistically associated with an increase in hematocrit and hemoglobin levels. There was no enhancement in the treatment effect by Lupron 7.5mg over that of Lupron 3.75mg

The uterine volume reduction results of Study M90-411 are consistent with those of the previously submitted Studies M86-034, M86-049, M86-062 in that a significantly greater percentage of Lupron 3.75mg patients experienced at least a 25% reduction in uterine volume than did placebo patients. Once again, the Lupron 3.75mg treatment effect was not enhanced by the use of Lupron 7.5mg.

Also, as with regard to the three previously submitted studies, there were statistical indications that Lupron 3.75mg is associated with the occurrence of vasodilation (hot flashes) and vaginitis. The Lupron 7.5mg vasodilation and vaginitis incidence rates were also significantly greater than the corresponding

placebo rates as were the dizziness, depression, arthralgia, and abdominal pain incidence rates.

In addition, there were statistical indications that Lupron is associated with a reduction in bone mineral density levels and an increase in total cholesterol and LDL levels.

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Mathematical Statistician

Concur: Dr. Nevius 8/12/94
For Dr. Dubey 8/15/94

cc:
Original NDA 19-943
HFD-510
HFD-510/Dr. Sobel
HFD-510/Dr. Rarick
HFD-510/Ms. ~~Galliers~~ Pauls
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: 1.3.2 NDA]
HFD-713/Group 2 File
HFD-713/Mr. Marticello
Chron.

This review consists of 6 pages of test and 6 pages of tables.

Table 1
Study M90-411
Frequent [+] Adverse Events

EVENT	LUPRON 7.5mg	LUPRON 3.75mg	PLACEBO
Vasodilation	72(67.3%)*	68(66.0%)*	27(27.6)
Dizziness	18(16.8%)*	11(10.7%)	5(5.1%)
Depression	16(15.0%)*	7(6.8%)	6(6.1%)
Arthralgia	16(15.0%)*	10(9.7%)	6(6.1%)
Vaginitis	14(13.1%)*	13(12.6%)*	4(4.1%)
Abdominal Pain	13(12.1%)*	9(8.7%)	4(4.1%)

+ Adverse events which occurred in at least 5% of the patients in at least one treatment group for which a statistically significant ($p<.05$) higher percentage occurred in a Lupron treatment group than in the placebo group.

* $p<.05$

Table 2
Study M90-411
Protocol + Responder Rates

	LUPRON 7.5mg	LUPRON 3.75mg	PLACEBO
Stratum A[a]	40/40(100.0%)	34/35(97.1%)	32/35(91.4%)
Stratum B[b]	61/66(92.4%)*	55/60(91.7%)#	48/60(80.0%)
Total	101/106(95.3%)**	89/95(93.7%)*	80/95(84.2%)

+Response is an increase of 2g/dl in hemoglobin and/or 6% in hematocrit.

#p<.10 in favor of Lupron over placebo

*p<.05 in favor of Lupron over placebo

**p<.01 in favor of Lupron over placebo

[a]Baseline hematocrit not in excess of 28%

[b]Baseline hematrocit greater than 28%

Table 3
Study M90-411
Clinical [+] Responder Rates

	LUPRON 7.5mg	LUPRON 3.75mg	PLACEBO
Stratum A[a]	31/40(77.5%)**	29/35(82.9%)***	17/35(48.6%)
Stratum B[b]	60/66(90.9%)***	52/60(86.7%)*	41/60(68.3%)
Total	91/106(85.8%)***	81/95(85.3%)***	58/95(61.1%)

\+ Response is the attainment of a hemoglobin level of at least 12g/dl and/or a hematocrit level of at least 36%.

[a] Baseline hematrocrit not in excess of 28%

[b] Baseline hematrocrit greater than 28%

* p<.05 in favor of Lupron over placebo

** p<.01 in favor of Lupron over placebo

*** p<.001 in favor of Lupron over placebo

Table 4
Study M90-411
Mean Hematocrit Levels

Stratum A[a]			
	LUPRON 7.5mg	LUPRON 3.75mg	PLACEBO
N	40	35	35
Baseline	24.9	24.6	24.4
Increase	14.5***	14.1***	10.3
Stratum B[b]			
	LUPRON 7.5mg	LUPRON 3.75mg	PLACEBO
N	66	60	60
Baseline	31.2	31.4	31.0
Increase	8.0**	8.3***	6.2
Total			
	LUPRON 7.5mg	LUPRON 3.75mg	PLACEBO
N	106	95	95
Baseline	28.0	28.0	27.7
Increase	10.5***	10.5***	7.5

[a] Baseline hematocrit not in excess of 28%

b Baseline hematocrit is greater than 28%

** $p<.01$ in favor of Lupron over placebo

*** $p<.001$ in favor of Lupron over placebo

Table 5
Study M90-411
Mean Hemoglobin Levels

Stratum A[a]			
	LUPRON 7.5mg	LUPRON 3.75mg	PLACEBO
N	40	35	35
Baseline	7.2	7.1	7.0
Increase	5.5***	5.3***	3.9
Stratum B[b]			
	LUPRON 7.5mg	LUPRON 3.75mg	PLACEBO
N	66	60	60
Baseline	9.1	9.2	9.1
Increase	3.7**	3.8***	2.9
Total			
	LUPRON 7.5mg	LUPRON 3.75mg	PLACEBO
N	106	95	95
Baseline	8.2	8.2	8.0
Increase	4.4***	4.3***	3.2

[a] Baseline hematocrit not in excess of 28%

b Baseline hematocrit is greater than 28%

** $p<.01$ in favor of Lupron over placebo

*** $p<.001$ in favor of Lupron over placebo

Table 6
Study M90-411
Bone Mineral Density Means (gm/cm^2)

	LUPRON 7.5mg	LUPRON 3.75mg	PLACEBO
N	18	20	23
Baseline	1.12	1.11	1.10
% Reduction	1.4#	2.7**	0.0

p = .13 Lupron 7.5mg versus placebo

** p<.01 Lupron 3.75mg versus placebo

NDA 19-943
Lupron® Depot (leuprolide acetate)
TAP Pharmaceuticals, Inc.

Advertising Material

No advertising material has been submitted.

Integrated Summary of Safety

Attached Safety Summary was submitted in NDA 19-943, Section VIII, Volume 1.25 and has the same page numbers as in the NDA.

Section VIII.H. Integrated Summary of Safety

Section VIII.H. Integrated Summary of Safety

1. Introduction

Table 1

Summary of Patients Enrolled, Evaluable, and Completed Therapy

Study	Number of Investigators	Patients Entered		Number of Evaluable Patients		Number Completed	
		Lupron Depot	Placebo	Lupron Depot	Placebo	Lupron Depot	Placebo
Controlled							
M90-411	50	211	98	188	77	197	84
M86-034	1	20	20	17	20	17	17
M86-049	5	22	22	22	21	20	10
M86-062	7	21	23	21	23	21	11
Total Controlled		274	163	248	141	255	122
Uncontrolled							
M86-048	12	56	--	50	--	50	--
Overall Total		330	163	298	141	305	122

The present clinical program was designed to demonstrate the safety and efficacy of Lupron Depot® 3.75 mg as treatment for uterine leiomyomas. This section of the NDA summarizes the safety information from studies evaluating Lupron Depot as treatment for up to 24 weeks for this condition.

For the safety database, exposure to Lupron Depot, demographic characteristics, adverse events, premature terminations, and laboratory abnormalities are grouped and analyzed by study category as follows: 1) study M90-411, a placebo-controlled study with a 12 week treatment period that required all patients to take iron and calcium supplements daily; 2) studies M86-034, M86-049, M86-062, placebo-controlled studies with a 24 week treatment period; and 3) study M86-048, an open-study with a 24 week treatment period.

GnRH analogs, including Lupron Depot, are known to affect changes in bone mineral density; therefore, changes in bone mineral density are also presented. These changes are grouped and analyzed according to the study categories outlined above.

2. Patient Accountability

The number of patients who received Lupron Depot treatment for uterine leiomyomas is summarized by study and treatment group in Table 2. A breakdown of all patients by study and investigator is found in Volume 1.5.

In study M90-411, one patient randomized to Lupron Depot 3.75 mg had no available results other than race. Although she is included in the table of patient accountability, she is not included in subsequent safety tables.

Of the 274 patients randomized to Lupron Depot, 255 (93%) completed the treatment period compared to 122 of 163 (75%) of patients randomized to placebo. Table 3 outlines the reasons for premature termination for the remaining 7% of Lupron Depot-treated patients and the remaining 25% of placebo-treated patients. For the randomized Lupron Depot treatment groups, a total of seven patients terminated prematurely due to an adverse event. For patients treated with placebo, one terminated prematurely due to an adverse event.

Table 2

Disposition of All Patients Treated in Lupron Depot Uterine Leiomyoma Studies

Study	Total Pts. Entered	Lupron Depot 7.5			Lupron Depot 3.75			Placebo		
		Number Entered	Number Completed	Number D/C'd due to AEs	Number Entered	Number Completed	Number D/C'd due to AEs	Number Entered	Number Completed	Number D/C'd due to AEs
Controlled										
M90-411	309	107	104	1	104	93	3	98	84	1
M86-034	60	--	--	--	20	17	2	20	17	0
M86-049	44	--	--	--	22	20	1	22	10	0
M86-062	44	--	--	--	21	21	0	23	11	0
Total Controlled	437	107	104	1	167	151	6	163	122	1
Uncontrolled										
M86-048	56	--	--	--	56	50	3	--	--	--
Overall Total	493	107	104	1	223	201	9	163	122	1

Table 3

Primary Reasons for Premature Discontinuation for All Patients

Reason	Treatment Group	Study M90-411	Study M86-034	Study M86-049	Study M86-062	Study M86-048	Total
Worsening of Disease/ or No Improvement	Lupron Depot 7.5	0	--	--	--	--	0
	Lupron Depot 3.75	1	0	1	0	0	2
	Placebo	2	3	12	10	--	27
Adverse Events	Lupron Depot 7.5	1	--	--	--	--	1
	Lupron Depot 3.75	3	2	1	0	3	9
	Placebo	1	0	0	0	--	1
Prestudy Criteria Not Met	Lupron Depot 7.5	1	--	--	--	--	1
	Lupron Depot 3.75	4	0	0	0	0	4
	Placebo	3	0	0	0	--	3
Lost to Follow-up	Lupron Depot 7.5	1	--	--	--	--	1
	Lupron Depot 3.75	1	1	0	0	1	3
	Placebo	2	0	0	0	--	2
Patient Request	Lupron Depot 7.5	0	--	--	--	--	0
	Lupron Depot 3.75	0	0	0	0	0	0
	Placebo	2	0	0	1	--	3
Other	Lupron Depot 7.5	0	--	--	--	--	0
	Lupron Depot 3.75	2	0	0	0	2	4
	Placebo	4	0	0	1	--	5
Total (% enrollment)	Lupron Depot 7.5	3 (3%)	--	--	--	--	3 (3%)
	Lupron Depot 3.75	11 (11%)	3 (15%)	2 (9%)	0	6 (11%)	22 (10%)
	Placebo	14 (14%)	3 (15%)	12 (55%)	12 (52%)	--	41 (25%)

Fifty-six patients who received placebo in one of three of the controlled trials, M86-034, M86-049, or M86-062, entered into an open six-month trial of Lupron Depot 3.75 mg. Six patients did not complete the study: three due to adverse events, two due to non-compliance with the visit schedule, and one who was lost to follow-up.

Patients who discontinued due to adverse events are discussed in Section 6.

3. Demographic Characteristics

A summary of age, height, and body weight for the patients from the four controlled studies and the one uncontrolled study is displayed in Table 4. For the controlled studies, ages ranged from 20 to 53 with a mean age of 39 years. Heights ranged from 52 to 72 inches with a mean height of 64.0 inches. Weights ranged from 99 to 350 pounds with a mean weight of 163.4 pounds.

Table 4

Summary of Demographic Characteristics and Disease History for All Patients

Variable	Study	Dose	Lupron Depot N	Lupron Depot Mean	Lupron Depot SE	Lupron Depot Range	Placebo N	Placebo Mean	Placebo SE	Placebo Range	P-Value
Age (yrs)											
	M90-411	7.5	107	39.3	0.6	26-52	98	39.4	0.6	23-51	0.821
		3.75	103	39.7	0.6	23-51					
	M86-034	3.75	20	41.1	1.4	29-53	20	39.3	1.4	29-49	0.360
	M86-049	3.75	22	36.5	1.1	25-47	22	35.0	1.1	28-45	0.358
	M86-062	3.75	21	34.5	1.3	28-47	23	33.0	1.3	20-44	0.426
	Combined	3.75	63	37.3	0.8	25-53	65	35.6	0.8	20-49	0.161
	M86-048	3.75	56	36.4	0.9	26-50					
Height (in)											
	M90-411	7.5	105	63.9	0.3	54-70	94	63.2	0.3	52-68	0.045†
		3.75	99	64.1	0.3	52-68					
	M86-034	3.75	20	64.9	0.7	57-72	20	64.1	0.7	58-69	0.431
	M86-049	3.75	22	65.5	0.5	61-70	22	64.8	0.4	61-68	0.259
	M86-062	3.75	20	64.9	0.7	61-72	23	63.2	0.6	59-70	0.059
	Combined	3.75	62	65.1	0.4	57-72	65	64.0	0.3	58-70	0.0239
	M86-048	3.75	56	64.1	0.4	58-70					
Body Weight (lbs)	M90-411	7.5	107	166.8	4.3	105-350	94	168.8	4.6	102-320	0.646
		3.75	99	163.7	4.4	102-250					
	M86-034	3.75	20	154.5	9.0	101-282	20	161.1	9.0	99-263	0.607
	M86-049	3.75	22	158.1	6.8	113-202	22	154.3	6.8	102-240	0.696
	M86-062	3.75	20	141.2	5.9	110-177	23	137.8	5.5	102-212	0.677
	Combined	3.75	62	151.5	4.3	101-282	65	150.6	4.2	99-263	0.876
	M86-048	3.75	56	153.8	5.5	99-261					

@ Significantly different ($p \leq 0.05$) between Lupron Depot and placebo
† Significantly different ($p \leq 0.05$) among all dosage groups

The only significant difference between Lupron Depot and placebo was for height, both for the combined analysis of the three smaller controlled trials and for M90-411. For the combined analysis, the mean height was 65.1 inches for the Lupron Depot group and 63.8 inches for the placebo group. For M90-411, the mean height was 64.0 inches for the Lupron Depot group and 63.2 inches for the placebo group.

4. Treatment Exposure

In studies M86-034, M86-049, M86-062 and M86-048, patients were scheduled to receive six monthly injections, while in Study M90-411, patients were scheduled to receive three monthly injections. The number of monthly injections received was distributed as follows.

Table 5

Number of Depot Injections for All Patients

	M90-411			M86-034, M86-049, M86-062		M86-048
Number of Injections	Lupron Depot 7.5	Lupron Depot 3.75	Placebo	Lupron Depot 3.75	Placebo	Lupron Depot 3.75
1	2	8	6	0	0	2
2	1	3	4	2	1	1
3	104	92	88	1	11	1
4	-	-	-	1	11	0
5	-	-	-	0	3	1
6	-	-	-	59	39	51
	107	103@	98	63	65	56

@ Tun #1028 - unknown number of injections.

5. Adverse Events

Adverse events were summarized using COSTART coding symbols from the Thesaurus of Adverse Reaction Forms (3rd Edition) prepared by the Department of Health and Human Services. A list of the COSTART terms used in the studies and the original medical terms from the raw data listings associated with them is provided in End-of-Text Table 1. All adverse events reported throughout the study and associated details for each patient are listed by treatment group in Appendices V.1.a. and V.1.b. of the Statistical Reports for each

of the individual studies for M86-034, M86-049, and M86-062. They are presented in Appendix C.13 of the study summary for M90-411 and Appendix C.10 of the study summary for M86-048. All 128 patients enrolled into studies M86-034, M86-049, and M86-062, all 56 patients enrolled into study M86-048, and 308 of the 309 patients enrolled into Study M90-411 were included in the adverse event analysis. The remaining patient in study M90-411 was excluded because there was no available data to evaluate.

End-of-Text Table 2 presents a summary of adverse events reported during the treatment period of the five studies for patients treated with Lupron Depot 3.75 mg or placebo by COSTART code, classified by body system. End-of-Text Table 3 summarizes the adverse events reported in Study M90-411 for the placebo, Lupron Depot 3.75 mg and Lupron Depot 7.5 mg treatment groups and End-of-Text Table 4 summarizes adverse events in this study for Black and non-Black race subgroups.

Adverse events were reported by 92% (N=204) of the 222 Lupron Depot 3.75 mg patients. The most frequently reported adverse event was hot flashes (COSTART="vasodilatation"). Of the 222 patients treated with Lupron Depot 3.75 mg, 76% (N=170) reported hot flashes. Aside from the hot flashes, the adverse events having the highest prevalence (≥ 10%) among Lupron Depot patients were headache (36%), vaginitis (15%), arthralgia (10%), and asthenia (10%).

Additionally, study M90-411 evaluated two doses of Lupron Depot, 7.5 mg and 3.75 mg. In study M90-411, 94% (101 of 107) of the Lupron Depot 7.5 mg group, 88% (91 of 103) of the Lupron Depot 3.75 mg group, and 89% (87 of 98) of the placebo group reported adverse events (End-of-Text Table 3). The most frequently reported adverse event was hot flashes, which was reported by 67% of the Lupron Depot 7.5 mg group, 56% of the Lupron Depot 3.75 mg group, and 28% of the placebo group.

Table 6 lists the adverse events which occurred in ≥ 10% of the Lupron Depot-treated patients in Study M90-411.

Table 6

Percent of Patients with Adverse Events with a Prevalence ≥ 10% Among Lupron Depot Patients from Study M90-411

Adverse Events (COSTART TERM)	Lupron Depot 7.5	Lupron Depot 3.75	Placebo
Vasodilatation	67#	66#	28
Headache	57	44	45
Pain	19	14	25
Nausea	18*	6	14
Dizziness	17#	11	5
Depression	15#	7	6
Arthralgia	15#	10	6
Asthenia	13	10	15
Vaginitis	13#	13#	4
Abdominal Pain	12#	9	4
Breast Pain	10*	3	9

* Significantly ($p \leq 0.05$) higher prevalence than Lupron Depot 3.75 mg
\# Significantly ($p \leq 0.05$) higher prevalence than placebo

A summary of adverse events in study M90-411 for Black and non-Black race subgroups is presented in End-of-Text Table 4. The overall occurrence of adverse events was comparable between race subgroups across the treatment groups. The relationship of treatment group and adverse event prevalence for the subset of Black patients was similar to that of the set of all patients. There was a higher prevalence of asthenia and insomnia among the non-Black patients, and a higher prevalence of chest pain among the Black patients for all treatment groups.

The severity of events in the Lupron Depot group was mostly mild or moderate with no single event having a disproportionate number of severe occurrences. End-of-Text Table 5 summarizes the distribution of severity ratings for all 329 patients who received either dose of Lupron Depot. Of these 329 patients, 17% (n=56) reported a severe adverse

event. The adverse events most commonly reported (> 1%) as severe were: hot flashes (9%) and headache (5%).

Most of the adverse events reported in the studies in the Lupron Depot groups were considered by the investigator to be probably or possibly related to Lupron Depot treatment. A summary of these events can be found in End-of-Text Table 6, for the patients who received Lupron Depot 3.75 mg in a double-blind study. This tabulation excludes occurrences for which the investigator indicated that the event was definitely not attributable to study drug. Significantly more patients reported an adverse event in the Lupron Depot group (83%) than in the placebo group (41%). Individual events reported by significantly more patients in the Lupron Depot group than in the placebo group were vasodilatation (72%), vaginitis (11%), insomnia (5%) and nervousness (5%). Adverse events for Study M90-411 that are probably or possibly related to treatment are summarized in End-of-Text Table 7.

COSTART terms were grouped with related events for summary in the labeling. The terms which were grouped together are listed in End-of-Text Table 8 and the summary of grouped terms is presented in End-of-Text Table 9 for the patients receiving Lupron Depot 3.75 mg in a double-blind study. Events that had a statistically significantly different prevalence between Lupron Depot 3.75 mg and placebo after the grouping of COSTART terms were vasodilatation (73%), depression (11%), vaginitis (11%) and nervousness (5%). Similar presentation of Study M90-411 results is included in End-of-Text Table 10.

6. Premature Terminations Due to Adverse Events

A total of eight patients terminated prematurely from the controlled trials due to adverse events: seven from a Lupron Depot group and one from a placebo group. In addition, three patients treated with Lupron Depot in the open trial discontinued prematurely due to an adverse event.

Three patients in the Lupron Depot group terminated prematurely from one of the studies M86-034, M86-049, and M86-062 due to adverse events. One patient terminated because of severe hot flashes, one because of a set of events including insomnia, fatigue, weight loss, hot flashes, pedal edema, headaches, and nausea, and one because of a dermatological reaction. This reaction, which was considered by the investigator and consulting dermatologist to possibly be related to Lupron Depot administration, involved the appearance of pruritic papules on the trunk and limbs which progressed into hypopigmented lesions (patient was Black).

There were five premature terminations from study M90-411 due to adverse events: one from the Lupron Depot 7.5 mg group, three from the Lupron Depot 3.75 mg group, and one from the placebo group. One patient treated with Lupron Depot 7.5 mg was discontinued at the time of hospitalization for pneumonia. Of the three patients treated with Lupron Depot 3.75 mg, one experienced an infarcted uterine myoma, followed by a prolapsed necrotic myoma that was surgically removed. The investigator judged the necrotic myoma to be of uncertain relationship to the study drug. Subsequently, she complained of continuing pelvic pain and requested to leave the study. A second patient discontinued with severe menometrorrhagia and pelvic cramps, and underwent early surgery. The third patient received one injection of Lupron Depot 3.75 mg and developed a rash on the day of the injection. The rash covered her chest, back, and distal extremities. She was discontinued from the study, and the investigator judged that there was a possible relationship between the rash and the study drug. The patient on placebo discontinued at the time of a hospitalization for a drug overdose.

Three patients discontinued Lupron Depot treatment prematurely from study M86-048. One patient discontinued due to slurred speech and increased urine volume. She had a history of taking street drugs. The second patient

discontinued due to hot flashes and insomnia, and the third patient discontinued due to nausea and vomiting.

There were no deaths during these studies.

7. Clinical Laboratory Determinations

7.a General Hematology and Clinical Chemistry

The hematology and clinical chemistry results are listed for each patient, by treatment group, in Appendices D.4 and D.19 of the Statistical Report for M90-411. For studies M86-034, M86-049, and M86-062 these data are provided in Appendices IV.3 and IV.4 and for M86-048 in Appendices C.8 and C.9. Normal ranges for the laboratories involved are also listed in the appendices of the individual reports.

A crosstabulation of results for each laboratory variable at baseline and at the end of the treatment period based on whether the value was below (L), within (N), or above (H) the normal range is presented for each treatment group in End-of-Text Table 11 for study M90-411, in End-of-Text Table 12 for the combined studies M86-034, M86-049, and M86-062, and in End-of-Text Table 13 for study M86-048. A few normal ranges were unavailable for certain centers, and data from these centers are not included in the crosstabulation. Several patients lacked values either at baseline or at the end of the treatment period; these patients were not included in the analysis of the specific variable or variables for which such values were not available.

There were no major adverse trends apparent in these analyses in either treatment group; the vast majority of values were within the normal range for a given variable at the end of the treatment period. There appeared to be a slight tendency for elevations to occur in lymphocytes, PT, PTT, glucose, alkaline phosphatase, SGOT, SGPT, LDH, cholesterol, LDL cholesterol, triglycerides, calcium and phosphorus in the Lupron Depot group, but these were not strong. Individual extreme values are reported in the study summaries.

End-of-Text Tables 14, 15, and 16 summarize mean changes from baseline to the end of the treatment period in the clinical laboratory variables for M90-411, the three combined studies, and for M86-048, respectively. For study M90-411 (End-of-Text Table 14), there were significant differences between both Lupron Depot dosage groups and placebo for mean changes in hemoglobin, hematocrit, RBC, neutrophils, lymphocytes, platelet count, BUN, creatinine, total protein, alkaline phosphatase, total bilirubin, calcium and phosphorus. Lupron Depot had greater mean increases for all parameters listed above when compared to placebo except for platelets and neutrophils, where Lupron Depot had a greater mean decrease compared to placebo. Additional significant differences from placebo seen only in the Lupron Depot 7.5 mg dosage group were in glucose, uric acid and albumin. Also, the mean change in LDH differed significantly between the placebo group (-15.9 IU/L) and Lupron Depot 3.75 mg (+36.6 IU/L) group, and between Lupron Depot 3.75 mg and 7.5 mg (+2.6 IU/L). Other than LDH, there were no significant differences between the two Lupron Depot dosage groups. For the combined study analysis (End-of-Text Table 15), there were significant differences between treatment groups for mean changes in hemoglobin, hematocrit, uric acid, BUN, albumin, alkaline phosphatase, SGOT, calcium and phosphorus.

The significant differences between treatment groups for most of the variables involved small mean increases in the Lupron Depot group and small mear decreases or no change in the placebo group.

For study M86-048, there were small but statistically significant mean increases from baseline to the end of treatment in hemoglobin, hematocrit, uric acid, BUN, total protein, albumin, alkaline phosphatase, calcium and phosphorus (End-of-Text Table 16).

The mean changes in most of these variables did not appear to be clinically significant, since the magnitudes of the mean changes for most of the variables within the Lupron

Depot group were small. Overall, the moderate mean increases in alkaline phosphatase, as well as the small mean increases in phosphorus and calcium, probably reflected changes in bone metabolism which can be expected with treatment with a GnRH analog.

7.b Lipids

End-of-Text Tables 17, 18, and 19 summarize mean changes in lipid variables from baseline to the end of the treatment period for study M90-411, the combined studies, and study M86-048, respectively. For study M90-411, there were significant mean increases from baseline to end-of-treatment in both Lupron Depot dosage groups for cholesterol, LDL cholesterol, LDL/HDL ratio and triglycerides. The increases within the placebo group were also significant for these parameters. The mean changes from baseline in the HDL cholesterol were not statistically significant in any group. The increases in cholesterol, LDL cholesterol and LDL/HDL ratio were significantly greater in the Lupron Depot groups than the placebo group. The results for the combined studies showed significant mean increases in cholesterol and LDL cholesterol for Lupron Depot, with only cholesterol being significantly different from placebo.

For study M86-048, there were significant increases in cholesterol (+20.0 mg/dl) and HDL cholesterol (+5.8 mg/dl). The mean LDL cholesterol and the LDL/HDL ratio did not change significantly.

The overall effect on cardiovascular risk as a result of these changes in lipid metabolism appear to be minimal, especially since the mean LDL/HDL ratio changed very slightly in the Lupron Depot groups. These negative directional changes in most lipid parameters were consistent with expected changes in lipid metabolism in estrogen-depleted individuals.

8. Vital Signs and Body Weight

Sitting blood pressure and pulse rate, and body weight are listed for each baseline and end-of-study visit for each

patient, by investigator and treatment group in Appendix C.8 of study summary M90-411, Appendix IV.1 of the Statistical Reports for each of the individual studies, M86-034, M86-049, M86-062, and in Appendix C.6 of study summary M86-048. End-of-Text Tables 20, 21, and 22 summarize mean changes in vital signs and body weight from baseline to the final visit for study M90-411, the combined studies, and M86-048, respectively.

For study M90-411, there were no statistically significant differences in vital signs or body weight between dosage groups or for Lupron Depot vs. placebo. For the combined studies, the only statistically significant difference between groups noted was for a mean decrease of 3.5 mmHg in diastolic blood pressure for the placebo group compared to the mean increase of 0.3 mmHg in the Lupron Depot group.

In study M86-048, the mean changes in vital signs were slight and not statistically significant. There was a small but statistically significant increase (mean change of 3.1 lbs) in body weight from baseline to the final visit.

9. Changes in Bone Mineral Density

Changes in bone mineral density were measured in the four placebo-controlled trials and in follow-up study M86-043, but not in uncontrolled study M86-048. However, studies M86-034, M86-049, M86-062, and M86-043 utilized technologies that have since, for the most part, become outdated.

9.a M90-411

For study M90-411, the determination of bone mineral density (BMD) was limited to sites using [redacted] QDR equipment for dual energy x-ray absorptiometry (DEXA) of whole vertebral body of the spine (L1-L4). An analysis of percent changes in bone mineral density, by treatment group, from baseline to Weeks 8, 12, and the final visit is presented in Appendix C.10 of the study summary.

To standardize the results across the 11 investigative sites where BMD was measured, the original data (original scan

information on computer disc) were read and analyzed by a central reader, Dr. J.C. Gallagher, Department of Medicine, Creighton University, Omaha, Nebraska, and by outside consultants at Providence Center for Osteoporosis, Portland, Oregon, all of whom remained blinded to treatment assignments. Sixty-one patients (18 Lupron Depot 7.5 mg patients, 20 Lupron Depot 3.75 mg patients and 23 placebo patients) were included in the analyses.

The mean percent changes in bone mineral density (by central reader) for study M90-411 are summarized in End-of-Te Table 23.

The mean percent changes from baseline to the final visit were -1.4% in the Lupron Depot 7.5 mg group, -2.7% in the Lupron Depot 3.75 mg group, and 0% in the placebo group. There was a significant difference in bone mineral density change between the Lupron Depot 3.75 mg group and the placebo group, but not between the Lupron Depot 7.5 mg group and the placebo group. There was no significant difference between Lupron Depot dosage groups.

Patients were given calcium carbonate 1250 mg tablets (500 mg elemental calcium) twice-a-day to minimize bone loss. There was comparable compliance with respect to consumption of calcium tablets among the three treatment groups.

The results of this analysis indicate that there is minimal bone mineral density loss, of about 2%, after three months of Lupron Depot treatment.

9.b <u>M86-034, M86-049, M86-062 and M86-043</u>

For studies M86-034, M86-049 and M86-062, bone mineral density measurements were performed prestudy and at the end of the six month treatment period, using either dual photon absorptiometry (DPA) or quantitative computerized tomography (QCT) of the spine, single photon absorptiometry (SPA) of the forearm to assess changes in cortical bone, and DPA of the hip.

Original bone mineral density data collected for the studies, except QCT measurements of the spine, dual-photon measurements of the hip (Ward's triangle and the trochanter), and cortical wrist density by SPA in study M86-049, were evaluated in a blinded manner by the central reader, Dr. J.C. Gallagher. Only the results of the central reader are included in this summary, except where noted. The original readings are included in the individual study summaries.

The largest site-by-method category for combined studies was spinal bone density measured by DPA (24 Lupron Depot and 12 placebo patients). Patients in the Lupron Depot group incurred a mean loss of 3.8% and placebo patients had a mean loss of 0.2%. This difference was significant.

Changes in spinal bone density measured by QCT showed a significantly greater mean loss (13.5%) in the Lupron Depot group (N=7), compared to the mean loss (2.8%) in the placebo group (N=3). The greater loss recorded with QCT compared to DPA was expected in view of the fact that QCT measures only trabecular bone.

In general, meaningful analyses were precluded due to the variety of methodologies used to measure bone density, small sample sizes, technical errors, and unexpected losses (mean and individual) in placebo patients.

Data from the no treatment follow-up (M86-043) showed a trend toward recovery, especially when measured by QCT, in most patients within one year following termination of treatment.

These findings are consistent with reported data from other clinical trials, using Lupron Depot or other GnRH analogs, in which similar losses in bone mineral density have been observed, as well as complete or nearly-complete recovery, generally within six months after cessation of treatment.[2,3,4] Gallagher[2], Fogelman[3] and Scialli[4] all noted the difficulties of comparing results obtained using

different methodologies. Fogelman[3] and Scialli[4] also questioned the clinical relevance of these statistically significant decreases in bone mineral density over a short period of time, especially in view of the subsequent recovery observed in most patients.

10. Results from TAP-144-SR/FO5

For the German multicenter study, TAP-144-SR-FO5, 22 patients discontinued treatment prematurely: 6 had fewer than 4 injections, 8 had 4, 3 patients had 5, and 5 patients had 6 injections. The majority of drop-outs were due to side-effects, a planned operation (enucleation of myomas) or because the patient stopped attending. The other 150 patients received six injections of TAP-144-SR (Lupon Depot 3.75 mg), as planned. The mean duration of treatment was 139 ± 27 days.

The 172 patients were aged between 18 and 49; mean age was 33 ± 6 years. One hundred eighteen patients (68.6%) were over the age of 30 and 17 patients (9.9%) were over 40. The patients' mean height was 167 ± 6 cm and bodyweight 63 ± 10 kg.

The treating physicians reported side-effects appearing for the first time during the treatment in 91.3% of patients, mainly in the form of hot flashes, sweating, insomnia, headaches, depressive moods and nausea. Five patients discontinued prematurely due to adverse events.

Laboratory tests were performed before, during and after treatment. Comparisons of patients with normal, elevated or reduced values at those stages were also carried out. Nearly all the parameters that were normal, reduced or elevated before treatment were found to be in the same categories during and after therapy in most cases. It was noticeable, however, that total cholesterol at the final measurement stage was increased in 19 out of 125 patients whose cholesterol had previously been normal. Hemoglobin

levels returned to normal during treatment in 18 out of 25 patients with previously reduced levels and hematocrit in 19 out of 25 patients.

The safety profile of leuprorelin acetate depot in this study supports the findings from the controlled studies and study M86-048.

11. Conclusions - Safety

Overall, changes in safety parameters as a result of Lupron Depot treatment did not exceed expected limits. Adverse events experienced by patients in the studies were primarily those symptoms characteristically experienced in the postmenopausal population, and reflecting the hormonal suppression (hypoestrogenism) which forms the basis of the therapeutic effect. The significant changes in laboratory parameters observed were mostly small. The observed tendency for lipid parameters to change slightly to moderately in a disadvantageous direction again reflects changes seen in postmenopausal patients. Bone loss after three months of Lupron Depot treatment was about 2%. Post-treatment follow-up of patients and literature citations indicate that bone mineral loss reverses in most patients after treatment termination.

12. References (copies of journal articles follow the End-of-Text Tables)

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2. Gallagher JC. Effect of gonadotropin-releasing hormone agonists on bone metabolism. Sem Reprod Endocrinol 1993;11:201-8.

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