

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:NDA 19-886/S-013**

**STATISTICAL REVIEW(S)**

## Statistical Review and Evaluation

NDA#: 19-886/S-013

DEC 21 1998

Applicant: Searle

Name of Drug: Synarel (nafarelin intranasal)

Documents Reviewed: Final Report of Trial NAF610/USA dated December 22, 1997,  
FAX's dated December 3, 1998.

Medical Officers: Theresa Van der Vlugt, M.D. and Shelley Slaughter, M.D, HFD-580

### Background

The sponsor has submitted one trial (NAF610/USA) in support of four (4) additions to the label for Synarel. The first states that Synarel is "equivalent to intramuscular leuprolide depot, 3.75 mg monthly, in the management of endometriosis." The second states that the "median percent of days on which woman receiving nafarelin experienced hot flashes was significantly less than those receiving leuprolide (66% vs 91%)". The third states that "the median percent of days with bleeding was 8% and 6% for nafarelin and leuprolide, respectively." The fourth states that "at the end of 6 months treatment, bone loss was less in the nafarelin group than in the leuprolide group (3.2% vs 4.5%,  $p=.002$ ). Bone loss was substantially reversed during the post-treatment period in both groups."

### Trial NAF610/USA

This randomized, single-blind, double-placebo parallel trial compared 200  $\mu$ g BID Synarel intranasal to 3.75 mg leuprolide once monthly for signs and symptoms of endometriosis. The study randomized 236 patients among 20 investigational sites. There was a 6 month treatment period followed by a 6 month follow-up period.

The protocol states that "clinical equivalence" between the two therapies will be assessed for each symptom, separately: [there are five in all: pelvic tenderness, induration (investigator-evaluated), dysmenorrhea, dyspareunia, and pelvic pain (patient-evaluated)], the percentage of patients on Synarel who improve at least one severity category from baseline (absent, mild, moderate, severe) is at least an absolute 20% within the percentage improvement on leuprolide. One-sided 95% confidence limits will be used. There is no statement as to how the confidence intervals will be computed.

For bone loss, it states that "absolute change and percent change from baseline in bone density will be analyzed using ANOVA as appropriate."

For hypoestrogenic symptoms, CMH will be used. The actual clinical endpoint (e.g. percentage with any experience, or number of days with experience) is not stated.

With 100 patients per group, there is 90% power to detect a treatment group difference in mean percentages in bone density of -4% and -6% with a standard deviation of 4%.

If "clinical response" as defined above is the same in each group, there is 90% chance that the trial will demonstrate equivalence as defined above.

There is 84% power to detect a 20% (absolute difference) between groups if one group has 20% incidence of hypoestrogenic symptoms and the other group has a 40% incidence.

### Results

Of the 236 randomized 208 actually received study drug: 99 Synarel and 93 leuprolide. There were 16 patients excluded from efficacy analyses: 14 for being on study drug for less than 3 months and 2 for drug protocol violations, leaving a total of 192: 93 Synarel and 83 leuprolide. (The protocol does not state that patients with less than 3 months treatment will be excluded from efficacy analyses.)

Table 1 displays the patient disposition throughout the trial. A total of 40 patients terminated the trial before the 6 month treatment period: 15 Synarel and 25 leuprolide. Half of all dropouts was due to adverse events. At baseline, the only visible imbalance was that there were more current smokers in the Synarel group (37% vs 18%)

### Signs and Symptoms of Endometriosis

Table 2 displays the results of the "clinical equivalence" analysis at the end of 6 months treatment provided by the sponsor. Note that it does not address the endpoint specified in the protocol. What the sponsor did *post hoc* was to assign scores of 0, 1, 2, 3 to the categories of absent, mild, moderate, severe, respectively, and then total these scores over the 5 symptoms. They then created four (4) *post hoc* "severity categories" based on these total scores: 0(none), 1-2(mild), 3-5(moderate), 6-10(severe), 11-15(very severe). **But the number and percentages in Table 2 are not even based on these *post hoc* categories. They are based on the number of patients who improved with respect to the total score itself, not any severity category. Thus the analysis bears virtually no relation to the endpoint in the protocol.**

The result of this *post hoc* analysis is that the lower limit of a 1-sided 95% confidence interval for the difference in percentage of "improved patients" is -11% which is greater than -20%, thus supposedly demonstrating "statistical equivalence" to leuprolide. The lower bound using a 2-sided 95% confidence interval is -12%.

### Hypoestrogenic Symptoms

Table 3 displays the results of the comparisons between the treatment groups for these symptoms. Note that out of seven (7) symptoms, one statistically favored Synarel (hot flashes,  $p < .001$ ), and one favored leuprolide (bleeding,  $p = .011$ ). However, the analyses producing these results do not follow from the plan in the protocol. This is understandable because nearly everyone got some hot flashes and everyone had some bleeding. Therefore a statistical analysis on merely the occurrence of these symptoms is moot. The sponsor then switched to "median % days in the trial with the symptom," and got the results in Table 3. According to the study report, the Wilcoxon Rank Sum test was used to compare the treatment groups.

### Bone Mineral Density (BMD)

Table 4 displays the treatment comparisons with respect to absolute and relative change from baseline in BMD, change from baseline and percent change from baseline. At the end of 6 months of treatment, there was a statistically significant difference in the lowering of bone density between the two arms. Leupron had a greater lowering from baseline.

### Reviewer's Comments

#### Signs and Symptoms of Endometriosis

The Medical Division requested the sponsor to do the analyses prescribed in the protocol for each of the signs and symptoms of endometriosis. The results of both completer and LOCF analyses were similar. For Pelvic Tenderness, the lower bound of the two-sided confidence interval was just -20% with a p-value for the test of equivalence of .03, just above the critical value of .025. For Rate of Induration, the p-value for equivalence was .396, so that equivalence was not shown for this sign. Equivalence was shown for the 3 symptoms: Dysmenorrhea, Dysparunia, and Pelvic Pain. The sample size for analyzing Dyspareunia was substantially below the number randomized due to patients' not having Dyspareunia at baseline. See Tables 5-9 which use LOCF.

#### Bone Density

This reviewer has re-analyzed and confirmed the sponsor's results showing that there is a statistically significant difference between change from baseline in bone density at end of treatment either using completers or LOCF ( $p < .01$ ) with treatment by investigator interaction in the model. The LOCF analysis includes 174 patients who had at least one post baseline bone density. When interaction between investigator and treatment is included in the model, the p-value for treatment effect rises to  $p = .03$  in the "completer" analysis. Figure 1 displays the empirical distribution functions using the 154 patients with bone density observations with prescribed windows. In any case, the change from baseline in the Synarel group was between -.035 and -.04, while that in the Lupron group was -.05.

## **Hypoestrogenic Symptoms**

There were a total of seven (7) hypoestrogenic symptoms analyzed by the sponsor. They have chosen to comment on the two which reached nominal statistical significance: hot flashes, which favored nafarelin, and bleeding, which favored Leupron. This reviewer has analyzed the 202 patients with information about the **percentage of days on drug that a patient had at least one hot flash:** N=102 Synarel, N=100 Leuprolide. ANOVA and Wilcoxon signed rank test produce p-values <.01. The median percentage for the Synarel group was 62% while the median percentage for the Leuprolide group was 87%. It should be noted that, on the database, there are patients for whom the percentage is greater than 1.0; i.e, they were 43 patients who recorded more days with hot flashes than the number of days they were on treatment.

With respect to the **percentage of days on drug that a patient experienced bleeding**, this reviewer used the same 202 patients available and produced a Wilcoxon rank sum p-value of .03, whereas the sponsor had gotten .011 with 191 efficacy patients. On the other hand, a two-way ANOVA produces a high p-value (.43) with the lsmeans nearly identical .106 vs .094 when investigator is in the model. Even when investigator is not in the model and the point estimates are essentially those in the sponsor's table (11% vs 9.7%), the p-value from this t-test is p=.33. The reason for the discrepancy is likely due to the long tails of both distributions. See Figure 2. Deletion of the 10 greatest observations (% days bleeding on treatment at least .30) produces a p-value of .06 with investigator in the model. By deleting these 10 observations, the MSE was reduced by 67%. Alternatively, a log transformation to increase the degree of normality results in a t-test p-value of .06. Aside from this consideration, the sponsor reports that the comparison of the distributions of the **maximum severity** favored Lupron (p=.008).

## **Conclusions**

1. The results of trial NAF610 fulfill the statistical condition for "equivalence" (really clinical comparability) of the given dose of Synarel to the given dose of Lupron with respect to Dysmenorrhea, Dyspareunia, and Pelvic Pain.
2. There is some statistical evidence (at the nominal .05 level) that the degree of bone loss, as measured in the trial, was statistically greater on Lupron than on Synarel.
3. Although nearly all patients experienced hot flashes, there was a statistically greater percentage of days on treatment with any hot flashes associated with being on Lupron as opposed to Synarel. A Bonferroni correction among the hypoestrogenic symptoms still results in statistically significant result.
4. There is "suggestive" statistical evidence that patients on Synarel experienced a greater percentage of days on treatment with bleeding (along with maximum severity of bleeding) than on Lupron.

/S/

David Hoberman, Ph.D.  
Mathematical Statistician HFD-715

Concur: Dr. Kammerman *JAK* 12/17/98  
Dr. Nevius *SN* 12/20/98

cc:

Archival NDA 19-886/S-013

HFD-580

HFD-580/Tvan der Vlugt, Mmann, SSlaughter, CKish

HFD-715/DHoberman, DOB2, Chron

Table 1

PATIENT DISPOSITION

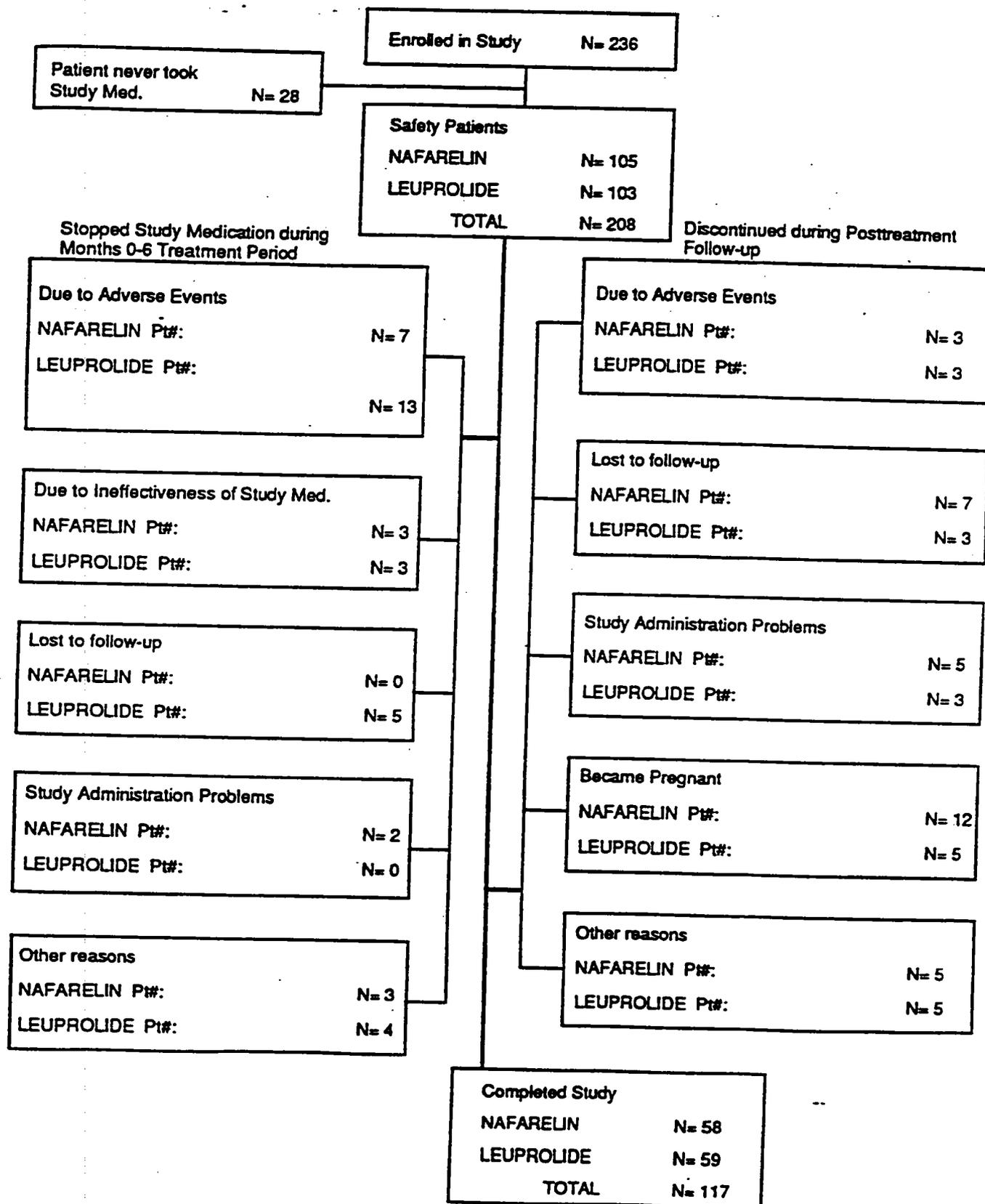


Table 2

**ESTABLISHMENT OF TREATMENT EQUIVALENCE BETWEEN NAFARELIN AND  
LEUPROLIDE BASED ON THE IMPROVEMENT RATE\* OF TOTAL SIGN AND  
SYMPTOM SEVERITY AT END OF ACTIVE TREATMENT  
ALL EFFICACY PATIENTS**

PATIENT POPULATION <sup>1</sup>	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVEMENT RATE	CONFIDENCE BOUND <sup>2</sup> ON TREATMENT DIFFERENCE (NAF-LEU)	p-VALUE <sup>3</sup>
<b>PRETREATMENT SEVERITY</b>						
MILD (1-2)	NAFARELIN	1	1	100%		
	400 MCG LEUPROLIDE 3.75 MG	3	3	100%		
MODERATE (3-5)	NAFARELIN	23	19	83%		
	400 MCG LEUPROLIDE 3.75 MG	20	14	70%	-0.13	0.016
SEVERE (6-10)	NAFARELIN	57	50	88%		
	400 MCG LEUPROLIDE 3.75 MG	58	56	97%	-0.19	0.030
VERY SEVERE (11-15)	NAFARELIN	18	17	94%		
	400 MCG LEUPROLIDE 3.75 MG	9	8	89%	-0.22	0.063
ALL SEVERITY	NAFARELIN	99	87	88%		
	400 MCG LEUPROLIDE 3.75 MG	90	81	90%	-0.11	<0.001

MISSING DATA WERE REPLACED THROUGH INTERPOLATION/EXTRAPOLATION FROM BASELINE. TOTAL SIGN AND SYMPTOM IS THE SUM OF PATIENT-ASSESSED AND INVESTIGATOR-ASSESSED SCORES.

NAFARELIN IS CONSIDERED TO BE CLINICALLY EQUIVALENT TO LEUPROLIDE IF THE POPULATION IMPROVEMENT RATE OF NAFARELIN (R<sub>naf</sub>) IS NOT LOWER THAN THAT OF LEUPROLIDE (R<sub>leu</sub>) BY 20% OR MORE.

\* PROPORTION OF PATIENTS WHOSE PRE-TREATMENT TOTAL SIGN AND SYMPTOM SEVERITY SCORE IS LARGER THAN THE END OF TREATMENT SCORE. AMENORRHEA PATIENTS INCLUDED IN THE ANALYSIS WITH A SCORE OF 0. PATIENTS FOR WHOM DYSpareunia WAS 'NOT APPLICABLE' WERE RECORDED AS A MISSING VALUE.

<sup>1</sup> ONLY PATIENTS WITH PRE-TREATMENT SYMPTOM SEVERITY SCORE > 0 WERE INCLUDED.

<sup>2</sup> THIS IS THE LOWER LIMIT OF 95% 1-SIDED CONFIDENCE INTERVAL OF R<sub>naf</sub> - R<sub>leu</sub>. IT DEFINES STRICTEST CRITERION OF CLINICAL EQUIVALENCE WHICH IS STATISTICALLY SUPPORTED BY THE OBSERVED DATA.

<sup>3</sup> THE p-VALUE TESTS THE NULL HYPOTHESIS H<sub>0</sub>: R<sub>naf</sub>-R<sub>leu</sub> ≤ -20%. TREATMENT EQUIVALENCE IS CONCLUDED WHEN P < .05.

CONFIDENCE BOUND AND p-VALUE GIVEN ONLY WHEN SAMPLE SIZE OF EACH TREATMENT GROUP IS NO LESS THAN 5.

Table 3

**NUMBER (%) OF PATIENTS WITH HYPOESTROGENIC SYMPTOMS  
TREATMENT PHASE\*\*  
ALL EFFICACY PATIENTS  
(PAGE 1 OF 3)**

	MAFARELIN 400 MCG	LEUPROLIDE 3.75 MG	P-VALUE
<b>NUMBER OF PATIENTS*</b>	98	93	
<b>BLEEDING</b>			
-----			
<b>NO. WITH BLEEDING</b>	98 (100%)	93 (100%)	1.000 [1]
<b>MEAN % DAYS WITH EVENT (SE)</b>	11% (1%)	9.2% (1%)	
<b>MEDIAN % DAYS WITH EVENT</b>	8.2%	5.9%	0.011 [2]
<b>MAXIMUM SEVERITY REPORTED:</b>			
<b>NO. (%) SPOTTING</b>	0	1 (1%)	0.008 [3]
<b>NO. (%) LIGHT</b>	10 (10%)	13 (14%)	
<b>NO. (%) MODERATE</b>	30 (31%)	44 (47%)	
<b>NO. (%) HEAVY</b>	58 (59%)	35 (38%)	
<b>HOT FLASHES</b>			
-----			
<b>WITH HOT FLASHES</b>	95 (97%)	93 (100%)	0.247 [1]
<b>MEAN % DAYS WITH EVENT (SE)</b>	62% (4%)	81% (3%)	
<b>MEDIAN % DAYS WITH EVENT</b>	66%	91%	<0.001 [2]
<b>MAXIMUM SEVERITY REPORTED:</b>			
<b>NO. (%) MILD</b>	10 (10%)	6 (6%)	0.065 [3]
<b>NO. (%) MODERATE</b>	25 (26%)	16 (17%)	
<b>NO. (%) SEVERE</b>	60 (61%)	71 (76%)	

Patients with symptoms are patients who had reported at least one occurrence of the specified symptoms in the daily diary during specified period.

\* PATIENT WHOSE DIARY DATA WAS NOT AVAILABLE.

\*\* TREATMENT PHASE INCLUDED A 30 DAYS OBSERVATION PERIOD AFTER THE END OF ACTIVE TREATMENT.

[1] TREATMENT DIFFERENCE IS TESTED BY FISHER'S EXACT TEST

[2] TREATMENT DIFFERENCE IS TESTED BY A WILCOXON RANK SUM TEST.

[3] TREATMENT DIFFERENCE IS TESTED BY A MANTEL-MAENSZEL TEST.

Table 4

**BONE DENSITOMETRY (LUMBAR SPINE) ANALYSIS  
SAFETY PATIENTS**

	MAFARELIN 400 MCG	LEUPROLIDE 3.75 MG	TREATMENT COMPARISON P-VALUE [1]
<b>BASELINE MEASUREMENT</b>			
N	102	98	0.658
MEAN (SE)	1.15 (0.015)	1.14 (0.016)	
MINIMUM			
25%	1.05	1.02	
MEDIAN	1.14	1.14	
75%	1.25	1.24	
MAXIMUM			
<b>END OF TREATMENT CHANGE FROM BASELINE</b>			
N	78	74	0.004
MEAN (SE)	-0.04 (0.004)	-0.05 (0.003)	
MINIMUM			
25%	-0.06	-0.07	
MEDIAN	-0.03	-0.05	
75%	-0.01	-0.04	
MAXIMUM			
<b>END OF TREATMENT PERCENT CHANGE FROM BASELINE</b>			
N	78	74	0.002
MEAN (SE)	-3% (0.3%)	-5% (0.3%)	
MINIMUM			
25%	-5%	-6%	
MEDIAN	-3%	-4%	
75%	-1%	-3%	
MAXIMUM			
<b>6 MONTHS FROM END OF TREATMENT CHANGE FROM BASELINE</b>			
N	41	49	0.100
MEAN (SE)	-0.02 (0.005)	-0.03 (0.004)	
MINIMUM			
25%	-0.04	-0.04	
MEDIAN	-0.02	-0.03	
75%	0.01	-0.01	
MAXIMUM			
<b>6 MONTHS FROM END OF TREATMENT PERCENT CHANGE FROM BASELINE</b>			
N	41	49	0.072
MEAN (SE)	-1% (0.4%)	-2% (0.3%)	
MINIMUM			
25%	-4%	-3%	
MEDIAN	-2%	-2%	
75%	1%	-1%	
MAXIMUM			

[1] P-VALUE ARE CALCULATED USING AN ANALYSIS OF VARIANCE MODEL.

Table 5

**Establishment of Treatment Equivalence Between Nafarelin and Leuprolide  
Based on the Improvement Rate of Induration at End of Active Treatment for  
All Efficacy Patients  
(Page 1 of 1)**

PATIENT POPULATION [1]	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVEMENT RATE	CONFIDENCE BOUND ON TREATMENT DIFFERENCE (NAF-LEU) [2]	p-VALUE [3]
<b>PRE-TREATMENT SEVERITY</b>						
MILD (1)	NAFARELIN 400 MCG	34	19	56%		
	LEUPROLIDE 3.75 MG	24	19	79%	-0.50	0.509
MODERATE (2)	NAFARELIN 400 MCG	19	18	95%		
	LEUPROLIDE 3.75 MG	24	23	96%	-0.19	0.015
SEVERE (3)	NAFARELIN 400 MCG	4	4	100%		
	LEUPROLIDE 3.75 MG	2	2	100%		
ALL SEVERITY	NAFARELIN 400 MCG	57	41	72%		
	LEUPROLIDE 3.75 MG	50	44	88%	-0.11	0.396

MISSING DATA WERE REPLACED THROUGH INTERPOLATION/EXTRAPOLATION FROM BASELINE.  
PATIENTS USED CONCOMITANT MEDICATION DUE TO ENDOMETRIOSIS/PELVIC PAIN WERE COUNTED  
AS NO IMPROVEMENT.

NAFARELIN IS CONSIDERED TO BE CLINICALLY EQUIVALENT TO LEUPROLIDE IF THE POPULATION IMPROVEMENT RATE OF  
NAFARELIN (R<sub>naf</sub>) IS NOT LOWER THAN THAT OF LEUPROLIDE (R<sub>leu</sub>) BY 20% OR MORE.  
IMPROVEMENT RATE IS THE PROPORTION OF PATIENTS WHOSE PRE-TREATMENT SYMPTOM SEVERITY  
SCORE IS LARGER THAN THE END OF TREATMENT SCORE. AMENORRHEA PATIENTS INCLUDED IN THE ANALYSIS WITH  
A SCORE OF 0. PATIENTS FOR WHOM DYSPARRENIA WAS 'NOT APPLICABLE' WERE RECORDED AS DYSPARRENIA MISSING.

- [1] ONLY PATIENTS WITH PRE-TREATMENT SYMPTOM SEVERITY SCORE > 0 WERE INCLUDED.  
[2] THIS IS THE LOWER LIMIT OF 97.5% 1-SIDED CONFIDENCE INTERVAL OF R<sub>naf</sub> - R<sub>leu</sub>. IT DEFINES STRICTEST  
CRITERION OF CLINICAL EQUIVALENCE WHICH IS STATISTICALLY SUPPORTED BY THE OBSERVED DATA.  
[3] THE p-VALUE TESTS THE NULL HYPOTHESIS H<sub>0</sub>: R<sub>naf</sub>-R<sub>leu</sub> < -20%. TREATMENT EQUIVALENCE IS CONCLUDED  
WHEN P < .025.  
CONFIDENCE BOUND AND p-VALUE GIVEN ONLY WHEN SAMPLE SIZE OF EACH TREATMENT GROUP IS NO LESS THAN 5.

SOURCE: /pub/studies/scarle/naf610nda/n610\_bndest/tables/induric.sas (02DEC98,21:14)

Table 6

Establishment of Treatment Equivalence Between Nafarelin and Leuprolide  
Based on the Improvement Rate of Pelvic Tenderness at End of Active  
Treatment for All Efficacy Patients  
(Page 1 of 1)

PATIENT POPULATION (1)	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVEMENT RATE	CONFIDENCE BOUND ON TREATMENT DIFFERENCE (RnaI - RLeu) (2)	P-VALUE (3)
<b>PRE-TREATMENT SEVERITY</b>						
<b>MILD (1)</b>	NAFARELIN 400 MG	35	19	54%		
	LEUPROLIDE 3.75 MG	37	23	62%	-0.33	0.211
<b>MODERATE (2)</b>	NAFARELIN 400 MG	51	40	78%		
	LEUPROLIDE 3.75 MG	40	36	90%	-0.28	0.210
<b>SEVERE (3)</b>	NAFARELIN 400 MG	4	4	100%		
	LEUPROLIDE 3.75 MG	2	1	50%		
<b>ALL SEVERITY</b>	NAFARELIN 400 MG	90	63	70%		
	LEUPROLIDE 3.75 MG	79	60	76%	-0.20	0.030

MISSING DATA WERE REPLACED THROUGH INTERPOLATION/EXTRAPOLATION FROM BASELINE.  
PATIENTS USED CONCOMITANT MEDICATION DUE TO ENDOMETRIOSIS/PELVIC PAIN WERE COUNTED  
AS NO IMPROVEMENT.

NAFARELIN IS CONSIDERED TO BE CLINICALLY EQUIVALENT TO LEUPROLIDE IF THE POPULATION IMPROVEMENT RATE OF  
NAFARELIN (RnaI) IS NOT LOWER THAN THAT OF LEUPROLIDE (RLeu) BY 20% OR MORE.  
IMPROVEMENT RATE IS THE PROPORTION OF PATIENTS WHOSE PRE-TREATMENT SYMPTOM SEVERITY  
SCORE IS LARGER THAN THE END OF TREATMENT SCORE. AMENORRHEA PATIENTS INCLUDED IN THE ANALYSIS WITH  
A SCORE OF 0. PATIENTS FOR WHOM DYSPARUNIA WAS 'NOT APPLICABLE' WERE RECORDED AS DYSPARUNIA MISSING.

[1] ONLY PATIENTS WITH PRE-TREATMENT SYMPTOM SEVERITY SCORE > 0 WERE INCLUDED.

[2] THIS IS THE LOWER LIMIT OF 97.5% 1-SIDED CONFIDENCE INTERVAL OF RnaI - RLeu. IT DEFINES STRICTEST  
CRITERION OF CLINICAL EQUIVALENCE WHICH IS STATISTICALLY SUPPORTED BY THE OBSERVED DATA.

[3] THE P-VALUE TESTS THE NULL HYPOTHESIS H<sub>0</sub>: RnaI - RLeu <= -20%. TREATMENT EQUIVALENCE IS CONCLUDED  
WHEN P < .025.

CONFIDENCE BOUND AND P-VALUE GIVEN ONLY WHEN SAMPLE SIZE OF EACH TREATMENT GROUP IS NO LESS THAN 5.

SOURCE: /pub/studies/searle/naf610nda/n610\_hndest/tables/pelvicic.sas (02DEC98,20:26)

Table 7

**Establishment of Treatment Equivalence Between Nafarelin and Leuprolide  
Based on the Improvement Rate of Dysmenorrhea at End of Active Treatment  
for All Efficacy Patients  
(Page 1 of 1)**

PATIENT POPULATION [1]	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVEMENT RATE	CONFIDENCE BOUND ON TREATMENT DIFFERENCE (Naf-Leu) [2]	p-VALUE [3]
<b>PRE-TREATMENT SEVERITY</b>						
MILD (1)	NAFARELIN 400 MCG	23	20	87%		
	LEUPROLIDE 3.75 MG	20	19	95%	-0.29	0.203
MODERATE (2)	NAFARELIN 400 MCG	44	38	86%		
	LEUPROLIDE 3.75 MG	41	40	98%	-0.25	0.137
SEVERE (3)	NAFARELIN 400 MCG	31	27	87%		
	LEUPROLIDE 3.75 MG	29	22	76%	-0.12	0.003
ALL SEVERITY	NAFARELIN 400 MCG	98	85	87%		
	LEUPROLIDE 3.75 MG	90	81	90%	-0.13	<0.001

MISSING DATA WERE REPLACED THROUGH INTERPOLATION/EXTRAPOLATION FROM BASELINE.  
PATIENTS USED CONCOMITANT MEDICATION DUE TO ENDOMETRIOSIS/PELVIC PAIN WERE COUNTED AS NO IMPROVEMENT.

NAFARELIN IS CONSIDERED TO BE CLINICALLY EQUIVALENT TO LEUPROLIDE IF THE POPULATION IMPROVEMENT RATE OF NAFARELIN (Rnaf) IS NOT LOWER THAN THAT OF LEUPROLIDE (Rleu) BY 20% OR MORE. IMPROVEMENT RATE IS THE PROPORTION OF PATIENTS WHOSE PRE-TREATMENT SYMPTOM SEVERITY SCORE IS LARGER THAN THE END OF TREATMENT SCORE. AMENORRHEA PATIENTS INCLUDED IN THE ANALYSIS WITH A SCORE OF 0. PATIENTS FOR WHOM DYSPARUNIA WAS 'NOT APPLICABLE' WERE RECORDED AS DYSPARUNIA MISSING.

- [1] ONLY PATIENTS WITH PRE-TREATMENT SYMPTOM SEVERITY SCORE > 0 WERE INCLUDED.  
[2] THIS IS THE LOWER LIMIT OF 97.5% 1-SIDED CONFIDENCE INTERVAL OF Rnaf - Rleu. IT DEFINES STRICTEST CRITERION OF CLINICAL EQUIVALENCE WHICH IS STATISTICALLY SUPPORTED BY THE OBSERVED DATA.  
[3] THE p-VALUE TESTS THE NULL HYPOTHESIS H0: Rnaf-Rleu <= -20%. TREATMENT EQUIVALENCE IS CONCLUDED WHEN P < .025.  
CONFIDENCE BOUND AND p-VALUE GIVEN ONLY WHEN SAMPLE SIZE OF EACH TREATMENT GROUP IS NO LESS THAN 5.

SOURCE: /pub/studies/scarla/naf610nda/n610\_hndest/tables/dynamic.sas (02DEC98,20:58)

Table 8

**Establishment of Treatment Equivalence Between Nafarelin and Leuprolide  
Based on the Improvement Rate of Dyspareunia at End of Active Treatment for  
All Efficacy Patients  
(Page 1 of 1)**

PATIENT POPULATION (1)	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVEMENT RATE	CONFIDENCE BOUND ON TREATMENT DIFFERENCE (RAF-LAU) (2)	P-VALUE (3)
<b>PRE-TREATMENT SEVERITY</b>						
<b>MILD (1)</b>	NAFARELIN 400 MCG	26	18	69%		
	LEUPROLIDE 3.75 MG	32	20	63%	-0.21	0.032
<b>MODERATE (2)</b>	NAFARELIN 400 MCG	20	10	50%		
	LEUPROLIDE 3.75 MG	18	12	67%	-0.53	0.548
<b>SEVERE (3)</b>	NAFARELIN 400 MCG	17	15	88%		
	LEUPROLIDE 3.75 MG	10	7	70%	-0.22	0.031
<b>ALL SEVERITY</b>	NAFARELIN 400 MCG	63	43	68%		
	LEUPROLIDE 3.75 MG	60	39	65%	-0.15	0.006

MISSING DATA WERE REPLACED THROUGH INTERPOLATION/EXTRAPOLATION FROM BASELINE. PATIENTS USED CONCOMITANT MEDICATION DUE TO ENDOMETRIOSIS/PELVIC PAIN WERE COUNTED AS NO IMPROVEMENT.

NAFARELIN IS CONSIDERED TO BE CLINICALLY EQUIVALENT TO LEUPROLIDE IF THE POPULATION IMPROVEMENT RATE OF NAFARELIN (RAF) IS NOT LOWER THAN THAT OF LEUPROLIDE (LAU) BY 20% OR MORE. IMPROVEMENT RATE IS THE PROPORTION OF PATIENTS WHOSE PRE-TREATMENT SYMPTOM SEVERITY SCORE IS LARGER THAN THE END OF TREATMENT SCORE. AMENORRHEA PATIENTS INCLUDED IN THE ANALYSIS WITH A SCORE OF 0. PATIENTS FOR WHOM DYSPAREUNIA WAS 'NOT APPLICABLE' WERE RECORDED AS DYSPAREUNIA MISSING.

[1] ONLY PATIENTS WITH PRE-TREATMENT SYMPTOM SEVERITY SCORE > 0 WERE INCLUDED.

[2] THIS IS THE LOWER LIMIT OF 97.5% 1-SIDED CONFIDENCE INTERVAL OF RAF - LAU. IT DEFINES STRICTEST CRITERION OF CLINICAL EQUIVALENCE WHICH IS STATISTICALLY SUPPORTED BY THE OBSERVED DATA.

[3] THE P-VALUE TESTS THE NULL HYPOTHESIS H<sub>0</sub>: RAF-LAU ≤ -20%. TREATMENT EQUIVALENCE IS CONCLUDED WHEN P < .025.

CONFIDENCE BOUND AND P-VALUE GIVEN ONLY WHEN SAMPLE SIZE OF EACH TREATMENT GROUP IS NO LESS THAN 5.

SOURCE: /pub/studies/searle/naf610nda/n610\_hmdest/tables/dysparic.sas (02DEC98,21:24)

Table 9

**Establishment of Treatment Equivalence Between Nafarelin and Leuprolide  
Based on the Improvement Rate of Pelvic Pain at End of Active Treatment for  
All Efficacy Patients  
(Page 1 of 1)**

PATIENT POPULATION (1)	TREATMENT	NUMBER OF PATIENTS	NUMBER OF IMPROVED PATIENTS	IMPROVEMENT RATE	CONFIDENCE BOUND ON TREATMENT DIFFERENCE (RAF-LEU) (2)	p-VALUE (3)
<b>PRE-TREATMENT SEVERITY</b>						
<b>MILD (1)</b>	NAFARELIN 400 MCG	28	22	79%		
	LEUPROLIDE 3.75 MG	36	21	58%	-0.05	0.001
<b>MODERATE (2)</b>	NAFARELIN 400 MCG	40	28	70%		
	LEUPROLIDE 3.75 MG	35	28	80%	-0.32	0.233
<b>SEVERE (3)</b>	NAFARELIN 400 MCG	20	16	80%		
	LEUPROLIDE 3.75 MG	16	11	69%	-0.23	0.040
<b>ALL SEVERITY</b>	NAFARELIN 400 MCG	88	66	75%		
	LEUPROLIDE 3.75 MG	87	60	69%	-0.08	<0.001

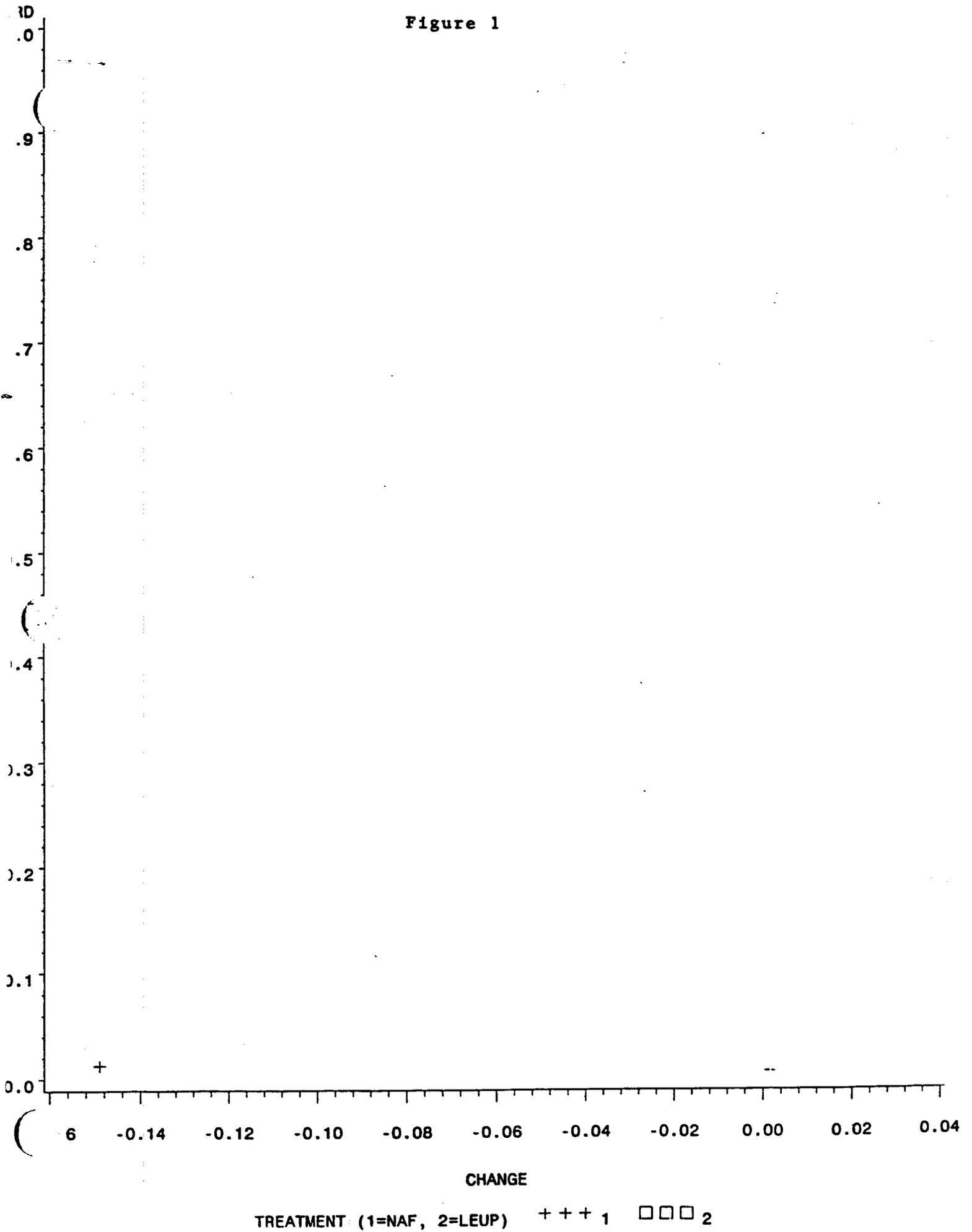
MISSING DATA WERE REPLACED THROUGH INTERPOLATION/EXTRAPOLATION FROM BASELINE. PATIENTS USED CONCOMITANT MEDICATION DUE TO ENDOMETRIOSIS/PELVIC PAIN WERE COUNTED AS NO IMPROVEMENT.

NAFARELIN IS CONSIDERED TO BE CLINICALLY EQUIVALENT TO LEUPROLIDE IF THE POPULATION IMPROVEMENT RATE OF NAFARELIN (R<sub>naf</sub>) IS NOT LOWER THAN THAT OF LEUPROLIDE (R<sub>leu</sub>) BY 20% OR MORE. IMPROVEMENT RATE IS THE PROPORTION OF PATIENTS WHOSE PRE-TREATMENT SYMPTOM SEVERITY SCORE IS LARGER THAN THE END OF TREATMENT SCORE. AMENORRHEA PATIENTS INCLUDED IN THE ANALYSIS WITH A SCORE OF 0. PATIENTS FOR WHOM DYSPARONIA WAS 'NOT APPLICABLE' WERE RECORDED AS DYSPARONIA MISSING.

- (1) ONLY PATIENTS WITH PRE-TREATMENT SYMPTOM SEVERITY SCORE > 0 WERE INCLUDED.  
 (2) THIS IS THE LOWER LIMIT OF 97.5% 1-SIDED CONFIDENCE INTERVAL OF R<sub>naf</sub> - R<sub>leu</sub>. IT DEFINES STRICTEST CRITERION OF CLINICAL EQUIVALENCE WHICH IS STATISTICALLY SUPPORTED BY THE OBSERVED DATA.  
 (3) THE p-VALUE TESTS THE NULL HYPOTHESIS H<sub>0</sub>: R<sub>naf</sub>-R<sub>leu</sub> < -20%. TREATMENT EQUIVALENCE IS CONCLUDED WHEN p < .025.  
 CONFIDENCE BOUND AND p-VALUE GIVEN ONLY WHEN SAMPLE SIZE OF EACH TREATMENT GROUP IS NO LESS THAN 5.

SOURCE: /pub/studies/ncic/naf610na/n610\_hndest/tables/palvpmc.sas (02DEC98,21:20)

Figure 1



**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 19-886/S-013**

**ADMINISTRATIVE DOCUMENTS**

DEC 21 1998

**Group Leader Memorandum**

**NDA:** 19-886  
**Drug:** Synarel®  
Intranasal nafarelin acetate 2 mg/mL solution

**Indications:** Equivalence to intramuscular leuprolide depot, 3.75 mg monthly, in the management of endometriosis;

Fewer days with hot flashes compared to intramuscular leuprolide depot

Less bone loss compared to intramuscular leuprolide depot

**Dose:** 200 ug (one spray) twice a day

**Formulation:** Nasal spray

**Applicant:** G.D. Searle and Co.

**Original Submission:** December 22, 1997  
**Review Completed:** December 22, 1998  
**Date of Memorandum:** December 21, 1998

---

Background

Synarel® is composed of nafarelin acetate, and is a gonadotropin-releasing hormone (GnRH) agonistic analog. It is approved for the indication of central precocious puberty at a recommended daily dose of 1600 ug (four sprays divided into each nostril twice a day). It is also approved for the management of endometriosis with a recommended dosage of 200 ug twice daily, which can be increased to 400 ug twice daily in those patients with persistent regular menstruation after 2 months of treatment.

In this NDA supplement, the sponsor reports the results of a single clinical trial entitled: "Comparison of Nafarelin Intranasal vs Leuprolide Depot Intramuscular in Patients with Endometriosis." The major labeling claims the sponsor desired from this study were:

- Intranasal Synarel® was clinically equivalent to intramuscular leuprolide depot, 3.75 mg monthly, in the management of endometriosis.
- Bone loss was less in the nafarelin group than in the leuprolide group (3.2% vs 4.5%, p=0.002).
- The median percent of days with bleeding was 8% and 6% for nafarelin and leuprolide, respectively.

- The median percent of days women experienced hot flushes was significantly less in the nafarelin arm (66%) compared to the leuprolide arm (91%).

#### Review of Clinical Study

The pivotal study for this NDA supplement was a randomized, single-blind, double-placebo, parallel trial of 6 months duration with an additional 6 months of follow-up. Patients with endometriosis were randomized 1:1 to receive either nafarelin (N) at a dose of 200 ug BID or leuprolide (L) at a dose of 3.75 mg once monthly. As discussed by the primary medical reviewer, the dose of 200 ug BID of N does not reflect the approved dosing recommendations for this product which allow increases to 400 ug BID if necessary, particularly if patients continue to menstruate. This flaw in study design is a major concern in addressing the safety claims that the sponsor desires of superiority over leuprolide (such as less bone mineral density loss or fewer hot flushes). To establish a truly superior safety profile, comparable approved doses of each product should have been studied.

A second concern raised in the review process regarding claims of superiority relate to the original protocol, which never stated that superiority claims were desired, or were a primary objective of the protocol. The protocol described analyzing changes from baseline in bone mineral density, but did not power the study to detect any particular change. A clinically meaningful difference between study arms regarding bone mineral density loss, for example, was never defined a priori. Thus, the findings of this study could be considered exploratory in nature, but not significant enough or definitive enough to support a claim of superiority.

Regarding clinical equivalence, the study protocol stated that for each symptom of endometriosis, the percentage of patients on nafarelin who improve at least one severity category from baseline (absent, mild, moderate, severe) will be at least within 20% of the percentage of improvement noted for patients on leuprolide. Five symptoms were to be examined: pelvic tenderness and induration (assessed by the examiner), and pelvic pain, dysmenorrhea, and dyspareunia (assessed by the patient). One-sided 95% confidence limits were to be calculated for each comparison, and this lower bound was to exclude any difference exceeding 20% (in favor of leuprolide).

The primary analysis of efficacy submitted by the sponsor, however, differed substantially from that defined by the protocol. All five symptoms were grouped together and analyzed with scores of 0, 1, 2, and 3 to correspond to the categories of absent, mild, moderate, and severe. Their results showed that the lower bound of the 95% confidence interval for the difference in the percentage of "improved patients" comparing nafarelin to leuprolide was -11%. Thus the sponsor claimed statistical and clinical equivalence. FDA analyzed efficacy based on the primary analytical plan set forth in the original protocol, and found that equivalence was only met for three of the five symptoms: pelvic pain, dysmenorrhea, and dyspareunia, while the two physician-assessed symptoms of pelvic tenderness and induration did not meet equivalence. As noted earlier, however, the sponsor only studied the lowest approved dose of nafarelin to make these comparisons, making these results fairly impressive. Therefore, I agree with the primary

medical officer that this study supports a claim of clinical comparability between nafarelin and leuprolide acetate for the relief of pelvic pain, dysmenorrhea, and dyspareunia associated with endometriosis.

/S/

, R.D.

12-21-98

Marianne Mann, M.D.  
Deputy Director, HFD-580

Synarel® (nafarelin acetate)  
Patent Information  
Supplemental New Drug Application

Page 1 of 1  
RA-SYN-03  
Dec. 09, 97

### Patent Information

1. Active Ingredient: nafarelin acetate
2. Strength/Dosage Form: 2 mg/mL (as nafareline base)/solution
3. Trade Name: SYNAREL
4. Route of Administration: intranasal
5. Applicant Firm Name: G. D. Searle & Co.
6. Applicable Patent Number: 4,234571/June 11, 2011

### PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 19886 Trade Name: SYNAREL NASAL SOLUTION  
 Supplement Number: 13 Generic Name: NAFARELIN ACETATE  
 Supplement Type: SE8 Dosage Form: SPR  
 Regulatory Action: PN Proposed Indication: 400 ug Synarel is comparable to 3.75 mg leuprolide (im depot) for dysmenorrhea, dyspareunia and pelvic pain

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?  
 NeoNates (0-30 Days )  Children (25 Months-12 years)  
 Infants (1-24 Months)  Adolescents (13-16 Years)

Label Status -  
 Formulation Status -  
 Studies Needed -  
 Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:  
will be approved by 12/24/98

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER CHRISTINA KISH

/S/  
Signature

12/21/98  
Date

Synarel® (nafarelin acetate)  
Drug Product  
Debarment Certification

Page 1 of 1  
RA-SYN-02  
Dec. 09, 1997

**DEBARMENT CERTIFICATION**

Pursuant to section 306(k) of the Federal Food, Drug and Cosmetic Act, the applicant did not employ or otherwise use in any capacity the services of any person debarred under subsection (a) or (b), in connection with this application.

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 19-886/S-013**

**CORRESPONDENCE**



Food and Drug Administration  
Rockville MD 20857

NDA 19-886/S-013

G.D. Searle & Company  
4901 Searle Parkway  
Skokie, IL 60077

JAN 14 1998

Attention: Doranne Frano  
Associate Director

Dear Ms. Frano:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Synarel (nafarelin acetate)

NDA Number: 19-886

Supplement Number: S-013

Date of Supplement: December 22, 1997

Date of Receipt: December 24, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on February 22, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Drug Products, HFD-580  
Office of Drug Evaluation II  
Attention: Document Control Room 17B-20  
5600 Fishers Lane  
Rockville, MD 20857

Sincerely,

/S/

Lana L. Pauls, M.P.H.  
Chief, Project Management Staff  
Division of Reproductive and Urologic  
Drug Products, HFD-580  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

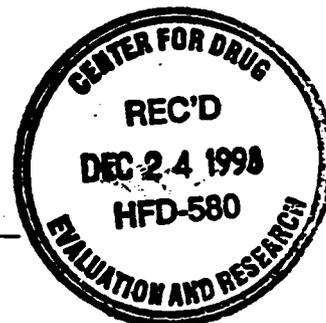
**SEARLE**

*Master*

December 22, 1998

SEARLE  
4901 SEARLE PARKWAY  
SKOKIE, ILLINOIS 60077  
PHONE (847) 982-7000  
FAX (847) 982-4701

Lisa Rarick, MD  
Division of Reproductive and Urology  
Drug Products (HFD-580)  
Center for Drug Evaluation and Research  
Room 17B45  
5600 Fishers Lane  
Rockville, MD 20857



Re: NDA 19-886/S-013  
Synarel (nafarelin acetate)  
AMENDMENT TO PENDING  
SUPPLEMENT

Dear Dr. Rarick:

In accordance with 21 CFR 314.120 G. D. Searle & Co. hereby amends the above mentioned SNDA with revised draft labeling and a Safety Update for Synarel.

If you have any questions regarding this matter, please do not hesitate to contact me.

Sincerely,

Doranne Frano  
Associate Director  
Regulatory Affairs  
(847) 982-7691  
(847) 982-8090 (fax)

DAF/hcl 122298W6.00P

SE8-013

# SEARLE ORIGINAL

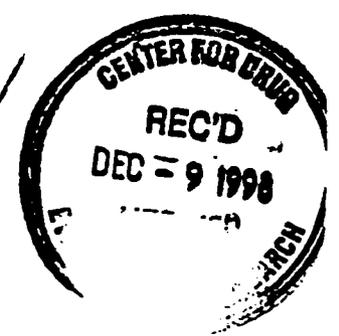
SUPPL NEW CORRESP

December 10, 1998

SEARLE  
4901 SEARLE PARKWAY  
SKOKIE, ILLINOIS 60077  
PHONE (847) 982-7000  
FAX (847) 982-4701

Dr. Lisa Rarick, Director  
Division of Reproductive and Urology  
Drug Products (HFD-580)  
Center for Drug Evaluation and Research  
Room 17B45  
5600 Fishers Lane  
Rockville, MD 20857

*N/A -  
Please  
file  
MMannMD  
12/14/98*



Re: NDA 19-886/S-013  
SYNAREL  
(nafarelin acetate)  
RESPONSE TO TELEPHONE REQUEST -  
DR. HOBERMAN

Dear Dr. Rarick:

A copy of the enclosed floppy disk containing the BMD data set requested by Dr. Hoberman was Federal Expressed directly to Dr. Hoberman on December 7, 1998. This copy is being submitted for your file.

If you have any questions regarding this submission, please do not hesitate to contact me.

Sincerely,

Doranne Frano  
Associate Director  
Regulatory Affairs  
(847)982-7691  
(847)982-8090 (fax)

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS _____ DATE _____

DRF/sai 121098W.doc

**ORIGINAL  
SEARLE**

SEARLE  
4901 SEARLE PARKWAY  
SKOKIE, ILLINOIS 60077  
PHONE (847) 982-7000  
FAX (847) 982-4701

December 3, 1998

Dr. Lisa Rarick, Director  
Division of Reproductive and Urology  
Drug Products (HFD-580)  
Center for Drug Evaluation and Research  
Room 17B45  
5600 Fishers Lane  
Rockville, MD 20857



Re: NDA 19-886/S-013  
SYNAREL  
(nafarelin acetate)  
RESPONSE TO TELEPHONE REQUEST

Dear Dr. Rarick:

Enclosed are the NAF 610 Case Report Forms for 26 patients as requested by Christina Kish on December 1, 1998.

If you have any questions regarding this information, please contact me.

Sincerely,

Doranne Frano  
Associate Director  
Regulatory Affairs  
(847)982-7691  
(847)982-8090 (fax)

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

DRF/ndr 120398W.doc

# SEARLE ORIGINAL

December 3, 1998

SEARLE  
4901 SEARLE PARKWAY  
SKOKIE, ILLINOIS 60077  
PHONE (847) 982-7000  
FAX (847) 982-4701

Dr. Lisa Rarick, Director  
Division of Reproductive and Urology  
Drug Products (HFD-580)  
Center for Drug Evaluation and Research  
Room 17B45  
5600 Fishers Lane  
Rockville, MD 20857



Re: NDA 19-886/S-013  
SYNAREL  
(nafarelin acetate)  
SUPPLEMENT TO  
PENDING APPLICATION

Dear Dr. Rarick:

Enclosed are the responses to Dr. Hoberman's requests of November 12, 1998. These responses were faxed to Dr. Hoberman on December 3, 1998. The BMD data on a floppy disk were Federal Expressed to his attention. A copy of the floppy disk will be sent to the division under separate cover.

If you have any questions regarding this information, please contact me.

Sincerely,

Doranne Frano  
Associate Director  
Regulatory Affairs  
(847)982-7691  
(847)982-8090 (fax)

NOT RECORDED	
COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

DRF/hai 120298W.doc

# SEARLE ORIGINAL

November 17, 1998

SEARLE  
4901 SEARLE PARKWAY  
SKOKIE, ILLINOIS 60077  
PHONE (847) 982-7000  
FAX (847) 982-4701

Lisa Rarick, MD  
Division of Reproductive and Urology  
Drug Products (HFD-580)  
Center for Drug Evaluation and Research  
Room 17B45  
5600 Fishers Lane  
Rockville, MD 20857



*Notice  
KR  
11/24/98*

Re: NDA 19-886/S-013  
Synarel (nafarelin acetate)  
AMENDMENT TO PENDING  
SUPPLEMENT

Dear Dr. Rarick:

In accordance with 21 CFR 314.70 and per a telephone request from Christina Kish on October 27, 1998, G. D. Searle & Co. hereby submits the attached responses to the reviewers questions and the Case Report Forms for the patients who were lost to follow-up.

If you have any questions regarding this submission, please do not hesitate to contact me.

Sincerely,

Doranne Frano  
Associate Director  
Regulatory Affairs  
(847) 982-7691  
(847) 982-8090 (fax)

DRF/mai 110598W.doc

*11/28/98  
Reviewed  
ADJ*

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS _____ DATE _____

**SEARLE**

S-013 BL  
NDA SUPP AMEND

November 16, 1998

SEARLE  
4901 SEARLE PARKWAY  
SKOKIE, ILLINOIS 60077  
PHONE (847) 982-7000  
FAX (847) 982-4701

Lisa Rarick, MD  
Division of Reproductive and Urology  
Drug Products (HFD-580)  
Center for Drug Evaluation and Research  
Room 17B45  
5600 Fishers Lane  
Rockville, MD 20857



Re: NDA 19-886/S-013  
Synarel (nafarelin acetate)  
AMENDMENT TO PENDING  
SUPPLEMENT

Dear Dr. Rarick:

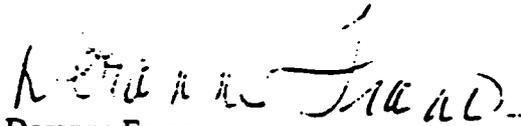
In accordance with 21 CFR 314.70 and per a telephone request from Christina Kish, Searle hereby submits an amendment to the pending labeling supplement (S-013) for Synarel.

The clinical pharmacology section of the physician labeling has been revised to be consistent with FDA guidelines.

Enclosed are 4 copies of the proposed revision to the Clinical Pharmacology Section of the Physician Labeling. A diskette containing the Synarel labeling for Supplements S-013, are being prepared and will be submitted to each pending supplement as soon as they are completed.

If you have any questions regarding this submission, please do not hesitate to contact me.

Sincerely,

  
Doranne Frano  
Associate Director  
Regulatory Affairs  
(847) 982-7691  
(847) 982-8090 (fax)

Searle  
4901 Searle Parkway  
Skokie, Illinois 60077  
Telephone 847 982 7000  
Fax 847 982 4701

ORIGINAL

December 22, 1997

Dr. Lisa Rarick, Director  
Division of Reproductive and Urology  
Drug Products (HFD-580)  
Center for Drug Evaluation and Research  
Room 17B45  
5600 Fishers Lane  
Rockville, MD 20857



**IRLE**

NDA NO. 19-886 REF. NO. 013  
NDA SUPPL FOR SLI

Re: NDA 19-886  
Synarel®  
(nafarelin acetate)

Dear Dr. Rarick:

In accordance with 21 CFR 314.70(b) G.D. Searle & Co. hereby supplements the above mentioned NDA for a labeling revision. This labeling revision incorporates an addition to the clinical pharmacology section to reflect additional data regarding bone loss results from an adequate well controlled study comparing Synarel® and Leupron (NAF610). Four copies of the draft proposed labeling revision, the study report NAF610, and the publication of this study, "Nafarelin vs. Leuprolide Acetate Depot for Endometriosis" are included in this submission.

If you have any questions regarding this submission, please do not hesitate to contact me.

Sincerely,

Doranne Frano  
Associate Director  
Regulatory Affairs  
(847) 982-7691  
(847) 982-8090 (fax)

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE