Appendix 11
Interim Study Report for Protocol NR15792

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1. STUDY POPULATION

1.1 Disposition of Patients

This document summarizes the pharmacodynamic and safety data for the first nine patients who completed all of the required pharmacokinetic visits for Roche Protocol NR15792 on or before February 23, 2000. The patient numbers for this subset are 25163/101, 25163/102, 25163/104, 25163/105, 25163/106, 25163/107, 25163/119, 25163/122, and 25163/123. The cut-off date for these data was February 23, 2000.

1.2 Demographic Data and Baseline Characteristics

A summary of the demographic data for the nine patients included in this document is presented in Table 1. A complete listing of demographic data for the individual study patients is presented in Appendix 1.

Table 1 Demographic Data Summary

Summary of Demographic Data by Trial Treatment
Protocol(s): NR15792/M01507
Analysis: ALL 9 PATIENTS Center: CRTN #25163

	Accutane NF/ Ortho Novum-7/7/7 N = 9
Sex	
MALE	-
FEMALE	9
n	9
Race	
CAUCASIAN	4
BLACK	3
ORIENTAL	2
OTHER	-
n	9
Age	
Mean	26.1
SD	4.26
SEM	1.42
Median	26.0
Min-Max	20 - 32
n	9
Weight in kg	
Mean	68.24
SD	21.465
SEM	7.155
Median	65.00
Min-Max	51.4 - 123.0
n	9
Height in cm	
Mean	166.6
SD	6.09
SEM	2.03
Median	165.0
Min-Max	157 - 175
n	9

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
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2. PHARMACODYNAMIC RESULTS

The pharmacodynamic results for these nine patients can be summarized as follows:

- The median values for progesterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH) on oral contraceptive pill days 6 and 20 for patients who received ethinyl estradiol and norethindrone as Ortho Novum 7/7/7™ and Accutane NF were not significantly changed from the corresponding values when patients received only Ortho Novum 7/7/7™.

2.1 Assessment of Progesterone, FSH and LH Serum Concentrations at Baseline and During Accutane NF Treatment

2.1.1 Progesterone, FSH and LH Serum Concentrations on Day 6 of Cycle 2 (Control, Before Accutane NF Treatment) and Day 6 of Cycle 4 (During Accutane NF Treatment)

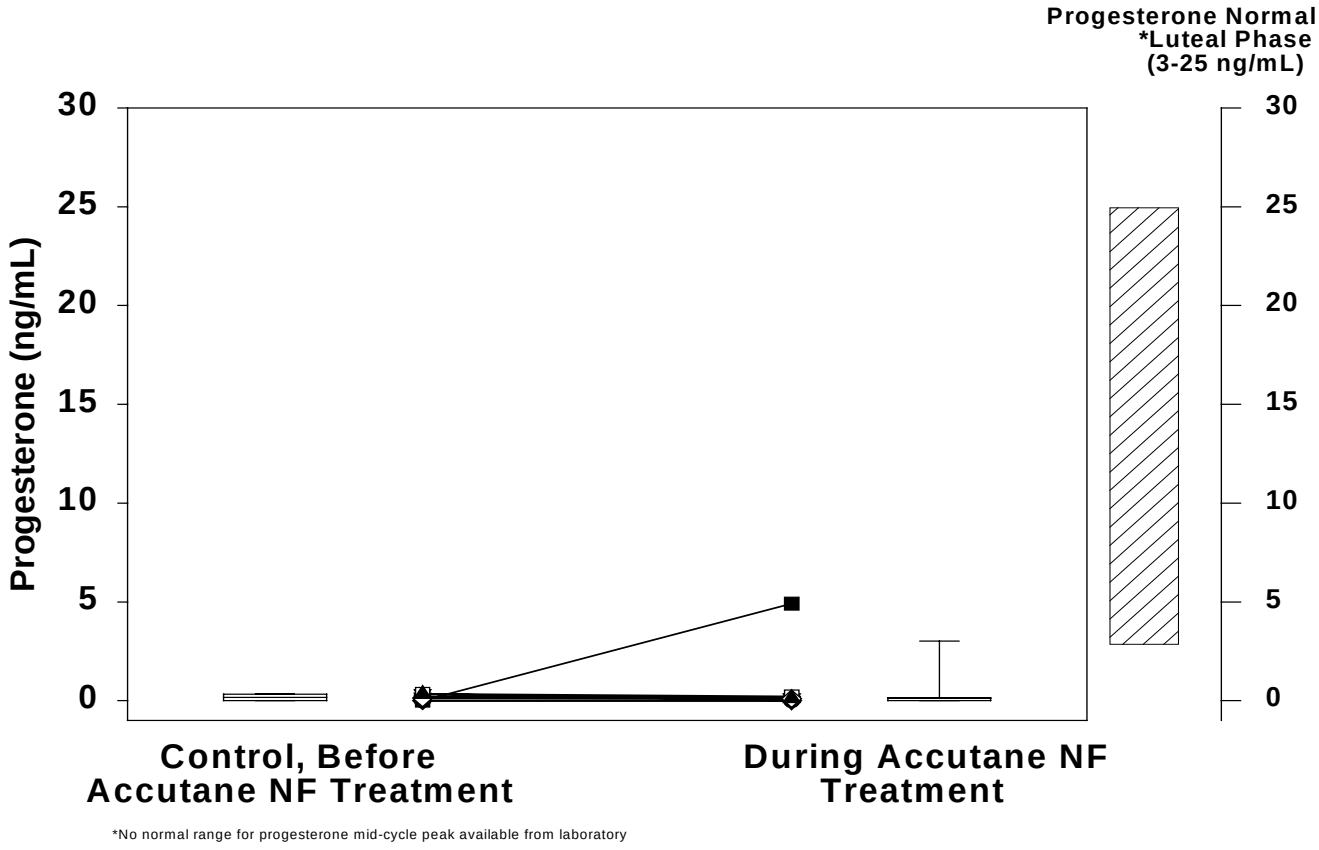
Descriptive statistical summaries for serum concentrations of progesterone, FSH and LH on day 6 of cycle 2 (control, before Accutane NF treatment) and on day 6 of cycle 4 (during Accutane NF treatment) are shown in Table 2.

Figures 1-3 show plots of individual serum concentrations of progesterone, FSH and LH on day 6 of cycle 2 (control, before Accutane NF treatment) and day 6 of cycle 4 (during Accutane NF treatment), respectively. The corresponding concentration values on day 6 of cycles 2 and 4 have been connected with a solid line for the values for each individual patient before and during Accutane NF treatment. The box plots represent the median, the upper and lower quartile, and the 5% and 95% percentile for the nine patients on day 6 of each cycle. Any values below the quantifiable limits of the analytic method were replaced by the value, zero, for purposes of data analysis and presentation. The normal concentration range of each hormone at the appropriate time in the menstrual cycle is represented by the bar graph to the right of the patient data.

Table 2 Summary of Progesterone, FSH and LH Serum Concentrations On Day 6 of Cycle 2 (Control, Before Accutane NF Treatment) and Day 6 of Cycle 4 (During Accutane NF Treatment)

		Day 6, Cycle 2 Control, Before Accutane NF Treatment	Day 6, Cycle 4 During Accutane NF Treatment
Progesterone (ng/mL)			
	N	9	9
	Mean	0.17	0.62
	SD	0.15	1.61
	Min	0.00	0.00
	Median	0.16	0.12
	Max	0.35	4.91
	CV%	86.95	259.21
FSH (mIU/mL)			
	N	9	9
	Mean	3.04	3.93
	SD	1.47	1.87
	Min	1.30	1.05
	Median	2.59	4.04
	Max	5.25	6.29
	CV%	48.43	47.58
LH (mIU/mL)			
	N	9	9
	Mean	4.33	7.70
	SD	2.42	5.94
	Min	0.57	0.07
	Median	4.69	7.44
	Max	8.24	21.13
	CV%	55.90	77.15

Figure 1 **Individual and Median Progesterone Serum Concentrations on Day 6 of Cycle 2 (Control, Before Accutane NF Treatment) and Day 6 of Cycle 4 (During Accutane NF Treatment)**



*No normal range for progesterone mid-cycle peak available from laboratory

Figure 2 **Individual and Median FSH Serum Concentrations on Day 6 of Cycle 2 (Control, Before Accutane NF Treatment) and Day 6 of Cycle 4 (During Accutane NF Treatment)**

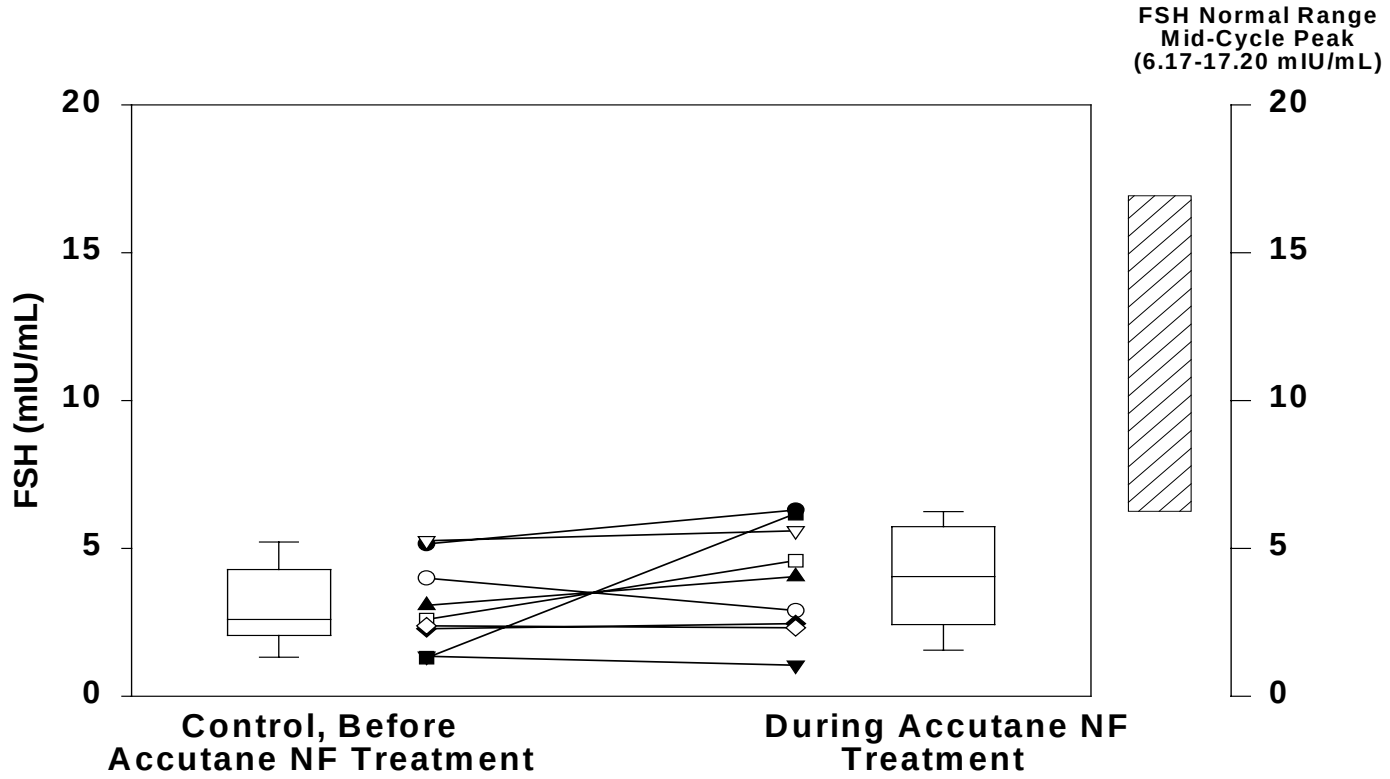
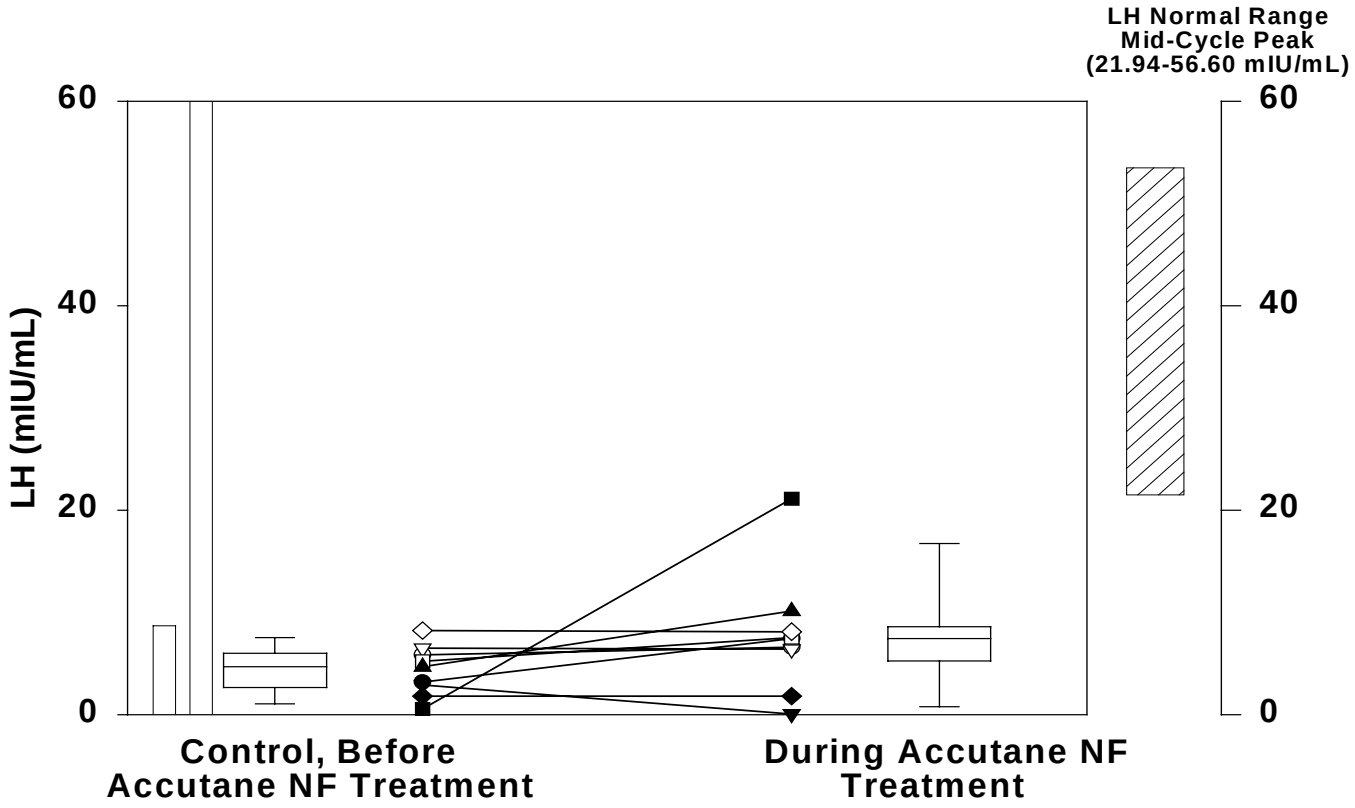


Figure 3 **Individual and Median LH Serum Concentrations on Day 6 of Cycle 2 (Control, Before Accutane NF Treatment) and Day 6 of Cycle 4 (During Accutane NF Treatment)**



2.1.2 Progesterone, FSH and LH Serum Concentrations on Day 20 of Cycle 2 (Control, Before Accutane NF Treatment) and Day 20 of Cycle 4 (During Accutane NF Treatment)

Descriptive statistical summaries for serum concentrations of progesterone, FSH and LH on day 20 of cycle 2 (control, before Accutane NF treatment) and day 20 of cycle 4 (during Accutane NF treatment) are shown in Table 3.

Figures 4–6 show plots of individual serum concentrations of progesterone, FSH and LH on day 20 of cycle 2 (control, before Accutane NF treatment) and day 20 of cycle 4 (during Accutane NF treatment), respectively. The corresponding concentration values on day 20 of cycles 2 and 4 have been connected with a solid line for the values for each individual patient before and during Accutane NF treatment. The box plots represent the median, the upper and lower quartile, and the 5% and 95% percentile for the nine patients on day 20 of each cycle. Any values below the quantifiable limits of the analytic method were replaced by the value, zero, for purposes of data analysis and presentation. The normal concentration range of each hormone at the appropriate time in the menstrual cycle is represented by the bar graph to the right of the patient data.

Table 3 Summary of Progesterone, FSH and LH Serum Concentrations On Day 20 of Cycle 2 (Control, Before Accutane NF Treatment) and Day 20 of Cycle 4 (During Accutane NF Treatment)

		Day 20, Cycle 2 Control, Before Accutane NF Treatment	Day 20, Cycle 4 During Accutane NF Treatment
Progesterone (ng/mL)			
	N	9	9
	Mean	0.20	0.05
	SD	0.21	0.08
	Min	0.00	0.00
	Median	0.15	0.00
	Max	0.69	0.21
	CV%	102.46	154.80
FSH (mIU/mL)			
	N	9	9
	Mean	2.03	2.23
	SD	1.08	1.79
	Min	0.61	0.27
	Median	1.91	2.16
	Max	3.85	5.05
	CV%	53.21	80.30
LH (mIU/mL)			
	N	9	9
	Mean	2.01	2.56
	SD	2.01	2.19
	Min	0.00	0.00
	Median	1.37	2.59
	Max	5.72	5.82
	CV%	99.91	85.37

Figure 4 **Individual and Median Serum Progesterone Concentrations on Day 20 of Cycle 2 (Control, Before Accutane NF Treatment) and Day 20 of Cycle 4 (During Accutane NF Treatment)**

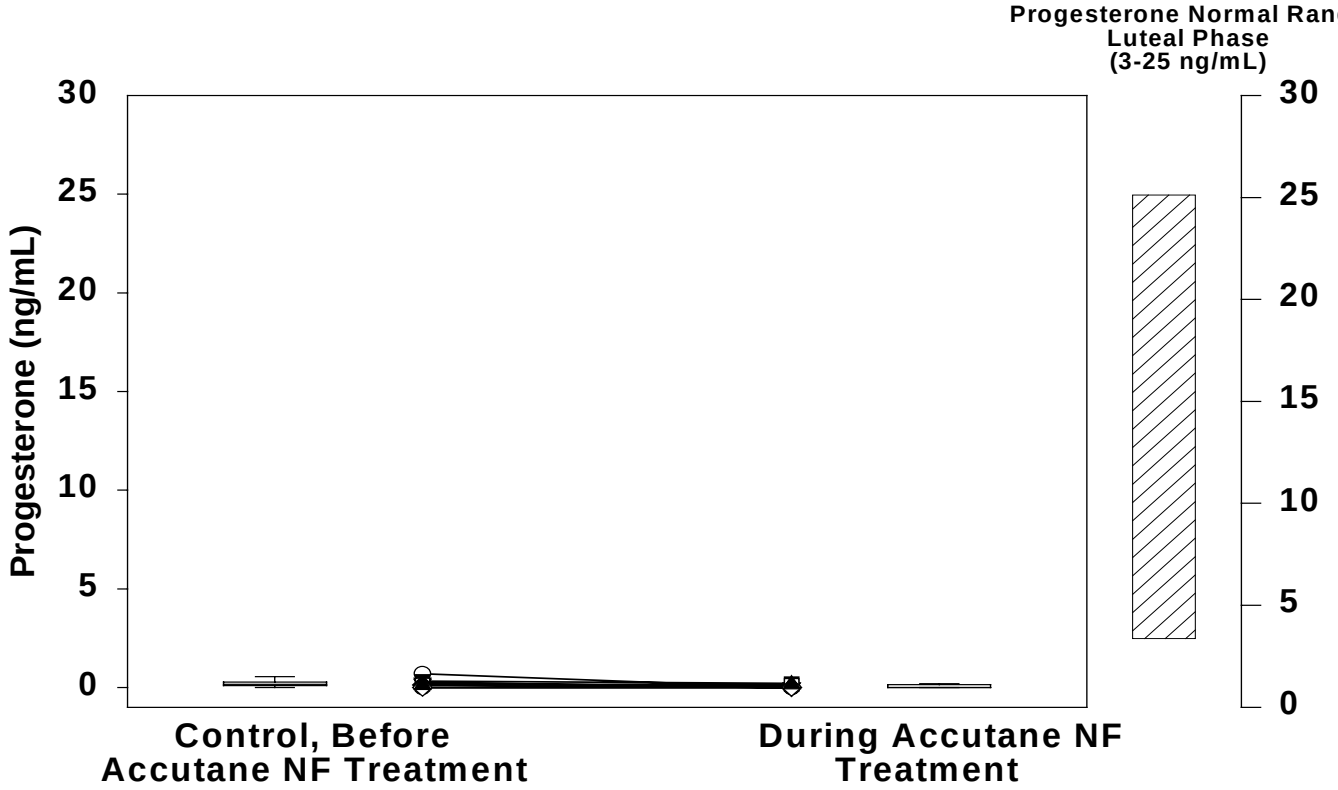


Figure 5 **Individual and Median FSH Serum Concentrations on Day 20 of Cycle 2 (Control, Before Accutane NF Treatment) and Day 20 of Cycle 4 (During Accutane NF Treatment)**

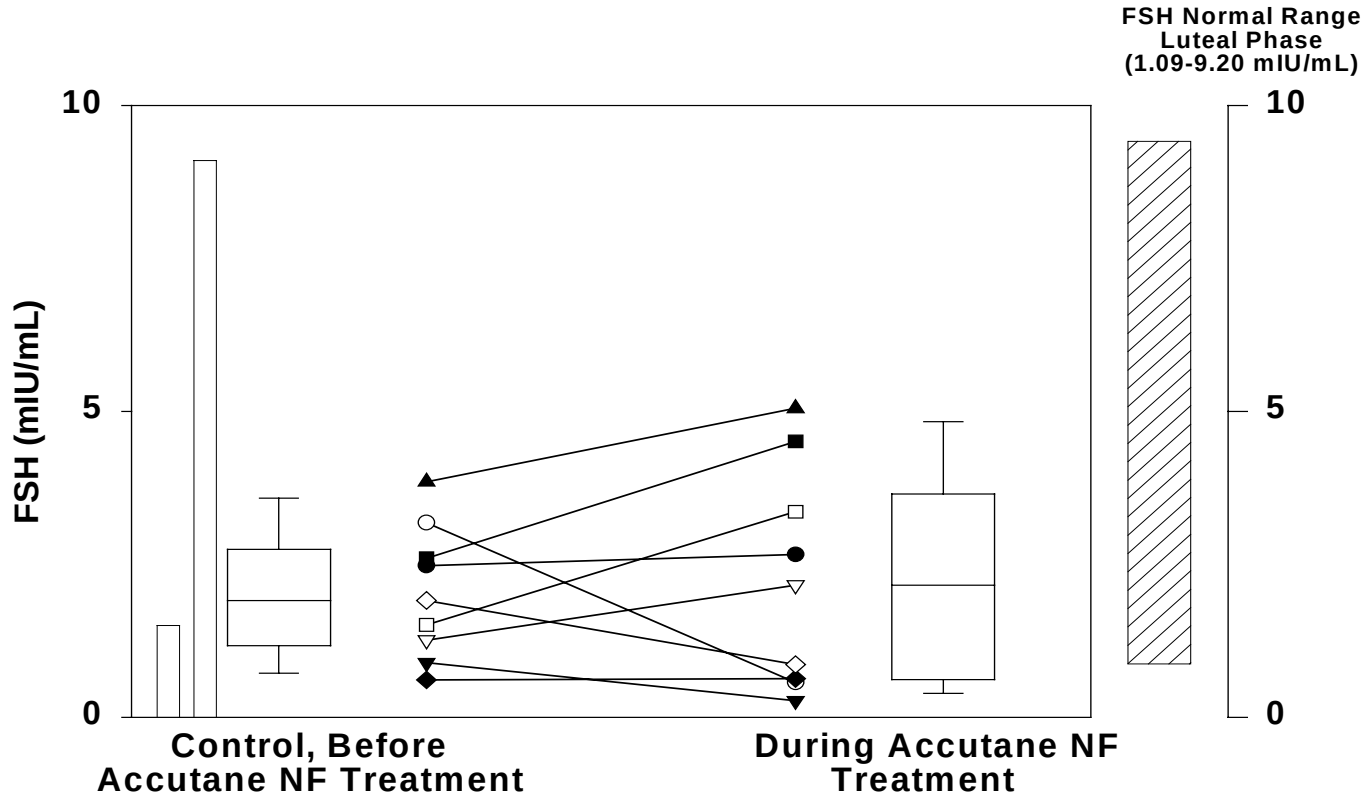
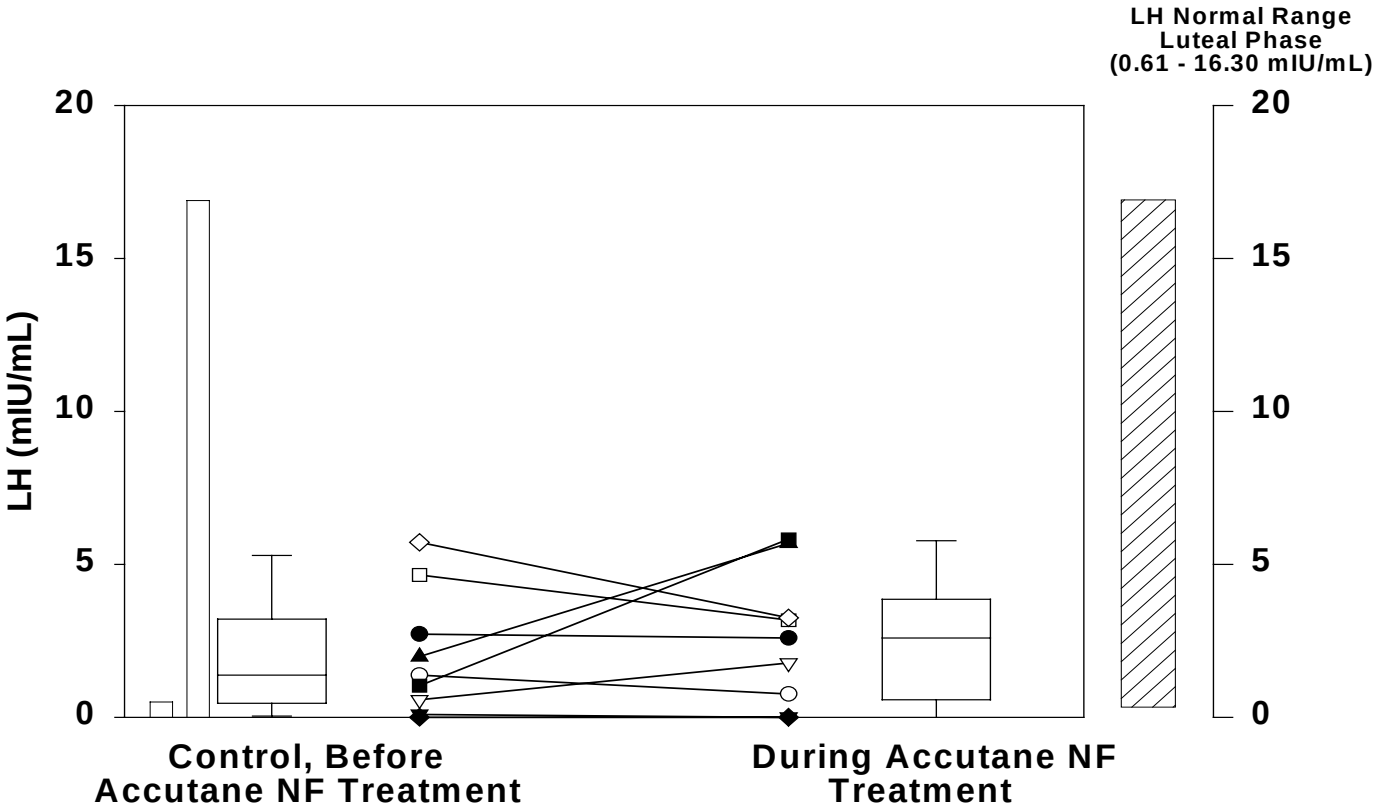


Figure 6 **Individual and Median LH Serum Concentrations on Day 20 of Cycle 2 (Control, Before Accutane NF Treatment) and Day 20 of Cycle 4 (During Accutane NF Treatment)**



3. SAFETY RESULTS

The overall safety results can be summarized as follows:

- There were no unexpected or serious adverse events related to the study treatment in this patient group evaluated through the data collection period of February 23, 2000.

3.1 Extent of Exposure to Trial Medication

This study is an open-label, drug interaction trial of ethinyl estradiol and norethindrone administered as Ortho Novum 7/7/7™ and isotretinoin administered as Accutane NF 0.4 mg/kg/day in adult women with severe, recalcitrant, nodular acne. All nine patients included in this interim document received two cycles of Ortho Novum 7/7/7™ before the start of Accutane NF treatment. Accutane NF and Ortho Novum 7/7/7™ were administered concomitantly for 16 to 20 weeks, followed by one month of Ortho Novum 7/7/7™ administered alone during the final month of study participation.

3.2 Adverse Events

3.2.1 Overview of Adverse Events

A summary of all adverse events (AEs) reported by the investigator is presented in Table 4. A listing of all adverse events that occurred in the nine study patients presented in this interim document is presented in Appendix 2.

Table 4 Summary of Adverse Events by Body System and Intensity

Body System/ Adverse Event	All Periods Accutane NF/ Ortho Novum-7/7/7 N = 9				All Periods Ortho Novum-7/7/7 N = 9			
	Tot No.	Mild No.	Mod No.	Sev No.	Tot No.	Mild No.	Mod No.	Sev No.
ALL BODY SYSTEMS								
Total Pts with at Least one AE	9	5	2	2	2	2	-	-
Total Number of AEs	24	7	3	2	2	2	-	-
SKIN & SUBCUTANEOUS TISSUE DISORDERS								
Total Pts With at Least one AE	9	1	2	-	-	-	-	-
DRY SKIN	8	1	2	-	-	-	-	-
LOCALISED EXFOLIATION	1	-	-	-	-	-	-	-
Total Number of AEs	9	1	2	-	-	-	-	-
GASTROINTESTINAL DISORDERS								
Total Pts With at Least one AE	8	1	1	2	-	-	-	-
LIP DRY	8	-	1	2	-	-	-	-
NAUSEA	1	1	-	-	-	-	-	-
Total Number of AEs	9	1	1	2	-	-	-	-
"RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS"								
Total Pts With at Least one AE	3	2	-	-	-	-	-	-
COUGH	1	1	-	-	-	-	-	-
EPISTAXIS	1	1	-	-	-	-	-	-
NASAL DRYNESS	1	-	-	-	-	-	-	-
Total Number of AEs	3	2	-	-	-	-	-	-
GENERAL DISORDERS								
Total Pts With at Least one AE	1	1	-	-	-	-	-	-
PAIN NOS	1	1	-	-	-	-	-	-
RIGORS	1	1	-	-	-	-	-	-
Total Number of AEs	2	2	-	-	-	-	-	-
DISORDERS OF THE REPRODUCTIVE SYSTEM AND BREAST								
Total Pts With at Least one AE	-	-	-	-	1	1	-	-
INTERMENSTRUAL BLEEDING	-	-	-	-	1	1	-	-
Total Number of AEs	-	-	-	-	1	1	-	-
INFECTIONS & INFESTATIONS								
Total Pts With at Least one AE	1	1	-	-	-	-	-	-
INFLUENZA	1	1	-	-	-	-	-	-
Total Number of AEs	1	1	-	-	-	-	-	-

Table 4 Summary of Adverse Events by Body System and Intensity (Cont.)

All Periods Body System/ Adverse Event	All Periods Accutane NF/ Ortho Novum-7/7/7 N = 9				 Ortho Novum-7/7/7 N = 9			
	Tot No.	Mild No.	Mod No.	Sev No.	Tot No.	Mild No.	Mod No.	Sev No.
NEUROLOGICAL DISORDERS								
Total Pts With at Least one AE	-	-	-	-	1	1	-	-
HEADACHE NOS	-	-	-	-	1	1	-	-
Total Number of AEs	-	-	-	-	1	1	-	-

Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual under a given treatment through the data collection period of February 23, 2000.
Any difference between the total number and sum of AEs is due to missing investigators assessment of the most severe intensity.

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3.2.2 Incidence of Adverse Events by Relationship to Study Drug

A summary of all adverse events (AEs) by body system and intensity reported by the investigator that occurred during the study reporting period is presented in Table 4. A listing of all adverse events that occurred in the nine study patients presented in this interim document is presented in Appendix 2.

3.3 Death, Serious Adverse Events, and Adverse Events Leading to Premature Withdrawal From the Study

No deaths, serious adverse events or adverse events leading to premature withdrawal from the study were reported for the nine study patients included in this interim document through the data cut-off date of February 23, 2000.

All nine patients reported at least one adverse event. Adverse events without intensity ratings are those which were ongoing at the time of the data cut-off date of February 23, 2000. Of the AEs which had resolved by the February 23, 2000, two were considered to be severe. Both were dry lips, reported for patients 25163/101 and 25163/122, and both were considered to be probably related to study treatment. Both patients received topical over-the-counter lip balm preparations as treatment. All other AEs were classified as either mild or moderate and those considered to be related to study treatment are known adverse events of oral contraceptives and/or isotretinoin.

4. DISCUSSION

Protocol NR15792 is an open-label, drug interaction study designed to determine if Accutane NF (0.4 mg/kg/day) administered in one daily dose without food alters the pharmacokinetics and/or surrogate markers of pharmacodynamic effectiveness of ethinyl estradiol and norethindrone administered as Ortho Novum 7/7/7™ in 24 women between the ages of 18 and 45 years who require isotretinoin treatment for severe, recalcitrant, nodular acne. This study was initiated in September 1999; as of February 23, 2000, 23 patients had been enrolled into the study, with nine of these 23 patients having completed all of their required pharmacokinetic study visits. At a meeting on January 20, 2000 between Roche and the FDA, Roche's plan for the evaluation of the potential for drug interactions between hormonal contraceptives and isotretinoin was discussed. During this meeting, Roche proposed submission of data from the first nine patients enrolled in Protocol NR15792 to provide preliminary information regarding any potential isotretinoin-oral contraceptive drug interaction. In a February 29, 2000 submission to NDA 18-662, Roche indicated that these data would be submitted to the Agency by May 30, 2000.

There were no unexpected or serious adverse events in these nine patients whose data were evaluable through February 23, 2000. Two of the adverse events which were reported were classified as severe. Patients 25163/101 and 25163/122 reported dry lips, which began 4 and 7 days after the initiation of Accutane NF, respectively. Both adverse events were classified by the investigator as severe in intensity and probably related to study drug; both were treated with topical, over the counter, lip balm preparations.

Surrogate markers for pharmacodynamic effectiveness, as assessed by serum concentrations of progesterone, FSH and LH were obtained on the same study days as the pharmacokinetic sampling for ethinyl estradiol and norethindrone concentrations. In healthy women not receiving systemic contraception, these three hormones are secreted in a cyclic manner.**[0001]** On or about menstrual cycle day 12, FSH and LH concentrations rise substantially which, in turn, allows for ovulation to occur. Subsequently, in the luteal phase of the menstrual cycle, progesterone concentrations rise to facilitate growth of the endometrial lining of the uterus. Progesterone levels become negligible by the start of the next menstrual cycle if pregnancy does not occur.

Administration of systemic, hormonal contraception suppresses the cyclic rises and falls in serum concentrations of progesterone, FSH and LH.**[0001]** The concentrations of these hormones in patients receiving adequate doses of oral contraceptives would be expected to remain low during the entire 28 day menstrual cycle. Women receiving oral contraceptives commonly begin their menstrual flow on or around the completion of the 21 day oral contraceptive pill cycle. By convention, then, this first day of menstrual flow is counted as the first day of the menstrual cycle.

Protocol NR15792 assessed serum concentrations of progesterone, FSH and LH on days 6 and 20 of the birth control pill dispensing pack; this approximates menstrual cycle days 12-14 (the mid point of the menstrual cycle, corresponding to the mid-cycle peak of FSH and LH) and 26-28 (during the luteal phase of the menstrual cycle), respectively. Comparisons of serum concentrations of progesterone, FSH and LH were made on birth control pill days 6 and 20 (menstrual cycle days of approximately 12-14 and 26-28, respectively) when patients were not receiving Accutane NF ("control, before Accutane NF treatment") compared with when they were receiving Accutane NF ("during Accutane NF treatment"). Evaluation of the individual patient data shows that Patient 25163/106 had a change in her progesterone and LH parameters on day 6, "during Accutane NF treatment" when compared with the same assessments on day 6 of the "before Accutane NF treatment". The significance of this change is not known, but will be more carefully evaluated once the pharmacokinetic data are available for analysis. Evaluation of all data for the nine patients included in this interim report show that the median values for progesterone, FSH and LH values at the assessments done at the "control, before Accutane NF treatment" and "during Accutane NF treatment" on birth control pill day 6 were well below normal. This suggests that there was no change in

the effectiveness of the oral contraceptive therapy, ethinyl estradiol and norethindrone, administered as Ortho Novum 7/7/7™ with concomitant Accutane NF administration. At birth control pill day 20, at the assessments done at the "control, before Accutane NF treatment" and the "during Accutane NF treatment", the median values for progesterone were below normal while the median FSH and LH values were in the low normal range at both assessments. This suggests that there is no change in the effectiveness of the oral contraceptive therapy, ethinyl estradiol and norethindrone, administered as Ortho Novum 7/7/7™, with concomitant Accutane NF administration.

5. REFERENCES

1. Bell ET, Christie SW. Gonadotrophin and steroid interrelationships during the normal menstrual cycle. *Steroidologia* 1970;1:152-174.

6. APPENDICES

Appendix 1 Listings of Demographic Data

Listing of Patient Demographic Data by Trial Treatment and CRTN/Patient Number
Protocol(s): NR15792/M01507
Analysis: ALL 9 PATIENTS Center: CRTN #25163
Treatment: Accutane NF/Ortho Novum 7/7/7; N = 9

CRTN/Pt. No.	Age yr	Sex	Weight kg	Height cm	Race
25163/0101	26	F	55	160	ORIENTAL
25163/0102	26	F	65	170	BLACK
25163/0104	20	F	66	163	ORIENTAL
25163/0105	32	F	68	165	BLACK
25163/0106	28	F	68	171	CAUCASIAN
25163/0107	20	F	51	165	CAUCASIAN
25163/0119	31	F	64	175	CAUCASIAN
25163/0122	24	F	55	157	BLACK
25163/0123	28	F	123	173	CAUCASIAN

CRTN = Clinical Research Task Number (center no.)
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Appendix 2 Listings of Patients with Adverse Events

Listing of Patients with Adverse Events by CRTN/Patient Number with Actually Received Treatment
All Adverse Events Protocol(s): NR15792/M01507
Analysis: ALL 9 PATIENTS Center: CRTN #25163

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Intensity	Day of Onset	Duration in days	Trial Treatment: Actually Received	Trial Treatment: Scheduled Visit	Trial Treatment: Days on TT	Time after Last Dose days	Relation to Trial Treatment	Outcome	Treatm. given	Discont or Dose Adjusted
25163/0101	26	F	55											
NAUSEA				MILD	30	63	Accutane NF/Ortho Novum 7/7/7	Period 2	1	**	PROBABLE	RESOLVED, NO SEQUELAE	NO	NONE
LIP DRY				SEVERE	33	?	Accutane NF/Ortho Novum 7/7/7	Period 2	4	**	PROBABLE	.	YES	NONE
LOCALISED EXFOLIATION				.	36	?	Accutane NF/Ortho Novum 7/7/7	Period 2	7	**	PROBABLE	.	NO	NONE
25163/0102	26	F	65											
LIP DRY				.	34	?	Accutane NF/Ortho Novum 7/7/7	Period 2	4	**	PROBABLE	.	YES	NONE
DRY SKIN				.	58	?	Accutane NF/Ortho Novum 7/7/7	Period 2	28	**	PROBABLE	.	NO	NONE
EPISTAXIS				MILD	58	32	Accutane NF/Ortho Novum 7/7/7	Period 2	28	**	PROBABLE	RESOLVED, NO SEQUELAE	YES	NONE
25163/0104	20	F	66											
DRY SKIN				MODERATE	35	54	Accutane NF/Ortho Novum 7/7/7	Period 2	4	**	PROBABLE	RESOLVED, NO SEQUELAE	NO	NONE
LIP DRY				.	35	?	Accutane NF/Ortho Novum 7/7/7	Period 2	4	**	PROBABLE	.	YES	NONE
25163/0105	32	F	68											
LIP DRY				.	41	?	Accutane NF/Ortho Novum 7/7/7	Period 2	7	**	PROBABLE	.	YES	NONE
DRY SKIN				.	47	?	Accutane NF/Ortho Novum 7/7/7	Period 2	13	**	PROBABLE	.	.	NONE
COUGH				MILD	53	6	Accutane NF/Ortho Novum 7/7/7	Period 2	19	**	UNRELATED	RESOLVED, NO SEQUELAE	YES	NONE
PAIN NOS				MILD	53	6	Accutane NF/Ortho Novum 7/7/7	Period 2	19	**	UNRELATED	RESOLVED, NO SEQUELAE	YES	NONE
RIGORS				MILD	53	6	Accutane NF/Ortho Novum 7/7/7	Period 2	19	**	UNRELATED	RESOLVED, NO SEQUELAE	YES	NONE
25163/0106	28	F	68											
DRY SKIN				MILD	90	30	Accutane NF/Ortho Novum 7/7/7	Period 2	57	**	PROBABLE	RESOLVED, NO SEQUELAE	NO	NONE
25163/0107	20	F	51											
DRY SKIN				.	36	?	Accutane NF/Ortho Novum 7/7/7	Period 2	7	**	PROBABLE	.	NO	NONE
LIP DRY				.	36	?	Accutane NF/Ortho Novum 7/7/7	Period 2	7	**	PROBABLE	.	YES	NONE
25163/0119	31	F	64											
DRY SKIN				.	36	?	Accutane NF/Ortho Novum 7/7/7	Period 2	6	**	PROBABLE	.	YES	NONE
LIP DRY				.	36	?	Accutane NF/Ortho Novum 7/7/7	Period 2	6	**	PROBABLE	.	YES	NONE

(patient continuing ...)

CRTN = Clinical Research Task Number (center no.)
'?' = At least one date is missing or invalid since AE is ongoing.
'**' = No derivation done because end of trial drug administration after AE onset.
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Listing of Patients with Adverse Events by CRTN/Patient Number with Actually Received Treatment
All Adverse Events Protocol(s): NR15792/M01507
Analysis: ALL 9 PATIENTS Center: CRTN #25163

CRTN/Pt. No. / Adverse Event	Age yr	Sex	Weight kg	Intensity	Day of Onset	Duration in days	Trial Treatment: Actually Received	Trial Treatment: Scheduled Visit	Trial Treatment: Days on TT	Time after Last Dose days	Relation to Trial Treatment	Outcome	Treatm. given	Discont. or Dose Adjusted
(... patient continuing)														
25163/0119	31	F	64											
INFLUENZA				MILD	53	6	Accutane NF/Ortho Novum 7/7/7	Period 2	23	**	UNRELATED	RESOLVED, NO SEQUELAE	NO	NONE
25163/0122	24	F	55											
INTERMENSTRUAL BLEEDING				MILD	11	94	Ortho Novum 7/7/7	Period 1	11	**	POSSIBLE	RESOLVED, NO SEQUELAE	NO	NONE
LIP DRY				SEVERE	37	?	Accutane NF/Ortho Novum 7/7/7	Period 2	7	**	PROBABLE	.	YES	NONE
DRY SKIN				.	39	?	Accutane NF/Ortho Novum 7/7/7	Period 2	9	**	PROBABLE	.	YES	.
25163/0123	28	F	123											
HEADACHE NOS				MILD	23	< 1	Ortho Novum 7/7/7	Period 1	23	< 1	UNRELATED	RESOLVED, NO SEQUELAE	YES	NONE
NASAL DRYNESS				.	42	?	Accutane NF/Ortho Novum 7/7/7	Period 2	12	**	PROBABLE	.	YES	NONE
DRY SKIN				MODERATE	44	?	Accutane NF/Ortho Novum 7/7/7	Period 2	14	**	PROBABLE	.	YES	NONE
LIP DRY				MODERATE	44	?	Accutane NF/Ortho Novum 7/7/7	Period 2	14	**	PROBABLE	.	YES	NONE

CRTN = Clinical Research Task Number (center no.)
'?' = At least one date is missing or invalid since AE is ongoing.
'**' = No derivation done because end of trial drug administration after AE onset.
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