Appendix 10
Interim Study Report for Protocol NR15888

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1. STUDY POPULATION

1.1 Disposition of Patients

This document summarizes the pharmacodynamic and safety data for the first eight patients who completed all of the required visits for Roche Protocol 15888 on or before September 30, 1999. The patient numbers for this subset are 24372/001, 24372/003, 24372/004, 24372/005, 24372/007, 24372/009, 24372/010 and 24372/011. The cut-off date for these data was September 30, 1999.

1.2 Demographic Data and Baseline Characteristics

A summary of the demographic data for the eight 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

	Accutane/Ortho Novum 7/7/7 N = 8
Sex	
MALE	-
FEMALE	8
n	8
Race	
CAUCASIAN	4
BLACK	1
ORIENTAL	2
OTHER	1
n	8
Age	
Mean	26.5
SD	2.98
SEM	1.05
Median	27.5
Min-Max	22 - 31
n	8
Weight in kg	
Mean	59.19
SD	3.893
SEM	1.376
Median	58.60
Min-Max	53.6 – 65.4
n	8
Height in cm	
Mean	163.9
SD	6.56
SEM	2.32
Median	164.0
Min-Max	152 - 175
n	8

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

Source Data: Appendix 1
DM11 16NOV1999:10:41:07 (1 of 1)

2. PHARMACODYNAMIC RESULTS

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

- No changes were seen in serum concentrations of progesterone, follicle stimulating hormone (FSH), or luteinizing hormone (LH) in patients receiving ethinyl estradiol and norethindrone as Ortho Novum 7/7/7™ and concomitant Accutane® treatment.

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

2.1.1 Progesterone, FSH and LH Serum Concentrations on Day 6 of Cycle 2 (Control, No Accutane®) and Day 6 of Cycle 4 (Accutane® Treatment)

Descriptive statistical summaries for serum concentrations of progesterone, FSH and LH on day 6 of cycle 2 (control, no Accutane®) and day 6 of cycle 4 (Accutane® 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, no Accutane®) and day 6 of cycle 4 (Accutane® treatment), respectively. The corresponding concentration values on day 6 of cycles 2 and 4 have been connected with a solid line to illustrate the changes in the values with respect to Accutane® treatment. 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. The box plots represent the median, the upper and lower quartile, and the 95% and 5% percentile for the eight subjects on the specified day.

Table 2 Summary of Progesterone, FSH and LH Serum Concentrations On Day 6 of Cycle 2 (Control, No Accutane®) and Day 6 of Cycle 4 (Accutane® Treatment)

		Day 6, Cycle 2 Control, No Accutane®	Day 6, Cycle 4 Accutane® Treatment
Progesterone (ng/mL)			
	N	8	8
	Mean	0.12	0.18
	SD	0.21	0.20
	Min	0.00	0.00
	Median	0.00	0.11
	Max	0.60	0.44
	CV%	176.10	113.30
FSH (mIU/mL)			
	N	8	8
	Mean	4.19	3.73
	SD	1.59	1.92
	Min	1.40	0.00
	Median	4.05	4.15
	Max	6.10	5.80
	CV%	38.00	51.60
LH (mIU/mL)			
	N	8	8
	Mean	5.30	5.35
	SD	4.31	4.82
	Min	0.00	0.00
	Median	5.20	3.95
	Max	12.00	12.70
	CV%	81.40	90.00

Figure 1 **Individual and Median Progesterone Serum Concentrations on Day 6 of Cycle 2 (Control, No Accutane®) and Day 6 of Cycle 4 (Accutane® Treatment)**

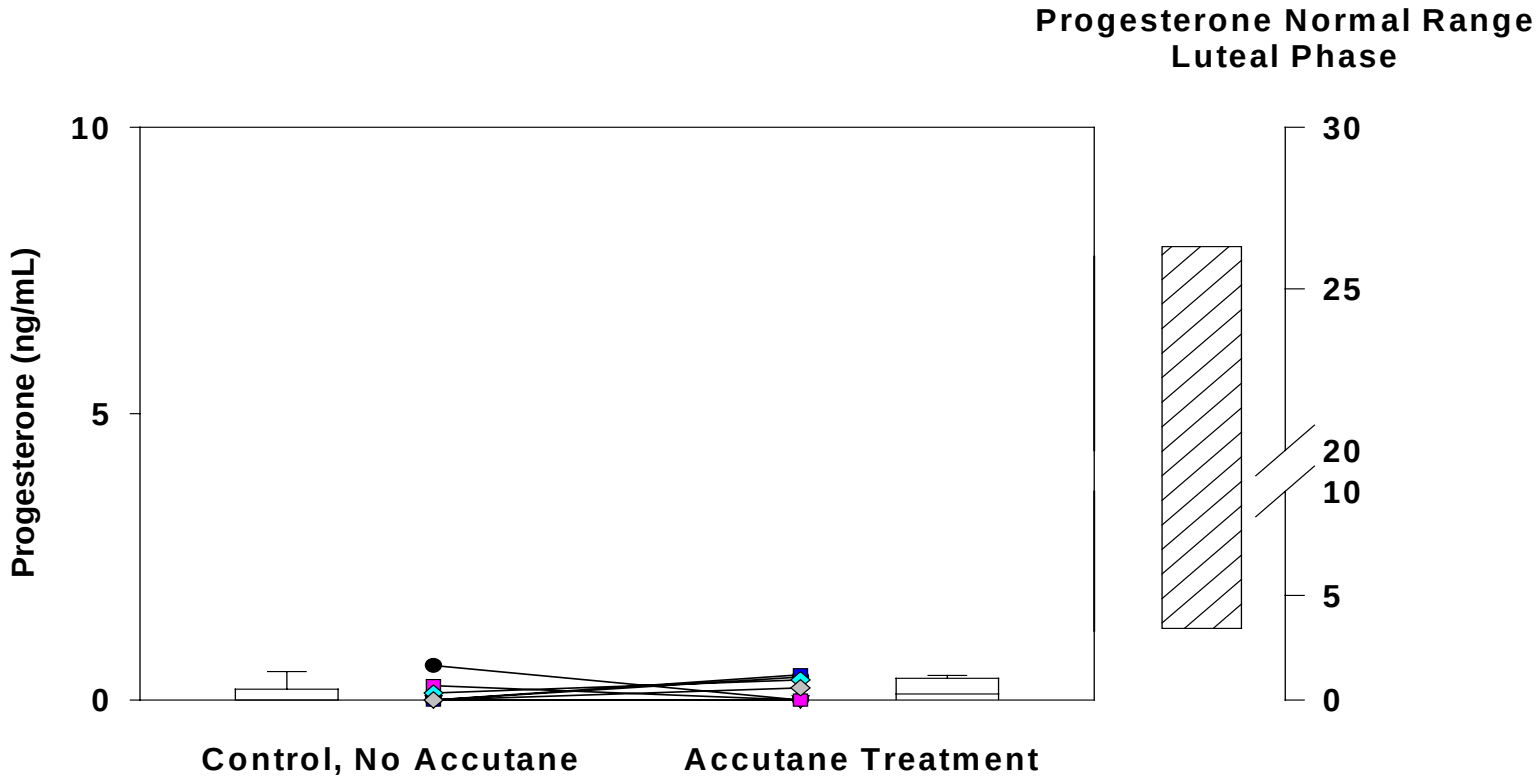


Figure 2 **Individual and Median FSH Serum Concentrations on Day 6 of Cycle 2 (Control, No Accutane®) and Day 6 of Cycle 4 (Accutane® Treatment)**

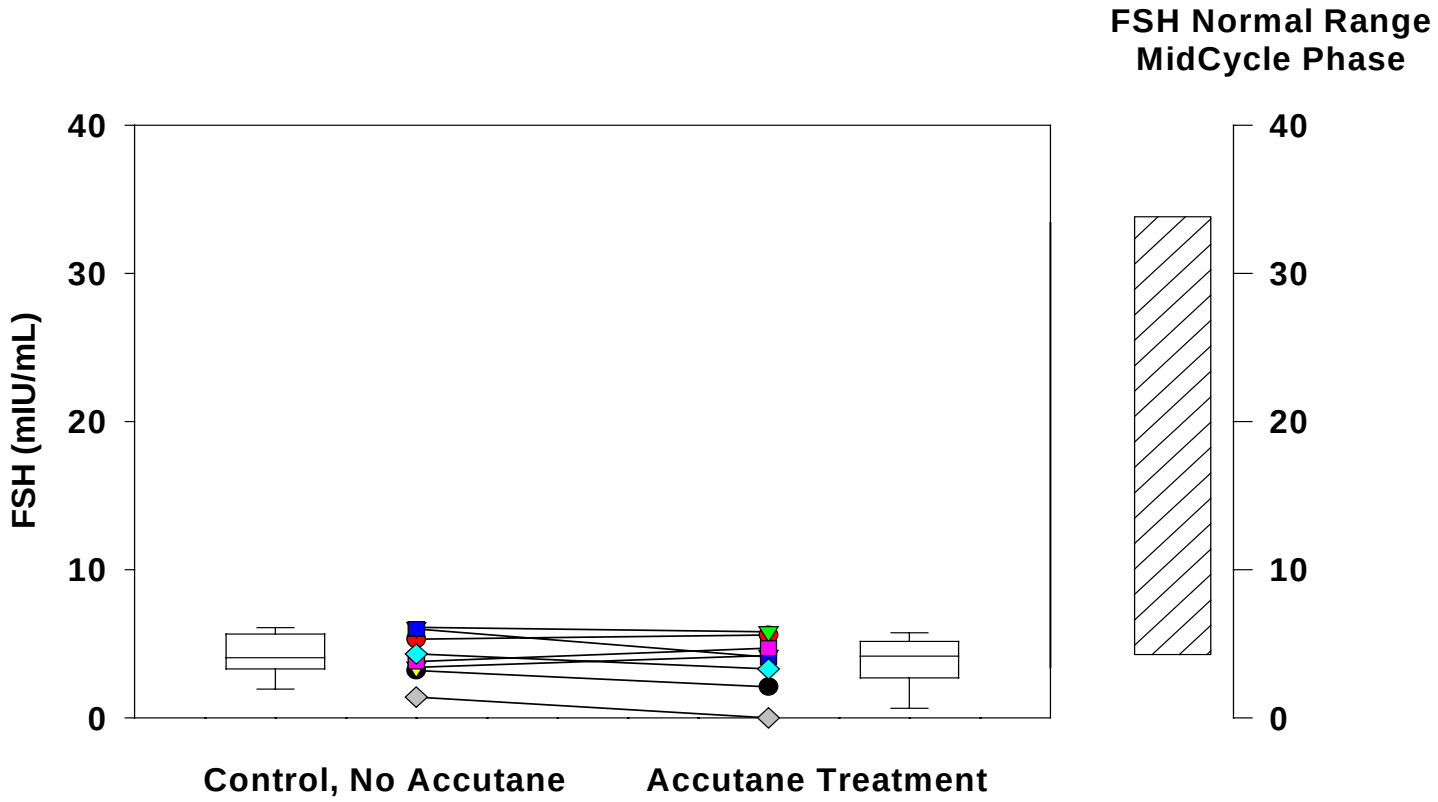
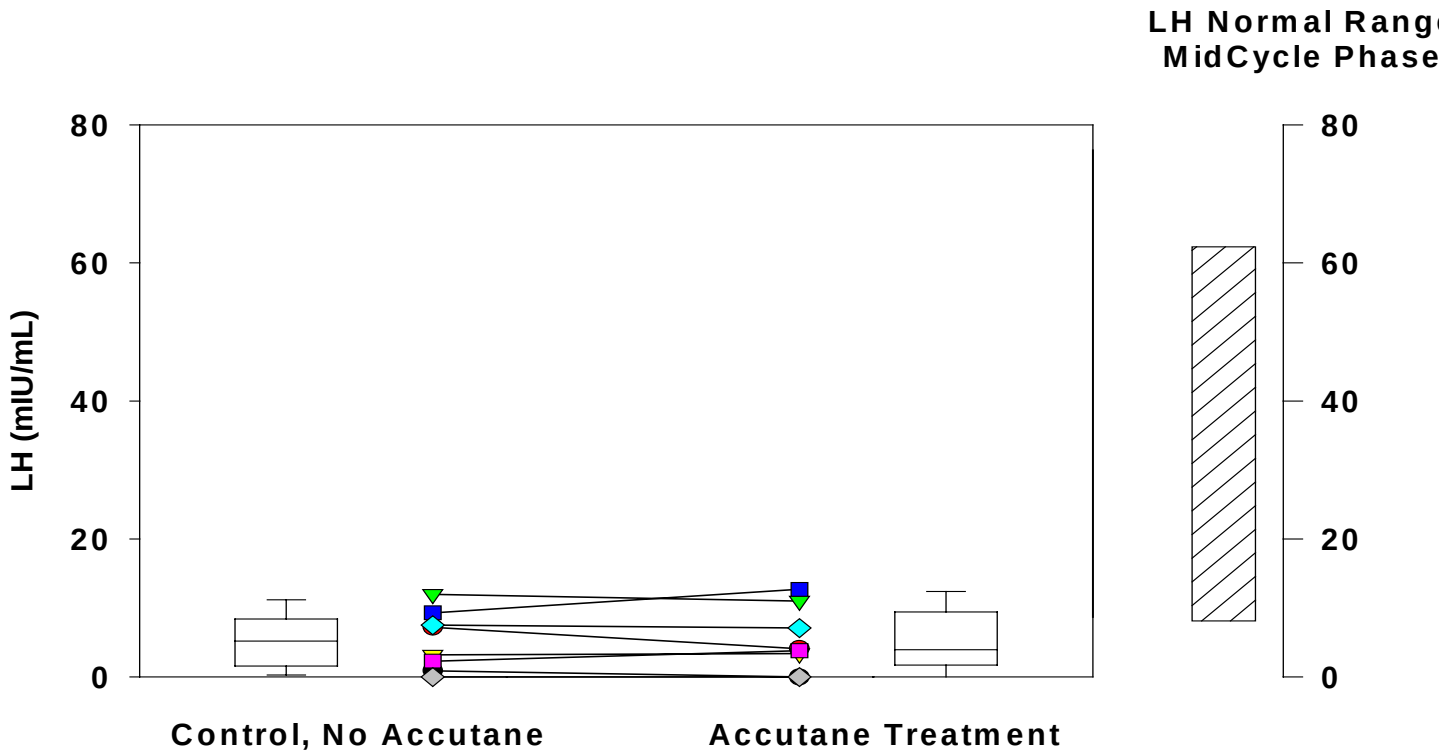


Figure 3 **Individual and Median LH Serum Concentrations on Day 6 of Cycle 2 (Control, No Accutane®) and Day 6 of Cycle 4 (Accutane® Treatment)**



2.1.2 Progesterone, FSH and LH Serum Concentrations on Day 20 of Cycle 2 (Control, No Accutane®) and Day 20 of Cycle 4 (Accutane® Treatment)

Descriptive statistical summaries for serum concentrations of progesterone, FSH and LH on day 20 of cycle 2 (control, no Accutane®) and day 20 of cycle 4 (Accutane® 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, no Accutane®) and day 20 of cycle 4 (Accutane® treatment), respectively. The corresponding concentration values on day 20 of cycles 2 and 4 have been connected with a solid line to illustrate the changes in the values with respect to Accutane® treatment. 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. The box plots represent the median, the upper and lower quartile, and the 95% and 5% percentile for the eight subjects on the specified day.

Table 3 Summary of Progesterone, FSH and LH Serum Concentrations On Day 20 of Cycle 2 (Control, No Accutane®) and Day 20 of Cycle 4 (Accutane® Treatment)

		Day 20, Cycle 2 Control, No Accutane®	Day 20, Cycle 4 Accutane® Treatment
Progesterone (ng/mL)			
	N	8	8
	Mean	0.16	0.17
	SD	0.23	0.13
	Min	0.00	0.00
	Median	0.00	0.18
	Max	0.52	0.35
	CV%	140.90	75.50
FSH (mIU/mL)			
	N	8	8
	Mean	1.78	0.99
	SD	1.36	1.43
	Min	0.70	0.00
	Median	1.40	0.00
	Max	4.80	3.50
	CV%	76.50	144.30
LH (mIU/mL)			
	N	8	8
	Mean	1.05	0.65
	SD	2.23	1.19
	Min	0.00	0.00
	Median	0.00	0.00
	Max	6.40	3.40
	CV%	211.90	183.70

Figure 4 **Individual and Median Serum Progesterone Concentrations on Day 20 of Cycle 2 (Control, No Accutane®) and Day 20 of Cycle 4 (Accutane® Treatment)**

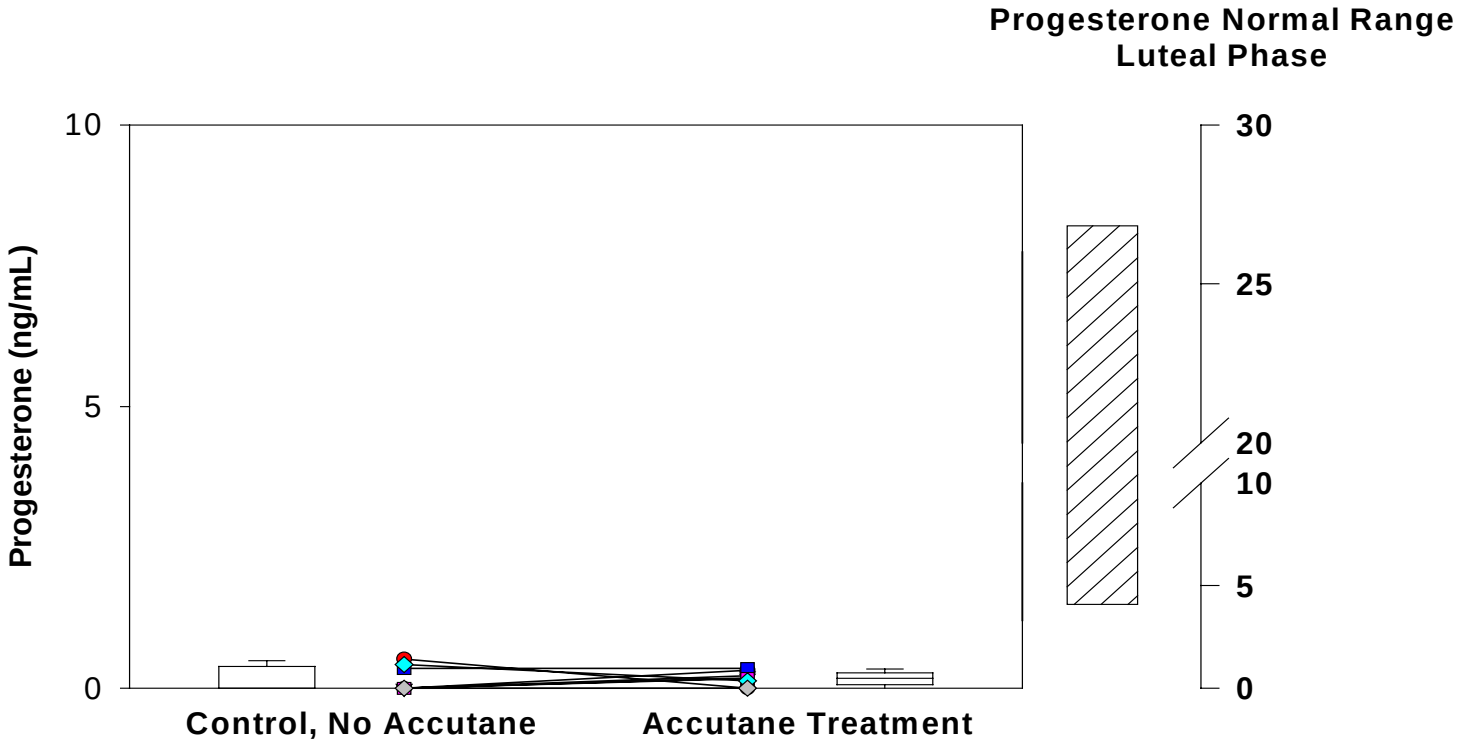


Figure 5 **Individual and Median FSH Serum Concentrations on Day 20 of Cycle 2 (Control, No Accutane®) and Day 20 of Cycle 4 (Accutane® Treatment)**

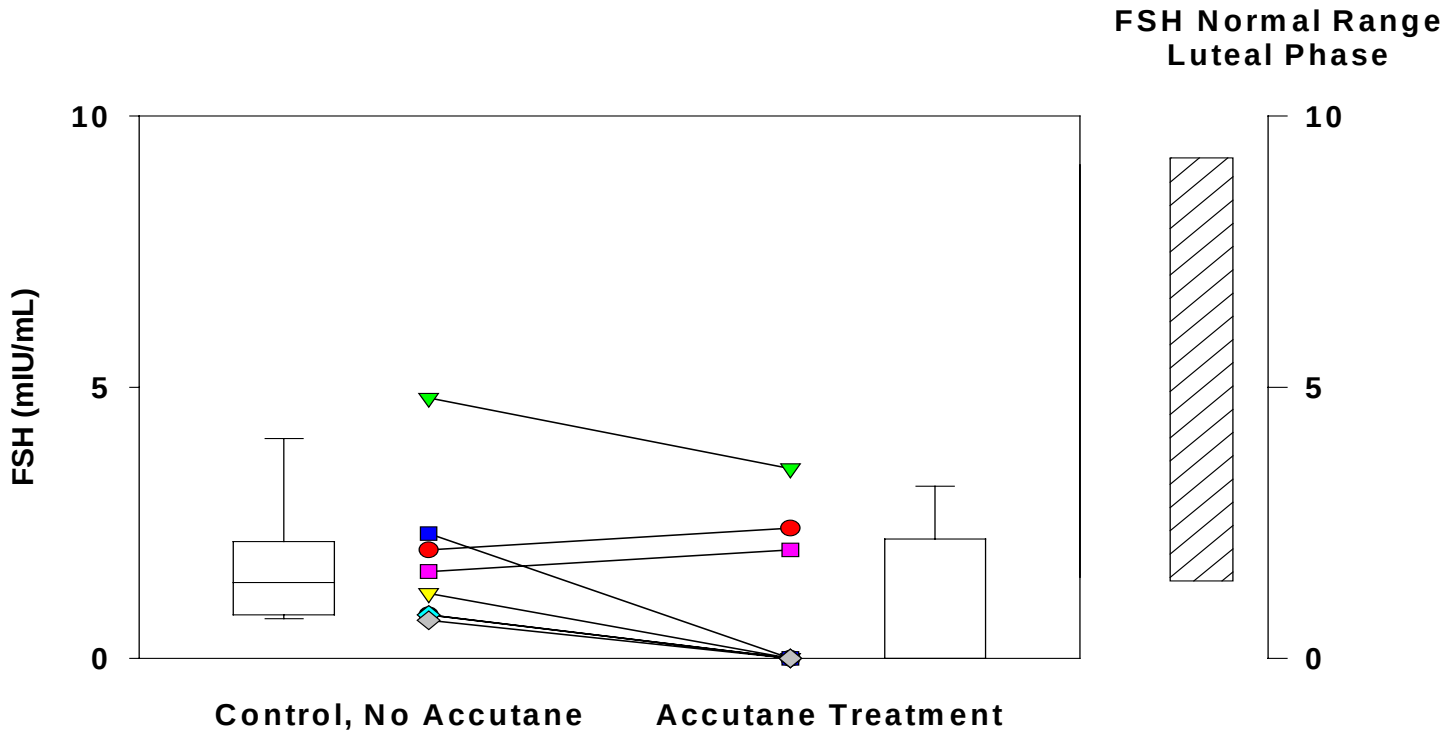
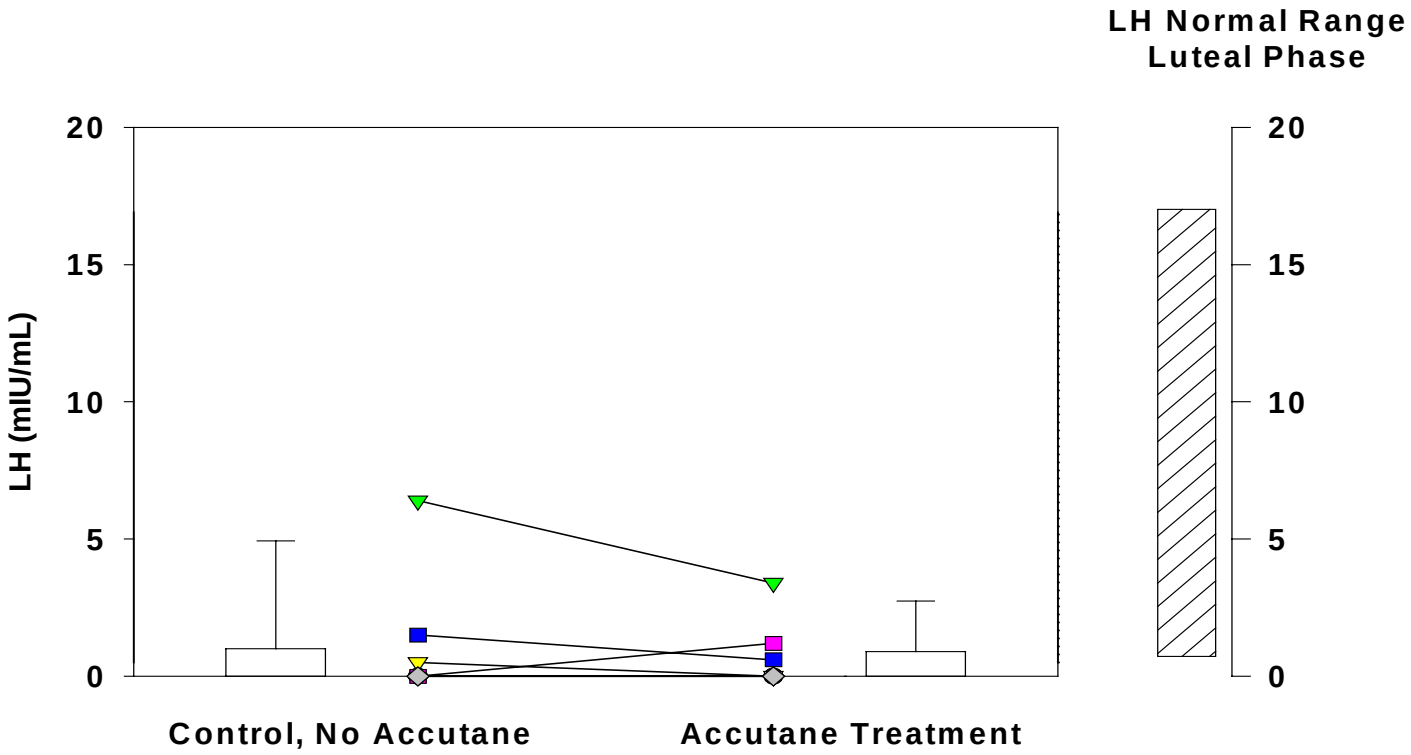


Figure 6 **Individual and Median LH Serum Concentrations on Day 20 of Cycle 2 (Control, No Accutane®) and Day 20 of Cycle 4 (Accutane® Treatment)**



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 September 30, 1999.

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® 1.0 mg/kg/day in adult women with severe, recalcitrant, nodular acne. All eight patients in this interim document received two cycles of Ortho Novum 7/7/7™ prior to the start of Accutane® treatment. Accutane® and Ortho Novum 7/7/7™ were administered concomitantly for 16 to 20 weeks, then one month of Ortho Novum 7/7/7™ was administered alone during the final month of study participation.

3.2 Clinical 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 eight study patients presented in this interim document is presented in Appendix 2.

All eight patients reported at least one adverse event. Patients who reported an identical adverse event on more than one occasion had the most severe AE listed in Table 4. The majority of the AEs were classified as mild in intensity. One severe AE was reported. Patient 24372/007 experienced a severe recurrent oral herpes simplex infection that was believed by the investigator to be unrelated to the study medication. No unexpected or serious adverse events were reported up to September 30, 1999 in these eight patients in the study.

Table 4 Summary of Adverse Events by Body System and Intensity

BODY SYSTEM / ADVERSE EVENT	Accutane/Ortho Novum 7/7/7 N = 8 TOTAL No.	(%)	MILD No.	MOD No.	SEV No.	UNSP No.	Ortho Novum 7/7/7 N = 8 TOTAL No.	(%)	MILD No.	MOD No.	SEV No.	UNSP No.
ALL BODY SYSTEMS												
Total patients with at least one AE	8		7	3	1	-	7		7	3	-	-
Total number of AEs	34		29	4	1	-	15		12	3	-	-
GASTROINTESTINAL DISORDERS												
Total patients with at least one AE	6		6	-	-	-	2		2	-	-	-
Total number of AEs	6		6	-	-	-	2		2	-	-	-
CHEILITIS	4		4	-	-	-	-		-	-	-	-
NAUSEA	1		1	-	-	-	1		1	-	-	-
ABDOMINAL PAIN NOS	-		-	-	-	-	1		1	-	-	-
GASTRITIS	1		1	-	-	-	-		-	-	-	-
NEUROLOGICAL DISORDERS												
Total patients with at least one AE	3		3	-	-	-	3		1	2	-	-
Total number of AEs	3		3	-	-	-	3		1	2	-	-
HEADACHE NOS	3		3	-	-	-	3		1	2	-	-
SKIN & SUBCUTANEOUS TISSUE DISORDERS												
Total patients with at least one AE	4		3	1	-	-	2		2	-	-	-
Total number of AEs	6		5	1	-	-	2		2	-	-	-
ACNE AGGRAVATED	2		2	-	-	-	-		-	-	-	-
ECZEMA NOS	1		1	-	-	-	1		1	-	-	-
CHLOASMA	-		-	-	-	-	1		1	-	-	-
DERMATITIS ATOPIC	1		-	1	-	-	-		-	-	-	-
DRY SKIN	1		1	-	-	-	-		-	-	-	-
RASH ERYTHEMATOUS	1		1	-	-	-	-		-	-	-	-
MUSCULOSKELETAL												
Total patients with at least one AE	4		3	1	-	-	-		-	-	-	-
Total number of AEs	4		3	1	-	-	-		-	-	-	-
BACK PAIN	1		-	1	-	-	-		-	-	-	-
GANGLION	1		1	-	-	-	-		-	-	-	-
MUSCLE SPASMS	1		1	-	-	-	-		-	-	-	-
MUSCULOSKELETAL PAIN	1		1	-	-	-	-		-	-	-	-

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LEGEND: MOD=Moderate, SEV=Severe, UNSP=Unspecified
NOTE: Percentages are based on N. If N < 10 percentages are omitted.
If a subject reports more than one identical adverse events the most severe is chosen

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

BODY SYSTEM / ADVERSE EVENT	Accutane/Ortho Novum 7/7/7 N = 8 TOTAL No.	(%)	MILD No.	MOD No.	SEV No.	UNSP No.	Ortho Novum 7/7/7 N = 8 TOTAL No.	(%)	MILD No.	MOD No.	SEV No.	UNSP No.
DISORDERS OF THE REPRODUCTIVE SYSTEM AND BREAST												
Total patients with at least one AE	2		2	-	-	-	2		2	-	-	-
Total number of AEs	3		3	-	-	-	2		2	-	-	-
DYSMENORRHOEA	1		1	-	-	-	1		1	-	-	-
AMENORRHOEA NOS	-		-	-	-	-	1		1	-	-	-
INTERMENSTRUAL BLEEDING	1		1	-	-	-	-		-	-	-	-
MENORRHAGIA	1		1	-	-	-	-		-	-	-	-
INFECTIONS & INFESTATIONS												
Total patients with at least one AE	2		1	1	1	-	2		1	1	-	-
Total number of AEs	4		2	1	1	-	2		1	1	-	-
BRONCHITIS NOS	-		-	-	-	-	1		-	1	-	-
HERPES SIMPLEX	1		-	-	1	-	-		-	-	-	-
NASOPHARYNGITIS	1		1	-	-	-	-		-	-	-	-
PHARYNGITIS NOS	-		-	-	-	-	1		1	-	-	-
PHARYNGITIS STREPTOCOCCAL	1		-	1	-	-	-		-	-	-	-
UPPER RESPIRATORY TRACT INFECTION NOS	1		1	-	-	-	-		-	-	-	-
DISORDERS OF THE EYE												
Total patients with at least one AE	3		3	-	-	-	-		-	-	-	-
Total number of AEs	3		3	-	-	-	-		-	-	-	-
BLINDNESS NIGHT	1		1	-	-	-	-		-	-	-	-
PAINFUL RED EYES	1		1	-	-	-	-		-	-	-	-
XEROPHTHALMIA	1		1	-	-	-	-		-	-	-	-
GENERAL DISORDERS												
Total patients with at least one AE	2		2	-	-	-	1		1	-	-	-
Total number of AEs	2		2	-	-	-	1		1	-	-	-
INFLUENZA LIKE ILLNESS	-		-	-	-	-	1		1	-	-	-
PAIN NOS	1		1	-	-	-	-		-	-	-	-
XEROSIS	1		1	-	-	-	-		-	-	-	-
RESPIRATORY												
Total patients with at least one AE	-		-	-	-	-	2		2	-	-	-
Total number of AEs	-		-	-	-	-	2		2	-	-	-
COUGH	-		-	-	-	-	1		1	-	-	-
RHINITIS SEASONAL	-		-	-	-	-	1		1	-	-	-

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LEGEND: MOD=Moderate, SEV=Severe, UNSP=Unspecified

NOTE: Percentages are based on N. If N < 10 percentages are omitted.
If a subject reports more than one identical adverse events the most severe is chosen.

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

BODY SYSTEM / ADVERSE EVENT	Accutane/Ortho Novum 7/7/7 N = 8						Ortho Novum 7/7/7 N = 8					
	TOTAL No.	(%)	MILD No.	MOD No.	SEV No.	UNSP No.	TOTAL No.	(%)	MILD No.	MOD No.	SEV No.	UNSP No.
INJURY & POISONING												
Total patients with at least one AE	1		-	1	-	-	1		1	-	-	-
Total number of AEs	1		-	1	-	-	1		1	-	-	-
DERMATITIS CONTACT	-		-	-	-	-	1		1	-	-	-
LIMB INJURY NOS	1		-	1	-	-	-		-	-	-	-
PSYCHIATRIC DISORDERS												
Total patients with at least one AE	2		2	-	-	-	-		-	-	-	-
Total number of AEs	2		2	-	-	-	-		-	-	-	-
DEPRESSION NOS	2		2	-	-	-	-		-	-	-	-

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LEGEND: MOD=Moderate, SEV=Severe, UNSP=Unspecified
NOTE: Percentages are based on N. If N < 10 percentages are omitted.
If a subject reports more than one identical adverse events the most severe is chosen.

3.2.2 Incidence of Adverse Events by Relationship to Study Drug

A listing of all adverse events that occurred during the study is presented in Appendix 2. Criteria for the analysis of adverse events and the definitions of intensity are presented in Appendix 2.

All eight patients reported one or more adverse event; a total of 34 AEs were reported. Twenty-nine (85%) of these AEs were considered mild in intensity, four (12%) were considered moderate in intensity (12%) and one (3%) was considered severe in intensity. The severe adverse event occurred in patient 24372/007 who developed recurrent oral herpes simplex infection; this was judged by the investigator to be unrelated to study treatment.

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 in the eight study patients included in this interim document through the data cut-off date of September 30, 1999.

4. DISCUSSION

Protocol NR15888 is an open-label, drug interaction study designed to determine if Accutane® (1 mg/kg/day) administered in two divided doses with 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 April 1999; as of September 30, 1999, 14 evaluable patients had been enrolled into the study, with eight of these patients having completed all of their required study visits. A pre-NDA meeting between Roche and the FDA was held on May 29, 1999 to discuss the NDA application for a new formulation of isotretinoin, Accutane NF. During the meeting, representatives from the FDA expressed an interest in reviewing as early as possible any data which addressed the issue of a potential isotretinoin-oral contraceptive drug interaction. In a teleconference between Roche and the FDA on 12/15/99, it was agreed that this document describing the pharmacodynamic and safety data for these first eight patients would be submitted to the FDA in January, 2000.

There were no unexpected or serious adverse events in these eight patients enrolled in this study in data evaluated through September 30, 1999. Only one severe adverse event was reported: patient 24372/007 experienced a severe recurrent oral herpes simplex infection that was judged by the study investigator to be unrelated to the study medication.

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 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 NR15888 assessed serum concentrations of progesterone, FSH and LH on days 6 and 20 of the birth control pill dispensing pack; this corresponds to menstrual cycle days 12-14 and 26-28, respectively. Comparisons of serum concentrations of progesterone, FSH and LH were made on birth control pill day 6 and 20 (menstrual cycle days 12-14 and 26-28, respectively) when patients were not receiving Accutane® ("baseline") compared to during Accutane® ("on Accutane®") treatment. The progesterone, FSH and LH values both at "baseline" and "on Accutane®" at birth control pill days 6 and 20 were well below normal, as would be expected for patients receiving effective hormonal contraception. These data suggest 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® administration.

5. REFERENCES

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

6. APPENDICES

Appendix 1 Listings of Demographic Data

Appendix 2 Listings of Subjects with Adverse Events