



Elements	Metrics
	Tracking forms for any calls from female patients and professionals will be completed on the day of the call with patient demographics
<b>Behavioral Research</b>	Discriminant Study 1 <sup>st</sup> Q 2001
<b>Annual Review with the Agency of Process Goals and Analysis of Assessment Data</b>	Continue to report pregnancy exposure quarterly for trend analysis. Reestablish annual FDA meeting to access methodologies and success rate

#### 4. HORMONAL CONTRACEPTIVE EVALUATION PROGRAM

- *A comprehensive in vitro and in vivo risk assessment program is underway to confirm the lack of interaction between isotretinoin and hormonal contraceptives.*
- *No evidence of any interaction has been observed in the preliminary data.*

##### 4.1 Background

The hormonal contraceptive evaluation program presented in the following sections was developed in collaboration with the FDA. This comprehensive program consists of both laboratory (*in vitro*) studies and clinical (*in vivo*) studies to evaluate whether isotretinoin and its metabolites alter the clinical pharmacology of hormonal contraceptive drugs. All of the study results will be submitted in the 3rd quarter 2001. This program was undertaken to insure that hormonal contraceptives remain an effective form of birth control for female patients during isotretinoin therapy.

##### 4.2 In Vitro Inhibition and Induction Studies

- *Isotretinoin and its major metabolites, 4-oxo-isotretinoin, tretinoin, and 4-oxo-tretinoin, do not inhibit CYP 1A, 2C9, 2C19, 2D6, 2E1, or 3A4 in human liver microsomes.*

*In vitro* drug interaction studies using human liver microsomes were conducted to assess the effects of isotretinoin and its three major metabolites on probe drugs metabolized by specific cytochrome P450 (CYP) enzymes. The results showed that isotretinoin and its major metabolites, 4-oxo-isotretinoin, tretinoin, and 4-oxo-tretinoin, do not inhibit CYP 1A, 2C9, 2C19, 2D6, 2E1, or 3A4 in human liver microsomes. Thus, isotretinoin and its metabolites would not be expected to inhibit the metabolism of drugs metabolized by these CYP enzymes.

In addition, there are ten ongoing *in vitro* inhibition and induction drug interaction studies using human liver cells to evaluate if isotretinoin and its major metabolites have any effect on the metabolism of the following progestin compounds: medroxyprogesterone acetate, progesterone, norethindrone, norgestimate, and levonorgestrel. Because these studies are conducted with primary cultures of liver cells, the timing of the studies and submission to the FDA depends upon

the availability of live human hepatocytes and the complexity of the studies. Table 15 lists the timelines for submission of the data from these experiments.

**Table 15 Submission Dates for the In Vitro Drug Interaction Studies**

Progestin Compound	Inhibition Study	Induction Study
Medroxyprogesterone acetate	Submitted (8/2/2000)	12/04/2000
Progesterone	09/01/2000	01/29/2001
Norethindrone	10/30/2000	04/02/2001
Norgestimate	01/01/2001	05/28/2001
Levonorgestrel	03/05/2001	08/06/2001

### 4.3 Clinical Studies

There are two ongoing, open-label, Phase I clinical studies: NR15888 and NR15792. Both studies were designed to determine the effect of isotretinoin on the pharmacokinetics and pharmacodynamics of oral contraceptive pills in pre-menopausal women with severe recalcitrant nodular acne. These studies are identical in design except for the isotretinoin formulation being studied: NR15888 is studying the effect of marketed Accutane on oral contraceptives, while NR15792 is studying the effect of a new investigational isotretinoin formulation (Accutane NF) on oral contraceptives.

#### 4.3.1 Hormonal Contraceptive Physiology

The clinical outcome for lack of contraceptive effectiveness is pregnancy. In the ongoing clinical studies, serum concentrations of progesterone, follicle stimulating hormone (FSH), and luteinizing hormone (LH) are being measured and used as surrogate markers for the pharmacodynamic effectiveness of oral contraceptives. These surrogate markers of pharmacodynamic effectiveness are widely used as predictors of reproductive capacity [Barditch-Crovo et al., 1999; Israel R, et al., 1972].

Administration of systemic contraception suppresses the cyclic rise and fall in serum concentrations of progesterone, FSH, and LH. The concentrations of these hormones in female 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, the first day of menstrual flow will be counted as the first day of the menstrual cycle.

#### 4.3.2 Ortho Novum 7/7/7

Ortho Novum 7/7/7™ was specifically chosen for use in the interaction studies because it contains a combination of both ethinyl estradiol, an estrogen component used in the majority of oral contraceptive products [Hatcher et al., 1998] and norethindrone, a progestin component used in a large number of oral contraceptive products. Moreover, the norethindrone is present at three concentrations (0.5, 0.75, 1.0 mg) in this contraceptive. It is believed that all progestins are metabolized via the same metabolic pathways, so the data obtained on norethindrone should be

generalizable to other progestins. Thus, the results from these studies will be helpful in understanding the potential for isotretinoin drug interactions with other hormonal contraceptives.

#### **4.3.3 Primary Objectives of the Clinical Studies**

The primary objectives of the clinical studies are (1) to determine if isotretinoin alters the pharmacokinetics of ethinyl estradiol and norethindrone when used as oral contraception, and (2) to determine if isotretinoin alters the surrogate markers of pharmacodynamic effectiveness of ethinyl estradiol and norethindrone when used as oral contraception.

#### **4.3.4 Patient Selection Criteria and Study Enrollment**

Both studies had identical patient selection criteria. Non-pregnant, non-lactating, non-smoking women of childbearing potential between the ages of 18 and 45 years with severe recalcitrant nodular acne for whom isotretinoin is indicated, as determined by the study dermatologist, were allowed to enter. The patients had to agree to use oral contraceptives as one of their two forms of contraception during isotretinoin therapy. Patients also had to have laboratory assessments (AST, ALT, total bilirubin, fasting triglycerides, BUN, and serum creatinine) with clinically acceptable ranges as determined by the investigator. Both studies enrolled sufficient patients so that each study would have a minimum of 24 patients evaluable for the pharmacokinetic and pharmacodynamic assessments.

#### **4.3.5 Study Design**

These open-label, drug interaction studies were designed to assess if concomitant administration of 1.0 mg/kg/day of marketed Accutane (NR15888) and 0.4 mg/kg/day of Accutane NF (NR15792) alter the pharmacokinetics and/or pharmacodynamic surrogate markers of ethinyl estradiol 35 µg / norethindrone 0.5, 0.75, 1.0 mg pills (Ortho Novum 7/7/7). During study month 1, oral contraceptive pills are initiated to allow patients to become stabilized on this therapy. During oral contraceptive pill cycle 2, blood is drawn on pill days 6 and 20 at regular intervals over a 24 hour dosing period for pharmacokinetic assessments of both ethinyl estradiol and norethindrone; a single blood sample is drawn on each of these days for pharmacodynamic assessments.

Isotretinoin therapy is initiated prior to the start of oral contraceptive pill cycle 3; patients continue to take oral contraceptive pills during isotretinoin therapy. During oral contraceptive pill cycle 4, when patients are taking both oral contraceptive pills and isotretinoin, blood is again drawn on pill days 6 and 20 that was previously described for oral contraceptive pill cycle 2. Patients continue in these studies, receiving both oral contraceptives and isotretinoin until each patient has completed a 16-20 week course of isotretinoin treatment. Oral contraceptive therapy is continued for one month following the cessation of isotretinoin treatment.

#### **4.3.6 Interim Results from Clinical Study NR15888**

The clinical study NR15888 is ongoing. The last patient visit is scheduled for September 30, 2000. At that time, a minimum of 24 patients evaluable for all pharmacodynamic assessments will have completed the study. A final study report will be submitted to the FDA during the 1<sup>st</sup> quarter 2001. Interim data for patients who have completed all pharmacodynamic and safety

assessments (through study visit 9) were recently submitted to the FDA in January 2000 (Appendix 10).

#### **4.3.6.1 Study Population**

All patients are female, of whom 50% are Caucasian, 12.5% Black, 25% Oriental, and 12.5% Other. Their mean ( $\pm$ SD) age is  $26.5\pm 3.0$  years (range: 27-31 years), the mean ( $\pm$ SD) weight is  $59.19\pm 3.89$  kg (range: 53.6-65.4 kg), and the mean ( $\pm$ SD) height is  $163.9\pm 6.6$  cm (range: 152-175 cm).

#### **4.3.6.2 Interim Pharmacodynamic Results**

- *There are no apparent changes in the concentrations of progesterone, FSH, and LH, the pharmacodynamic surrogate markers of hormonal contraceptive effectiveness, with concomitant administration of Accutane.*

The three surrogate markers, progesterone, FSH, and LH are suppressed during all four pharmacodynamic assessments of the study. This suggests that there are no changes in the pharmacodynamics of oral contraceptive therapy in the presence of Accutane.

#### **4.3.6.3 Safety Results**

None of the patients became pregnant during the reporting period for this interim report. There were no deaths, serious adverse events, or adverse events leading to premature withdrawal from the study. Each of the patients reported at least one adverse event on or before study visit 9. All of the adverse events 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 Accutane.

#### **4.3.7 Results from Clinical Study NR15792**

The clinical study NR15792 is ongoing. The last patient visit is scheduled for September 30, 2000. At that time, a minimum of 24 patients evaluable for all pharmacokinetic and pharmacodynamic assessments will have completed the study. A final study report will be submitted to the FDA during the 1<sup>st</sup> quarter 2001. Interim pharmacodynamic and safety data were recently submitted to the FDA in June 2000 (Appendix 11).

#### **4.3.7.1 Study Population**

All patients are female, of whom 44.4% are Caucasian, 33.3% black, and 22.2% Oriental. The mean ( $\pm$ SD) age of the patients is  $26.1\pm 4.3$  years (range: 20-32 years), the mean ( $\pm$ SD) weight is  $68.24\pm 21.47$  kg (range: 51.4-123.0 kg), and the mean ( $\pm$ SD) height is  $166.6\pm 6.1$  cm (range: 157-175 cm).

#### 4.3.7.2 Pharmacodynamic Results

- *There are no apparent changes in the concentrations of progesterone, FSH, and LH, the pharmacodynamic surrogate markers of hormonal contraceptive effectiveness, with concomitant administration of Accutane NF.*

The pharmacodynamic results can be summarized as follows—the median values for progesterone, FSH, and 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. These three surrogate markers are suppressed during all four pharmacodynamic assessments of the study. This suggests that there are no changes in the pharmacodynamics of oral contraceptive therapy in the presence of Accutane NF.

#### 4.3.7.3 Safety Results

None of the patients became pregnant during the reporting period for this interim report. There were no deaths, serious adverse events, or adverse events leading to premature withdrawal from the study. Each of the patients reported at least one adverse event on or before study visit 9. Two of the adverse events were considered severe; both events (chapped lips) were considered probably related to study treatment. All other adverse events were classified as mild or moderate, and those considered to be related to study treatment are known adverse events of oral contraceptives and/or isotretinoin.

#### 4.4 Overall Conclusions

The current package insert states in the boxed CONTRAINDICATIONS AND WARNINGS section that: "Although hormonal contraceptives are highly effective, there have been reports of pregnancy from women who have used oral contraceptives, as well as injectable/implantable contraceptive products." This warning is the basis for using two effective means of contraception. Based on more than 18 years of experience with Accutane and on more than 450,000 female Accutane patients who have provided voluntary information about their contraceptive use, it is unlikely that the effect of hormonal contraceptives is affected by the use of Accutane. However, two forms of contraception provide a safety margin that ensures effective pregnancy prevention when both forms are used as directed.

It is now feasible to evaluate possible mechanisms of contraceptive drug interactions by both *in vitro* laboratory experiments and clinical trials. Roche has implemented a comprehensive program in this regard, as has been described in this section.

Results from the *in vitro* mechanistic studies indicate that isotretinoin and its metabolites do not inhibit the metabolism of probe drugs whose metabolism is via the most common CYP enzymes. Furthermore, from studies using live human hepatocytes, it can be concluded that isotretinoin and its metabolites do not inhibit the metabolism of medroxyprogesterone. In addition, interim data for patients who have completed their pharmacodynamic assessments suggest that Accutane does not affect the surrogate markers for pharmacodynamic effectiveness of ethinyl estradiol and norethindrone.