CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-864

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	21-864 (s042)
Generic Name:	Levonorgestrel (LNG)/ Ethinyl Estradiol (EE)
Proprietary Drug Name:	**Lybrel™**
Indication:	Oral contraceptive
Dosage Form:	Immediate Release Film-Coated Tablet
Strengths:	90 µg LNG/ 20 µg EE
Route of Administration:	Oral
Applicant:	Wyeth
Clinical Division:	DRUP (HFD-580)
Type of Submission:	NDA
Submission Date:	December 22, 2006
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader:	Myong-Jin Kim, Pharm. D.

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1. EXECUTIVE SUMMARY

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology III (OCP / DCP-III) has reviewed amendment s042 submitted to NDA 21-864 on December 22, 2006. We found this amendment acceptable from an OCP standpoint provided that the sponsor agrees with the Agency's labeling recommendations made during the review of original NDA submission.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology Findings

Lybrel™ film-coated tablets contain levonorgestrel (LNG) (90 µg) and ethinyl estradiol (EE) (20 µg) a progestin and an estrogen, respectively. Lybrel™ is a low dose combination oral contraceptive (COC) containing 28 days of LNG/EE tablets to be taken continuously with no hormone free period. This regimen differs from current oral contraceptives regimens which have a placebo or 'pill free' period that usually lasts for 4 or 7 days in a month. The formulation of Lybrel™ is similar to the currently marketed product Alesse (100 µg LNG/20 µg EE) with a slight adjustment to the LNG and lactose content.

NDA 21-864 for Lybrel™ tablets was submitted on May 25, 2005 and included the data from one Phase I, one Phase II and two Phase III studies. During the NDA review it was found that the two Phase III clinical trials used products manufactured using different procedures. On March 2, 2006 the sponsor was informed that the change in manufacturing process was considered as a Level III change according to the Guidance for Industry: Immediate Release Solid Oral Dosage Forms- Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (SUPAC-IR) and that a bioequivalence (BE) study was needed to bridge these 2 manufacturing processes. The sponsor replied with an amendment on March 6, 2006 which included a request for a waiver for the in vivo BE study since, according to the sponsor, LNG and EE met the Biopharmaceutics Classification System (BCS) Class 1 classification.

At a meeting held on March 8, 2006, the sponsor agreed to provide additional information to address the BCS classification information submitted earlier. On May 5, 2006 the FDA sent a facsimile to the sponsor informing that Lybrel™ could not be classified as BSC class 1 as EE is not highly permeable and the product does not dissolve rapidly (within 15 minutes). On June 2, 2006, the sponsor submitted a study protocol (Protocol 0858A2-108-US) under IND 65,693 (s067) entitled "Single-dose, randomized, 2-period, crossover, bioequivalence study to compare 2 manufacturing processes for LNG 90 µg / EE 20 µg in healthy cycling women". On June 27, 2006, the Agency sent an approvable letter and Wyeth's complete response was received on August 22, 2006.

The present submission (s042) is an amendment to NDA 21-864 and is part of a second review cycle for this NDA. This submission contains the results of the bioequivalence study under Protocol 0858A2-108-US. Lybrel™ tablets (LNG 90 µg/EE 20 µg; Test Tablets) manufactured using the ——— equipment were bioequivalent to Lybrel™ tablets (LNG 90 µg/EE 20 µg; Reference Tablets) manufactured using a ——— procedure. The ratio of geometric means for Cmax, AUCt and $AUC_{0\rightarrow\infty}$ values were within the 80-125 goal post for BE for both LNG and EE (Table 1). b(4)

Table 1. Point estimates and 90% confidence intervals for the log-transformed Cmax, AUCt, and $AUC_{0\rightarrow\infty}$ values of LNG and EE following single administration of the treatments

Comparison	PK parameter	Point estimates	90% CI
	LNG		
TRT T /TRT R	Cmax	98	90-107
	AUCt	105	98-113
	$AUC_{0\rightarrow\infty}$	101	94-109
	EE		
TRT T/ TRT R	Cmax	97	91-103
	AUCt	99	94-104
	$AUC_{0\rightarrow\infty}$	99	94-103

In summary, there are no clinical pharmacology issues. Below is a summary of the pharmacokinetics of Lybrel™, the majority of which has previously been reported under original NDA submission (refer to Dr. Julie Bullock's review for NDA 21-864 DFSed on 3/09/06).

Absorption and Elimination

LNG is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first-pass metabolism. Ethinyl estradiol is rapidly and almost completely absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of ethinyl estradiol is between 38% and 48%.

The most important metabolic pathways of LNG are reduction of the Δ4-3-oxo group and hydroxylation at positions 2α, 1β, and 16β, followed by conjugation. Most of the circulating metabolites are sulfates of 3α, 5β-tetrahydro-levonorgestrel, while excretion occurs predominantly in the form of glucuronides. Some of the parent LNG also circulates as 17β-sulfate. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users.

Cytochrome P450 enzymes (CYP3A4) in the liver are responsible for the 2-hydroxylation that is the major oxidative reaction of EE. The 2-hydroxy metabolite is further transformed by methylation, sulfation, and glucuronidation prior to urinary and fecal excretion. Levels of CYP3A4 vary widely among individuals and can explain the variation in rates of ethinyl estradiol 2-hydroxylation. EE also undergoes enterohepatic recirculation.

The terminal elimination half-life for LNG in Lybrel™ is about 36 hours. LNG and its metabolites are excreted in the urine (40% to 68%) and in feces (16% to 48%). The terminal elimination half-life of EE in Lybrel™ is about 21 hours.

Effect of Race

The effect of race on the PK of Lybrel™ has not been addressed.

Effect of Renal Impairment

The effect of renal function on the pharmacokinetics of Lybrel™ has not been evaluated.

Effect of Liver Impairment

The effect of hepatic impairment on the PK of Lybrel™ has not been formally evaluated. However, steroid hormones may be poorly metabolized in patients with impaired liver function.

Drug-Drug Interactions (DDI)

Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, rifabutin, barbiturates, primidone, phenylbutazone, phenytoin, dexamethasone, carbamazepine, felbamate, oxcarbazepine, topiramate, griseofulvin, and modafinil. In such cases a nonhormonal back-up method of birth control should be considered.

Combination hormonal contraceptives containing some synthetic estrogens (eg. EE) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone and other corticosteroids, and theophylline have been reported with concomitant administration of oral contraceptives. Decreased plasma concentrations of acetaminophen and lamotrigine, and increased clearance of temazepam, salicylic acid, morphine, and clofibric acid, due to induction of conjugation (particularly glucuronidation), have been noted when these drugs were administered with oral contraceptives

Dissolution

The proposed dissolution method for Lybrel™ (LNG 90 µg/ EE 20 µg) film-coated tablets is determined as directed in the USP monograph for LNG and EE Tablets.

Table 1. Proposed method and specifications for Lybrel™ (LNG 90 µg/ EE 20 µg) film-coated tablets

Apparatus	Paddle stirred vessel (USP, dissolution apparatus 2)
Dissolution medium	5 ppm (w/w) Polysorbate 80 in dionized water
Volume of dissolution medium	500 mL
Temperature	37 ± 0.5 °C
Stirring speed	75 r.p.m.
Sampling volume	15 mL
Proposed specification	LNG: Q=NLT — in 30 minutes EE: Q=NLT — in 30 minutes

b(4)

The specifications for LNG 90 mg/EE 20 mg tablets are based on those of the approved market product, Alesse® (LNG 100 mg/EE 20 mg) tablets, NDA number 20-683. On a meeting with the sponsor dated May 4, 2006, the Agency agreed to consider Wyeth's proposal to use the USP monograph dissolution method for LNG/EE Tablets. The Agency has previously agreed upon the proposed dissolution specifications for Lybrel™.

Reviewer

Sandra Suarez-Sharp, Ph.D.
Office of Clinical Pharmacology
Division of Clinical Pharmacology III

Final version signed by Myong-Jin Kim Pharm. D.
Team leader
Office of Clinical Pharmacology
Division of Clinical Pharmacology III

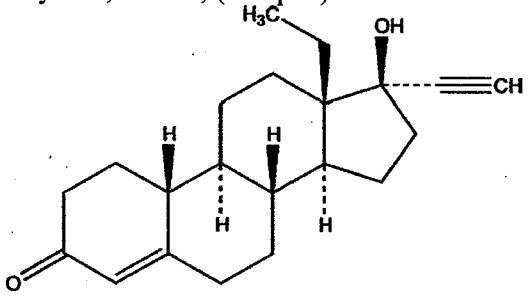
cc:
NDA 21-864 (S042): Division File
OCP/DCPIII: Bashaw, Kim, Suarez-Sharp
HFD-580: Kim, Price, Slaughter

2. QUESTION BASED REVIEW

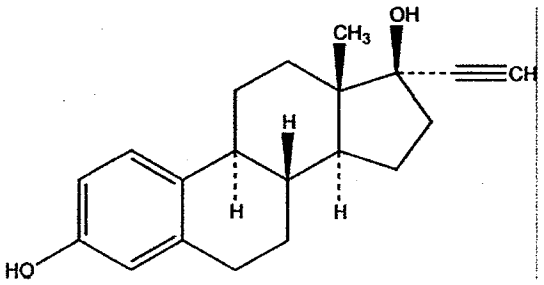
2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

The chemical formula of levonorgestrel USP is 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17 alpha)-, (-)-, and the chemical formula of ethinyl estradiol USP is 19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17alpha)-. The structural formulas are as follows:



Levonorgestrel
$C_{21}H_{28}O_2$ M.W. 312.45



Ethinyl Estradiol
$C_{20}H_{24}O_2$ M.W. 296.40

FORMULATION

Lybrel™ is formulated as a round, yellow, biconvex film-coated tablet with 90 µg LNG)and 20 µg EE. The tablets are debossed with "1117"on one side and "W" on the other side. A — process overage of both LNG and EE components is utilized to compensate for observed manufacturing losses (i.e., losses due to equipment surfaces). The product is packaged in — single unit dispensers. The composition of Lybrel™ is shown in Table 2.1.1.1. b(4)

Table 2.1.1.1. Composition Statement

Ingredient	Reference to Standards	Function	Unit Dose (mg/tablet)
	Tablet Core		
Active Ingredients:			
Levonorgestrel, Micronized [a]	USP	Active	0.090 [b]
Ethinyl Estradiol, Micronized [a]	USP	Active	0.020 [b]
Other Ingredients:			
Microcrystalline Cellulose	NF		
Lactose Monohydrate [a]	NF		
Magnesium Stearate	NF		
Polacrilin Potassium	NF		b(4)
Polyethylene Glycol 1450 [d]	NF		
Montanic Ester Wax	USP DAB [e]		
Total Weight (Coated Tablets)			70.5

a. The amount of each drug substance is adjusted against the lactose content.
b. Theoretical amount of drug substance per tablet. A — overage of each drug substance is used in the formulation to account for manufacturing losses on the equipment.
d. Used in the manufacturing process, but does not appear in the final product.
e. DAB = Deutsches Arzneibuch (German Pharmacopoeia) b(4)

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?
Mechanism of Action:

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

INDICATION (as per proposed label)
The proposed indication is for the prevention of pregnancy.

2.1.3 What are the proposed dosage(s) and route(s) of administration?
DOSAGE AND ADMINISTRATION (as per proposed label)

The dosage of Lybrel™ is one tablet daily.

2.2 General Clinical Pharmacology

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

Not applicable.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Plasma samples were analyzed for LNG and EE by a validated high performance liquid chromatography (HPLC) assay with tandem mass spectroscopy (MS/MS) detection. The compounds and their respective internal standards were extracted and ethinyl estradiol was derivatized prior to chromatographic separation and detection. The limit of quantitation (LOQ) for LNG was 50.0 pg/mL and the LOQ for EE was 2.0 pg/mL.

Calibration curves ranged from 50 to 12500 pg/ and from 2 to 250 pg/mL for LNG and EE, respectively. The method was linear, precise, and accurate.

2.2.3 Exposure Response

2.2.3.1 What are the characteristics of the dose-systemic exposure relationships for efficacy?

Not applicable

2.2.3.3 Does this drug prolong the QT or QTc interval?

Not applicable

2.2.4 What are the PK characteristics of the drug?

2.2.4.1 What are the single and multiple dose PK parameters? What are the characteristics of drug distribution? How do the PK parameters change with time following chronic dosing?

A summary of the single dose and multiple dose LNG and EE pharmacokinetic parameters for 18 women under fasting conditions is provided in Table 2.2.4.1.1. The plasma concentrations of LNG and EE reached steady-state by approximately day 12. LNG and EE concentrations did not increase from days 14 to 28, but did increase from Days 1 to 28.

Table 2.2.4.1.1. Mean (SD) Pharmacokinetic Parameters of Lybrel™ Over a 28-Day Dosing Period*

Day	Cmax (ng/mL)	Tmax (h)	t1/2 (h)	AUC0-24 (ng•h/mL)
LNG				
1 28	2.4 (0.9) 5.7 (2.1)	1.2 (0.4) 1.3 (0.8)	- 36 (19)	16 (8) 74 (41)
EE				
Day	Cmax (ng/mL)	Tmax (h)	t1/2 (h)	AUC0-24 (ng•h/mL)
1 28	47.7 (20.1) 74.4 (29.7)	1.3 (0.5) 1.4 (0.5)	- 21 (7)	378 (140) 717 (351)

*Data taken from Dr. Bullock's review for NDA 21-864.

2.3 Intrinsic Factors

2.3.1 Does age or race affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

Effect of Race

The effect of race and age on the PK of Lybrel™ has not been addressed.

2.3.2 Does renal impairment affect the PK of the drug? Is dosage regimen adjustment recommended?

The effect of renal function on the pharmacokinetics of Lybrel™ has not been evaluated. Literature suggests that ethinyl estradiol clearance in renal failure patients was found to be decreased relative to normal healthy women.

2.3.3 Does liver impairment affect the PK of the drug? Is dosage adjustment recommended?

The effect of hepatic impairment on the PK of Lybrel™ and its metabolites has not been formally evaluated.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of herbal products, diet, smoking and alcohol use were not evaluated.

2.4.2 Drug-Drug Interactions (DDI)

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

No formal drug-drug interactions were performed. The sponsor will use the FDA class labeling for DDI's in their label. The class labeling covers the known interactions with anti-infective agents, anti-HIV protease inhibitors, herbal products, CYP3A4 inhibitors and other drugs that are altered pharmacokinetically by estrogens.

2.5 General Biopharmaceutics

2.5.1 What is the BCS classification for Lybrel™?

Lybrel™ does not belong to BCS Class 1.

2.5.2 Was the to-be-marketed formulation used in the PK/clinical trials?

Two different batch products of Lybrel™ tablets were used in the two clinical trials (Studies 313 and 315) (Table 2.5.2.2). These two batches of products differ in the manufacturing process used.

Formulation 0931760C was used in three trials including one phase 3 trial (pivotal trial 313) and formulation 0931921C was used in one phase 3 trial (Study 315). The ——— process used for formulation 0931760C was changed to the ——— process ——— (formulation 0931921C) to improve the content uniformity of the tablets during the ——— stage. This manufacturing process change was considered as a Level III change according to SUPAC guidance.

b(4)

Table 2.5.2.2. Quantitative Composition comparison Lybrel™ clinical trial formulations

Batch No.	**A22646**	**A59604**
Formulation No.	**0931760C**	**0931921C**
Used in Clinical Trials	106, 208, 313	315
Manufacturing		
Overage	None	for EE for LNG
Input	**Tablets (kg)**	
LNG Micronized		
EE Micronized		
Other Ingredients		
Microcrystalline Cellulose		
Lactose Monohydrate		
Magnesium Stearate		
Polacrilin Potassium		
Polyethylene Glycol		
Montanic Ester Wax		
Tablet Coated Weight	388	388

b(4)

2.5.3 Were the tablets manufactured using different manufacturing processes bioequivalent?

Study 0858A2-108-US was conducted to determine the BE between formulations manufactured using different manufacturing processes. This was an open-label, single-dose, 2-period, randomized to sequence, crossover study in healthy, cycling women conducted at a single site. Each dose was administered within days 3 and 10 within a menstrual cycle, for 2 menstrual cycles. Subjects (21) were randomly assigned to 1 of 2 sequences, to receive the following 2 test articles:

b(4)

A: Single dose of LNG 90 µg/EE 20 µg tablet [reference])
B: Single dose of LNG 90 µg/EE 20 µg tablet test])

Each treatment was preceded by an overnight fast of at least 10 hours and administered with 240 mL of room-temperature water. Each subject received a single, oral dose of each treatment within days 3 and 10 of each menstrual cycle, for 2 menstrual cycles.

Plasma samples were analyzed for LNG and EE by a validated high performance liquid chromatography (HPLC) assay with tandem mass spectroscopy (MS/MS) detection.

The results of this study can be summarized as follows:

- The LNG 90 µg/EE 20 µg Test Tablet manufactured using the equipment was bioequivalent to the LNG 90 µg/EE 20 µg Reference Tablet manufactured The ratio of geometric means for Cmax, AUCt, and $AUC_{0\rightarrow\infty}$ values were within the 80-125 goal post for BE for both LNG and EE (Table 2.5.3.1, Figures 2.5.3.1 and 2.5.3.2)

Table 2.5.3.1. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of LNG and EE following single administration of the treatments

Comparison	PK parameter	Point estimates	90% CI
	Levonogestrel		
TRT T /TRT R	Cmax	98	90-107
	AUCt	105	98-113
	AUCinf	101	94-109
	Estradiol		
TRT T/ TRT R	Cmax	97	91-103
	AUCt	99	94-104
	AUCinf	99	94-103

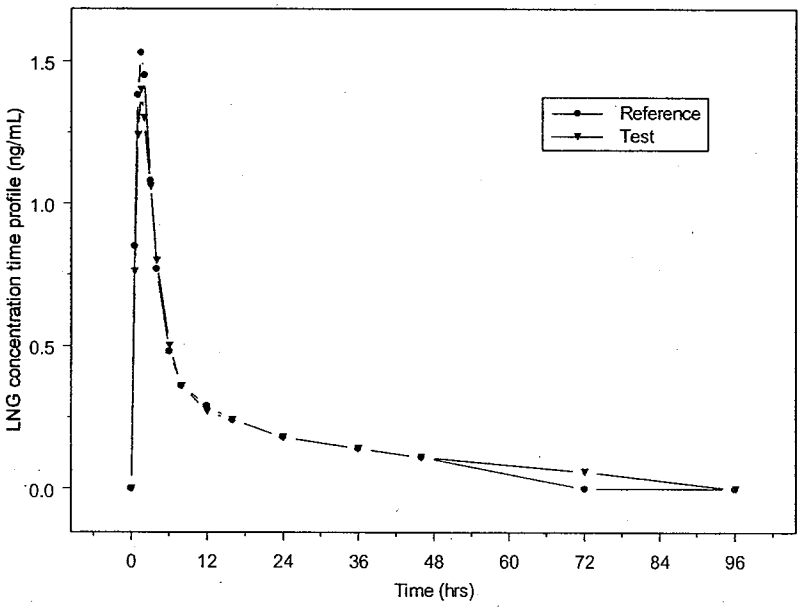


Figure 2.5.3.1. Mean LNG plasma concentration-time profiles following single administration of **TRT Reference:** LNG 90 mcg/EE 20 mcg (and **TRT Test: :** LNG 90 mcg/EE 20 mcg to 21 female healthy volunteers. b(4)

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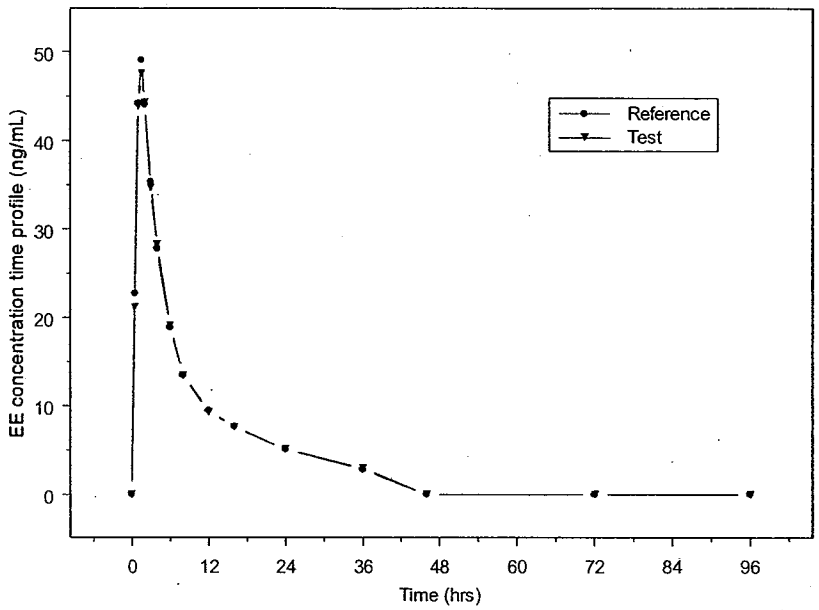

Figure 2.5.3.2. Mean EE plasma concentration-time profiles following single administration of the treatments: **TRT Reference:** LNG 90 mcg/EE 20 mcg and TRT **Test:** LNG 90 mcg/EE 20 mcg to 21 female healthy volunteers.

2.5.5 What is the effect of food on the BA of the drug?

This has not been evaluated.

2.6 Analytical Section

2.6.1 Was the suitability of the analytical method supported by the submitted information?

Plasma samples were analyzed for LNG and EE by a validated high performance liquid chromatography (HPLC) assay with tandem mass spectroscopy (MS/MS) detection. The compounds and their respective internal standards were extracted and ethinyl estradiol was derivatized prior to chromatographic separation and detection. The limit of quantitation (LOQ) for LNG was 50.0 pg/mL and the LOQ for EE was 2.0 pg/mL.

Calibration curves ranged from 50 to 12500 pg/ and from 2to 250 pg/mL for LNG and EE, respectively. The method was linear, precise, and accurate (Table 2.6.1.1).

Table 2.6.1.1. Assay performance for LNG and EE

	LNG	EE
Limit of quantitation	50 pg/mL	2 pg/mL
Linearity	Satisfactory: Standard curve range from 50 to 12500 pg/mL; r^2>0.997	Satisfactory: Standard curve range from 2 to 250 pg/mL; r^2>0.9990
Inter-day Accuracy	Satisfactory: QC % Bias: -4.0 at 125 pg/mL; -3.5 at 250 pg/mL; -2.7 at 800 pg/mL; -1.2 at 2500 pg/mL; 0.46 at 10000 pg/mL.	Satisfactory: QC % Bias: -3.5 at 4 pg/mL; -2.2 at 8 pg/mL; -1.2 at 22.5 pg/mL; -1.04 at 60 pg/mL; -1.0 at 190 pg/mL.
Inter-day Presicion	Satisfactory: QC % CV: 10 at 125 pg/mL; -5.8 at 250 pg/mL; 4.9 at 800 pg/mL; 3.2 at 2500 pg/mL; 3.1 at 10000 pg/mL.	Satisfactory: QC % CV: -7.3 at 4 pg/mL; 3.4 at 8 pg/mL; 2.5 at 22.5 pg/mL; 2.6 at 60 pg/mL; 2.2 at 190 pg/mL.
Specificity	Satisfactory: sample chromatograms submitted	Satisfactory: sample chromatograms submitted

Long Term Stability

17α-ethinyl estradiol and norgestrel in frozen human plasma containing potassium oxalate/sodium fluoride was evaluated by analyzing stability samples stored under the same conditions as study samples. Results indicate a frozen-state stability of approximately 811 days at -70°C.

Data on stock stability, bench top stability, freeze-thaw cycle stability, percentage of recovery was not provided.

3. Labeling Comments

Not applicable. See Dr. Julie Bullock's review for proposed labeling comments suggested during the review for the original submission of this NDA.

4. APPENDIX

"AN OPEN-LABEL, SINGLE-DOSE, RANDOMIZED, 2-PERIOD, CROSSOVER, BIOEQUIVALENCE STUDY TO COMPARE 2 MANUFACTURING PROCESSES FOR LEVONORGESTREL 90 mg/ETHINYL ESTRADIOL 20 mg IN HEALTHY, CYCLING WOMEN"

Study no.:	0858A2-108-US
Development Phase of Study:	Phase I
Principal investigator:	Stuart I Harris, MD, PhD SeaView Research in Miami, FL. 3898 N.W. 7th St. Miami, FL 33126
Study Dates:	June 2006 to October 2006

Background

Most of the clinical development program for continuous-use LNG 90 µg/EE 20 µg utilized a formulation manufactured by a ——— process. A new formulation has been developed for marketing, which utilizes a ——— process with ——— equipment. This study assessed the bioequivalence of these 2 formulations. b(4)

Objectives

Primary:

- To determine the bioequivalence between the clinical batch process and the new processes for manufacturing LNG/EE.

Secondary:

- To obtain additional safety and tolerability data concerning LNG/EE in healthy, cycling women.

Study Population

A total of 22 subjects were enrolled and 20 subjects completed the study. Two (2) subjects were withdrawn from the study after completing the first treatment period. Subject 108-001-000013 was withdrawn because of an adverse event (polycystic kidney) after receiving the reference formulation. Subject 108-001-000022 failed to return after receiving the test formulation of LNG 90 µg/EE 20 µg.

The volunteers (females only) averaged 27.95 ± 4.9 years of age (mean ± SD) with a range of 20 years to 35 years of age. They were 162.6 ± 5.3 cm. They weighed 65.7 ± 6.9 kg with a range of 54 to 81 kg. Twenty volunteers (90.9%) were white (Hispano or Latino) and 2 were black.

STUDY DESIGN, TREATMENT AND ADMINISTRATION

This was an open-label, single-dose, 2-period, randomized to sequence, crossover study in healthy, cycling women conducted at a single site. Each dose was administered within days 3 and 10 within a menstrual cycle, for 2 menstrual cycles.

Subjects were randomly assigned to 1 of 2 sequences, to receive the following 2 test articles: b(4)

A: Single dose of LNG 90 µg/EE 20 µg tablet (process [reference])

B: Single dose of LNG 90 µg/EE 20 µg tablet process [test])

Each treatment was preceded by an overnight fast of at least 10 hours and administered with 240 mL of room-temperature water. Each subject received a single, oral dose of each treatment within days 3 and 10 of each menstrual cycle, for 2 menstrual cycles.

The timing of dose administration within the same timeframe for each cycle was to allow for consistent measurement of LNG/EE, because LNG/EE is bound by SHBG, a hormone that fluctuates within a cycle.

There was about 30-day washout between treatments.

FORMULATION

The formulation, strength, and batch numbers of the study drug are summarized in Table 6-3.

Table 6-3: Study Drug Information

Study Drug	Dosage	Batch Number	Formulation Number
process (reference)	LNG 90 µg/EE 20 µg	B65454	0931760C
process (test)	LNG 90 µg/EE 20 µg	A67975	0932127C

b(4)

PHARMACOKINETIC MEASUREMENTS

Blood samples for pharmacokinetic analysis were taken at predose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours post dose.

Analytical Method

Plasma samples were analyzed for LNG and EE by a validated high performance liquid chromatography (HPLC) assay with tandem mass spectroscopy (MS/MS) detection. The compounds and their respective internal standards were extracted and ethinyl estradiol was derivatized prior to chromatographic separation and detection. The limit of quantitation (LOQ) for LNG was 50.0 pg/mL and the LOQ for EE was 2.0 pg/mL.

SAFETY MEASUREMENTS

Safety was evaluated from the results of spontaneously reported signs and symptoms, scheduled physical examinations, measurements of vital signs, 12-lead ECGs, and clinical laboratory evaluations. All adverse events were recorded.

Concomitant therapy

Concomitant therapy was not permitted throughout the study. However, concomitant therapy was received by 4 (18%) subjects during treatment with study drug. The sponsor

considered the use of these concomitant therapies not to have affected the PK behavior of LNG or EE in the study.

DATA ANALYSIS

Pharmacokinetic Data Analysis

A noncompartmental method of analysis was used to analyze the plasma concentrations of LNG and EE. The WinNonlin Professional Version 4.1 (Pharsight, Mountain View, CA) was used for pharmacokinetic calculations.

Statistical Analysis

Descriptive statistics were calculated for the LNG and EE mean plasma concentrations and for estimates of PK parameters. Statistical comparisons of mean plasma concentrations and estimates of the PK parameters between the 2 treatment groups were made using analysis of variance (ANOVA) for a 2-treatment, 2-period crossover study. Estimates of the PK parameters were analyzed using mixed-effects ANOVA, where fixed terms were fitted to the model for treatment, sequence, and period, and subjects were fitted as a random effect.

Comparisons between the treatments were performed by using the two 1-sided tests BE procedure for log-transformed data on C_{max}, AUC_T, and AUC. The 90% confidence intervals (CI) for the geometric mean ratios (test/reference) were calculated based on least squares means and the mean square error obtained from the 2-period crossover ANOVA using fixed and random effects. The test treatment was to be judged to be bioequivalent to the reference treatment if the 90% CI was contained by the interval (0.80 to 1.25).

RESULTS

Analytical Method

Stability and % of Recovery: Not reported

Freeze/Thaw of Plasma: not reported

Bench Top Stability: Not reported

Long Term Stability

17α-ethinyl estradiol and norgestrel in frozen human plasma containing potassium oxalate/sodium fluoride was evaluated by analyzing stability samples stored under the same conditions as study samples. Results indicate a frozen-state stability of approximately 811 days at -70°C.

In-Study Validation

Table 1. Assay performance for LNG and EE

	LNG	EE
Limit of quantitation	50 pg/mL	2 pg/mL
Linearity	Satisfactory: Standard curve range from 50 to 12500 pg/mL; r^2>0.997	Satisfactory: Standard curve range from 2 to 250 pg/mL; r^2>0.9990
Inter-day Accuracy	Satisfactory: QC % Bias: -4.0 at 125 pg/mL; -3.5 at 250 pg/mL; -2.7 at 800 pg/mL; -1.2 at 2500 pg/mL; 0.46 at 10000 pg/mL.	Satisfactory: QC % Bias: -3.5 at 4 pg/mL; -2.2 at 8 pg/mL; -1.2 at 22.5 pg/mL; -1.04 at 60 pg/mL; -1.0 at 190 pg/mL.
Inter-day Presicion	Satisfactory: QC % CV: 10 at 125 pg/mL; -5.8 at 250 pg/mL; 4.9 at 800 pg/mL; 3.2 at 2500 pg/mL; 3.1 at 10000 pg/mL.	Satisfactory: QC % CV: -7.3 at 4 pg/mL; 3.4 at 8 pg/mL; 2.5 at 22.5 pg/mL; 2.6 at 60 pg/mL; 2.2 at 190 pg/mL.
Specificity	Satisfactory: sample chromatograms submitted	Satisfactory: sample chromatograms submitted

Pharmacokinetic Results

The mean plasma concentration-time profiles for LNG and EE following administration of the treatments are shown in Figures 1 and 2, respectively. The mean pharmacokinetic parameters for LNG and EE are summarized in Table 2. Individual LNG Cmax and AUCt values following the administration of the treatments are shown in Figures 3 and 4, respectively. Likewise, individual Cmax and AUCt EE following administration of the treatments are represented in Figures 5 and 6, respectively.

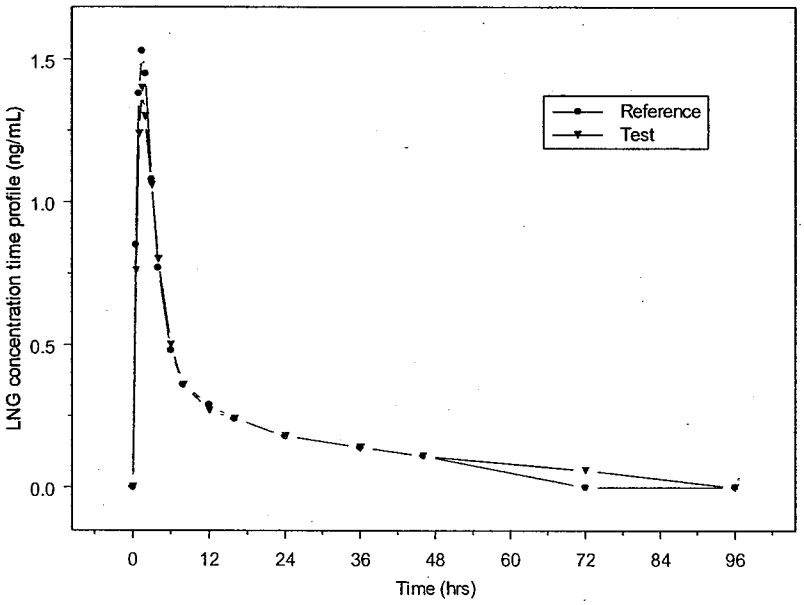

Figure 1. Mean LNG plasma concentration-time profiles following single administration of **TRT Reference:** LNG 90 mcg/EE 20 mcg and **TRT Test: :** LNG 90 mcg/EE 20 mcg to 21 female healthy volunteers.

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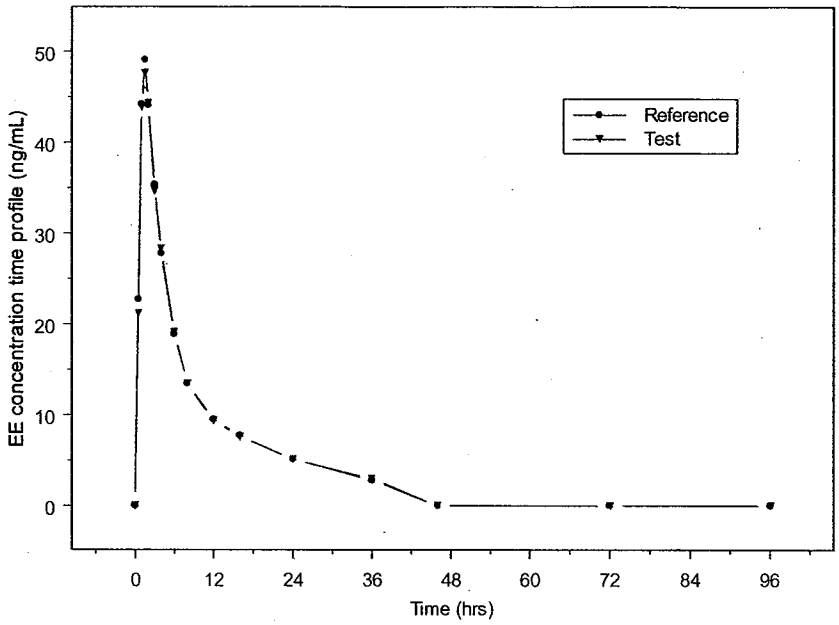

Figure 2. Mean EE plasma concentration-time profiles following single administration of the treatmemts:**TRT Reference:** LNG 90 mcg/EE 20 mcg and **TRT Test: :** LNG 90 mcg/EE 20 mcg to 21 female healthy volunteers.

Table 2. Mean (%CV) pharmacokinetic parameters of EE and LNG following single administration of the treatments

	Mean (SD) PK Parameters				
Treatment	**Cmax (ng/mL)**	**Tmax (hr)**	**AUCt (ng*hr/mL)**	**AUCinf (ng*hr/mL)**	**T1/2 (hr)**
	EE				
TRT R	49.7 (13.5)	1.45 (0.22)	408 (128)	475.6 (140)	16.3 (3.9)
TRT T	48.4 (12.2)	1.6 (0.3)	389.6 (108)	454.6 (112)	16.1 (3.1)
	LNG				
TRT R	1.66 (0.6)	1.5 (0.4)	16.1 (1.7)	19.3 (12.4)	34.6 (25)
TRT T	1.58 (0.6)	1.5 (1.1)	15.9 (1.3)	18. (10.9)	30.2 (12.8)

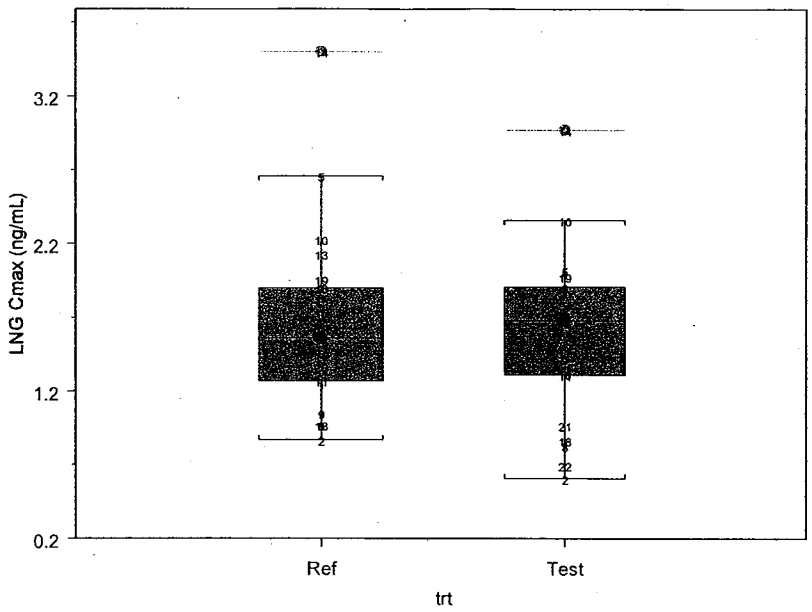

Figure 3. Individual LNG Cmax values following single administration of the treatments: **TRT Reference:** LNG 90 µg/EE 20 µg and **TRT Test: :** LNG 90 µg /EE 20 µg to 21 female healthy volunteers.

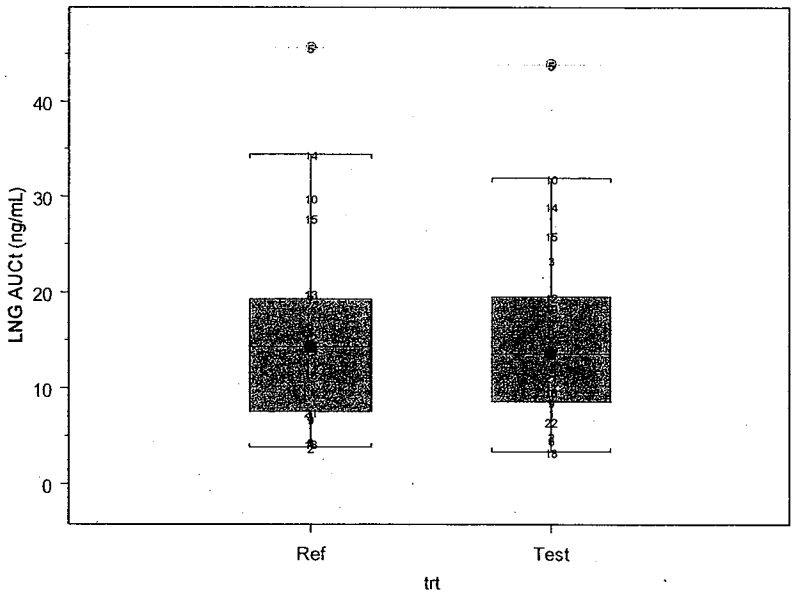

Figure 4. Individual LNG AUCt values following single administration of the treatments: **TRT Reference:** LNG 90 µg/EE 20 µg and **TRT Test: :** LNG 90 µg /EE 20 µg to 21 female healthy volunteers.

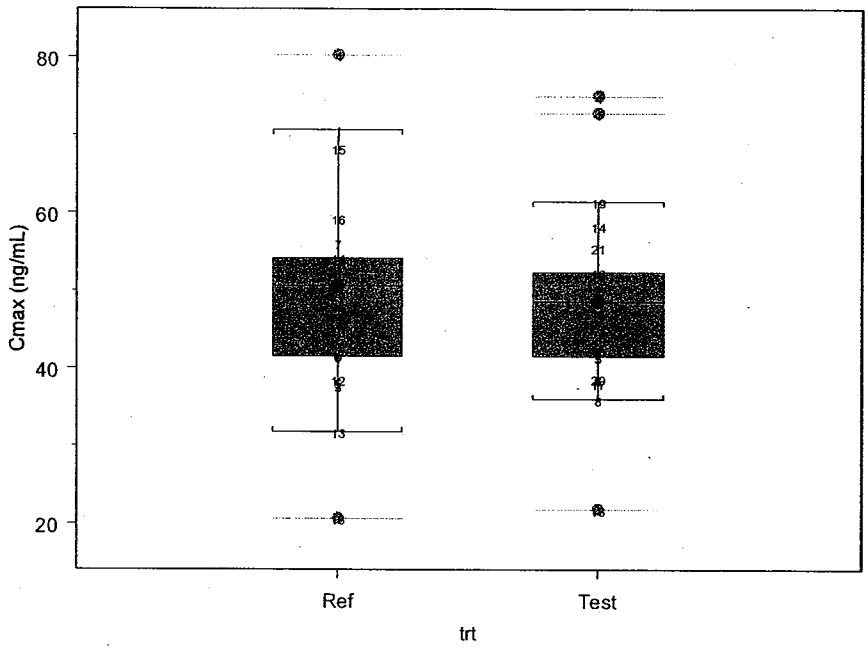

Figure 4. Individual EE Cmax values following single administration of the treatments: **TRT Reference:** LNG 90 µg/EE 20 µg and **TRT Test:** LNG 90 µg /EE 20 µg to 21 female healthy volunteers.

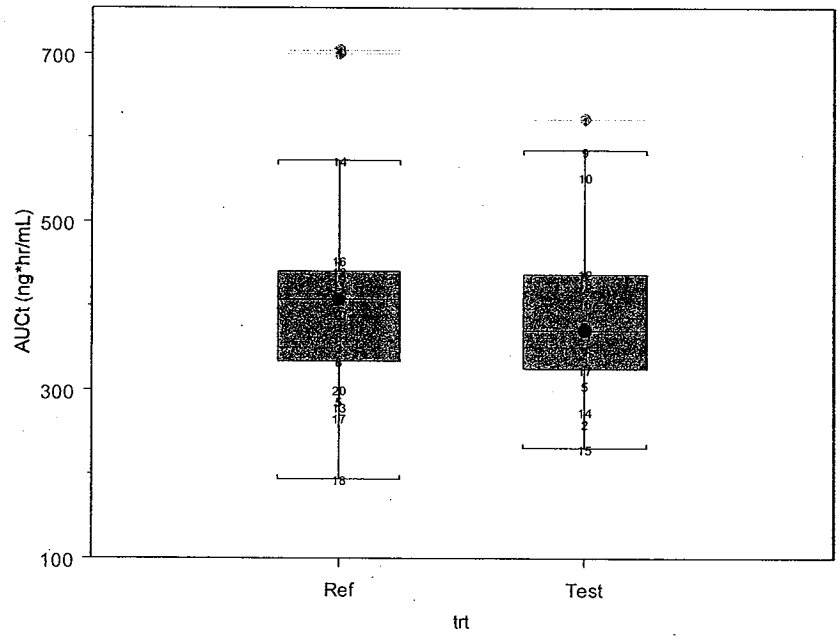

Figure 4. Individual EE AUCt values following single administration of the treatments: **TRT Reference:** LNG 90 µg/EE 20 µg and **TRT Test:** : LNG 90 µg /EE 20 µg to 21 female healthy volunteers.

The point estimates and the 90% CIs for the log-transformed Cmax, AUCt and AUCinf for LNG and EE are presented in Table 3. The AUC(t), AUCinf, and Cmax CI for LNG and EE of R vs. T met the 80-125% bioequivalence guideline.

Table 3. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of LNG and EE following single administration of the treatments

Comparison	PK parameter	Point estimates	90% CI
	Levonogestrel		
TRT T /TRT R	Cmax	98	90-107
	AUCt	105	98-113
	AUCinf	101	94-109
	Estradiol		
TRT T/ TRT R	Cmax	97	91-103
	AUCt	99	94-104
	AUCinf	99	94-103

CONCLUSION

- The LNG 90 µg/EE 20 µg Test Tablet manufactured using the [redacted] equipment was bioequivalent to the LNG 90 µg/EE 20 µg Reference Tablet manufactured using [redacted]. The ratio of geometric means for Cmax, AUCt, and AUCinf values were within the 80-125 goal post for BE for both LNG and EE. b(4)

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/s/

Sandra Suarez
3/20/2007 09:33:23 AM
BIOPHARMACEUTICS

Myong-Jin Kim
3/20/2007 11:02:25 AM
PHARMACOLOGIST/TOXICOLOGIST

Clinical Pharmacology Review

NDA	21-864
Submission Date	May 27, 2005
PDUFA Goal Date	March 27, 2006
Brand Name	Lybrel™
Generic Name	Levonorgestrel (LNG) 90µg / Ethinyl Estradiol (EE) 20µg
Formulation	Tablets
Reviewer	Julie M. Bullock, Pharm.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB Division	Division of Clinical Pharmacology III
ORM Division	Division of Reproductive & Urologic Products
Sponsor	Wyeth Pharmaceuticals
Submission Type; Code	Original NDA; 000
Dosing regimen	Once daily
Indication	Prevention of Pregnancy

OCP Briefing on February 23, 2006 attended by: John Hunt, Sandra Suarez, Phil Price, Donna Christner, Ameeta Parekh, Donny Tran, Sandhya Apparaju, and Shelley Slaughter.

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1 Executive Summary

NDA 21-864 for Lybrel™ (Levonorgestrel (LNG) 90µg / Ethinyl Estradiol (EE) 20µg) tablets was submitted on May 25, 2005. Lybrel™ is a low dose oral contraceptive intended for continuous use, which differs from current oral contraceptives which have a placebo or 'pill free' period that usually lasts for 7 days.

This NDA includes the data from one Phase I, one Phase II and two Phase III studies which were performed to support approval of Lybrel™. They are summarized as follows:

- Study 106: A 28-day pharmacokinetic study in 18 healthy female subjects.
- Study 208: An 84-day ovulation inhibition study in 58 healthy female subjects.
- Study 313: An open label long term efficacy and safety study in 2134 healthy females for 1 year.
- Study 315: An open label, active controlled study in 641 healthy females for 1 year.

The formulation of Lybrel™ is similar to the currently marketed product Alesse® (100µg LNG/20µg EE) with a slight adjustment to the LNG and lactose content. Two Lybrel™ products were used in the 4 clinical studies submitted and differed only in their manufacturing process. The final to-be-marketed product is a yellow biconvex, debossed film coated tablet [redacted]. Dissolution data was provided to compare the clinical trial batches and the registration/validation batches and showed similar dissolution results using the USP method and the method developed by the sponsor with no surfactant. b(4)

Only one human study was submitted that pertained to Clinical Pharmacology. The study was a pharmacokinetic study which looked at the single and multiple dose pharmacokinetics of Lybrel™ after 28 days of continuous administration using the non-to-be marketed manufacturing process product.

1.1 Pending Issues

The Chemistry review for NDA 21-864 is ongoing and preliminary review indicates a Level 3 manufacturing change between the Lybrel™ products used in Study 313 and Study 315. The Clinical review is also ongoing and preliminary discussions with the medical team have implied that only Study 313 will be used to support the efficacy of NDA 21-864.

If only Study 313 is considered evaluable by the Clinical Division, then the manufacturing equipment and process change between the Study 313 product and that to-be-marketed (used in Study 315) could require in vivo bioequivalence documentation. Chemistry and Clinical reviews are ongoing.

The sponsor was notified on March 2, 2006 of Chemistry's perspective regarding the Level 3 change and what is required to support this manufacturing change according to the SUPAC Guidance. The sponsor replied with an amendment on March 6, 2006 which included in its conclusion that LNG and EE met BCS Class 1 classification. Additional multipoint dissolution data in different pH media was also submitted (will be reviewed at a later date).

A meeting was held with the sponsor on March 8, 2006 to discuss clinical study 313 and the chemistry issues. At the conclusion of this meeting the sponsor agreed to provide additional information to address the BCS classification (mentioned in the March 6, 2006

amendment) for each drug substance and the additional in-vitro dissolution profile data.

Once the new information is provided and reviewed an addendum to this review will be provided.

1.2 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed the information provided NDA 21-864 submitted on May 27, 2004. Pharmacokinetic study 106 is found to be an acceptable study as is the in-vitro dissolution data provided in this submission. An addendum to this review will be provided once the newly requested information from the sponsor meeting on March 8, 2006 is provided.

Reviewer: Julie M. Bullock, Pharm.D.

Team Leader: Ameeta Parekh, Ph.D.

Summary of Clinical Pharmacology and Biopharmaceutics Findings

Lybrel™ is a continuous use combination oral contraceptive (COC) containing 28 days of combination LNG/EE 90/20 µg tablets to be taken continuously with no hormone free period. Lybrel™ differs from other currently marketed COC's by its dose of LNG/EE which is lower than other approved products such as Seasonale® which is the only approved 84 day COC which contains LNG 150µg/EE 30µg. The LNG 90µg/EE 20µg dose for Lybrel™ was chosen as the lowest daily dose of progestin and estrogen that would provide good contraceptive efficacy and safety. The sponsor's rationale behind the continuous use of LNG/EE to inhibit withdrawal bleeding is to avoid the symptoms associated with the menses such as premenstrual dysphoric disorder (PMDD).

Because of the lower dose of Lybrel™ there is not an increased cumulative dose of LNG/EE over the course of a year as seen below in Table 1 as compared to other products containing LNG/EE combination tablets.

TABLE 1: Cumulative Annual Dosages of Levonorgestrel and Ethinyl Estradiol for the Continuous-Use LNG 90µg/EE 20µg Regimen and Approved Oral Contraceptives

Parameter	LNG 90 µg/EE 20 µg	Alesse/Loette	Nordette	Seasonale
Regimen	Continuous use	21-Day cyclic	21-Day cyclic	Extended use
Active tablets/interval	28/pill pack	21/28 day cycle	21/28 day cycle	84/91 day interval
Active tablets/year	364	273	273	336
Dose/tablet (µg)				
LNG	90	100	150	150
EE	20	20	30	30
Total dose/year (mg)				
LNG	32.76	27.30	40.95	50.40
EE	7.28	5.46	8.19	10.08

A 28 day multiple dose study was reviewed in support of this NDA. Study 0858A2-106 assessed the pharmacokinetic profile of Lybrel™ at key points across 28 days. PK samples were drawn on Day 1, 14, and 28. The study confirmed that increasing the duration of uninterrupted combination oral contraceptive treatment from the conventional 21 days does not result in any further accumulation of drug. This is consistent with the information concluded from other extended cycle oral contraceptives using an LNG/EE combination tablet.

Two clinical trial products were used in the development of Lybrel™. From a clinical pharmacology perspective there was no difference in the quantitative composition of the clinical trial formulations and therefore we had no issues regarding the similarity of these two products. In addition, the only difference seen between the proposed commercial tablets and the clinical tablets are the —— color coat (yellow versus white, respectively) and was supported by dissolution. b(4)

However, the two clinical trial products used did differ in their manufacturing processes, which was defined as a SUPAC Level 3 change by CMC on February 22, 2006, and was supported only by dissolution. A Level 3 change needs supporting in vivo bioequivalence data to bridge this difference according to the SUPAC Immediate Release Oral Dosage form Guidance. A bioequivalence study was not submitted with the NDA. The sponsor was notified on March 2, 2006 of CMC's perspective regarding the Level 3 change and what is required to support this manufacturing change according to the SUPAC Guidance.

2 Question Based Review

2.1 General Attributes

What is the proposed dosage and route of administration?

The proposed indication is for the prevention of pregnancy. The dosage of Lybrel™ is one yellow LNG 90µg/EE 20µg tablet daily. This was chosen as the lowest daily dose of progestin and estrogen that would provide good contraceptive efficacy and safety.

What is the proposed mechanism of drug action and therapeutic indications?

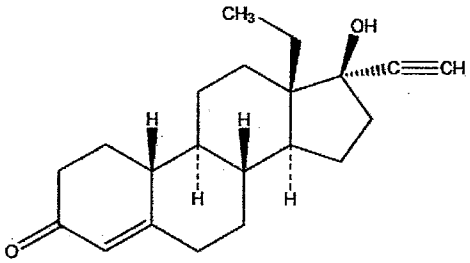
Combinational hormonal contraceptives act by suppression of gonadotropins. The primary mechanism of action is inhibition of ovulation. Other alterations include changes in cervical mucus that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

The continuous use LNG/EE may be beneficial to women because the discontinuation of cyclic hormonal fluctuations should decrease or eliminate the menstrual bleeding and cycle-related symptoms such as dysmenorrhea, mood swings, and other physical complaints.

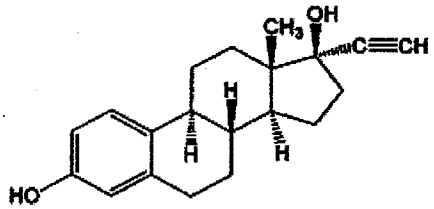
What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Physico-chemical properties

- Structural properties



LNG



EE

- Established name: Levonorgestrel, USP (LNG), Ethinyl Estradiol, USP (EE)
- Molecular Weight: 296.4 (EE); 312.45 (LNG)
- Molecular Formula: $C_{20}H_{24}O_2$ (EE); $C_{21}H_{28}O_2$ (LNG)
- Chemical Name: (-) 13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one (LNG); 19-Norpregna-1,3,5(10)-triene-20-yne -3,17-diol, (17α)- (EE)

2.2 Formulation

2.2.1 Clinical Trial Drug Formulation

What are the differences between the clinical trial formulations used in the four clinical trials?

Two clinical trial products were used during development. From a clinical pharmacology perspective the two clinical trial products are identical with regards to quantitative

composition.

TABLE 2: Quantitative Composition comparison Lybrel clinical trial formulations

Batch No. **Formulation No.**	**A22646** **0931760C**	**A59604** **0931921C**
Used in Clinical Trials	106, 208, 313	315
Manufacturing		
Overage	None	for EE & for LNG
	Input/	**Tablets (kg)**
LNG Micronized		
EE Micronized		
Other Ingredients		
Microcrystalline Cellulose		
Lactose Monohydrate		
Magnesium Stearate		
Polacrilin Potassium		
Polyethylene Glycol		
Montanic Ester Wax		
Tablet Coated Weight	388	388

b(4)

The main difference between the products used in clinical trials 313 and 315 was the manufacturing process. Table 2 outlines the formulations used in the clinical trials. Formulation 0931760C was used in three trials including one phase 3 trial and formulation 0931921C was used in one phase 3 trial. The process used for formulation 0931760C was changed to the process (formulation 0931921C) to improve the content uniformity of the tablets during the stage. It was noted at a recent meeting with the Clinical Division that the trial 315 is not considered pivotal (review ongoing).

It was brought to our attention by Moo-Jong Rhee Ph.D. at a meeting on February 22, 2006, that this manufacturing change between the two clinical trial products could be considered as a SUPAC Level 2 or Level 3 process change (meeting attended by: Julie Bullock, Pharm.D. Ameeta Parekh, Ph.D., John Hunt, Donna Christner, Ph.D., Moo-Jong Rhee, Ph.D., and Phil Price, M.D.). It was decided on Feb 22, 2006 by the Chemistry Division Director that the manufacturing change from the Agency's perspective was a SUPAC Level 3 change.

A SUPAC Level 3 change requires chemistry, dissolution, and *in vivo* bioequivalence documentation. The dissolution documentation needed is multi-point dissolution profiles in the application or compendial medium at 15, 30, 45, 60 and 120 minutes. This data was provided and is explained further below in section 3.3 In vitro Dissolution. The sponsor did not submit a bioequivalence trial with the NDA. The sponsor was notified of Chemistry's perspective regarding the SUPAC Level 3 change on March 2, 2006. Once the Chemistry and Clinical reviews are complete, and a final decision has been made regarding this issue an amendment will be posted to this review if necessary.

2.2.2 Commercial Formulation

The main differences between the clinical trial products and the commercial product are tablet color and the manufacturing process (Table 3). ——— white was used to coat the core tablets of the clinical batches (Formulation 0931760C: lot A22646 and Formulation 0931921C: lot A59604). ~ Yellow was used in the registration/validation batches (Formulation 0931923C: Lots A53036, A53038, A54657) which will be used for the to-be-marketed formulation. There is also an increase in the overage for the commercial formulation 0931923C for EE due to manufacturing losses.

b(4)

TABLE 3: Differences between the Clinical Trail formulations and the Registration/Validation formulations

	Clinical	Clinical	Registration Validation	Registration Validation Stability Commercial Tablet
Formulation number	0931760C	0931921C	0931922C	0931923C
Drug Product Lot numbers	**A22646**	A44624 A44625 **A59604** A64014	A44624 A44625	A44624 A44625 **A53036** **A53038** **A54657**
Overage				G
Tablet Color	White	White	Yellow	Yellow
Manufacturing Process				

b(4)

The change in the color coat is not a significant change and was supported with dissolution (see Dissolution section 3.3 below). The overage of EE in the formulation is of no clinical concern (Table 4). In addition, the Chemist was consulted and she did not have a concern with the increase in overage for EE because in the sponsor's batch analysis the dose of both LNG and EE is at or slightly above 100%.

TABLE 4: Quantitative Composition comparison of Clinical Trial Formulation and Commercial Formulation

Formulation No.	**Clinical Trial Tablet 0931921C**	**Commercial Tablet 0931923C**
Used in Clinical Trial	315	
Manufacturing Overage	for EE & for LNG	overage for EE & LNG
	Input/Tablets (mg)	
LNG Micronized	0.090	
EE Micronized	0.020	
Other Ingredients		
Microcrystalline Cellulose		
Lactose Monohydrate		
Magnesium Stearate		
Polacrilin Potassium		
Polyethylene Glycol		

b(4)

Formulation No.	Clinical Trial Tablet 0931921C	Commercial Tablet 0931923C
Montanic Ester Wax		
Tablet Coated Weight	70.5	70.5

b(4)

Of note, the sponsor had also developed additional Registration/Validation batches using . These batches (B11603, B11605, and B11606) were intended to be used for the commercial product. However, due to the Chemistry Division's concerns with a decline in stability seen with accelerated conditions by 3 months, the sponsor elected to go back to the Original Registration/Validation batches using the manufacturing process formulation 0931921C. For more details regarding these manufacturing changes and stability please see Dr. Donna Christner's Chemistry review in DFS and the minutes from the teleconference with the sponsor on January 31, 2006.

2.3 In Vitro Dissolution

2.3.1 Dissolution Method

Dissolution testing of LNG/EE combination tablets is typically done following the USP monograph for LNG/EE tablets. In this submission the USP method was replaced by . The only difference between the compendial method and the sponsors developed method is the absence of the surfactant (tween 80) and the dissolution volume. Table 5 below outlines the components of both methods. There was no justification provided from the sponsor regarding the use of instead of the more common USP method. appears to be more discriminating than the USP method.

b(4)

TABLE 5: Comparison of the USP dissolution Method and

	USP Method
	Dissolution Parameter
Equipment	USP Apparatus 2 (Paddles)
Dissolution medium	5 ppm Tween 80 solution
Dissolution Volume	500 mL
Agitation Speed	75 RPM
Filter	
HPLC Parameters	
Column	Packing L7 (RP, C8), 150 x 4 mm
Mobile Phase	Acetonitrile: Water (60:40)
Injection Volume	100 µL
UV Detection	247 nm (for LNG)
Fluorescence Detection	Excitation wavelength at 285 nm, Emission wavelength at 310 nm (For EE)
Flow Rate	About 1.5 mL/minute

b(4)

2.3.2 Dissolution Comparison of Clinical Trial Batches

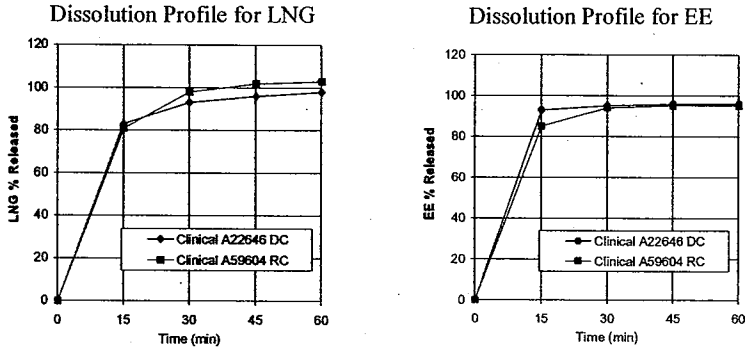
A comparison of the dissolution profile of the clinical batches A22646 and A59604 was provided using the USP Method. The two clinical batches were different in regards to manufacturing as noted in Table 3 and their dissolution profiles are provided in Figure 1.

b(4)

Both LNG and EE had release by 30 mins; therefore the results met the stage 1 release requirements of NLT (Q) in 30 minutes. An f_2 calculation for dissolution

comparison needs three to four dissolution time points to be valid. In this case only two time points can be included in the f_2 calculation since ~~~ was released after 45 and 60 mins (see Table 6), therefore an f_2 comparison for these batches is not needed. Based on visual inspection of the dissolution curves, and that both formulations meet the stage one release requirements we can conclude that the two clinical trial formulations are similar in regards to dissolution. b(4)

FIGURE 1: Mean dissolution profiles of LNG/EE tablets using the USP Method for Clinical Trial tablets Batch A22646 and Batch A59604



2.3.3 Dissolution Comparison of Clinical and Commercial Batches

b(4)

The sponsor used both the USP and the new dissolution method, ~~~ to test the clinical trial Lot A59604 to the Registration/Validation Lots (A53036, A53038, and A54657). The Registration/Validation Lot A53036 was the stability batch and is also used to graphically compare dissolution below (Figures 2 & 3).

USP Method

b(4)

For the USP method all of the Registration/Validation Lots met the release requirements of NLT ~~~ (Q) in 30 minutes for LNG and for EE (see Table 6). Once again an f_2 calculation for comparison is not appropriate in this circumstance because ~~~ of the drug was released after 30 mins.

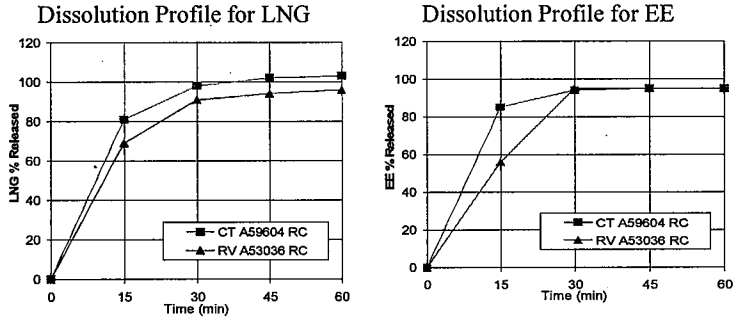
It is not explained by the sponsor why the release of EE at 15 minutes for the Registration/Validation batches resulted in such a range of values. Figure 2 shows graphically the lag in release for EE for the Registration/Validation (R/V) batch compared to the Clinical Trial tablet. The R/V A53038 batch showed similar results to what is normally seen for an EE dissolution profile. The decrease seen in the other batches could be due to sampling or assay error.

TABLE 6: Comparison of Dissolution Profiles for Clinical Batches and Registration/Validation Batches using the USP Method.

	Clinical Trial Tablets		Registration/Validation Tablets		
Time (min)	**A22646**	**A59604**	**A53036**	**A53038**	**A54657**
Levonorgestrel					
15	83	81	69	68	68
30	93	98	91	91	90
45	96	102	94	95	93
60	98	103	96	95	94
Ethinyl Estradiol					

15	93	75	56	91	54
30	95	94	95	97	96
45	96	95	95	98	97
60	96	95	95	96	97

FIGURE 2: Mean dissolution profiles of LNG/EE tablets using the USP Method for Clinical Batch A59604, and the Registration/Validation Batch A53036

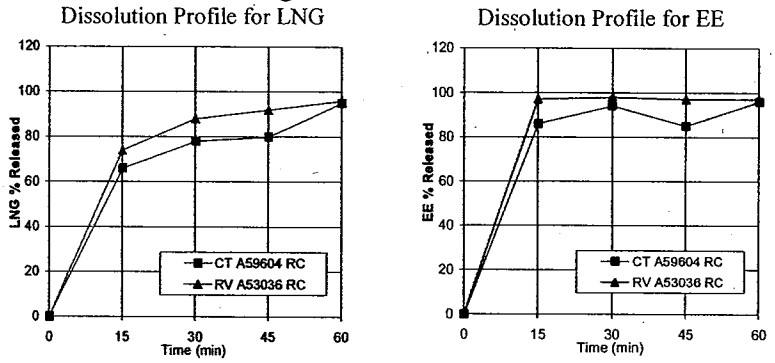


For dissolution ——— the NLT — (Q) at 30 minutes release requirement for LNG was used because ——— was more discriminating towards LNG. The release requirement of NLT — (Q) at 30 mins was used for EE. An f_2 calculation for EE is not needed in this circumstance because — of EE was released after 30 mins (Table 7). However, due to the more discriminating properties of this dissolution method LNG released more slowly. An f_2 was calculated for LNG using the 15, 30 and 45 min timepoints and it showed similarity between the two products (f_2 = 56.7). b(4)

TABLE 7: Comparison of Dissolution Profile of Clinical Batches and Registration Validation Batches using

	Clinical Trial Tablets		**Registration/Validation Tablets**		
Time (min)	**A22646**	**A59604**	**A53036**	**A53038**	**A54657**
			Levonorgestrel		
15	Not tested	66	74	71	70
30	Not tested	78	88	84	84
45	Not tested	80	92	90	90
60	Not tested	85	96	93	92
			Ethinyl Estradiol		
15	Not tested	86	97	94	95
30	Not tested	87	98	94	97
45	Not tested	85	97	95	97
60	Not tested	86	97	95	97

FIGURE 3: Mean dissolution profiles of LNG/EE tablets using ——— for Clinical Batch A59604, and the Registration/Validation Batch A53036 b(4)



In conclusion, the clinical trail batch A59604 can be considered equal to its registration validation batches (which will be used for marketing), even though the —— color was different (white to yellow). b(4)

2.4 General Clinical Pharmacology

Do PK parameters change with time following chronic dosing?

A single-treatment, multiple dose, steady state PK study in 18 normal healthy female adult subjects was conducted to asses the pharmacokinetic profile of Lybrel™ at key points across 28 days of once daily dosing. PK samples were drawn on Day 1, Day 14 and Day 28. The study confirmed that increasing the duration of uninterrupted combination oral contraceptive treatment from the conventional 21 days to continuous use (in this case 28 days) does not result in any further accumulation of the drug. This is consistent with the PK of LNG and EE seen with other oral contraceptive products. Table 6 and 7 in Appendix 5.1.1 summarizes the pharmacokinetic parameters calculated for LNG and EE

2.4.1 Exposure-Response Information

What are the characteristics of the exposure response relationships (dose-response, concentration-response) for efficacy?

Comment: no formal exposure response relationships were studied in Phase II. No measurements of study drug concentrations were made during the efficacy studies.

2.5 Intrinsic Factors (renal, hepatic)

No formal studies to evaluate the effect of race or hepatic or renal disease on the disposition of Lybrel™ have been conducted. Literature suggests that ethinyl estradiol clearance in renal failure patients was found to be decreased relative to normal healthy women.

Comment: Other LNG/EE products have performed no formal studies for race or renally or hepatically impaired patients. Their labels include the generic statements of: "No formal studies have been conducted to study the effect of (race, renal impairment, hepatic impairment) on the pharmacokinetics of...".

2.6 Extrinsic Factors (DDI)

No Formal drug-drug interactions were performed. The sponsor will use the FDA class labeling for DDI's in their label. The class labeling covers the known interactions with anti-infective agents, anti-HIV protease inhibitors, herbal products, CYP3A4 inhibitors and other drugs that are altered pharmacokinetically by estrogens.

Comment: For more information see the label.

2.7 General Biopharmaceutics

2.7.1 Food effect

No food effect study was performed

Comment: The other LNG/EE products have not performed formal food effect studies. A literature search found no published food effect study with LNG/EE combination tablets.

2.8 Analytical Section

All assays for levonorgestrel and ethinyl estradiol were performed and validated [redacted] b(4)
[redacted]. HPLC-MS/MS assay method for determination of LNG/EE in plasma was used on all human plasma samples in Study 0858A2-106. The lower limit of quantitation was 50.0 pg/mL for norgestrel and 2.00 pg/mL for ethinyl estradiol.

3 Detailed Labeling Recommendations

Only relevant clinical pharmacology sections were included in this section. Red double underlines indicate text that was added and ~~strikethroughs~~ represent text that is recommended to be removed.

[redacted]

b(4)

[redacted]

2 Page(s) Withheld

_____ Trade Secret / Confidential

__X__ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

b(4)

4 Appendices

4.1 Individual Study Review

4.1.1 Study 0858A2-106 (Study 106)

Objective

To determine the PK profiles of LNG and EE during a multiple dose regimen. In addition the effects of SHBG on the PK of LNG were examined.

Subjects

24 subjects were planned, 18 were enrolled and 18 completed the study. Plasma EE concentrations for 2 subjects (0005 and 0009) were not available on all 3 days of pharmacokinetic analysis (Days 1, 14 and 28) do to analytical problems. The data from these two subjects was excluded from concentration summary statistics and PK analysis for EE on all 3 days.

Ages ranged from 19 to 34 years (mean age 24.6 years) and body weight ranged from 47.7 to 85.4 kg (mean 61.7 kg).

Study Design

Open-label, multiple dose, steady state, pharmacokinetic study.

Each subject received one LNG 90µg/EE 20µg combination tablet (LNG/EE tablet) orally each morning at approximately 8 AM for 28 days.

On Days 1 each subject received the LNG/EE tablet with 240mL of room-temperature water after fasting for at least 10 hours. PK for LNG and EE were drawn at for 24-hours after dosing on Day 1. After completion of the 24-hour blood collections and measurements each subject received their 2nd dose of LNG/EE with 240 mL of water and were discharged from the study unit. The LNG/EE tablet was to be self dispensed on Days 3-11 at approximately 8AM each day.

Subjects returned to the unit on Day 12 at approximately 7:30 AM. The subjects underwent safety measurements as well as predose samples for SHBG and LNG protein binding analysis and predose samples for LNG/EE analysis. Their dose was administered at 8AM in the study unit with 240mL of room-temperature water.

Subjects returned on Day 13, and 24-hour PK was drawn on Day 14 under fasting

conditions. Days 15-25 subjects self administered the LNG/EE tablet and returned to the unit on Days 26 and 27 for safety procedures. On the morning of Day 28 following a 10 hour fast 24-hour PK was drawn. Patients were discharged on Day 29 after the 24 hour blood draw.

Treatments

Days 1-28: 1 x levonorgestrel 90µg/ethinyl estradiol 20µg tablets, USP; Lot no. A22646 (Formulation 0931760C).

Sample Collection

Blood samples were collected on the following days for the PK of orally administered LNG/EE and determination of SHBG concentrations and LNG protein binding:

Day 1:	SHBG and LNG protein binding – predose & 2, 7 & 24 hours post dose LNG/EE – predose & 1, 2, 4, 7, 12, 16, & 24 hours post dose
Day 12:	SHBG and LNG protein binding – predose LNG/EE – predose
Day 13:	SHBG and LNG protein binding – predose LNG/EE – predose
Day 14:	SHBG and LNG protein binding – predose & 2, 7 & 24 hours post dose LNG/EE – predose & 1, 2, 4, 7, 12, 16, & 24 hours post dose
Day 26	SHBG and LNG protein binding – predose LNG/EE – predose
Day 27:	SHBG and LNG protein binding – predose LNG/EE – predose
Day 28	SHBG and LNG protein binding – predose & 2, 7 & 24 hours post dose LNG/EE – predose and 1, 2, 4, 7, 12, 16, 24, 36, 48, & 72 hours post dose

PK Analysis

Unbound LNG plasma concentrations were used for pharmacokinetic analysis. The mean estimate of the fraction of unbound LNG on each day for individual subjects was used to calculate the unbound LNG plasma concentration.

Noncompartmental analysis was used to analyze the plasma concentrations of LNG, unbound LNG, and EE. Cmax, Cmin, Tmax, AUC, CL/F, Thalf, Cavg, apparent volume of distribution (Vz/F) and Accumulation Index (R) were calculated.

PK Results

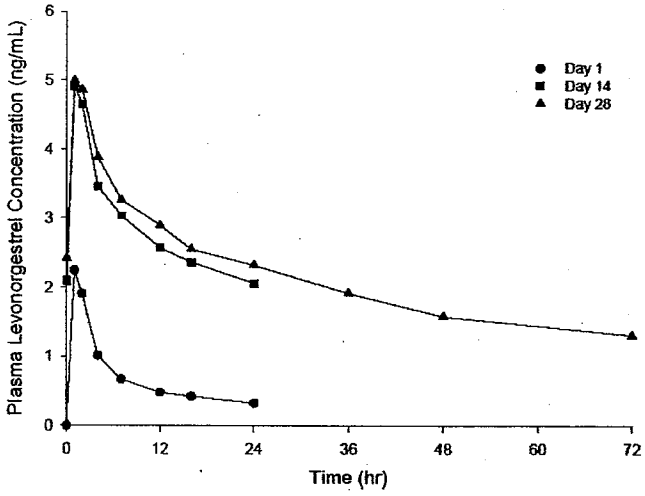
Levonorgestrel

- Mean AUC and Cmax on Day 14 are similar to those seen on Day 28.
- The plasma concentrations of LNG appeared to reach steady state by Day 12
- No long term accumulation occurs (Cmin: Day 14 2.0 ± 1.3, Day 28 3.08 ± 1.7).
- LNG is highly protein bound. The Unbound LNG accounted for only 0.8% of the total LNG on Day 1. There was an approximate 30% decrease in the percentage of unbound LNG from Day 1 to Day 28.
- SHBG concentrations increased approximately 2-fold and remained constant from Day 12 to Day 28. The unbound LNG decrease from Day 1 to Day 28 was in proportion to the increase in SHBG concentrations.

TABLE 8: Mean (SD) LNG and Unbound LNG Plasma Pharmacokinetic Parameters Following Single and Multiple Oral Administration of Lybrel™ to Healthy Women.

Parameter	Levonorgestrel (N=18)		Unbound Levonorgestrel (N=18)	
	Unit	Mean (SD)	Unit	Mean (SD)
Day 1				
Cmax	ng/mL	2.40 (0.910)	pg/mL	18.8 (3.66)
tmax	hr	1.2 (0.38)	hr	1.2 (0.38)
AUC_T	ng·hr/mL	16.3 (7.71)	pg·hr/mL	125 (33.1)
$AUC_{0-\infty}$	ng·hr/mL	35.5 (27.0)	pg·hr/mL	266 (147)
CL/F	L/hr	3.6 (1.9)	L/hr	407 (153)
Day 14				
Cmax ss	ng/mL	5.35 (2.12)		-
tmax ss	hr	1.7 (1.4)		-
AUC0-τ	ng·hr/mL	67.6 (36.0)		-
Cmin	ng/mL	2.0 (1.3)		
Cavg	ng/mL	2.82 (1.50)		-
CLss/F	L/hr	1.66 (0.763)		-
Day 28				
Cmax ss	ng/mL	5.72 (2.11)	pg/mL	31.6 (8.06)
tmax ss	hr	1.3 (0.83)	hr	1.3 (0.83)
AUC0-τ	ng·hr/mL	73.8 (40.8)	pg·hr/mL	397 (155)
Cmin	ng/mL	1.9 (1.5)	pg/mL	10.5 (6.1)
Cavg	ng/mL	3.08 (1.70)	pg/mL	16.5 (6.45)
t½	hr	35.7 (18.9)	hr	35.7 (18.9)
CLss/F	L/hr	1.53 (0.693)	L/hr	261 (98.7)
Vz ss/F	L	73.2 (44.2)	L	13009 (7828)
R	-	2.69 (1.12)	-	2.69 (1.12)

FIGURE 4: Mean Plasma Concentrations of LNG Following Single and Multiple Oral Administration of Lybrel™ to Healthy Women.



Ethinyl Estradiol

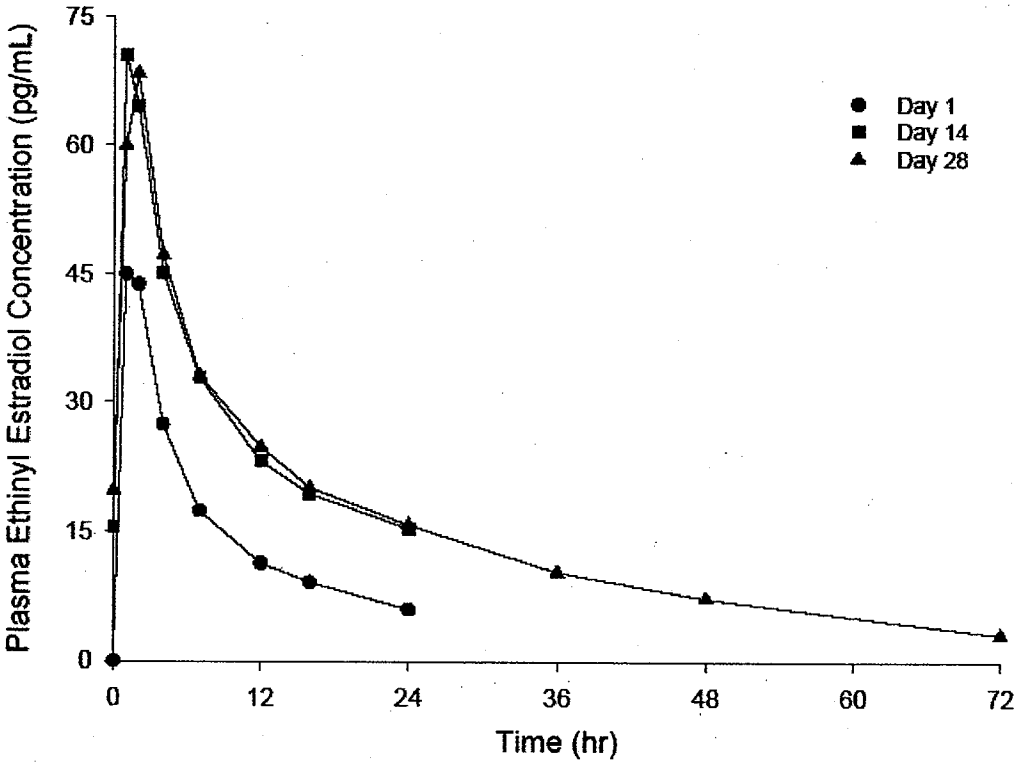
- Mean Plasma concentrations of EE were similar on Days 14 and 28 but higher than those on Day 1, indicating accumulation of EE in plasma with multiple doses
- Plasma concentrations of EE appeared to reach steady state by Day 12.

TABLE 9: Mean (SD) EE Plasma Pharmacokinetic Parameters Following Single and

Multiple Oral Administration of Lybrel™ to Healthy Women.

Parameter		Ethinyl Estradiol (N=16)		
	Unit	Day 1 Mean (SD)	Day 14 Mean (SD)	Day 28 Mean (SD)
Cmax	pg/mL	47.7 (20.1)	72.7 (37.2)	74.4 (29.7)
tmax	hr	1.3 (0.45)	1.4 (0.50)	1.4 (0.51)
AUC0-τ	pg·hr/mL	378 (140)	695 (361)	717 (351)
AUC0-∞	pg·hr/mL	567 (249)	-	-
Cavg	ng/mL	-	29.0 (15.1)	29.9 (14.6)
t½	hr	-	15.6 (7.03)	20.7 (7.12)
CL/F	L/hr	41.9 (19.9)	36.2 (20.8)	35.0 (19.9)
Vz ss/F	L	-	-	969 (462)
R	-	-	-	1.82 (0.406)

FIGURE 5: Mean Plasma Concentrations of EE Following Single and Multiple Oral Administration of Lybrel™ to Healthy Women.



Conclusions

For both LNG and EE the pharmacokinetic parameters estimated after Day 28 of dosing were similar to the estimates obtained after dosing on Day 14. Steady state levels of Lybrel™ during longer dosing duration are similar to the steady state levels of LNG/EE for a typical 21 day combination contraceptive regimen.

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/s/

Julie Bullock
3/9/2006 09:49:12 AM
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John P. Hunt
3/9/2006 11:04:54 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

GENERAL INFORMATION ABOUT THE SUBMISSION

	Information		Information
NDA Number	21-864	**Brand Name**	TRADENAME™
OCPB Division (I, II, III)	DPE II (HFD 870)	**Generic Name**	levonorgestrel 90µg/ethinyl estradiol 20µg tablets
Medical Division	DRUDP (HFD 580)	**Drug Class**	Oral Contraceptives
OCPB Reviewer	Julie Bullock, Pharm.D.	**Indication(s)**	Prevention of pregnancy
OCPB Team Leader	Ameeta Parekh, Ph.D.	**Dosage Form**	Tablet
OCPB Pharmacometrics Reviewer		**Dosing Regimen**	Once Daily
Date of Submission	05/27/2005	**Route of Administration**	Oral
Est. Due Date of OCPB Review	07/19/2005	**Sponsor**	Wyeth Pharmaceuticals.
PDUFA Due Date	03/27/2006	**Priority Classification**	N/A
Division Due Date			

CLIN. PHARM. AND BIOPHARM. INFORMATION

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE		[redacted]	[redacted]	
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X	1		**PK drawn on Day 1, 14 and 21 giving SD and MD data**
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	1		

Phase 3:	X	2		
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]			

FILABILITY AND QBR COMMENTS

	"X" if yes	Comments
Application fileable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Filing Memo

Clinical Pharmacology and BioPharmaceutics Review

NDA: **21-864**

Compound: **Levonorgestrel (LNG) 90µg / Ethinyl Estradiol (EE) 20µg**

Sponsor: **Wyeth Pharmaceuticals**

Filing Date: **July 27, 2005**

Reviewer: **Julie M. Bullock, Pharm.D.**

Background:

This NDA includes the data from one Phase I, one Phase II and 2 Phase III studies which were performed to support approval of TRADENAME. TRADENAME is a low dose continuous use oral contraceptive to be taken every day, without a pill free or placebo interval. The formulation of TRADENAME is similar to the currently marketed product Alesse® (100µg LNG/20µg EE) with a slight adjustment to the LNG and lactose content. The final formulation is a yellow biconvex, debossed film coated tablet. Dissolution data was provided to compare the clinical trial batches to the registration/validation batches and showed similar dissolution results according to the sponsor.

Pharmacokinetic Studies

-Conducted in healthy, non-pregnant, female subjects

- SD/MD Pharmacokinetic Study
    - Study 106: Multiple dose study of the PK of LNG 90µg and EE 20µg administered orally for 21 days. 24 subjects were enrolled and 18 were analyzed. Plasma samples were analyzed for LNG and EE and serum samples were analyzed for SHBG and LNG protein binding. Intensive PK samples were taken on Day 1, 14, and Day 28.

The sponsor provided the following:

1. Human Pharmacokinetics and Bioavailability section summary, full study reports and proposed labeling
2. Drug formulation
3. Bioanalytical methods
4. In-vitro dissolution data
5. A list of references
6. Sponsor provided dissolution data confirming that the to-be-marketed formulation and clinical trial formulations are the same.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II find that the Human Pharmacokinetics and Bioavailability section for NDA 21-864 fileable.

_____ _____

Julie M. Bullock, Pharm.D. Date

_____ _____

Ameeta Parekh, Ph.D., Team Leader Date

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/s/

Julie Bullock
7/12/05 03:24:50 PM
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Ameeta Parekh
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