

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204654Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**NDA Number:** 204654

**Stamp Date:** 09/28/2012

**Applicant:** Warner Chilcott Company, LLC

**Drug Name:** (b) (4) (norethindrone acetate and ethinyl estradiol chewable tablets, ethinyl estradiol tablets, and ferrous fumarate tablets)

On **initial** review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?			x	new formulation, use the information from the reference product
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			Pivotal study
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	

1 3	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
1 4	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
1 5	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
1 6	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	The Sponsor requests a full pediatric waiver for pre-menarcheal children
1 7	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
<b>General</b>					
1 8	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
1 9	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?** \_\_\_ Yes \_\_\_

**The following are reviews issues to be conveyed to the sponsor:**

The labeling of the new dosing instruction to include volume and type of liquid will be a review issue.

Li Li	10/26/2012
Reviewing Clinical Pharmacologist	Date
Myong Jin Kim	10/26/2012
Team Leader/Supervisor	Date

## Filing Memo

### Clinical Pharmacology Review

**NDA:** 204654  
**Compound:** (b) (4) (norethindrone acetate and ethinyl estradiol chewable tablets, ethinyl estradiol tablets, and ferrous fumarate tablets)  
**Sponsor:** Warner Chilcott Company, LLC  
**Date:** 10/26/2012  
**Reviewer:** Li Li, Ph.D.

#### Introduction:

The Sponsor submitted a New Drug Application (NDA) for a combination oral contraceptive (COC) (b) (4). The dose and dosing regimen of (b) (4) is

- Cycle Days 1-24: one mint-flavored, chewable tablet containing 1 mg norethindrone acetate (NETA)/10 µg ethinyl estradiol (EE) (referred to as (b) (4) 1/10 Tablet)
- Cycle Days 25-26: one 10 µg EE tablet (Referred to as WC3016 EE10 Tablet)
- Cycle Days 27-28: one inactive tablet containing ferrous fumarate

One tablet is to be taken daily for 28 consecutive days.

(b) (4) has the same NETA/ EE dose and dosing regimen as the reference product Lo Loestrin Fe (NDA 022501, Warner Chilcott Company, approved on October 21, 2010). The difference is in the mode of administration for tablets in the first 24-day of each cycle. In particular, (b) (4) 1/10 tablet can be “chewed” (b) (4) whereas WC3016 1/10 tablet in Lo Loestrin Fe should be “swallowed whole”. In addition, a (b) (4) and spearmint flavor is added to (b) (4) 1/10 tablet to enhance the chewability of the formulation. The 10 µg EE tablets and ferrous fumarate tablets in (b) (4) are identical to those in Lo Loestrin Fe.

The Sponsor seeks the approval of (b) (4) based on the demonstration of bioequivalence (BE) in norethindrone (NE) and EE exposure between (b) (4) 1/10 chewable tablets and WC3016 1/10 tablets in Lo Loestrin Fe (Study PR12111).

#### Clinical Development of (b) (4)

This application contains a full report of:

- BE and food effect study (Study PR-12111):  
A Randomized, Single-Dose, Three-Way Crossover Study conducted in healthy female volunteers to
  - assess the BE in NE and EE exposure from (b) (4) 1/10 chewable tablets and the approved Lo Loestrin Fe (WC3016 1/10) tablets
  - assess the effect of food on bioavailability of NE and EE from the (b) (4) 1/10 chewable tablets
- Food effect study on WC3016 EE10 tablet (Study PR-14106, previously submitted under NDA 022501)
- Single- and multiple-dose study of Lo Loestrin Fe (WC3016 1/10) tablet (Study PR-14206, previously submitted under NDA 022501)
- Oral safety study of (b) (4) chewable tablets (Study PR-10007)

#### Drug Product Formulation:

The (b) (4) 1/10 chewable tablet formulation was based on the formulation for the approved WC3016 1/10 tablets. The (b) (4) 1/10 chewable tablet formulation has added flavor and (b) (4) mannitol. A comparison of the unit-dose composition for the (b) (4) 1/10 chewable tablet formulation and the reference product, WC3016 1/10 tablet formulation is provided in **Table 1**.

**Table 1: Unit-Dose Composition of (b) (4) 1/10 Chewable Tablets and WC3016 1/10 Tablets**

Component	(b) (4) 1/10 chewable tablets (Formulation (b) (4))		WC3016 1/10 tablets (Formulation WC3016-21C)	
	mg/tablet	% w/w	mg/tablet	% w/w
Norethindrone acetate	1.000	(b) (4)	1.000	(b) (4)
Ethinyl estradiol*	0.010	(b) (4)	0.010	(b) (4)
Povidone (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Vitamin E (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Lactose Monohydrate (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Mannitol (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Mannitol (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Microcrystalline Cellulose (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
FD&C Blue #1, Aluminum Lake	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Spearmint Flavor (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sucralose	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium Starch Glycolate	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Magnesium Stearate	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total	(b) (4)	(b) (4)	(b) (4)	(b) (4)

**BE Assessment**

A single-dose, three way-crossover study was conducted in 42 healthy female volunteers. All subjects received the following 3 treatments:

- Treatment A: WC3016 1/10 tablet administered under fasted conditions
- Treatment B: (b) (4) 1/10 chewable tablet administered under fasted conditions
- Treatment C: (b) (4) 1/10 chewable tablet administered with a high fat meal

All tablets were administered orally with about 240 mL water following at least a 10-hour fast or following consumption of a standard high fat meal (Treatment C). Blood samples (10 mL) were collected at predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 60 hours postdose. Treatment periods were separated by at least 7 days.

Per Sponsor, statistical analysis on PK parameters (i.e.,  $C_{max}$  and AUC) of NE and EE indicated that the (b) (4) chewable 1/10 tablet is bioequivalent to WC3016 1/10 tablet. When (b) (4) 1/10 chewable tablets were administered with food,  $C_{max}$  values were decreased by 46% for NE and 41% for EE. The extent of NE and EE absorption was not significantly different.

**Absorption, Distribution, Metabolism, and Excretion (ADME)**

Specific studies describing the ADME of (b) (4) were not conducted. The Sponsor is proposing to use the available information of the reference product (i.e., Lo Loestrin Fe).

**Drug-Drug Interactions:**

No DDI studies were conducted with (b) (4)

**Specific Populations:**

- Pediatric use: No pediatric studies were conducted; the Sponsor requests a full waiver of the requirement for pediatric studies associated with the submission of this NDA
- Geriatric use: No geriatric studies were conducted
- Renal or hepatic impairment: No studies were conducted in patients with renal or hepatic impairments
- Contraindicated for pregnant women

**Bioanalytical Method:**

Plasma NE and EE concentrations were determined using GC/MS method; the bioanalytical work was performed by (b) (4)

**Recommendation:**

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 204654 is fileable.

**Office of Scientific Investigation (OSI) Inspection Request**

Study PR-12111 (pivotal BE study) was conducted by (b) (4). The bioanalytical work was done by (b) (4). Given that there were several recent inspections of these sites and that no major issues were identified, the inspection of the clinical and bioanalytical sites will not be requested.

**Reviewer's Comments:**

In the BE study, the chewable tablet ((b) (4) 1/10 tablet) was taken with 240 mL water. This is not consistent with the proposed drug product label, i.e., (b) (4). It should be noted that some liquids such as grapefruit juice may affect the CYP3A4 activity and in turn change the systemic exposure of NE and EE.

Per product label, (b) (4) 1/10 tablet can also be taken as (b) (4). Given the minor changes in the formulation, i.e., added flavor and (b) (4), a dedicated BE study may not be necessary. However, the final decision will be made by the CMC reviewer.

The clinical formulation for (b) (4) 1/10 is identical to the to-be-marketed (TBM) formulation. The TBM batch scale is (b) (4) larger than that of clinical study tablets. Per CMC lead Dr. Donna Christner, less than (b) (4) of scale change is acceptable without the need for comparative dissolution testing.

Incurred Sample Reanalysis (ISR) was conducted in the BE study.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

LI LI  
11/27/2012

MYONG JIN KIM  
11/27/2012

## OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA 204654	Submission Date(s)	09/28/12, 11/27/12, 01/23/13, 04/04/13, 05/18/13, 05/22/13, 07/16/13, 07/23/13
Brand Name	Lo Minastrin Fe	
Generic Name	Norethindrone acetate (NA) / Ethinyl estradiol (EE) / Ferrous fumarate (Fe)	
Reviewer	Li Li, PhD	
Acting Team Leader	Myong Jin Kim, PharmD	
OCP Division	Division of Clinical Pharmacology 3	
OND Division	Division of Bone, Reproductive and Urologic Products	
Sponsor	Warner Chilcott Company, LLC	
Submission Type	Original	
Formulation; Strengths; Regimen	One chewable tablet containing 1 mg NA/10 µg EE for 24 days, followed by one tablet containing 10 µg EE for 2 days and one tablet containing 75 mg Fe for 2 days (28 day regimen), daily oral administration	
Proposed Indication	Prevention of pregnancy	

### 1 Executive Summary

The Clinical Pharmacology review of NDA 204654 (DARRTS, June 20, 2013) stated that NDA 204654 was acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert labeling. The final agreement was reached on July 23, 2013 and there are no pending issues from the Office of Clinical Pharmacology. The highlights of the prescribing information and Clinical Pharmacology relevant sections of the final agreed upon package insert labeling are included in Section 2 of this addendum.

#### 1.1 Recommendation

The Division of Clinical Pharmacology-3, Office of Clinical Pharmacology finds the NDA 204654 acceptable.

8 Pags of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

1

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

LI LI  
07/24/2013

MYONG JIN KIM  
07/24/2013

---

## Clinical Pharmacology Review

---

<b>NDA Number:</b>	204654
<b>Submission Date:</b>	09/28/12, 11/27/12, 01/23/13, 04/04/13, 05/18/13, 05/22/13
<b>Brand Name:</b>	TBD
<b>Generic Name:</b>	Norethindrone acetate (NA) / Ethinyl estradiol (EE) / Ferrous fumarate (Fe)
<b>OCP Reviewer:</b>	Li Li, Ph.D
<b>OCP Team Leader:</b>	Myong Jin Kim, Pharm. D
<b>OCP Division:</b>	Division of Clinical Pharmacology III
<b>OND Division:</b>	Division of Bone, Reproductive and Urologic Products
<b>Sponsor:</b>	Warner Chilcott Company, LLC
<b>Submission Type:</b>	Original NDA; Standard review
<b>Relevant NDA:</b>	022501, Lo Loestrin Fe® Tablets
<b>Formulation; strength:</b>	One chewable tablet containing 1 mg NA/10 µg EE for 24 days, followed by one tablet containing 10 µg EE for 2 days and one tablet containing 75 mg Fe for 2 days (28 day regimen), daily oral administration
<b>Indication:</b>	Prevention of pregnancy

---

### Table of Contents

1	Executive Summary .....	2
1.1	Recommendations .....	2
1.3	Summary of Clinical Pharmacology Findings .....	2
2	Question Based Review .....	4
2.1	General Attributes .....	4
2.2	General Clinical Pharmacology.....	6
2.3	Intrinsic Factors.....	9
2.4	Extrinsic Factors.....	9
2.5	General Biopharmaceutics.....	11
2.6	Analytical Section .....	11
3	Detailed Labeling Recommendations .....	12
4	Appendix	
4.1	Individual Study Review.....	13

## Executive Summary

The Sponsor submitted an original New Drug Application (NDA) for a combination oral contraceptive (COC) (b) (4) on September 28, 2012.

The dose and dosing regimen of (b) (4) are as follows:

- Cycle Days 1-24: one mint-flavored, chewable tablet containing 1 mg NA/10 µg EE (referred to as (b) (4) 1/10 Tablet)
- Cycle Days 25-26: one 10 µg EE tablet
- Cycle Days 27-28: one inactive tablet containing 75 mg Fe

One tablet is to be taken daily for 28 consecutive days without regard to meals.

(b) (4) has the same NA/ EE dose and dosing regimen as the reference product Lo Loestrin Fe® (NDA 022501, Warner Chilcott Company, approved on October 21, 2010). The difference is in the mode of administration for tablets in the first 24-day of each cycle. Specifically, (b) (4) 1/10 tablet containing 1 mg NA/10 µg EE should be “chewed” and “swallowed” whereas the respective tablets in Lo Loestrin Fe® (referred to as WC3016 1/10 tablets) should be “swallowed whole”. The formulations of 10 µg EE tablets and ferrous fumarate tablets in (b) (4) are identical to those in Lo Loestrin Fe® and are to be administered as “swallowed whole”.

The Sponsor seeks the approval of (b) (4) based on the demonstration of bioequivalence (BE) in norethindrone (NE) and EE exposure between (b) (4) 1/10 chewable tablets and WC3016 1/10 tablets in Lo Loestrin Fe® (Study PR-12111). In addition, the effect of food on the bioavailability (BA) of NE and EE from (b) (4) 1/10 chewable tablets was evaluated in the same study.

For the pivotal BE study (Study PR-12111), a formal consult to the Office of Scientific Investigations (OSI) was made for inspections of the clinical and bioanalytical study sites.

### 1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) finds NDA 204654 acceptable provided that agreement is reached between the Sponsor and the Division regarding the language in the package insert.

#### • Phase IV Commitment/Requirement

None

### 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

**BE assessment of (b) (4) 1/10 chewable tablets and WC3016 1/10 tablets in Lo Loestrin Fe ®**  
Study PR-12111 demonstrated the BE in NE and EE exposure between (b) (4) 1/10 chewable tablets and WC3016 1/10 tablets (Lo Loestrin Fe®) following a single dose administration under a fasting condition in 38 healthy premenopausal women. The 90% confidence intervals (CI) for the test (b) (4) 1/10 to reference (WC3016 1/10) ratio in  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-inf}$  are within the 80.00% to 125.00% BE limit for both NE and EE (Table 1).

**Table 1** BE analysis of NE and EE PK parameters following a single dose administration of (b) (4) 1/10 chewable tablets (Test) or a WC3016 1/10 tablets in Lo Loestrin Fe® (Reference) under a fasting condition in 38 healthy female volunteers

Analyte	Parameter	Ratio (Test/Reference)	90% CI
NE	AUC <sub>0-t</sub> (pg·hr/mL)	102.79	97.76 – 108.07
	AUC <sub>inf</sub> (pg·hr/mL)	102.52	97.52 – 107.79
	C <sub>max</sub> (pg/mL)	109.74	100.17 – 120.22
EE	AUC <sub>0-t</sub> (pg·hr/mL)	109.85	102.84 – 117.34
	AUC <sub>inf</sub> (pg·hr/mL)	105.38	97.14 – 114.31
	C <sub>max</sub> (pg/mL)	117.20	111.22 – 123.50

### Absorption, Distribution, Metabolism, and Excretion (ADME)

The Sponsor determined NE and EE PK profiles after a single dose of (b) (4) 1/10 chewable tablets under fasting and fed conditions in study PR-12111. The respective PK parameters are summarized in Table 2. No other specific studies describing the DME of NE and EE were conducted.

**Table 2** Arithmetic means (%CV) of PK parameters of NE and EE following a single dose administration of (b) (4) 1/10 chewable tablets in healthy female subjects under a fasting condition (N=38, data from study PR-12111)

Parameters	NE	EE
AUC <sub>0-t</sub> (pg·hr/mL)	43396 (71)	317.5 (42)
AUC <sub>inf</sub> (pg·hr/mL)	44607 (74)	394.1 (47)
C <sub>max</sub> (pg/mL)	7613 (47)	39.0 (25)
T <sub>max</sub> (hr)*	1.5 (0.5 – 6.0)	1.5 (1.0 – 2.5)
T <sub>1/2</sub> (hr)	10.2	8.2

\* median (range)

### Food Effect:

A high fat meal reduced the rate, but not the extent of NE and EE absorption from WC (b) (4) 1/10 chewable tablet (Study PR-12111) compared to a fasting condition. Specifically, a high fat meal reduced the mean NE and EE C<sub>max</sub> values by 46 and 41%, respectively and increased the median NE and EE t<sub>max</sub> values by 2.5 hours. However, the 90% CI for test (fed) to reference (fasted) ratio in NE and EE AUC values were within the 80.00% to 125.00% BE limits.

### Drug-Drug Interactions:

No new DDI studies were conducted for (b) (4) tablets. The Sponsor is proposing to use the information from Lo Loestrin Fe® for their product labeling.

### Specific Populations:

#### Renal or Hepatic Impairment

No studies have been conducted to evaluate the effect of renal or hepatic impairment on the disposition of Lo Loestrin Fe® or the current product. In general, steroid hormones may be poorly metabolized in patients with impaired liver function. Lo Loestrin Fe® tablets are contraindicated for women with liver tumors or liver disease.

#### Pediatric subjects

The Sponsor has submitted a pediatric waiver request. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because the current submission is just for a new mode of administration, this NDA is not subject to PREA.

### **Bioanalytical Method Validation:**

Plasma concentrations of NE and EE were determined by a validated Gas Chromatography/Mass Spectrometry (GC/MS) method. Acceptance criteria and assay performance for are found to be acceptable.

An OSI consult requesting inspections of the clinical and bioanalytical sites of the pivotal BE study PR-12111 was made on January 18, 2013. There were no significant objectionable issues identified in the clinical site of the BE study. However, following the inspection on the analytical site in (b) (4), Form FDA-483 was issued on April 19, 2013 based on the observation listed below: “Not all aspects of study conduct were documented. For example: failure to maintain documentation for individual QC sets used during sample processing.” (b) (4) submitted a written response to Form FDA-483 on May 14, 2013. Following the review of the Form FDA 483 and the response from (b) (4) OSI recommended that that the clinical and analytical data generated for study PR-12111 were not affected by the cited deficiency and thus are accepted for further agency review. Details of the OSI inspection findings can be found in Dr. Adrindam Dasgupta OSI consult review dated May 30, 2013 in DARRTS.

## **2 QUESTION BASED REVIEW**

### **2.1 GENERAL ATTRIBUTES**

#### **2.1.1 What pertinent regulatory background or history contributes to the current assessment of the Clinical Pharmacology and Biopharmaceutics of this drug?**

The Sponsor submitted an NDA for a 28-day regimen COC (b) (4). It has the same NA/ EE dose and dosing regimen as the reference product Lo Loestrin Fe® (NDA 022501, approved on October 21, 2010). The difference is in the mode of administration for tablets in the first 24-day of each cycle. In particular, (b) (4) 1/10 tablet should be “chewed” and “swallowed” whereas WC3016 1/10 tablet in Lo Loestrin Fe® should be “swallowed whole”. In addition, a (b) (4) and spearmint flavor are added to (b) (4) 1/10 chewable tablets to enhance the chewability of the formulation. The 10 µg EE tablets and ferrous fumarate tablets in (b) (4) are identical to those in Lo Loestrin Fe® and are to be administered as “swallowed whole”.

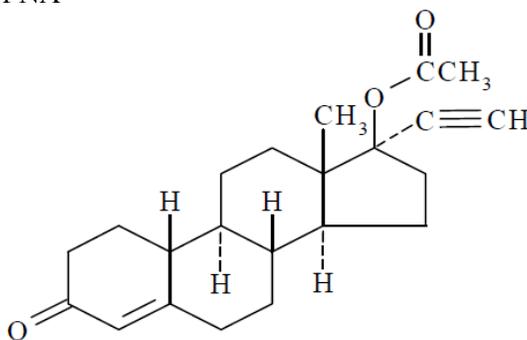
The Sponsor seeks the approval of (b) (4) based on the demonstration of BE in NE and EE exposures between (b) (4) 1/10 chewable tablets and WC3016 1/10 tablets in Lo Loestrin Fe® (Study PR-12111).

#### **2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance as they relate to clinical pharmacology and biopharmaceutics review?**

##### Active substance:

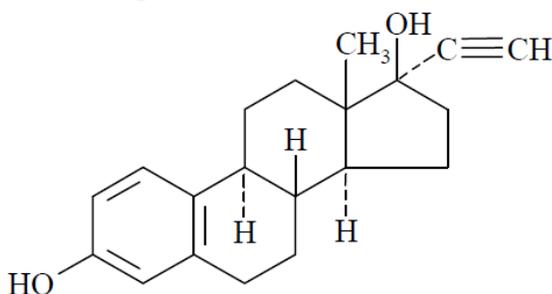
The chemical name of NA is [19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17α)-] and the empirical formula is C<sub>22</sub>H<sub>28</sub>O<sub>3</sub>. The structural formula is shown in Figure 1.

**Figure 1** Chemical structure of NA



The chemical name of EE is [19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 $\alpha$ )-] and the empirical formula is C<sub>20</sub>H<sub>24</sub>O<sub>2</sub>. The structural formula is shown in Figure 2.

**Figure 2** Chemical structure of EE



### 2.1.3 What are the proposed mechanism of action and therapeutic indication?

Indication:

Prevention of pregnancy

Mechanism of Action:

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

### 2.1.4 What are the proposed dose and dosing regimen?

The proposed dose and dosing regimen of (b) (4) are as follows:

- Cycle Days 1-24: one mint-flavored, chewable tablet containing 1 mg NA/10  $\mu$ g EE (referred to as (b) (4) 1/10 Tablet)
- Cycle Days 25-26: one 10  $\mu$ g EE tablet (Referred to as WC3016 EE10 Tablet)
- Cycle Days 27-28: one inactive tablet containing 75 mg Fe

One tablet is to be taken daily for 28 consecutive days without regard to meals.

### 2.1.5 What clinical and clinical pharmacology data are submitted to support the approval of (b) (4)?

This application contains a full report of:

- BE and food effect study (Study PR-12111):  
A Randomized, Single-Dose, Three-Way Crossover Study conducted in healthy female

volunteers to

- assess the BE in NE and EE exposure from (b) (4) 1/10 chewable tablets and the WC3016 1/10 tablets in Lo Loestrin Fe®
- assess the effect of food on BA of NE and EE from the (b) (4) 1/10 chewable tablets
- Food effect study on WC3016 EE10 tablet (Study PR-14106, previously submitted under NDA 022501)
- Single- and multiple-dose study of Lo Loestrin Fe (WC3016 1/10) tablet (Study PR-14206, previously submitted under NDA 022501)
- Oral safety study of (b) (4) chewable tablets (Study PR-10007)

The Sponsor is relying on the previous Phase 3 study of Lo Loestrin Fe® tablets for the demonstration of safety and efficacy.

## 2.2 GENERAL CLINICAL PHARMACOLOGY

### 2.2.1 Is (b) (4) 1/10 chewable tablet BE to the WC3016 1/10 tablet in Lo Loestrin Fe®?

Yes. Study PR-12111 demonstrated the BE in NE and EE exposure between (b) (4) 1/10 chewable tablets and WC3016 1/10 tablets in Lo Loestrin Fe®.

#### Study Design:

This is a single-dose, three way-crossover study conducted in 42 healthy female volunteers. All subjects received the following 3 treatments:

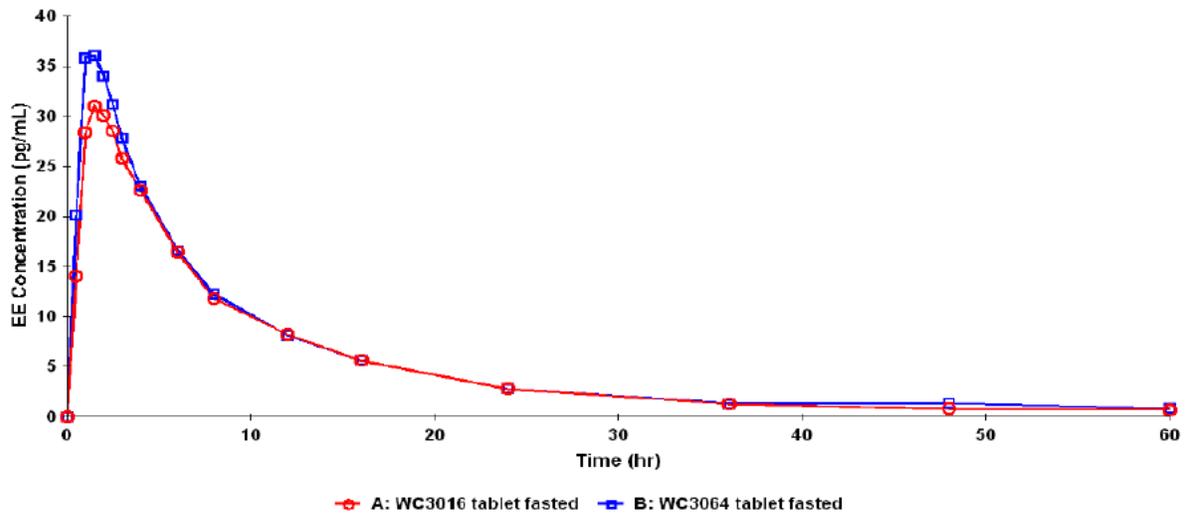
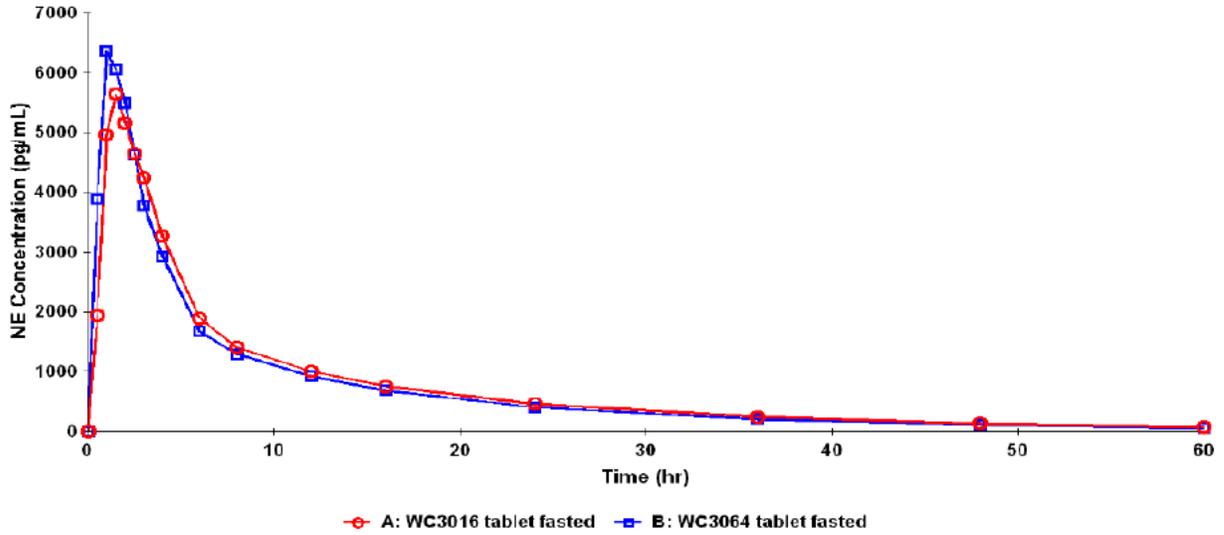
- Treatment A: WC3016 1/10 tablet administered under fasted conditions
- Treatment B: (b) (4) 1/10 chewable tablet administered under fasted conditions
- Treatment C: (b) (4) 1/10 chewable tablet administered with a high fat meal

All tablets were administered orally with about 240 mL water following at least a 10-hour fast (Treatment A and B) or following consumption of a standard high fat meal (Treatment C). Blood samples (10 mL) were collected at predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 60 hours postdose. Treatment periods were separated by at least 7 days.

#### Study Results:

As shown in Figure 3, the test (b) (4) 1/10 chewable tablet) and reference (WC3016 1/10 tablet in Lo Loestrin Fe®) products displayed similar PK profiles. The 90% CI for test to reference ratio in  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-inf}$  are within the BE limits of 80.00 to 125.00% for both NE and EE (Table 3).

**Figure 3:** Mean NE and EE Concentration-Time Profiles following a single dose of a (b) (4) chewable tablet (Test) or a WC3016 tablet (Reference) to fasted healthy female volunteers (N=38)



**Table 3** BE analysis of NE and EE PK parameters following a single dose of <sup>(b)(4)</sup> 1/10 chewable tablets (Test) or a WC3016 1/10 tablets (Reference) to fasted healthy female volunteers (N=38)

Analyte	Parameter	Geometric Mean		Ratio (Test/Reference)	90% CI
		Test	Reference		
NE	AUC <sub>0-t</sub> (pg·hr/mL)	37540	36522	102.79	97.76 – 108.07
	AUC <sub>0-inf</sub> (pg·hr/mL)	38390	37445	102.52	97.52 – 107.79
	C <sub>max</sub> (pg/mL)	6924	6309	109.74	100.17 – 120.22
EE	AUC <sub>0-t</sub> (pg·hr/mL)	293	267	109.85	102.84 – 117.34
	AUC <sub>0-inf</sub> (pg·hr/mL)	359	341	105.38	97.14 – 114.31
	C <sub>max</sub> (pg/mL)	37.7	32.2	117.20	111.22 – 123.50

### 2.2.2 What are PK characteristics of NE and EE from (b) (4) 1/10 chewable tablet?

The Sponsor determined NE and EE PK profiles after a single dose of (b) (4) 1/10 chewable tablets under fasting and fed condition in study PR-12111. The respective PK parameters were summarized in Table 4 and Table 5. No other specific studies describing the DME of NE and EE were conducted.

**Table 4** Arithmetic means (%CV) of PK parameters of NE and EE following a single dose administration of (b) (4) 1/10 chewable tablets to fasted healthy female subjects (N=38, data from study PR-12111)

Parameters	NE	EE
AUC <sub>0-t</sub> (pg·hr/mL)	43396 (71)	317.5 (42)
AUC <sub>0-inf</sub> (pg·hr/mL)	44607 (74)	394.1 (47)
C <sub>max</sub> (pg/mL)	7613 (47)	39.0 (25)
T <sub>max</sub> (hr)*	1.5 (0.5 – 6.0)	1.5 (1.0 – 2.5)
T <sub>1/2</sub> (hr)	10.2	8.2

\* median (range)

**Food Effect:** A High fat meal reduced the rate, but not the extent of NE and EE absorption from (b) (4) 1/10 chewable tablets (Study PR-12111). (b) (4) 1/10 chewable tablets can be taken without regard to meal.

Study Design: Refer to Section 2.2.1

#### Study Results:

High fat meal reduced the mean NE and EE C<sub>max</sub> values by 46 and 41%, respectively and increased the median NE and EE t<sub>max</sub> values by 2.5 hours, indicating a decreased rate of absorption in the presence of food. However, the extent of NE and EE absorption was not affected by food as the 90% CI for the test (fed) to reference (fasted) ratio in NE and EE AUC were within the 80.00% to 125.00% BE limits (Table 5).

**Table 5** Statistical analysis of NE and EE PK parameters following a single dose administration of a (b) (4) 1/10 chewable tablets to healthy female volunteers under fasted (reference) and fed (test) conditions (N=37)

Analyte	Parameter <sup>1</sup>	Geometric Mean		Ratio (Test/Reference)	90% CI
		Test	Reference		
NE	AUC <sub>0-t</sub> (pg·hr/mL)	41687	37706	110.56	105.02 – 116.39
	AUC <sub>0-inf</sub> (pg·hr/mL)	42918	38561	111.30	105.76 – 117.13
	C <sub>max</sub> (pg/mL)	3740	6941	53.88	48.48 – 59.88
	T <sub>max</sub> (hr)*	4.00 ( 1.50 – 12.00)	1.50 (0.50 – 6.00)		
EE	AUC <sub>0-t</sub> (pg·hr/mL)	298	294	101.38	93.14 – 110.35
	AUC <sub>0-inf</sub> (pg·hr/mL)	393	360	109.02	98.12 – 121.12
	C <sub>max</sub> (pg/mL)	22.4	37.7	59.32	54.29 – 64.82
	T <sub>max</sub> (hr)*	4.00 ( 1.50 – 12.00)	1.50 (0.50 – 2.50)		

\* Median (range)

## **Distribution**

Based on Lo Loestrin Fe® labeling, volume of distribution of NE and EE ranges from 2 to 4 L/kg. Plasma protein binding of both steroids is extensive (>95%); NE binds to both albumin and SHBG, whereas EE binds only to albumin. Although EE does not bind to SHBG, it induces SHBG synthesis.

## **Metabolism**

Based on Lo Loestrin Fe® labeling, NE undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites. A small amount of NA is metabolically converted to EE.

EE is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of EE and glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy EE, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of EE is believed to occur in gastrointestinal mucosa. EE may undergo enterohepatic circulation.

## **Excretion**

Based on Lo Loestrin Fe® labeling, NE and EE are excreted in both urine and feces, primarily as metabolites. Plasma clearance values for NE and EE are similar (approximately 0.4 L/hr/kg). Elimination half-lives of NE and EE following administration of tablets containing the combination of 1 mg NA and 10 µg EE are approximately 10 hours and 16 hours, respectively.

## **2.3 INTRINSIC FACTORS**

**2.3.1 What intrinsic factors (age, race, weight, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?**

### Renal or Hepatic Impairment

No studies have been conducted to evaluate the effect of renal or hepatic impairment on the disposition of Lo Loestrin Fe® or current product.

In general, steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Lo Loestrin Fe® tablets are contraindicated for women with liver tumors or liver disease.

### Pediatric subjects

The Sponsor has submitted pediatric waiver request. Under the PREA (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because the current submission is just for a new mode of administration, this NDA is not subject to PREA.

## **2.4 EXTRINSIC FACTORS**

No formal studies were conducted with (b) (4). The Sponsor is proposing to use the following publicly available information from Lo Loestrin Fe® label.

Changes in contraceptive effectiveness associated with co-administration of other products:

If a woman on hormonal contraceptives takes a drug or herbal product that induces enzymes, including CYP3A4, that metabolize contraceptive hormones, counsel her to use additional contraception or a different method of contraception. Drugs or herbal products that induce such enzymes may decrease the plasma concentrations of contraceptive hormones, and may decrease the effectiveness of hormonal contraceptives or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include barbiturates, bosentan, carbamazepine, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, St. John's wort, topiramate.

HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of the estrogen and progestin have been noted in some cases of co-administration of HIV protease inhibitors or of non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Increase in plasma levels of estradiol associated with co-administered drugs:

Co-administration of atorvastatin and certain combination oral contraceptives containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

Changes in plasma levels of co-administered drugs:

Combination hormonal contraceptives containing some synthetic estrogens (e.g., EE) may inhibit the metabolism of other compounds. (b) (4)

(b) (4)

**2.5 GENERAL BIOPHARMACEUTICS**

**2.5.1 What is the quantitative composition of the drug products used in the clinical trials of this application?**

The (b) (4) 1/10 chewable tablet formulation was based on the formulation for the approved WC3016 1/10 tablets in Lo Loestrin Fe®. The (b) (4) 1/10 chewable tablet formulation has added flavor and (b) (4) mannitol. A comparison of the unit-dose composition for the (b) (4) 1/10 chewable tablet formulation and the reference product, WC3016 1/10 tablet formulation is provided in **Table 6**.

**Table 6: Unit-Dose Composition of (b) (4) 1/10 Chewable Tablets and WC3016 1/10 Tablets**

Component	(b) (4) 1/10 chewable tablets (Formulation (b) (4))		WC3016 1/10 tablets (Formulation WC3016 (b) (4))	
	mg/tablet	% w/w	mg/tablet	% w/w
Norethindrone acetate	1.000	(b) (4)	1.000	(b) (4)
Ethinyl estradiol*	0.010	(b) (4)	0.010	(b) (4)
Povidone (b) (4)		(b) (4)		(b) (4)
Vitamin E (b) (4)				
Lactose Monohydrate (b) (4)				
Mannitol (b) (4)				

Mannitol	(b) (4)		(b) (4)		(b) (4)
Microcrystalline Cellulose	(b) (4)				
FD&C Blue #1, Aluminum Lake					
Spearmint Flavor	(b) (4)				
Sucralose					
Sodium Starch Glycolate					
Magnesium Stearate					
Total					

The formulations of EE tablets and ferrous fumarate tablets in (b) (4) are identical to those from Lo Loestrin Fe®.

### 2.5.2 Is the clinical formulation same to the TBM formulation?

The clinical formulation for (b) (4) 1/10 is identical to the to-be-marketed (TBM) formulation. The TBM batch scale is (b) (4) than that of clinical study tablets. Per CMC lead Dr. Donna Christner, less than 10-fold of scale change is acceptable without the need for comparative dissolution testing.

## 2.6 ANALYTICAL SECTION

### 2.6.1 What bioanalytical methods are used to assess concentrations?

Bioanalytical measurement was conducted at (b) (4) Bioanalytical Report (b) (4). Plasma concentrations of NE and EE were determined by a validated GC/MS method with (b) (4) EE as internal standards. The analytes were extracted from plasma into toluene, followed by several clean-up steps. After extraction, the samples were derivatized in two steps and 1-3 µL of the derivatized samples were injected into the GC/MS system. GC/MS measurements were performed in the chemical ionization mode (negative ions) using ammonia as reagent gas. The GC-MS method was developed and validated with the dynamic range of 25.0 - 25000 pg/mL for NE and 2.5-250 pg/mL for EE. For each quality control (QC) concentration level (7.5, 30 and 200 pg/mL for EE; 75, 2500 and 20000 pg/mL for NE), the precision and accuracy were within 10%. The detailed analytical conditions are presented in Table 7 and 8.

**Table 7** GC-MS analysis for plasma NE concentration

Calibration range	25.0 – 25000 pg/mL
Lower limit of quantification (LLOQ)	25.0 ng/mL
Calibration Standard Precision (% CV)	3.0 ~ 7.4 %
Calibration Standard Accuracy (% Bias)	-3.5 ~ 3.4 %
QC precision (% CV)	6.1 ~ 7.8 %
QC Accuracy (% Bias)	-4.6 ~ 8.0 %
Extraction Recovery (%)	75.8% ~ 106 %
Stability in plasma at room temperature	at least 144 hour
Stability in plasma at - 20°C	3 years
Stability of plasma samples at 3 thawing/freezing cycles	no problems observed

**Table 8** GC-MS analysis for plasma EE concentration

<b>Calibration range</b>	2.5 – 250 pg/mL
<b>LLOQ</b>	2.5 pg/mL
<b>Calibration Standard Precision (% CV)</b>	2.6 ~ 8.6 %
<b>Calibration Standard Accuracy (% Bias)</b>	-6.5 ~ 2.9 %
<b>QC precision (% CV)</b>	6.1 ~ 10.1 %
<b>QC Accuracy (% Bias)</b>	-3.5 ~ -2.2 %
<b>Extraction Recovery (%)</b>	68.7% ~ 96.5 %
<b>Stability in plasma at room temperature</b>	at least 94 hour
<b>Stability in plasma at - 20°C</b>	at least 97 days
<b>Stability of plasma samples at 3 thawing/freezing cycles</b>	no problems observed

### **3 DETAILED LABELING RECOMMENDATIONS**

Detailed labeling recommendations will be incorporated into DRUP’s proposed label.

The Clinical Pharmacology relevant edits to the proposed label include the following:

- Under Section 2 Dosage and Administration and Section 17 Patient Counseling Information, remove (b) (4)
- Update Section 7 Drug Interactions to align with current COC labels.
- Under Section 12.3 Pharmacokinetics, add the description of the BE study to show that the new method of administration (chewed and swallowed) is BE to approved method (swallowed whole) for the reference product (Lo Loestrin Fe®).

## 4 APPENDIX

### 4.1 INDIVIDUAL STUDY REVIEW

#### Study 03-0415-001

---

**A study to assess the comparative bioavailability of norethindrone acetate and ethinyl estradiol from WC3016 tablets and (b) (4) tablets and to assess the effect of food on bioavailability from (b) (4) tablets in healthy female volunteers**

**Protocol No:** PR-12111  
**Phase:** 1  
**Principal Investigator:** Maria Gutierrez, MD  
**Clinical Study Center:** Comprehensive Clinical Development, 3400 Enterprise Way  
Miramar, FL 33025  
**Clinical Study Dates:** 04 April 2012 to 20 April 2012  
**Analytical Study Facility:** (b) (4)

---

#### OBJECTIVES

- To assess the comparative BA of NE and EE following oral administration of WC3016 1/10 tablets and (b) (4) 1/10 chewable tablets in healthy female subjects
- To assess the effect of a high fat meal on the BA of NE and EE following oral administration of (b) (4) 1/10 chewable tablets in healthy female subjects

#### STUDY ENDPOINTS

The PK parameters used for BE evaluation were  $AUC_{0-t}$ ,  $AUC_{0-inf}$  and  $C_{max}$  of NE and EE

#### STUDY DESIGN

This is a randomized, single-dose, three-way crossover study in 42 healthy women. All subjects received the following 3 treatments:

- Treatment A: WC3016 1/10 tablet administered under fasted conditions
- Treatment B: (b) (4) 1/10 chewable tablet administered under fasted conditions
- Treatment C: (b) (4) 1/10 chewable tablet administered with a high fat meal

All tablets were administered orally with about 240 mL water following at least a 10-hour fast (Treatment A and B) or following consumption of a standard high fat meal (Treatment C). Treatment periods were separated by at least 7 days.

#### Disposition of Study Subjects

Forty-two (42) healthy, non-smoking female subjects were enrolled into the study, and 40 completed the study. Thirty-eight (38) were evaluable for PK analysis. The age of study subjects ranged between 20-45 years old with average body mass index (BMI) of 26.0 kg/m<sup>2</sup> (range: 20.7-29.7 kg/m<sup>2</sup>). Of the 42 subjects, there were 39 White and 3 Black or African American.

#### Inclusion Criteria

- Healthy non-smoking female, aged 18-45 years inclusive at the time of first signing the informed consent form (ICF)
- Weigh at least 45 kg and have a BMI between 19.0 to 29.9 kg/m<sup>2</sup>
- Have a history of regular menstrual period in the last year or at least 12 consecutive cycles defined as a usual length of 21-35 days and a variability of  $\pm 3$  days

- Use non-hormonal products for pregnancy avoidance/prevention
- Negative test for selected drugs of abuse and cotinine at the Screening visit (does not include alcohol) and on Day -1, Period 1 (includes alcohol)
- Negative hepatitis panel and negative Human Immunodeficiency Virus (HIV) antibody tests
- Negative test for pregnancy at the Screen visit and on Day -1, Period 1

### **Exclusion Criteria**

- Pregnant or lactating
- Use of any over-the-counter (OTC), non-prescription preparations (including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations) within the 14 days prior to Day -1, Period 1 unless deemed acceptable by the Investigator in consultation with Warner Chilcott
- Use of any prescription medications / products within the 14 days prior to Day -1, Period 1 unless deemed acceptable by the Investigator in consultation with Warner Chilcott
- Use of any oral contraceptive containing estrogens or any form of hormone therapy by any route during the 28 days prior to Day -1, Period 1 or use of medroxyprogesterone acetate contraceptive injection (eg, Depo-Provera®) during the year prior to Day -1, Period 1
- Use of any substances known to be strong inhibitors of cytochrome P450 (CYP) enzymes (such as cimetidine, fluoxetine, quinidine, erythromycin, fluconazole, and ketoconazole) or strong inducers of CYP enzymes (such as barbiturates, carbamazepine, glucocorticoids, phenytoin, and rifampin) within 28 days prior to Day -1, Period 1
- History or presence of any significant metabolic, allergic, cardiovascular, pulmonary,
- hepatic, renal, hematologic (including bleeding disorders), gastrointestinal, endocrine, immunologic, dermatologic, muscular, neurological, psychiatric, neoplastic, or other disease, that, in the opinion of the Investigator, could interfere with the course of the study or expose the subject to undue risk by participating in this study
- Relevant history or known presence of: migraines or severe headaches during previous estrogen therapy, thrombotic disorders, , breast cancer or undiagnosed breast nodules, severe hypertension, cerebrovascular accident, transient ischemic attacks, or undiagnosed vaginal bleeding
- Hypersensitivity, idiosyncratic reaction, or intolerance to estrogens, progestogens, or other hormonal agents or to any component of the formulations or test meal, eg, lactose intolerance
- History of cancer within the past 5 years, except for basal cell carcinoma with documentation of a 6-month remission at the Screening visit
- History of jaundice with previous use of oral contraceptives
- Consumption of:
  - caffeine- or xanthine-containing foods or beverages within the 24 hours prior to dose administration
  - alcohol-containing foods or beverages within 72 hours prior to dose administration
  - grapefruit-containing foods or beverages within the 7 days prior to dose administration
- History or presence of alcoholism or drug abuse or dependence

Detailed exclusion criteria can be found in the study protocol.

### **Formulations**

#### Reference Formulation

WC3016 Tablet (1 mg NA/ 10 µg EE): manufactured by Warner Chilcott Company, LLC, Fajardo, PR 00738 on October 22, 2011 (Lot No. 508556T).

#### Test Formulations

(b) (4) 1/10 Chewable Tablet (1 mg NETA/ 10 µg EE): manufactured by Warner Chilcott Company, LLC, Fajardo, PR 00738 on November 15, 2011 (Lot No. 509921X).

The (b) (4) 1/10 chewable tablet formulation was based on the formulation for the approved WC3016 tablets from Lo Loestrin Fe®. The (b) (4) 1/10 chewable tablet formulation has added flavor and (b) (4) and a corresponding reduction of the amount of mannitol. A comparison of the unit-dose composition for the (b) (4) chewable tablet formulation and the reference product, WC3016 1/10 tablet formulation is provided in Table 1.

**Table 1: Unit-Dose Composition of (b) (4) 1/10 Chewable Tablets (test) and WC3016 1/10 Tablets from Lo Loestrin Fe® (reference)**

Component	(b) (4) chewable tablets (Formulation (b) (4))		WC3016 tablets (Formulation WC3016-21C)	
	mg/tablet	% w/w	mg/tablet	% w/w
Norethindrone acetate	1.000	(b) (4)	1.000	(b) (4)
Ethinyl estradiol*	0.010		0.010	
Povidone (b) (4)	(b) (4)		(b) (4)	
Vitamin E (b) (4)				
Lactose Monohydrate (b) (4)				
Mannitol (b) (4)				
Mannitol (b) (4)				
Microcrystalline Cellulose (b) (4)				
FD&C Blue #1, Aluminum Lake				
Spearmint Flavor (b) (4)				
Sucralose				
Sodium Starch Glycolate				
Magnesium Stearate				
Total				

**Concomitant Food, Drinks and Therapy**

No medication (including over-the-counter products) was allowed during the 14 days preceding the study and throughout the entire study. This prohibition included vitamin supplements and herbal remedies.

Subjects were prohibited from smoking for the duration of the study. The consumption of caffeine- or xanthine-containing foods or beverages was prohibited for 24 hours before each dose and throughout the blood sampling periods. The consumption of alcohol-containing foods or beverages was prohibited for 72 hours before each dose and throughout the blood sampling periods. The consumption of grapefruit-containing foods or beverages was prohibited for 7 days before each dose and throughout the blood sampling periods.

Subjects who tested positive for cotinine, alcohol, or drugs in tests performed prior to dosing in each treatment period were to be withdrawn from the study.

**Protocol Deviation**

Two subjects each took one concomitant medication (acetaminophen) during the study. In particular, subject 506104 took 1000 mg acetaminophen and subject 506117 took 500 mg acetaminophen at about 10 hours post dose. However, it may not interfere with the outcome of the study.

**Reviewer’s Comments:**

$T_{max}$  of NE and EE is about 1.5 hours. Therefore, administration of acetaminophen at 10 hour postdose is not expected to affect NE and EE systemic exposure.

## PHARMACOKINETIC EVALUATION

### Blood Sampling

Blood samples (10 mL) were collected at predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 60 hours postdose.

### Bioanalytical method

Bioanalytical measurement was conducted at (b) (4) Bioanalytical Report (b) (4). Plasma concentrations of NE and EE were determined by a validated Gas Chromatography/Mass Spectrometry (GC/MS) method (b) (4) as internal standards. The analytes were extracted from plasma into toluene, followed by several clean-up steps. After extraction, the samples were derivatized in two steps and 1-3  $\mu$ L of the derivatized samples were injected into the GC/MS system. GC/MS measurements were performed in the chemical ionization mode (negative ions) using ammonia as reagent gas. The GC-MS method was developed and validated with the dynamic range of 25.0 - 25000 pg/mL for NE and 2.5-250 pg/mL for EE. For each quality control (QC) concentration level (7.5, 30 and 200 pg/mL for EE; 75, 2500 and 20000 pg/mL for NE), the precision and accuracy were within 10%. The detailed analytical conditions are presented in **Table 2-3**.

**Table 2** GC-MS analysis for plasma NE concentration

<b>Calibration range</b>	25.0 – 25000 pg/mL
<b>Lower limit of quantification (LLOQ)</b>	25.0 ng/mL
<b>Calibration Standard Precision (% CV)</b>	3.0 ~ 7.4 %
<b>Calibration Standard Accuracy (% Bias)</b>	-3.5 ~ 3.4 %
<b>QC precision (% CV)</b>	6.1 ~ 7.8 %
<b>QC Accuracy (% Bias)</b>	-4.6 ~ 8.0 %
<b>Extraction Recovery (%)</b>	75.8% ~ 106 %
<b>Stability in plasma at room temperature</b>	at least 144 hour
<b>Stability in plasma at - 20°C</b>	3 years
<b>Stability of plasma samples at 3 thawing/freezing cycles</b>	no problems observed

**Table 3** GC-MS analysis for plasma EE concentration

<b>Calibration range</b>	2.5 – 250 pg/mL
<b>LLOQ</b>	2.5 pg/mL
<b>Calibration Standard Precision (% CV)</b>	2.6 ~ 8.6 %
<b>Calibration Standard Accuracy (% Bias)</b>	-6.5 ~ 2.9 %
<b>QC precision (% CV)</b>	6.1 ~ 10.1 %

<b>QC Accuracy (% Bias)</b>	-3.5 ~ -2.2 %
<b>Extraction Recovery (%)</b>	68.7% ~ 96.5 %
<b>Stability in plasma at room temperature</b>	at least 94 hour
<b>Stability in plasma at - 20°C</b>	at least 97 days
<b>Stability of plasma samples at 3 thawing/freezing cycles</b>	no problems observed

**Incurred Sample Reanalysis (ISR):**

ISR was conducted on 98 out of 1952 study samples (approximately 5%). These incurred samples were selected as follows: one sample in the range of  $C_{max}$  and one sample from the elimination phase with a lower quantifiable level (but > low QC level). Of the 98 samples, 95 (95%) were within 20% of the original NE concentration value and 89 (89%) were within 20% of the original EE concentration value. These ISR results confirmed the reproducibility of the bioanalytical method.

**Reviewer’s Comment:** *Acceptance criteria and assay performance for NE and EE bioanalysis are in compliance with the Agency’s Bioanalytical Method Validation Guidance and the bioanalytical method are acceptable.*

An OSI consult requesting inspections of the clinical and bioanalytical sites of the pivotal BE study was made on January 18, 2013. There is no significant objectionable issues identified in the clinical site of the BE study. Following inspection on the analytical site in (b) (4) Form FDA-483 was issued on April 19, 2013 based on the observation listed below: “Not all aspects of study conduct were documented. For example: failure to maintain documentation for individual QC sets used during sample processing.” A written response to the inspectional findings from (b) (4) was received on May 14, 2013. After reviewing and the evaluation of the Form FDA 483 observation and response from (b) (4) OSI recommended that the data for clinical and analytical portions of study PR-12111 be accepted for further agency review. Details of the OSI inspection findings can be found in Dr. Adrindam Dasgupta OSI consult review dated May 30, 2013 in DARRTS.

**SAFETY ASSESSMENTS**

Vital signs and clinical laboratory assessments were monitored. All adverse events were recorded.

**DATA ANALYSIS**

BE will be established if the 90% CI for the geometric mean ratios (GMR) of test versus reference formulation based on  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-inf}$  for NE and EE were contained within the regulatory acceptance range of 80.00 to 125.00%.

**Data sets analyzed:** Forty two (42) healthy, non-smoking female volunteers were enrolled into the study, and 40 completed the study. Subject 506104 was withdrawn per protocol due to emesis within 2 hours after dosing in Period 3; her Period 1 and 2 samples were analyzed and included in the primary dataset (BE analysis). Subject 506132 was withdrawn after failing to return for dosing in Period 2. Therefore, PK analysis did not include the data from subject 506132. The data from a further 3 subjects was withdrawn from the primary dataset per protocol due to the measurable EE concentrations in one or more predose samples; the subject numbers were 506109, 506122, and 506129.

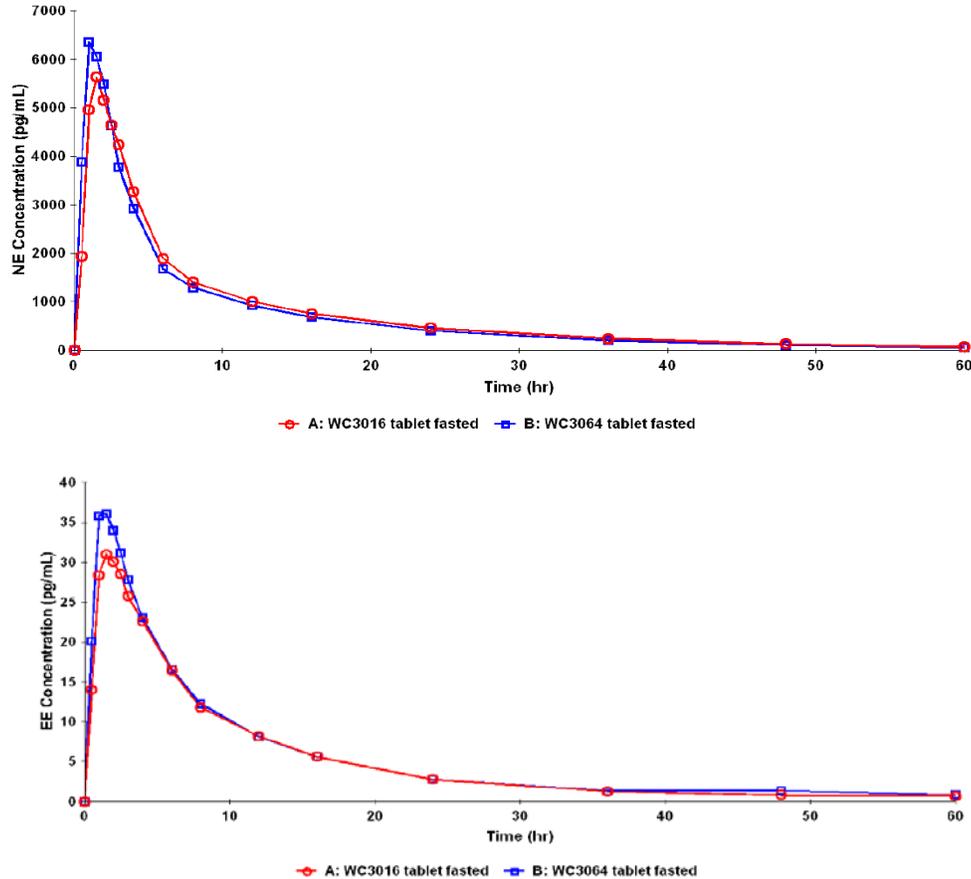
**Reviewer’s comments:** *The Sponsor did not calculate the statistical power based on the current sample size. Regardless, the sample size of 38 subjects seems to be adequate for the BE analysis for NE and EE.*

## PHARMACOKINETIC RESULTS

### BE Evaluation

NE and EE concentration-time profiles following a single dose of (b) (4) 1/10 chewable tablet (test) and WC3016 1/10 tablet in Lo Loestrin® (reference) are presented in **Figure 1** with PK parameters summarized in **Table 4**. The 90% CI for the test to reference ratio in  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-inf}$  are within the 80.00% to 125.00% BE limit for both NE and EE.

**Figure 1:** Mean NE and EE Concentration-Time Profiles following a single dose of a (b) (4) 1/10 chewable tablet (Test) or a WC3016 1/10 tablet from Lo Loestrin Fe® (Reference) to fasted healthy female volunteers (N=38)



**Table 4** BE analysis of NE and EE PK parameters following a single dose of a (b) (4) 1/10 chewable tablets (Test) or a WC3016 1/10 tablets from Lo Loestrin Fe® (Reference) to fasted healthy female volunteers (n=38)

Analyte	Parameter	Geometric Mean		Ratio (Test/Reference)	90% CI
		Test	Reference		
NE	$AUC_{0-t}$ (pg·hr/mL)	37540	36522	102.79	97.76 – 108.07
	$AUC_{0-inf}$ (pg·hr/mL)	38390	37445	102.52	97.52 – 107.79
	$C_{max}$ (pg/mL)	6924	6309	109.74	100.17 – 120.22
	$T_{max}$ (hr)	1.5 (0.5 – 6.0)	1.50 (1.0 – 6.0)	-	-
EE	$AUC_{0-t}$ (pg·hr/mL)	293	267	109.85	102.84 – 117.34

AUC <sub>0-inf</sub> (pg·hr/mL)	359	341	105.38	97.14 – 114.31
C <sub>max</sub> (pg/mL)	37.7	32.2	117.20	111.22 – 123.50
T <sub>max</sub> (hr)	1.5 (1.0 – 2.5)	1.50 (1.0 – 4.0)	-	-

1. C<sub>max</sub> = Maximum plasma concentration (pg/mL); AUC<sub>0-t</sub> = Area under the plasma concentration versus time curve from time 0 to time of last determinable concentration (pg-h/mL); AUC<sub>0-inf</sub> = Area under the plasma concentration versus time curve from time 0 to infinity (pg-h/mL); t<sub>max</sub> = Time of the maximum measured plasma concentration (h); t<sub>1/2</sub> = Terminal phase half-life (h)

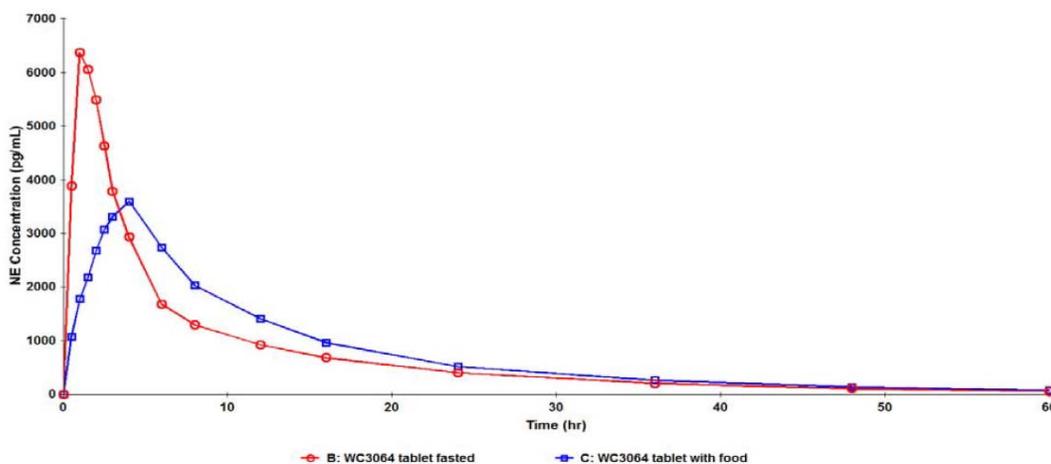
### Reviewer's comments:

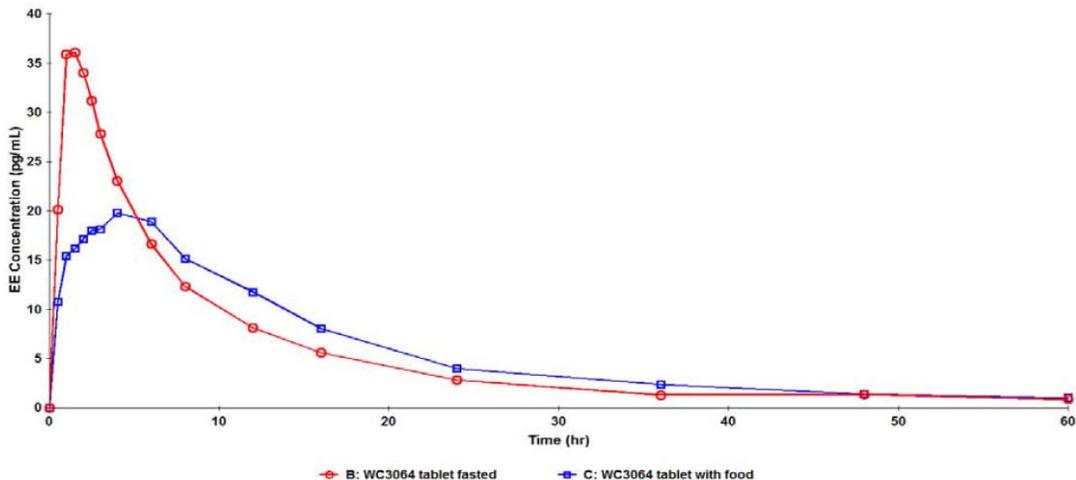
This reviewer agrees that BE in NE and EE exposure between (b) (4) 1/10 chewable tablets and WC3016 1/10 tablets from Lo Loestrin Fe® has been adequately established.

### Food Effect

The NE and EE concentration-time profiles following a single dose of (b) (4) 1/10 chewable tablet under fasted and fed condition are presented in **Figure 2** with PK parameters summarized in **Table 5**. High fat meal reduced the mean NE and EE C<sub>max</sub> values by 46 and 41%, respectively and increased the median NE and EE t<sub>max</sub> values by 2.5 hours, indicating a decreased rate of absorption in the presence of food. However, the extent of NE and EE absorption was not affected by food as the 90% CI for the test (fed) to reference (fasted) ratio in NE and EE AUC were within the 80.00% to 125.00% BE limits.

**Figure 2** Mean NE and EE Concentration-Time Profiles following single-dose oral administration of a (b) (4) 1/10 chewable tablet with food (Test) or fasted (Reference) to healthy female volunteers (N=37)





**Table 5** Statistical analysis of NE and EE PK parameters following oral administration of a (b) (4) 1/10 chewable tablet with food (Test) or a (b) (4) 1/10 chewable tablet fasted (Reference) to healthy female volunteers (N=37)

Analyte	Parameter	Geometric Mean		Ratio (Test/Reference)	90% CI
		Test	Reference		
NE	AUC <sub>0-t</sub> (pg·hr/mL)	41687	37706	110.56	105.02 – 116.39
	AUC <sub>inf</sub> (pg·hr/mL)	42918	38561	111.30	105.76 – 117.13
	C <sub>max</sub> (pg/mL)	3740	6941	53.88	48.48 – 59.88
	T <sub>max</sub> (hr)	4.00 ( 1.50 – 12.00)	1.50 (0.50 – 6.00)		
EE	AUC <sub>0-t</sub> (pg·hr/mL)	298	294	101.38	93.14 – 110.35
	AUC <sub>inf</sub> (pg·hr/mL)	393	360	109.02	98.12 – 121.12
	C <sub>max</sub> (pg/mL)	22.4	37.7	59.32	54.29 – 64.82
	T <sub>max</sub> (hr)	4.00 ( 1.50 – 12.00)	1.50 (0.50 – 2.50)		

### SAFETY RESULTS

No significant abnormalities were noted in blood pressure, heart rate, respiration rate or temperature. Results from the Screening 12-lead ECG measurements were within normal limits or were not clinically significant. The overall nature and frequency of AEs seen in this study were consistent with what would be expected in subjects receiving single doses of orally administered NE and EE. WC3016 1/10 tablets fasted and (b) (4) 1/10 chewable tablets fasted or with food were generally well tolerated.

### CONCLUSIONS

- (b) (4) 1/10 chewable tablets are BE to WC3016 1/10 tablets from Lo Loestrin Fe®.
- High fat meal decreased the rate, not the extent of NE and EE absorption from (b) (4) 1/10 chewable tablets.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

LI LI  
06/20/2013

MYONG JIN KIM  
06/20/2013