CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209405
Priority or Standard	Standard
Received Date(s)	May 30, 2019
PDUFA Goal Date	March 20, 2020
Division/Office	Office of New Drugs/ODE3/DBRUP
Reviewer Name(s)	Anandi Kotak, MD, MPH
Review Completion Date	February 26, 2020
Established/Proper Name	Levonorgestrel/ethinyl estradiol (EV402)
(Proposed) Trade Name	(b) (4)
Applicant	Exeltis USA, Inc.
Dosage Form(s)	Chewable tablets
Applicant Proposed Dosing Regimen(s)	Levonorgestrel 0.10 mg/ethinyl estradiol 0.02 mg (b) (4) tablet once daily by mouth for 21 days followed by one inactive tablet daily for 7 days
Applicant Proposed Indication(s)/Population(s)	Prevention of pregnancy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Females of childbearing potential

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Glossary

AC	advisory committee
AE	adverse event
ANDA	abbreviated new drug application
ANOVA	Analysis of Variance
AR	adverse reaction
AUC	area under the concentration versus time curve
BA	bioavailability
BE	bioequivalence
BLA	biologics license application
BMI	body mass index
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHC	combination hormonal contraceptive
CMC	chemistry, manufacturing, and controls
COC	combination oral contraceptive
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EE	ethinyl estradiol
EV402	levonorgestrel 0.1 mg/ethinyl estradiol 0.02 mg
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice

GRMP	good review management practice
HRT	hormone replacement therapy
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IUD	intrauterine device
IUS	intrauterine system
LNG	levonorgestrel
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
POP	progestin-only oral contraceptives
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RLD	Reference Listed Drug
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	system organ class
TEAE	treatment-emergent adverse event

1. Executive Summary

1.1. Product Introduction

This application seeks approval for levonorgestrel (LNG) 0.1 mg/ethinyl estradiol (EE) 0.02 mg (b) (4) tablets. The Applicant referred to the product as EV402 and that designation will be used in this review. The proposed proprietary name for this product is (b) (4) This is a progestin/synthetic estrogen-containing oral combination hormonal contraceptive indicated for the prevention of pregnancy in females of reproductive potential. (b) (4) . It will be provided in blister packs containing 28 tablets each (21 active tablets and 7 placebo tablets). This product should be taken once daily at the same time every day.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This application meets the regulatory requirement for substantial evidence of effectiveness based on the definition of bioequivalence per 21 CFR §320.1. Study EXS-P3-239 demonstrates the pharmacokinetics of EV402 (b) (4) tablets are within the bioequivalence margin. I recommend approval of EV402 tablets for prevention of pregnancy.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The EV402 chewable tablet provides an additional contraceptive option for women who prefer or require a chewable tablet. The product demonstrates bioequivalence to the reference listed drug – levonorgestrel 0.1 mg/ethinyl estradiol 0.02 mg tablets (Lutera®). Because food and liquid effect studies have not been repeated with the final to-be-marketed formulation, this chewable tablet must be taken exactly as directed to ensure its safety and efficacy.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Prevention of pregnancy (See Section 2.1 for further information)	Contraceptive options provide women with choices for their family planning needs.
Current Treatment Options	• Chewable combination oral contraceptive tablets (See Section 2.2 for further information)	Several combination oral contraceptives have been approved in chewable dosage form. This dosage form may provide benefit to women who prefer not to or are unable to swallow tablets.
Benefit	• Bioequivalence is demonstrated (See Section 6.1 for further information	This product provides a chewable dosage form of levonorgestrel 0.1 mg/ethinyl estradiol 0.02 mg tablets.
Risk and Risk Management	• Chewable tablet is well-tolerated • Food and liquid effect studies have not been repeated with the final to-be-marketed formulation	This chewable tablet must be taken exactly as directed to ensure its safety and efficacy.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	☐ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	☐ Patient reported outcome (PRO)	
	☐ Observer reported outcome (ObsRO)	
	☐ Clinician reported outcome (ClinRO)	
	☐ Performance outcome (PerfO)	
	☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	☐ Observational survey studies designed to capture patient experience data	
	☐ Natural history studies	
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	
	☐ Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
	☐ Input informed from participation in meetings with patient stakeholders	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	☐ Observational survey studies designed to capture patient experience data	
	☐ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Unplanned pregnancy represents a major public health concern. Women who experience unplanned pregnancy are less likely to receive early prenatal care and to breastfeed. Their infants are more likely to be low birthweight. These women are also more likely to suffer social and economic hardship. Providing women of reproductive potential with contraceptive options will have a significant positive impact on women's health.

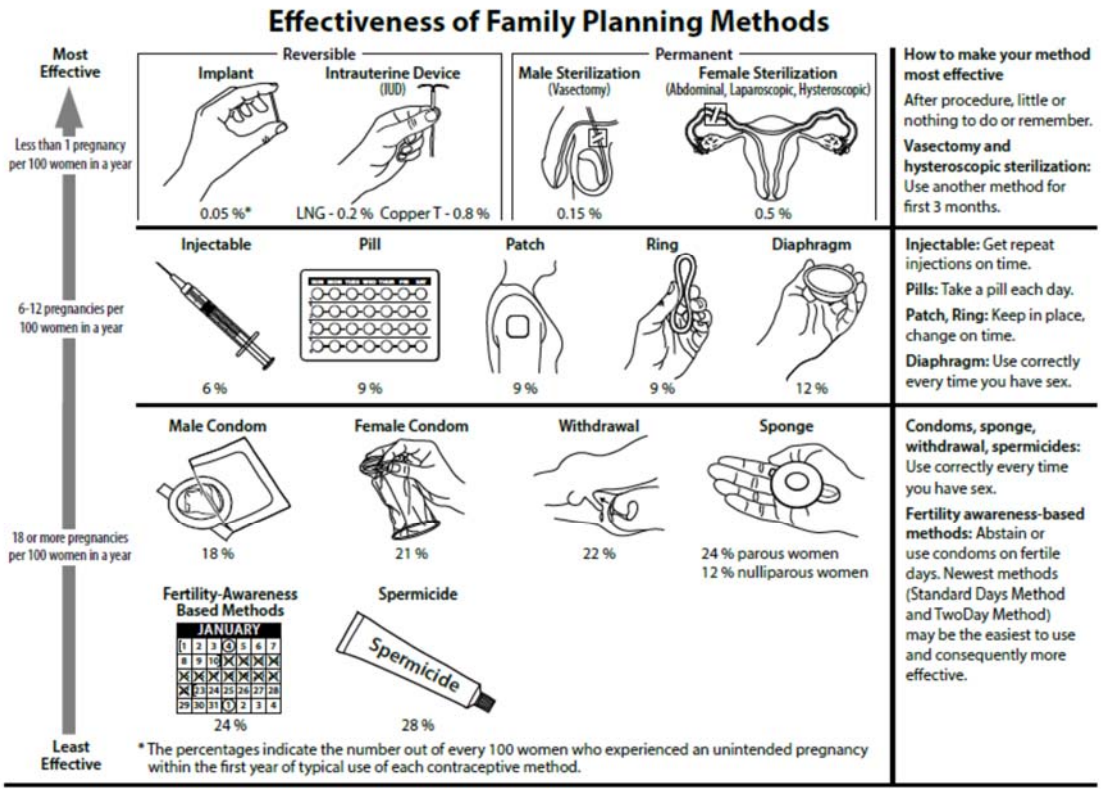
2.2. Analysis of Current Treatment Options

Current options for prevention of pregnancy include:

- Combination hormonal contraceptives (CHCs)
  - Combination oral contraceptives (COCs)
  - Intravaginal ring
  - Transdermal system
- Progestin-only hormonal contraceptives
  - Progestin-only oral contraceptives (POPs)
  - Implant
  - Injectable
  - Hormone releasing intrauterine system (IUS)
- Non-hormone releasing intrauterine systems
- Sterilization methods
- Barrier methods and spermicidal agents
- Natural-planning methods
- Abstinence

The efficacy of currently available contraceptive methods is dependent on mechanism of action as well as consistency of hormone levels, which can be user-dependent. Figure 1 below illustrates the overall effectiveness of the currently available contraceptive methods.

Figure 1: Effectiveness of Family Planning Methods



Source: Centers for Disease Control and Prevention.
file:///C:/Users/Anandi.Kotak/Documents/Clinical%20Review%20Resources/Contraceptive%20Efficacy/Contraceptive_methods_508.pdf

COCs that were approved in a chewable dosage form are listed in Table 1 below. Chewable tablets may be beneficial to women who have difficulty swallowing tablets. The only difference between COCs that are swallowed and those that are chewed are rare cases of oral irritation.

Table 1: Summary of Approved Contraceptive Chewable Tablets

Product (s) Name NDA #	Relevant Indication	Year of Approval for components	Route and Frequency of Administration	Efficacy Information (Pearl Index)	Components	Other Comments (e.g. subpopulation not addressed)
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
Minastrin 24 FE 203667	Prevention of pregnancy	1968	One tablet daily chewed and swallowed or swallowed whole	1.82	EE = 0.02 mg NETA = 1.0 mg	Women with BMI > 35 kg/m^2 excluded
Generess Fe 022573	Prevention of pregnancy	1974	One tablet daily, chewed without water	2.01	EE = 0.025 mg NET = 0.8 mg	
Femcon Fe 021490	Prevention of pregnancy	1975	One tablet daily, chewed or swallowed	1.48	N/A EE = 0.035 mg NET = 0.4 mg	

EE = ethinyl estradiol; NETA = norethindrone acetate; NET = norethindrone
Source: product labels

Reviewer Comment:
The main difference between EV402 and the products listed above is the progestin (levonorgestrel vs norethindrone based). Large epidemiologic safety studies have not detected any differences between these progestins.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Norgestrel/ethinyl estradiol-containing oral contraceptive tablets were initially approved in the United States in 1968. The reference product – Alesse (NDA 20683) – was approved in 1997. While the reference product is not currently marketed in the United States, multiple levonorgestrel/ethinyl estradiol contraceptives remain in circulation worldwide.

3.2. Summary of Presubmission/Submission Regulatory Activity

The design and conduct of pharmacokinetic studies and oral tolerability studies as well as pre-NDA submission discussions with the Division occurred under PIND (b) (4).

Reviewer Comment:
Initial interaction with Everett Laboratories (initial sponsor) mainly revolved around using

Lutera (generic for Alesse) in the bioequivalence (BE) study and quality issues (manufacturing, dissolution, and stability). There were no major clinical issues that arose during the development phase or at the time of the Pre-NDA meeting.

3.3. Foreign Regulatory Actions and Marketing History

There are no relevant foreign regulatory actions on this chewable product. Multiple levonorgestrel/ethinyl estradiol COC products that are swallowed remain in use worldwide. The generic equivalent of the RLD, Alesse (no longer marketed) is Lutera (ANDA 76625).

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Study Integrity and Surveillance (OSIS) determined that on-site inspections were not warranted at this time because a clinical inspection and analytical inspection had been conducted within the surveillance interval (both occurred in 2017). The final classification was No Action Indicated (NAI).

4.2. Product Quality

See Quality review.

4.3. Clinical Microbiology

See Quality Review.

4.4. Nonclinical Pharmacology/Toxicology

The primary Pharm/tox reviewer, Miyun Tsai-Turton PhD, MS found that the application for EV402, (b) (4) tablets did not raise any toxicological concerns and recommended approval.

4.5. Clinical Pharmacology

The Clinical Pharmacology team has determined that EV402 meets the bioequivalence criteria for approval. Dr. Jihong Shon, MD, PhD stated in his primary review:

> The Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology has reviewed the clinical pharmacology information submitted for

NDA 209405 (EV402). We find the current application acceptable and recommend approval from the clinical pharmacology standpoint.

The key clinical pharmacology review assessment is summarized below:

Study EXS-P3-239 compared the pharmacokinetic (PK) profile of EE and LNG following single dose administration of EV402 (Batch F02951A [the to-be-marketed formulation], chewed and swallowed with water) and Lutera® (Reference, swallowed with water) at fasting state in healthy female subjects. The 90% confidence intervals (CI) of geometric mean ratios (GMRs) of the PK parameters, maximum observed concentration (C_{max}) and area under the concentration-time curve (AUC) values, of both EE and LNG were within the specified no-effect boundary of 80% to 125% (Table 2.2-2). This finding demonstrated PK comparability between EV402 (chewed and swallowed with water) and Reference.

In conclusion, the PK results submitted in this NDA provided evidence that relevant exposure parameters met the standard bioequivalence criteria when EV402 was chewed and swallowed with water at fasting state and compared to Lutera®.

Source: Shon, J. NDA 209405 Levonorgestrel Ethinyl Estradiol (b) (4) tablets, Clinical Pharmacology Question-Based Review, February 25, 2020.

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2 summarizes the clinical studies submitted in support of this application.

Table 2: Listing of Clinical Studies

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	Subject DSP	Study Population	No. of Centers and Countries
Studies to Support Safety							
EXS-P1-531	Oral irritation Safety/tolerability Open-label 1-period Chewable formulation only	EV402 once daily in the morning for 21 consecutive days of active tablet followed by 7 consecutive days of inactive tablet	Oral irritation and abrasion Adverse events	Multiple-dose treatment 29 days	40 ENR 2 DC 40 AN	Healthy female volunteers Age 18-45	Single-center Canada
EHE-P4-471	Oral irritation potential/safety/tolerability Open-label 1-period Chewable formulation only	EV402 once daily in the morning for 21 consecutive days of active tablet followed by 7 consecutive days of inactive tablet	Oral irritation and abrasion Adverse events	Multiple-dose treatment 29 days	40	Healthy female volunteers Age 18-42	Single-center Canada
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
EXS-P3-239	Comparative BA Randomized Laboratory-blinded 3-period 6-sequence Crossover Chewable vs RLD Fasting only	**Test-1** = EV402 lot LF09251A, chewed thoroughly then swallowed with water **Test-2** = EV402 lot LFD0556A, chewed thoroughly then swallowed with water **Reference** = 1 Lutera® tablet swallowed whole with water	Pharmacokinetics	Single dose 28-day washout	36 ENR 4 DC 32 AN	Healthy female volunteers Age 20-44	Single-center Canada
EXS-P3-821	Comparative BA Randomized Laboratory-blinded 3-period 3-sequence Crossover	**Test** = EV402 **Reference** = 1 x Lutera® tablet Treatment 1 = Test chewed without water	Pharmacokinetics	Single dose	36	Healthy female volunteers Age 18-45	Single-center Canada

	Chewable vs RLD With/without water	Treatment 2 = Test chewed with water Reference = swallowed whole with water					
EHE-P4-469	Comparative BA Randomized Laboratory-blinded 3-period 6-sequence Crossover Chewable vs RLD Fasting/Fed	**Test** = EV402 chewable **Reference** = 1 x Lutera® tablet **Test Fast** = 10h fast; chew thoroughly, swallow, then drink water **Reference Fast** = 10h fast; swallowed whole with water **Test Fed** = 10h fast; high fat/high calorie meal; wait 30 minutes, chew thoroughly, swallow, then drink water	Pharmacokinetics	Single dose	36	Healthy female volunteers Age 18-45	Single-center Canada

EE = ethinyl estradiol; LNG = levonorgestrel; EV402 = EE/LNG 0.02mg/0.1mg chewable; BA = bioavailability; RLD= reference listed drug; DC = discontinued; AN= analyzed; DSP = disposition; Lutera® = LNG 0.1 mg/EE 0.02mg tablet

5.2. Review Strategy

The clinical review approach entailed review of five individual studies. Three pharmacokinetic studies and two oral tolerability studies were submitted. The pivotal pharmacokinetic study, EXS-P3-239, is reviewed in detail (see Section 6.1).

The safety of the study product was evaluated through review of all adverse event data collected for all studies in which subjects received at least one dose of the investigational product. In addition, the comprehensive safety update submitted with the application - including current references and global postmarketing data - was reviewed.

An integrated summary of safety was not required for submission. However, my analysis of the adverse event data included independently pooling the safety data across all submitted studies.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. EXS-P3-239

6.1.1. Study Design

Overview and Objective

This 3-period, 6-sequence, randomized, laboratory-blinded crossover study – EXS-P3-239 – compared the bioavailability of the study drug EV402 chewable tablet to the reference listed drug (0.02 mg EE/0.1 mg LNG oral tablet).

The primary objective was to evaluate the relative bioavailability of ethinyl estradiol and levonorgestrel in the study drug compared to RLD. The secondary objective was to evaluate the safety and tolerability of the study drug.

Trial Design

This study employed a crossover design to account for intra-subject variability in pharmacokinetic studies. Screening and enrollment of all 36 healthy female volunteers occurred at a single-center located in (b) (4). Subjects were domiciled for 10 hours prior to drug administration and for 24 hours post drug administration. Subjects received one each of three treatments for three treatment periods. Subjects were randomly assigned to one of six sequences. Treatment groups were laboratory-blinded. Figure 2 illustrates the 3-period, 6-sequence crossover study design.

Figure 2: EXS-P3-239 Study Sequences

	Period 1	Period 2	Period 3
Sequence 1 (n= 6)	Treatment-1	Treatment-2	Treatment-3
Sequence 2 (n= 6)	Treatment-2	Treatment-3	Treatment-1
Sequence 3 (n= 6)	Treatment-3	Treatment-1	Treatment-2
Sequence 4 (n= 6)	Treatment-3	Treatment-2	Treatment-1
Sequence 5 (n= 6)	Treatment-1	Treatment-3	Treatment-2
Sequence 6 (n= 6)	Treatment-2	Treatment-1	Treatment-3

*Treatment 1 = Test-1 (test drug from lot LF09251A)
Treatment 2 = Test-2 (test drug from lot LFD0556A)
Treatment 3 = RLD
Source: EXS-P3-239, Study Report Body, Table 2

Key inclusion criteria consisted of the following:

1. Healthy female volunteers
2. Ages 18-45
3. Non-pregnant
4. Child-bearing potential
5. Use of one of the following forms of contraception
    a. Abstinence
    b. Non-hormonal IUD
    c. Condom with spermicide
    d. Permanent sterilization
6. BMI 18.5-30.0 kg/m^2
7. Non-smoker or ex-smoker for at least 6 months

Key exclusion criteria consisted of the following:

1. Pregnant or lactating
2. Use of systemic hormonal contraception or hormone replacement therapy (HRT) for 28 days prior to Day 1
3. Injection or implant systemic contraception 13 weeks prior to Day 1
4. Tongue piercings, braces, or dentures
5. Postmenopausal

Subjects received a fixed-dose combination of 0.02 mg EE and 0.1 mg LNG. The fixed-dose combination was administered as either the test chewable tablet formulation or reference oral

tablet. Subjects received a single dose of test drug from one of two different batches (Test-1 = Lot LF09251A and Test-2 = Lot LFD0556A) or RLD in each treatment period. Subjects received treatment after a 10-hour fast under direct supervision.

Subjects receiving test drug were instructed to chew the tablet thoroughly and then swallow the saliva with 240 mL of water. Subjects receiving the reference drug were instructed to swallow the tablet whole with 240 mL of water. Hands and mouth were to be checked after drug administration to confirm consumption of the medication. Subjects had blood samples drawn at baseline and then at pre-determined intervals after study drug administration. A 28-day washout period followed Periods 1 and 2. Figure 3 illustrates the schedule of study events.

Figure 3: Schedule of Study Events

	Pre-Trial	Period 1			Wash-Out	Period 2			Wash-out	Period 3			End of Study
Days [a]	-28 to 0	0	1	2-4	1-28	28	29	30-32	29-56	56	57	58-60	60
Informed Consent Form Signed b	X	X	X	X	X	X	X	X	X	X	X	X	X
Admission to Unit	X	X	X	X		X[c]	X	X		X[d]	X	X	X
Medical History	X		X			X	X			X	X		
Physical Examination	X	X											X
Laboratory Tests	X					X				X			X
HIV Ag/Ab Combo, HBsAg (B) (Hepatitis B) and HCV (C) Tests	X	X											X[d]
Alcohol and Drugs of Abuse Screening	X					X				X			
ECG	X												
Pregnancy Test	X												
Vital Signs	X												
Drug Administration													
Blood Sampling	X												
Adverse Event Monitoring													

a The days assigned to each period may change according to the exact wash-out determined between the drug administrations.
b The last version must be signed prior to subject's inclusion (first drug administration).
c Hematology only.
d Any adverse events spontaneously reported by subjects for a period of 5 days following the last blood sample of the study will be documented.
Source: Study EXS-P3-239, 16.1.1 Protocol or Amendment

The study restricted the use of the following medications:

1. Systemic contraceptives in the previous 13 weeks before day one of the study until study completion: injections, implant, or hormone-releasing IUD.
2. Systemic contraceptives or hormone replacement therapy in the previous 28 days before day one of the study until study completion: oral, patch, vaginal ring.
3. Any prescription medication for 28 days prior to the first dose of the study and during the study.
4. Any over-the-counter products for seven days prior to the first dosing and during the study.
5. Vitamins used as nutritional supplements and non-therapeutic doses for 48 hours prior to the first dosing and during the study.

The protocol further restricted the use of the following:

1. Alcohol for 58 hours prior to each dosing and during each study period.
2. Cigarette smoking: only non- or ex-smokers for at least six months.
3. Xanthines: food or beverages containing xanthines (i.e. tea, coffee, cola drinks, energy drinks, or chocolate) for 58 hours prior to each dosing and during each study period.
4. Fluids: fluid intake other than water will be controlled for each housing period and for all subjects.
    i. Treatments 1 & 2: Water would be provided *ad libitum* until 1-hour pre-dose. 240 mL of room temperature water would be consumed after chewing the tablet. Water would be allowed *ad libitum* beginning 1-hour post-dose.
    ii. Treatment 3: Water would be provided *ad libitum* until 1-hour pre-dose. The tablet would be given with 240 mL of room temperature water. Water would be allowed *ad libitum* beginning 1-hour post-dose.
5. Food: food will be controlled and standardized for each housing period and for all subjects. Subjects will begin fasting 10 hours prior to drug administration and continue fasting for at least four hours post drug administration.
6. Grapefruit and pomelo-containing beverages and food will be avoided for seven days prior to dosing and during each study period.
7. Posture and physical activities: subjects would remain seated or ambulatory for the first four hours after drug administration. Subjects would not engage in strenuous activity at any time during the housing periods.
8. Female volunteers of childbearing potential would use an acceptable method of non-hormonal contraception for 28 days prior to first dose, during the study, and for at least 30 days after the last dose of study drug.

Subjects withdrawn from the study prior to first drug administration would not be considered drop-outs and would be replaced. Subjects withdrawn from the study after first drug administration would be considered drop-outs and would not be replaced. Data points collected from withdrawn subjects would still be considered in the final analysis.

Study Endpoints

The primary endpoints were the pharmacokinetic parameters of ethinyl estradiol and levonorgestrel. The PK parameters of interest included C_{max}, $AUC_{0-\tau}$, and $AUC_{0-\infty}$. For LNG, AUC_{0-72} was used in lieu of $AUC_{0-\tau}$, and $AUC_{0-\infty}$. The secondary endpoints included adverse events, clinical laboratory test results, and physical examination.

The study protocol planned 46 blood samples on 24 occasions for a total of 60 hours post drug administration. The protocol deviation plan allowed a 2-minute window for blood sampling. All deviations greater than 2 minutes from the scheduled blood sampling time were to be reported.

Statistical Analysis Plan

Statistical analysis of all pharmacokinetic parameters would use Analysis of Variance (ANOVA). The fixed factors were: 1) treatment received, 2) the period during which treatment was given, and 3) the sequence in which treatment was given. A random factor was added for subject effect (nested within sequence). The 90% confidence interval would be calculated for each comparison of interest.

Protocol Amendments

There were no significant protocol amendments submitted.

6.1.2. Study Results

Compliance with Good Clinical Practices

The sponsor attests to conducting the study in accordance with Good Clinical Practices.

Financial Disclosure

There were no financial disclosures reported.

Patient Disposition

Of the 36 study participants who were enrolled and subsequently randomized, 32 completed the study. Three subjects withdrew for personal reasons and one subject was removed from the study by the investigator due to a positive pregnancy test – a protocol removal criterion. In total, 36 subjects received Treatment 1 (Test-1), 34 subjects received Treatment 2 (Test-2), and 32 subjects received Treatment 3 (Reference).

The analysis population for EE and LNG concentrations consisted of 32 subjects. The statistical analysis included all 32 analyzed subjects.

Table 3 summarizes subject disposition.

Table 3: EXS-P3-239 Study Subject Disposition

Category	Number of Subjects
Subjects Included (N)	36
Subjects Discontinued Prior to End of Study	4
Reasons for Study Discontinuation [n (%)]	
Adverse Event	0
Withdrawal by Subject	3 (8)
Study Terminated by Sponsor	0
Physician Decision	0
Protocol Deviation	0
Death	0
Lost to Follow-up	0
Protocol Removal Criterion	1 (3)
Other	0

Source: EXS-P3-239 Study Report Body, Table 14.1.1

Protocol Violations/Deviations

There were no significant protocol violations or deviations reported.

Table of Demographic Characteristics

The demographic characteristics of the primary efficacy population for EXS-P3-239 are summarized in tables 4 and 5.

Table 4: EXS-P3-239 - Demographic characteristics of primary efficacy population - Ethinyl Estradiol

Demographic Parameters	Treatment Group			
	Treatment 1* (N= 32) n (%)	**Treatment 2†** (N= 31) n (%)	**Treatment 3‡** (N= 32) n (%)	**Total** (N= 32) n (%)
Gender				
Female	32 (100.0)	31 (100.0)	32 (100.0)	32 (100.0)
Age				
Mean years (SD)	34 (6)	34 (6)	34 (6)	34 (6)
Median (years)	35.0	35.0	35.0	35.0
Min, max (years)	23, 44	24, 44	23, 44	23, 44
Race				
White	29 (90.6)	28 (90.3)	29 (90.6)	29 (90.6)
Black or African American	1 (3.1)	1 (3.2)	1 (3.1)	1 (3.1)
Asian	2 (6.3)	2 (6.5)	2 (6.3)	2 (6.3)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity				
Hispanic or Latino	16 (50.0)	16 (51.6)	16 (50.0)	16 (50.0)
Not Hispanic or Latino	16 (50.0)	15 (48.4)	16 (50.0)	16 (50.0)
Region				
United States	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rest of the World				
Canada	32 (100.0)	31 (100.0)	32 (100.0)	32 (100.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Body Mass Index (kg/m^2)				
Mean (SD)	24.4 (2.8)	24.3 (2.8)	24.4 (2.8)	24.4 (2.8)
Median	24.80	24.80	24.80	24.80
Min, max	19.0, 28.4	19.0, 28.4	19.0, 28.4	19.0, 28.4

*Test 1 = EV402 (Lot LF09251A)
†Test 2 = EV402 (Lot LFD0556A)
‡RLD
Source: EXS-P3-239 Study Report Body, Table 14.1.2.2

Table 5: EXS-P3-239 - Demographic characteristics of primary efficacy population - Levonorgestrel

Demographic Parameters	Treatment Group			
	Treatment 1* (N= 32) n (%)	**Treatment 2†** (N= 31) n (%)	**Treatment 3‡** (N= 32) n (%)	**Total** (N= 32) n (%)
Gender				
Female	32 (100.0)	31 (100.0)	32 (100.0)	32 (100.0)
Age				
Mean years (SD)	34 (6)	34 (6)	34 (6)	34 (6)
Median (years)	35.0	35.0	35.0	35.0
Min, max (years)	23, 44	24, 44	23, 44	23, 44
Race				
White	29 (90.6)	28 (90.3)	29 (90.6)	29 (90.6)
Black or African American	1 (3.1)	1 (3.2)	1 (3.1)	1 (3.1)
Asian	2 (6.3)	2 (6.5)	2 (6.3)	2 (6.3)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity				
Hispanic or Latino	16 (50.0)	16 (51.6)	16 (50.0)	16 (50.0)
Not Hispanic or Latino	16 (50.0)	15 (48.4)	16 (50.0)	16 (50.0)
Region				
United States	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rest of the World				
Canada	32 (100.0)	31 (100.0)	32 (100.0)	32 (100.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Body Mass Index (kg/m^2)				
Mean (SD)	24.4 (2.8)	24.3 (2.8)	24.4 (2.8)	24.4 (2.8)
Median	24.8	24.8	24.8	24.8
Min, max	19.0, 28.4	19.0, 28.4	19.0, 28.4	19.0, 28.4

*Test 1 = EV402 (Lot LF09251A)
†Test 2 = EV402 (Lot LFD0556A)
‡RLD
Source: EXS-P3-239 Study Report Body, Table 14.1.2.3

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Treatment groups were similar in baseline characteristics.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Subjects were monitored for treatment compliance via directly observed treatment administration. Subjects were domiciled for 10 hours preceding drug administration until 24 hours post drug administration. Hands and mouth were inspected to ensure complete consumption of the administered drug. Treatment compliance issues were not reported.

Between the screening visit and the first dosing, two subjects disclosed taking ibuprofen for symptomatic relief of headache and menstrual cramps. Subjects were allowed to proceed with drug administration in Period 1.

Efficacy Results – Primary Endpoint

Tables 6 and 7 illustrate the pharmacokinetic parameters of EE and LNG respectively.

Table 6: EXS-P3-239 - Plasma Ethinyl Estradiol Pharmacokinetic Parameters

Parameter	Treatment -1* (n=32)		Treatment-2† (n=31)		Treatment-3‡ (n=32)	
	Mean	C.V. (%)	Mean	C.V. (%)	Mean	C.V. (%)
C_{max} (pg/mL)	53.22	(33.9)	56.99	(35.9)	46.24	(38.0)
$AUC_{0-\tau}$ (pg•h/mL)	476.97	(33.1)	502.37	(31.6)	425.67	(28.9)
$AUC_{0-\infty}$ (pg•h/mL)	514.18	(31.5)	538.27	(31.1)	460.77	(27.9)

Source: EXS-P3-239 Study Report Body, Table 6

Table 7: EXS-P3-239 - Plasma Levonorgestrel Pharmacokinetic Parameters

Parameter	Treatment -1* (n=32)		Treatment-2† (n=31)		Treatment-3‡ (n=32)	
	Mean	C.V. (%)	Mean	C.V. (%)	Mean	C.V. (%)
C_{max} (pg/mL)	3225.0	(33.1)	3347.4	(33.4)	3034.7	(35.5)
AUC_{0-72} (pg•h/mL)	27868.5	(38.8)	27887.3	(40.3)	25822.7	(35.4)

Source: EXS-P3-239 Study Report Body, Table 11

*Treatment 1 = Test 1
†Treatment 2 = Test 2
‡Treatment 3 = RLD

Tables 8 and 9 summarize the main statistical analysis for EE and LNG pharmacokinetic parameters. Note that the comparative analysis of Treatment 1 and Treatment 3 demonstrates bioequivalence and is the basis for approval.

Table 8: EXS-P3-239 - Summary of Main Statistical Analysis of Ethinyl Estradiol

Parameter	Global Intra-Subject c.v. (%)	Geometric LSmeans[a]			Comparison	Ratio (%)	90% Confidence Limits	
		TREATMENT-1† (n=32) b	TREATMENT-2‡ (n=31)	TREATMENT-3¶ (n=32)			Lower	Upper
C_{max}	11.2	50.88	53.76	44.01	Treatment-1 *vs* Treatment-3	115.61	110.32	121.15*
					Treatment-2 *vs* Treatment-3	122.14	116.50	128.06
$AUC_{0-\tau}$	9.1	460.92	490.56	415.78	Treatment-1 *vs* Treatment-3	110.86	106.63	115.25*
					Treatment-2 *vs* Treatment-3	117.98	113.49	122.66
$AUC_{0-\infty}$	9.0	500.21	527.62	451.43	Treatment-1 *vs* Treatment-3	110.81	106.63	115.15*
					Treatment-2 *vs* Treatment-3	116.88	112.48	121.45

a units are pg/mL for C_{max} and pg•h/mL for $AUC_{0-\tau}$ and $AUC_{0\infty}$
b n=31 for $AUC_{0-\tau}$ and $AUC_{0-\infty}$
Source: EXS-P3-239 Report Body, Table 7

†Treatment 1 = Test 1
‡Treatment 2 = Test 2
¶Treatment 3 = RLD
*Demonstrates bioequivalence

Table 9: EXS-P3-239 - Summary of Main Statistical Analysis of Levonorgestrel

Parameter	Global Intra-Subject c.v. (%)	Geometric LSmeansa			Comparison	Ratio (%)	90% Confidence Limits (%)	
		TREATMENT-1† (n=32) b	TREATMENT-2‡ (n=31)	TREATMENT-3 (n=32)			Lower	Upper
C_{max}	11.9	3026.1	3092.9	2794.9	Treatment-1 *vs* Treatment-3	108.27	102.99	113.83
					Treatment-2 *vs* Treatment-3	110.66	105.21	116.40
AUC_{0-72}	9.8	25705.8	25778.1	24260.6	Treatment-1 *vs* Treatment-3	105.96	101.62	110.48
					Treatment-2 *vs* Treatment-3	106.26	101.91	110.79

a units are pg/mL for C_{max} and pg•h/mL for AUC_{0-72}
b n=31 for AUC_{0-72}
Source: EXS-P3-239 Report Body, Table 12

†Treatment 1 = Test 1
‡Treatment 2 = Test 2
¶Treatment 3 = RLD

Data Quality and Integrity

Data quality and integrity issues were not identified.

Efficacy Results – Secondary and other relevant endpoints

Analysis of secondary or exploratory endpoints was not applicable to this review.

Dose/Dose Response

The study drug is comprised of a fixed dose combination of 0.1 mg LNG and 0.02 mg EE. Alternate doses and dose response were not investigated.

Durability of Response

This single-dose pharmacokinetic study did not evaluate the drug's effect over time.

Persistence of Effect

This single-dose pharmacokinetic study did not evaluate the drug's persistent effects.

Additional Analyses Conducted on the Individual Trial

Additional analyses were not conducted.

6.2. EXS-P3-821

6.2.1. Study Design

Overview and Objective

This 3-period, 3-sequence, randomized, laboratory-blinded crossover study compared the bioavailability of the test drug (0.02mg EE/0.1mg LNG chewable tablet) versus RLD in the fasting state. Subjects received a single dose of test drug with water, test drug without water, or RLD with water.

Trial Design

This study employed a crossover design to account for intra-subject variability in pharmacokinetic studies. Screening and enrollment of all 36 healthy female volunteers occurred at a single-center located in (b) (4). Subjects were domiciled for 10 hours prior to drug administration and for 24 hours post drug administration. Subjects received one each of three treatments for three treatment periods. Subjects were randomly assigned to one of three sequences. Treatment groups were laboratory-blinded. Figure 4 illustrates the 3-

period, 3-sequence crossover study design.

Figure 4: EXS-P3-821 Study Sequences[1]

	Period 1	Period 2	Period 3
Sequence 1 (n= 12)	Treatment-1	Treatment-2	Treatment-3
Sequence 2 (n= 12)	Treatment-2	Treatment-3	Treatment-1
Sequence 3 (n= 12)	Treatment-3	Treatment-1	Treatment-2

1 Treatment 1 = Test[2] chewed and swallowed without water
Treatment 2 = Test chewed and swallowed, then drink water[4]
Treatment 3 = RLD[3] swallowed whole with water[4]
2 Test = 1 x LNG 0.1 mg/EE 0.02 mg chewable tablet
3 RLD = 1 x Lutera® (LNG 0.1 mg/EE 0.02 mg)
4 Subjects consumed 240 mL of room temperature water
Source: EXS-P3-821 Study Report Body, Table 2

All other aspects of the study design were identical to EXS-P3-239 (see Section 6.1.1) including: diagnostic criteria, inclusion and exclusion criteria, procedures and schedule, dietary restrictions, as well as handling of subject completion, discontinuation, or withdrawal.

Study Endpoints

The primary endpoints were the pharmacokinetic parameters of ethinyl estradiol: C_{max}, $AUC_{0-\tau}$, and $AUC_{0-\infty}$; and levonorgestrel: C_{max} and AUC_{0-72}.

Statistical Analysis Plan

The statistical analysis plan was identical to Study EXS-P3-239 (see Section 6.1.1).

Protocol Amendments

There were no significant protocol amendments submitted.

6.2.2. Study Results

Compliance with Good Clinical Practices

The sponsor attests to conducting the study in accordance with Good Clinical Practices.

Financial Disclosure

There were no financial disclosures of interest reported.

Patient Disposition

A total of 36 subjects were included in the study. After randomization, 34 subjects received Treatment 1, 33 subjects received Treatment 2, and 33 subjects received Treatment 3.

33 subjects were analyzed, and 32 subjects included in the pharmacokinetic and statistical analysis for ethinyl estradiol. For levonorgestrel, 33 subjects were analyzed and 30 were included in PK and statistical analyses.

Five subjects discontinued the study: one subject withdrew consent for personal reasons related to clinical events; one subject withdrew consent for personal reasons not related to clinical events; two subjects were removed due to protocol removal criterion; and one subject was withdrawn for safety reasons per investigator's decision. Table 10 summarizes subject disposition.

Table 10: EXS-P3-821 Study Subject Disposition

Category	Number of Subjects [n (%)]
Subjects Included (N)	36
Subjects Discontinued Prior to End of Study	5
Reasons for Study Discontinuation [n (%)]	
Adverse Event	0
Withdrawal by Subject	2
Study Terminated by Sponsor	0
Physician Decision	1
Protocol Deviation	
Death	0
Lost to Follow-up	0
Protocol Removal Criterion	2
Other	0

Source: EXS-P3-821 Study Report Body, Table 14.1.1

Protocol Violations/Deviations

Protocol violations or deviations were not reported.

Table of Demographic Characteristics

The demographic characteristics of the primary efficacy population for EXS-P3-239 are summarized in tables 11 and 12.

Table 11: EXS-P3-821 Demographic characteristics of primary efficacy population - Ethinyl Estradiol

Demographic Parameters	Treatment Group			
	Treatment 1* (N= 32)	**Treatment 2†** (N= 31)	**Treatment 3‡** (N= 32)	**Total** (N= 32)
Gender				
Female	32 (100.0)	31 (100.0)	32 (100.0)	32 (100.0)
Age				
Mean years (SD)	35 (7)	34 (6)	35 (7)	35 (7)
Median (years)	33.5	33.0	33.5	33.5
Min, max (years)	22, 44	22, 44	22, 44	22, 44
Race				
White	30 (93.8)	29 (93.5)	30 (93.8)	30 (93.8)
Black or African American	2 (6.3)	2 (6.5)	2 (6.3)	2 (6.3)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity				
Hispanic or Latino	13 (40.6)	13 (41.9)	13 (40.6)	13 (40.6)
Not Hispanic or Latino	19 (59.4)	18 (58.1)	19 (59.4)	19 (59.4)
Region				
United States	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rest of the World				
Canada	32 (100.0)	31 (100.0)	32 (100.0)	32 (100.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Body Mass Index (kg/m^2)				
Mean (SD)	25.0 (2.6)	25.0 (2.7)	25.0 (2.6)	25.0 (2.6)
Median	25.2	25.3	25.2	25.2
Min, max	20.7, 29.6	20.7, 29.6	20.7, 29.6	20.7, 29.6

*Treatment 1 = Test chewed and swallowed without water
†Treatment 2 = Test chewed and swallowed, then drink water
‡Treatment 3 = RLD swallowed whole with water
Source: EXS-P3-821 Study Report Body, Table 14.1.2.2

Table 12: EXS-P3-821 Demographic characteristics of primary efficacy population for - Levonorgestrel

Demographic Parameters	Treatment Group			
	Treatment 1* (N= 30)	Treatment 2† (N= 29)	Treatment 3‡ (N= 30)	Total (N= 30)
Gender				
Female	30 (100.0)	29 (100.0)	30 (100.0)	30 (100.0)
Age				
Mean years (SD)	35 (7)	34 (7)	35 (7)	35 (7)
Median (years)	34.0	33.0	34.0	34.0
Min, max (years)	22, 44	22, 44	22, 44	22, 44
Race				
White	28 (93.3)	27 (93.1)	28 (93.3)	28 (93.3)
Black or African American	2 (6.7)	2 (6.9)	2 (6.7)	2 (6.7)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity				
Hispanic or Latino	12 (40.0)	12 (40.0)	12 (40.0)	12 (40.0)
Not Hispanic or Latino	18 (60.0)	17 (58.6)	18 (60.0)	18 (60.0)
Region				
United States	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rest of the World				
Canada	30 (100.0)	29 (100.0)	30 (100.0)	30 (100.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Body Mass Index (kg/m^2)				
Mean (SD)	24.9 (2.7)	24.9 (2.7)	24.9 (2.7)	24.9 (2.7)
Median	24.9	24.8	24.9	24.9
Min, max	20.7, 29.6	20.7, 29.6	20.7, 29.6	20.7, 29.6

*Treatment 1 = Test chewed and swallowed without water
†Treatment 2 = Test chewed and swallowed, then drink water
‡Treatment 3 = RLD swallowed whole with water
Source: EXS-P3-821 Study Report Body, Table 14.1.2.3

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Treatment groups were similar in baseline characteristics.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was achieved through directly observed treatment administration. Subjects were domiciled for 10 hours pre- and 24 hours post- drug administration.

There were no reported instances of concomitant medication use.

Efficacy Results – Primary Endpoint

Tables 13 and 14 summarize the statistical analysis of ethinyl estradiol and levonorgestrel respectively. Both the lower bound and upper bound are well below the bioequivalence margin when EV402 is taken without water.

Table 13: EXS-P3-821 - Summary of Main Statistical Analysis of Ethinyl Estradiol

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSmeans[a]			Comparison	RATIO (%)	90% CONFIDENCE LIMITS (%)	
		Treatment-1[†] (n=32)[b]	Treatment-2[‡] (n=31)[c]	Treatment-3[*] (n=32)[b]			LOWER	UPPER
C_{max}	12.4	63.94	52.52	42.71	Trt-1 vs Trt-3	149.70	142.14	157.67[#]
					Trt-2 vs Trt-3	122.97	116.70	129.59
$AUC_{0-\tau}$	8.9	541.67	481.18	415.58	Trt-1 vs Trt-3	130.34	125.57	135.29
					Trt-2 vs Trt-3	115.78	111.50	120.23
$AUC_{0-\infty}$	9.1	587.50	520.52	453.90	Trt-1 vs Trt-3	129.43	124.52	134.54
					Trt-2 vs Trt-3	114.68	110.27	119.26

a units are pg/mL for C_{max} and pg•h/mL for AUC $_{0-\tau}$ and $AUC_{0\infty}$
b n=31 for $AUC_{0-\tau}$ and $AUC_{0-\infty}$
c n=30 for $AUC_{0-\infty}$
Source: EXS-P3-821 Study Report Body, Table 9

† Treatment 1 = Test chewed and swallowed without water
‡ Treatment 2 = Test chewed and swallowed, then drink water
* Treatment 3 = RLD swallowed whole with water
# C_{max} of EE is significantly increased when EV402 is taken without water

Table 14: EXS-P3-821 - Summary of Statistical Analysis of Levonorgestrel

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSmeans [a]			Comparison	RATIO (%)	90% CONFIDENCE LIMITS (%)	
		Treatment-1† (n=30)	Treatment-2‡ (n=29)	Treatment-3* (n=30)			LOWER	UPPER
C_{max}	13.4	2868.4	2982.8	2748.2	Trt-1 vs Trt-3	104.37	98.50	110.59#
					Trt-2 vs Trt-3	108.54	102.36	115.08
AUC_{0-72}	12.0	26866.1	25355.7	24521.9	Trt-1 vs Trt-3	109.56	104.02	115.40#
					Trt-2 vs Trt-3	103.40	98.11	108.98

a units are pg/mL for C_{max} and pg•h/mL for AUC_{0-72}
Source: EXS-P3-821 Study Report Body, Table 12

† Treatment 1 = Test chewed and swallowed without water
‡ Treatment 2 = Test chewed and swallowed, then drink water
* Treatment 3 = RLD swallowed whole with water
# Bioavailability of LNG is unaffected by water intake

Data Quality and Integrity

No data quality or integrity issues were identified.

Efficacy Results – Secondary and other relevant endpoints

Analysis of secondary or exploratory endpoints was not applicable to this review.

Dose/Dose Response

Dose and dose response were not evaluated for the study product.

Durability of Response

This single-dose pharmacokinetic study did not evaluate the drug's effect over time.

Persistence of Effect

This single-dose pharmacokinetic study did not evaluate the drug's persistent effects.

Additional Analyses Conducted on the Individual Trial

Additional analyses were not conducted.

6.3. EHE-P4-469

6.3.1. Study Design

Overview and Objective

This 3-period, 6-sequence crossover study aimed to measure the comparative bioavailability of the study drug versus RLD in the fasting and fed states.

The primary objective was to assess the relative bioavailability of the study product compared to RLD when taken without food, and to evaluate the food effect on the bioavailability of the study product.

The secondary objective was to determine the safety and tolerability of the study drug.

Trial Design

This study was a single center, randomized, single-dose, laboratory-blinded, 3-period, 6-sequence crossover design in healthy volunteers.

Subjects were domiciled for 10.5 hours before dosing and underwent a supervised overnight fast.

Subjects were randomly assigned to one of three treatment groups for three treatment periods (see Figure 5 below):

- Treatment 1: Test product administered in fasting conditions.
- Treatment 2: RLD administered in fasting conditions.
- Treatment 3: Test product administered in fed conditions.

Figure 5: EHE-P4-469 Study Sequences

	Period 1	Period 2	Period 3
Sequence 1 (n= 6)	Treatment-1	Treatment-2	Treatment-3
Sequence 2 (n= 6)	Treatment-2	Treatment-3	Treatment-1
Sequence 3 (n= 6)	Treatment-3	Treatment-1	Treatment-2
Sequence 4 (n= 6)	Treatment-1	Treatment-3	Treatment-2
Sequence 5 (n= 6)	Treatment-2	Treatment-1	Treatment-3
Sequence 6 (n= 6)	Treatment-3	Treatment-2	Treatment-1

Source: EHE-P4-469 Study Report Body, Table 2

All other aspects of the study design were identical to EXS-P3-239 (see Section 6.1.1) including: diagnostic criteria, inclusion and exclusion criteria, procedures and schedule, dietary restrictions, as well as handling of subject completion, discontinuation, or withdrawal.

Study Endpoints

The primary endpoints were the pharmacokinetic parameters of ethinyl estradiol: C_{max}, $AUC_{0-\tau}$, and $AUC_{0-\infty}$; and levonorgestrel: C_{max} and AUC_{0-72}. The secondary endpoints included adverse events, clinical laboratory test results, and physical examination.

Statistical Analysis Plan

The statistical analysis plan was identical to Study EXS-P3-239 (see Section 6.1.1).

Protocol Amendments

There were no significant protocol amendments submitted.

6.3.2. Study Results

Compliance with Good Clinical Practices

The sponsor attests to conducting the study in accordance with Good Clinical Practices.

Financial Disclosure

There were no financial disclosures reported.

Patient Disposition

A total of 36 subjects were included in the study. After randomization, 34 subjects received Treatment-1 (Test fast), 33 subjects received Treatment-2 (Reference fast), and 32 subjects received Treatment-3 (Test fed).

Five subjects discontinued the study: two withdrew consent for personal reasons not related to clinical events; three were withdrawn per protocol removal criterion as listed below:

1. 1 positive serum pregnancy test.
2. 1 positive test for amphetamines.
3. 1 positive test for alcohol.

The pharmacokinetic and statistical analysis for ethinyl estradiol and levonorgestrel included 32 and 31 subjects, respectively.

Table 15 summarizes subject disposition.

Table 15: EHE-P4-469 Study Subject Disposition

Category	Number of Subjects [n (%)]
Subjects Included (N)	36
Subjects Discontinued Prior to End of Study	5 (13.9)
Reasons for Study Discontinuation [n (%)]	
Adverse Event	0
Withdrawal by Subject	2 (5.6)
Study Terminated by Sponsor	0
Physician Decision	0
Protocol Deviation	
Death	0
Lost to Follow-up	0
Protocol Removal Criterion	3 (8.3)
Other	0

Source: EHE-P4-469 Study Report Body, Table 14.1.1

Protocol Violations/Deviations

Protocol violations or deviations were not reported.

Table 16 summarizes the demographic characteristics of the overall study population.

Table 16: EHE-P4-469 Demographic characteristics of overall population

Demographic Parameters	Overall[1,2] (N= 36)
Gender	
Female	36 (100.0)
Age	
Mean years (SD)	32 (7)
Median (years)	32.0
Min, max (years)	19, 43
Race	
White	31 (86.1)
Black or African American	4 (11.1)
Asian	0 (0.0)
American Indian or Alaska Native	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)
Other	1 (2.8)
Ethnicity	
Hispanic or Latino	8 (22.2)
Not Hispanic or Latino	28 (77.8)
Region	
United States	0 (0.0)
Rest of the World	
Canada	32 (100.0)
Other	0 (0.0)
Body Mass Index (kg/m^2)	
Mean (SD)	23.6 (2.9)
Median	23.0
Min, max	19.6, 29.9

1 All enrolled subjects
2 One subject excluded from pharmacokinetic and statistical analysis of LNG due to pre-dose LNG concentration > 5% of C_{max} in period 2
Source: EHE-P4-469 Study Report Body, Table 14.1.1

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Treatment groups were similar in baseline characteristics.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was achieved through administration of test drug under direct supervision. Subjects were domiciled for 10 hours prior to and for 24 hours post- drug administration.

There were no reported instances of concomitant medication use.

Efficacy Results – Primary Endpoint

Tables 17 and 18 summarize the food effect statistical analyses for EV402. The upper and lower bounds of the 90% confidence interval are well below the bioequivalence margin. Therefore, EV402 must be taken on an empty stomach. This will be communicated in labeling.

Table 17: Summary of Food Effect Statistical Analysis of Ethinyl Estradiol for Study EHE-P4-469

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSmeans*		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		Treatment-3‡ Test Fed (n=31)	Treatment-1† Test Fast (n=32)		LOWER	UPPER
C_{max}	16.3	34.23	61.23	55.91	52.20	59.88#
$AUC_{0-\tau}$	10.9	489.93	497.77	98.42	94.01	103.05
$AUC_{0-\infty}$	10.7	528.77	531.63	99.46	95.07	104.06

*units are pg/ml for C_{max} and pg•h/mL for $AUC_{0-\tau}$ and $AUC_{0-\infty}$
Source: EHE-P4-469 Study Report Body, Table 10

Table 18: Summary of Food Effect Statistical Analysis of Levonorgestrel for Study EHE-P4-469

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSmeans*		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		Treatment-3‡ Test Fed (n=30)	Treatment-1† Test Fast (n=31)		LOWER	UPPER
C_{max}	25.5	1153.2	2621.8	43.99	39.49	49.00#
AUC_{0-72}	11.8	26072.8	24589.4	106.03	100.79	111.54

*units are pg/ml for C_{max} and pg•h/mL for AUC_{0-72}
Source: EHE-P4-469 Study Report Body, Table 14

* Treatment 1 = Test Fast
† Treatment 2 = Reference Fast
‡ Treatment 3 = Test Fed
# C_{max} of EV402 in fed state is lower than in fasting state

Data Quality and Integrity

No data quality or integrity issues were identified.

Efficacy Results – Secondary and other relevant endpoints

Analysis of secondary or exploratory endpoints was not applicable to this review.

Dose/Dose Response

Dose and dose response were not evaluated for the study product.

Durability of Response

This single-dose pharmacokinetic study did not evaluate the drug's effect over time.

Persistence of Effect

This single-dose pharmacokinetic study did not evaluate the drug's persistent effects.

Additional Analyses Conducted on the Individual Trial

Additional analyses were not conducted.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Efficacy of EV402 is supported by a single pharmacokinetic study demonstrating bioequivalence. Therefore, assessment of efficacy across clinical trials is not applicable.

7.1.1. Primary Endpoints

The primary endpoints of the pharmacokinetic studies evaluating EV402 included the pharmacokinetic parameters of EE and LNG as stated in Section 6.

Reviewer Comment:

The pharmacokinetic parameters of LNG were limited to C_{max} and AUC_{0-72}. Discussion occurred between Clinical Pharmacology and the Sponsor. The Clinical Pharmacology team determined the parameters to be appropriate.

7.1.2. Secondary and Other Endpoints

The secondary endpoints included adverse events, clinical laboratory test results, and physical examination as stated in Section 6.

Reviewer Comment:

The secondary endpoints were used in combination with results from 2 clinical studies to support the safety and tolerability of EV402.

7.1.3. Subpopulations

Analysis of subpopulations is not applicable to review of this application.

7.1.4. Dose and Dose-Response

Analysis of dose and dose-response is not applicable to review of this application.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Analysis of onset, duration, and durability of efficacy effects is not applicable to review of this application.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The pharmacokinetics of EE and LNG were evaluated in subjects was not evaluated by body mass index (BMI). Present thinking on the impact of BMI on drug metabolism suggests that there could be differences in pharmacokinetic parameters, and therefore, contraceptive efficacy, of oral contraceptives. The lack of evaluation of PK parameters by BMI will be communicated in labeling.

Although the study population was demographically less diverse compared to the target population in the US, this is unlikely to significantly impact the efficacy of EV402.

7.2.2. Other Relevant Benefits

The chewable formulation of EV402 may benefit those desiring an oral contraceptive who have difficulty swallowing pills.

7.3. Integrated Assessment of Effectiveness

EV402 demonstrates bioequivalence per regulations based on the pharmacokinetic profile in study EXS-P3-239 (see Section 6.1.2). The geometric LSmeans ratio of EE and LNG falls within the 80-125% range with the upper bound of the confidence interval at 121%.

It is notable that PK parameters are affected by food and water intake. When taken with food, C_{max} of EE and LNG is decreased. When taken without water, C_{max} of EE and LNG is increased.

However, this will have labeling implications as these studies were not repeated for the final to-be-marketed formulation. See Section 10 for further discussion.

8. Review of Safety

8.1. Safety Review Approach

The safety review of EV402 consisted of analysis of all adverse events in the safety population, i.e. all subjects who received at least one dose of EV402. The Applicant submitted individual adverse event datasets for each of the three pharmacokinetics studies and two oral tolerability and safety studies as agreed upon by the Agency in the pre-NDA meeting. This reviewer integrated the adverse event data from all five studies (see Section 5.1 for list of studies).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety analysis included all study subjects exposed to at least one dose of EV402. Three pharmacokinetic studies and two oral tolerability and safety studies contributed to the analysis. Overall exposure to EV402 consisted of 188 healthy volunteers. All subjects were exposed to at least one dose of study drug. One hundred eight subjects were exposed to the reference product. Overall exposure was adequate for evaluation. Table 19 summarizes the safety population.

Table 19: Safety Population

Safety Database for EV402[1] Individuals exposed to any treatment in this development program for the indication under review N[2] = 188		
Clinical Trial Groups	EV402[1]	Reference[3]
Healthy volunteers (N)	188	108
All trials conducted for this indication	5	3

1 Three pharmacokinetic studies (EXS-P3-239, EXS-P3-281, EHE-P4-469) and 2 oral irritation studies (EXS-P1-531, EHE-P4-471)
2 N is the sum of all subjects exposed
3 Pharmacokinetic studies only

The safety population primarily consisted of non-Hispanic White subjects with normal BMI. Table 20 summarizes the demographics of the safety population.

Table 20: Demographics of the Safety Population

Demographic Parameters	**All Subjects Exposed to EV402*** (N= 188) n (%)
Gender	
Female	188 (100.0)
Age	
Mean years (SD)	31.8 (8.1)
Median (years)	32
Min, max (years)	18, 45
Race	
White	166 (88.3)
Black or African American	16 (8.5)
Asian	3 (1.6)
American Indian or Alaska Native	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)
Other	3 (1.6)
Ethnicity	
Hispanic or Latino	70 (37.2)
Not Hispanic or Latino	118 (62.8)
Region	
United States	0 (0.0)
Rest of the World	
Canada	188 (100.0)
Other	0 (0.0)
Body Mass Index (kg/m^2)	
Mean (SD)	24.4 (2.9)
Median	24.0
Min, max	19.0, 29.9

*Includes all subjects receiving at least one dose of EV402 in studies EXS-P3-239, EXS-P3-281, EHE-P4-469, EXS-P1-531, and EHE-P4-471

Subjects in pharmacokinetic studies received a single dose of study product or reference during each of three treatment periods. Only subjects in clinical studies received multiple consecutive doses. In these two studies, subjects received 21 consecutive days of active chewable tablets, followed immediately by 7 consecutive days of placebo tablets as per intended real-world product use. The duration of exposure is adequate to assess oral irritation potential of the study product. Table 21 summarizes duration of exposure to the study product.

Table 21: Duration of Exposure

	Number of patients exposed to EV402		
	Single dose[1]	Multiple doses[2]	All subjects exposed
Number of subjects (N)	108	80	188

[1] Pharmacokinetic studies only (EXS-P3-239, EXS-P3-281, EHE-P4-469)
[2] One 28-day cycle (21 consecutive days of active chewable tablets, followed by 7 consecutive days of placebo tablets) (EXS-P1-531, EHE-P4-471)

8.2.2. Relevant characteristics of the safety population:

Study subjects had mean BMI ≤ 25 kg/m^2. Approximately 30% of the US population is obese, with BMI ≥ 30 mg/m^2. The lack of studies in the obese population is notable and will be accounted for in labeling.

The composition of the safety population adequately informs the intended purpose. Subjects were primarily Caucasian (See Section 6). While the target population in the United States is more diverse, these differences are unlikely to impact adverse event outcomes for this product.

8.2.3. Adequacy of the safety database:

The safety database adequately represents the frequency of adverse events related to EV402. Significant differences from the target population are not expected. The database consisted of healthy females of child-bearing potential. This is consistent with studies evaluating tolerability and safety of a new dosage form or formulation of existing contraceptive products.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Data integrity concerns were not identified and did not impact the safety review.

8.3.2. Categorization of Adverse Events

Adverse events were categorized appropriately. Definitions of serious adverse events and treatment-emergent adverse events were acceptable and appropriate.

Adverse events were elicited from study subjects through open-ended questioning. Reporting and recording of adverse events occurred through 5 days after last drug administration in pharmacokinetic studies and 8 days after last drug administration in clinical studies. This is acceptable given the elimination half-lives of EE and LNG.

Adverse event follow-up, categorization, and causality assessment were adequately described prior to study initiation.

8.3.3. Routine Clinical Tests

Clinical tests performed in the safety evaluation included:

1) General Biochemistry: Sodium, potassium, chloride, BUN, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, and albumin
2) Hematology: White cell count with differential (absolute values of neutrophil, lymphocyte, monocyte, eosinophil, and basophil), red cell count, hemoglobin, hematocrit, MCV, and platelet count
3) Urinalysis: Color appearance, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination for leukocyte, blood, nitrite, or protein count outside of reference range only.

The clinical tests to support safety of the study product were adequate. Clinical tests for pharmacokinetic studies were performed during pre-trial evaluation, at the beginning of periods 2 and 3 and at the end of study visit. During clinical studies, the clinical test evaluation was performed at the start and end of the study.

8.4. Safety Results

8.4.1. Deaths

No deaths occurred.

8.4.2. Serious Adverse Events

No serious adverse events occurred.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Two subjects in Study EXS-P3-821 did not complete the study due to adverse events. Subject (b) (6) withdrew consent after experiencing migraine headache. See Reviewer Comment below. Subject (b) (6) was withdrawn from the study by the investigator due to an adverse event that was unrelated to study product (complications following a car accident).

Reviewer Comment:

An information request was sent to the Applicant on November 9, 2019 to clarify the categorization of an adverse event of "migraine headache." Migraine headache is a labeled

adverse event associated with COCs; this instance of "migraine headache" was reported as unrelated to study drug and therefore warranted in depth review.

Subject (b) (6) experienced "migraine headache" and subsequently withdrew consent from participation in the study. Additional details clarified that the subject experienced additional symptoms consistent with influenza infection at the time of "migraine headache." These events were remote from study drug administration; therefore, the event was categorized as unlikely related to study drug. I agree with the Applicant's assessment of severity and causality of the adverse event of migraine headache in Subject (b) (6).

8.4.4. Significant Adverse Events

There were no significant adverse events reported.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most frequently reported adverse events were headache, nausea, and menstrual irregularities. The adverse event "dizziness" occurred more frequently than expected. (See Section 8.5.1 for details). Additionally, the adverse event "oropharyngeal pain" occurred more frequently than has been reported with traditional oral contraceptive tablets. Table 22 below illustrates the frequency of adverse events in the safety population (i.e. all subjects receiving at least one dose of EV402 in studies EXS-P3-239, EXS-P3-281, EHE-P4-469, EXS-P1-531, and EHE-P4-471).

Table 22: Frequency of Adverse Events – Safety Population

Preferred Term	N (# of subjects)	% (total = 188)
Headache	53	15.7
Nausea	29	8.6
Menstruation irregular	20	5.9
Metrorrhagia	13	3.8
Dizziness†	12	3.6
Abdominal pain	10	3.0
Fatigue	10	3.0
Cough	9	2.7
Oropharyngeal pain*	9	2.7
Dysmenorrhoea	8	2.4
Nasal congestion	8	2.4
Diarrhoea	7	2.1

*Oropharyngeal pain is not an adverse reaction reported with Lutera®
†Dizziness occurred more frequently than expected
Source: EXS-P3-239, EXS-P3-281, EHE-P4-469, EXS-P1-531, EHE-P4-471

8.4.6. Laboratory Findings

Significant laboratory findings were not reported.

8.4.7. Vital Signs

Significant vital sign findings were not reported.

8.4.8. Electrocardiograms (ECGs)

Abnormal electrocardiogram findings were not reported.

8.4.9. QT

QT prolongation studies were not required.

8.4.10. Immunogenicity

Immunogenicity studies were required.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Adverse Event Dizziness

The adverse event "dizziness" [Preferred Term (dizziness)] was reported with a higher than expected frequency of 3.6% (12 out of 188 subjects). The Sponsor provided additional details in response to an Information Request.

Analysis revealed no specific pattern for the occurrence of dizziness in trial subjects. Of 12 subjects experiencing dizziness, six are identified as having a reasonable possibility of relatedness to the study product. Of these six subjects, two were enrolled in pharmacokinetic studies (Study EHE-P4-469 and Study EXS-P3-239); four subjects were enrolled in clinical studies (Study EXS-P1-531). Table 23 summarizes the details of the adverse event "dizziness."

Table 23: Summary of Subjects Experiencing Adverse Event Dizziness (PT Dizziness)

Study ID	Subject ID	Description of Event	Causality Assessment	Additional details	Actions taken	Product received*
Pharmacokinetic Studies	(b) (6)					
EHE-P4-469		Dizziness that lasted for 10 minutes after leaving study site	reasonable possibility	resolved, mild	None	Study product
EHE-P4-469		dizziness occurred prior to study drug administration	NA	resolved, mild	NA	NA
EHE-P4-469		dizziness following catheter insertion	no reasonable possibility	resolved, mild	NA	NA
EHE-P4-469		dizziness due to catheter site painful	no reasonable possibility	resolved, mild	Additional Safety Assessment and Non Drug Therapy Administered	NA
EXS-P3-821		dizziness 2 days after intake of reference product	reasonable possibility	resolved, mild	Additional Safety Assessment	RLD
EXS-P3-239		dizziness 27 days after study treatment; same day of reference	no reasonable possibility	resolved, mild	NA	NA

		product administration but 1 hour prior to dose				
EXS-P3-239		dizziness on day of intake - reference product	reasonable possibility	resolved, mild	NA	RLD
EXS-P3-239		dizziness on day of intake - reference product	reasonable possibility	resolved, mild	NA	RLD
EXS-P3-239		dizziness 8 days after study drug	reasonable possibility	resolved, mild	NA	Study product
Clinical Studies						
EXS-P1-531		intermittent dizziness on study day 4	reasonable possibility	resolved, mild	None	Study product
EXS-P1-531		dizziness occurred on 4th day of inactive pills (study day 25)	reasonable possibility	resolved, mild	None	Study product
EXS-P1-531		dizziness on study day 16	reasonable possibility	resolved, mild	None	Study product
EXS-P1-531		dizziness on study day 7	reasonable possibility	resolved, mild	None	Study product

(b) (6)

*NA indicates adverse event occurred prior to administration of assigned treatment

Reviewer Comment:

An information request was sent to the Applicant regarding the adverse event "dizziness" on October 29, 2019. This reviewer reviewed the information submitted by the Applicant in response to our request. All cases of dizziness were mild and resolved spontaneously. Two cases required additional assessments but did not require hospitalization. There were no reported adverse events of syncope associated with dizziness. I agree with the causality assessments as determined by the Applicant. I conclude that there is no evidence of a new safety signal with regard to dizziness.

8.6. Safety Analyses by Demographic Subgroups

Not applicable.

8.7. Specific Safety Studies/Clinical Trials

No specific safety studies/clinical trials were performed.

8.8. Additional Safety Explorations

Not applicable.

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable.

8.8.2. Human Reproduction and Pregnancy

Not applicable.

8.8.3. Pediatrics and Assessment of Effects on Growth

An Agreed initial Pediatric Study Plan is in place. Clinical studies are not planned.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.9. Safety in the Postmarket Setting

After nearly 50 years of use, the risks associated with LNG/EE COCs are well-known and consistent with COC class safety labeling. Voluntary reporting and epidemiologic studies have generally supported data indicating that levonorgestrel-based COCs have less venous thromboembolic events than certain other COCs with different progestins. There have been no recent new safety signals for LNG/EE.

8.9.1. Additional Safety Issues From Other Disciplines

Not applicable.

8.10. Integrated Assessment of Safety

Significant safety issues did not arise in pharmacokinetic or oral tolerability studies of this product. Adverse event frequencies in the study population were comparable to adverse event frequencies in the reference product.

The risk of serious adverse events - such as venous thromboembolism and thrombotic disorders, liver disease, high blood pressure, carbohydrate and lipid metabolic effects and

headache – is not expected to differ from the risk of these events in the reference product or other products containing LNG/EE.

Aside from rare mild oral irritation, there is no reason to suspect that a chewable tablet would have any other additional safety concerns that differ from a COC that is swallowed.

Overall, the safety of EV402 chewable tablets has been demonstrated.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling recommendations have been made to align product labeling with that of the reference product, FDA's guidance for industry: "Labeling for Combined Hormonal Contraceptives," and current knowledge of drug class effects.

Product labeling updates for this drug implement Physician Labeling Rule (PLR) as well as Pregnancy and Lactation Labeling Rule (PLLR) requirements. Additionally, changes to the Dosing and Administration (Section 2) and Patient Counseling (Section 17) were recommended to clearly convey the importance of taking the product exactly as directed. Changes to Adverse Reactions (Section 6) have been recommended to reflect class labeling for COCs.

Please refer to Dr. Willett's CDTL review for final labeling agreements.

10.2. Nonprescription Drug Labeling

Not applicable.

11.Risk Evaluation and Mitigation Strategies (REMS)

Risk Evaluation and Mitigation Strategies are not required for this product.

12.Postmarketing Requirements and Commitments

Postmarketing Requirements/Commitments are not necessary for this product.

13.Appendices

13.1. References

Reviewer Comment:
There are no clinically related references in the section 2 summaries of this submission that negatively impact approval of EV402. This reviewer is not aware of any recent medical literature that negatively impacts approval.

13.2. Financial Disclosure

There were no financial disclosures to report.

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 13		

Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANANDI D KOTAK
02/26/2020 03:56:56 PM

GERALD D WILLETT
02/26/2020 03:59:04 PM
I concur with Dr. Kotak's review