OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA Number	209405
Link to EDR	\\cdsesub1\evsprod\NDA209405
Submission Dates	05/30/19, 09/27/19, 10/30/19 and 12/13/19
Submission Type	Resubmission
PDUFA Date	03/30/2020
Brand Name	A brand name has not been determined. The indicated name for the proposed product in the current submission is EV402.
Generic Name	Levonorgestrel/Ethinyl Estradiol
Dosage Form and Strength	Levonorgestrel/Ethinyl Estradiol (b) (4) tablets, 0.1 mg/0.02 mg
Route of Administration4	Oral
Proposed Indication	Prevention for pregnancy
Applicant	Exeltis USA, Inc
Associated IND	IND (b) (4)
OCP Review Team	Jihong Shon, M.D., Ph.D. Lu Yanhui, Ph.D.

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1 EXECUTIVE SUMMARY

EV402 consists of 28 (b) (4) tablets, 21 tablets containing 0.10 mg of levonorgestrel (LNG) and 0.02 mg of ethinyl estradiol (EE) and 7 inactive tablets. The Applicant is seeking approval via the 505(b)(2) pathway using Alesse® (LNG 0.10 mg / EE 0.02 mg, NDA 20-683 approved on April 1997) as the listed drug. The Applicant proposed to rely on the Agency's safety and efficacy findings of the listed drug. Since Alesse® is no longer marketed in the U.S., the Applicant used Lutera® (ANDA 76-625 by Mayne Pharma, Inc.), the current reference standard, as a reference product (Reference) in their comparative bioavailability studies. In support of this NDA, the Applicant conducted three comparative bioavailability clinical studies in healthy females.

1.1 Recommendations

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:

Review issue	Key assessments
PK comparability	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 Luteo® (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®.

1.2 Post-Marketing Requirement and Commitment

None.

2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 General Pharmacology

Twenty-one active tablets of EV402 contain 0.10 mg of LNG, a synthetic progestogen, and 0.02 mg of EE, a synthetic estrogen. Seven inactive tablets contain inactive ingredients. Combination oral contraceptives like EV402 acts by suppressing gonadotropins. The primary mechanism of action is inhibitory action on ovulation and other alterations include changes in the cervical mucus (which

increases the difficulty of sperm entry into the uterus) and the endometrium (which reduces the likelihood of implantation).

2.2 Clinical Pharmacokinetics

PK results of EE and LNG following single dose administration of EV402 or Reference in Study EXS-P3-239 are summarized in Table 2.2-1. The 90% CI for GMR of primary PK parameters, C_{max} and AUC values, of EE and LNG were within the no-effect boundary of 80% to 125% for EV402 (to-be-marketed formulation [Batch LF09251A] was chewed and swallowed with water) compared to Reference (Table 2.2-2).

Table 2.2-1. Summary of PK parameters of EE and LNG for EV402 and Reference (Lutera®)

Parameters	**EV402** (n=32)		**Reference** (n=32)	
	Mean (C.V. %)		Mean (C.V. %)	
	EE	LNG	EE	LNG
C_{max} (pg/mL)	53.218 (33.9%)	3225.00 (33.1%)	46.237 (38.0%)	3034.70 (35.5%)
T_{max} (hours)[a]	1.50 (1.00-2.25)	0.75 (0.50-1.00)	1.27 (0.75-2.25)	0.75 (0.50-4.00)
AUC_t (pg·h/mL)	477.75 (32.5%)	27586.0 (39.0%)	425.67 (28.9%)	25823.0 (35.4%)
AUC_{inf} (pg·h/mL)	515.51 (31.0%)	34099.0 (36.8%)[b]	460.77 (27.9%)	32249.0 (34.3%)[b]
$T_{1/2}$ (hours)	16.421 (25.0%)	33.673 (31.8%)[b]	15.953 (23.7%)	33.871 (38.2%)[b]

Mean = arithmetic mean; C.V. = the coefficient of variation; [a]median (range); [b]n=30
T_{max} = the time of C_{max}; AUC_t and AUC_{inf} = AUC from time 0 to time of last observed concentration and from time 0 to infinity, respectively. Source: Original Clinical Study Report and additionally submitted report (exp-p3-239-additional-tables dated 12/13/19) for Study EXS-P3-239

Table 2.2-2. PK parameters and pariwise comparison statistical results of EE and LNG following a single dose of EV402 or Reference (Lutera®) in healthy subjects.

	EV402	n	**Reference**	n		**Statistics**
EE	Mean		Mean			GMR (90% CI)
C_{max} (pg/mL)	50.88	32	44.01	32		115.61 (110.32, 121.15)
AUC_t (pg·h/mL)	462.12	32	415.65	32		111.18 (107.00, 115.53)
AUC_{inf} (pg·h/mL)	501.54	32	451.28	32		111.14 (107.00, 115.43)
LNG	Mean		Mean			GMR (90% CI)
C_{max} (pg/mL)	3026.1	32	2794.9	32		108.27 (102.99, 113.83)
AUC_t (pg·h/mL)	25793.6	32	24250.7	32		106.36 (102.05, 110.86)
AUC_{inf} (pg·h/mL)	32571.7	30	31040.7	30		104.93 (100.22, 109.87)

Mean = geometric mean; GMR = geometric mean ratio; CI = confidence interval
Source: Original Clinical Study Report and additionally submitted report (exs-p3-239-additional-tables dated 12/13/19) for Study EXS-P3-239

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology provides the following labeling recommendations:

- The dose administration instruction should be consistent in the sections of DOSAGE AND ADMINISTRATION and PATIENT COUNSELING INFORMATION: (b) (4)

(b) (4)

- Information of drug interaction (Section 7 DRUG INTERACTION) should include a description of the clinical implication in relation to concomitant use with Hepatitis C drug therapy – liver enzyme elevation.
- Section 12.3 Pharmacokinetics should include the updated PK results of Study EXS-P3-239 that the Applicant submitted (dated December 13, 2019) as a response to the Agency's Information Request.

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Progestin and estrogen combination hormonal products are commonly used to prevent pregnancy. The Applicant has developed EV402, a (b) (4) oral tablet formulation. EV402 consists of 28 (b) (4) tablets, 21 tablets containing 0.10 mg of LNG and 0.02 mg of EE and 7 inactive tablets. The Applicant submitted the NDA via the 505(b)(2) pathway using Alesse® (LNG 0.10 mg / EE 0.02 mg, NDA 20-683) as the listed drug. Alesse® was initially approved for the prevention of pregnancy in women in 1997, also containing 21 active tablets. Since Alesse® is no longer marketed in the U.S., the Applicant used Lutera® (ANDA 76-625 by Mayne Pharma, Inc.), the current reference standard, as a reference product in their comparative bioavailability studies.

The Applicant originally submitted this NDA on January 7, 2019 (SDN001). The Agency refused to file the NDA because datasets submitted were incomplete for review (letter dated March 8, 2019). No major filing issues were identified by the Clinical Pharmacology review team for the initial submission.

3.2 Clinical Pharmacology Questions

3.2.1 What are the design features of the clinical pharmacology and/or clinical studies to support this NDA?

The NDA is based on demonstration of relative bioavailability/bioequivalence (similar C_{max} and AUC) of EV402 to the reference standard. No clinical safety and efficacy trials were conducted with the proposed product.

The Applicant conducted three comparative bioavailability studies in healthy female subjects in support of this NDA as summarized in Table 3.2-1. Study EXP-P3-239 was deemed as the pivotal study because the batch (Batch LF09251A) used in the study is identical to the to-be-marketed drug product.

Table 3.2-1. List of clinical studies submitted in NDA 209405.

Study No.	Objectives	Study design	Test products	Subjects
EXS-P3-239	The relative bioavailability of two batches of EV402 compared to Reference	A randomized, single-dose, 3-period, 6-sequence, cross-over study	· EV402 (Formulation B, Batch LF09251A) chewed and swallowed with water · EV402 (Formulation B, Batch LFD0556A) chewed and swallowed with water · Lutera (Reference) swallowed with water	36 healthy female subjects (32 analyzed)

EXP-P3-821	The relative bioavailability of different administration methods of EV402 compared to Reference	A randomized, single-dose, 3-period, 3-sequence, cross-over study	· EV402 (Formulation B, Batch LFD0415A) chewed and swallowed without water · EV402 (Formulation B, Batch LFD0415A) chewed and swallowed with water · Lutera (Reference) swallowed with water	36 healthy female subjects (33 analyzed)
EHE-P4-469	The relative bioavailability of an initial formulation (Formulation A) compared with the Reference and the effect of food	A randomized, single-dose, 3-period, 6-sequence, cross-over study	· Formulation A, chewed/swallowed without water, followed by consumption of water · Formulation A chewed/ swallowed followed by water at 30 minutes after high-fat meal breakfast · Lutera (Reference) swallowed with water	36 healthy female subjects (32 analyzed)

Formulation A: the initial formulation; Formulation B: the to-be-marketed formulation

Two formulations (Formulation A and B) were used in the completed clinical PK studies. The originally developed formulation (Formulation A) was used in the first study, EHE-P4-469. Multiple batches (LF09251A, LFD0556A and LFD0415A) of Formulation B, the to-be-marketed formulation, were used in the other two comparative bioavailability studies, EXS-P3-239 and EXS-P3-821. Formulation A and B had different excipients (Refer to 2.7.1 Summary of Biopharmaceutics Studies and Associated Analytical Methods). Batch LF09251A used in Study EXS-P3-239 is identical to the to-be-marketed product based on the submitted pharmaceutical development report (3.2.P.2 Pharmaceutical Development). The manufacturing process of Batch LF09251A differed from that of the other two batches, LFD0556A and LFD0415A, (b) (4) for Batch LF09251A. The manufacturing process was identical for Batches LFD0556A and LFD0415A. Study EXS-P3-821 assessed the bioavailability of EE and LNG following administration of EV402 under different conditions in relation to water intake compared to that of Reference. Study EHE-P4-469 evaluated the food effect on the bioavailability of the EE and LNG (b) (4) tablet using the initial formulation compared to that of Reference. In all three studies, C_{max}, AUC_t, and AUC_{inf}, were used to assess the relative bioavailability of LNG and EE following single dose administration of EV402 compared to that of Reference.

3.2.2 Are the study design and the bioanalytical assay adequate to assess PK comparability?

Yes.

The pivotal relative bioavailability study, Study EXS-P3-239, is considered adequate to assess PK comparability between EV402 and Reference based on the following reasons:

- The study design (three-way, 6-sequence, cross-over study crossover, randomized study design) was reasonable to compare the PK between the two products, EV402 vs Reference. This study used Batch LF09251A which is identical to the proposed to-be-marketed product.
- The number of subjects was determined to achieve adequate power based on the proposed study design and predefined null hypothesis (the ratio of the test mean to the reference mean of the PK parameters is below 80% or above 125%).
- Conducting the study in healthy female subjects to compare the PK of EE and LNG between the two products is acceptable.
- This study collected PK samples for LNG up to post-dose 72 hours. The PK sampling time (i.e. 72 hours) is less than three terminal elimination half-lives of LNG (half-life of LNG is approximately 36±13 hours according to Alesse® Prescribing information). Considering that LNG is rapidly and completely absorbed after oral administration [mean (SD) of T_{max} is 1.6 ± 0.9 hours and

bioavailability is about 100% according Alesse® Prescribing information], the sampling time of up to 72 hours for LNG is acceptable (Refer to Section 4.3.2).

- A validated bioanalytical method was used to measure the plasma concentrations of EE and LNG (Refer Section 4.1).

The other two PK studies, EXS-P3-239 and EXS-P3-821, were conducted in similar design and methodologies but not considered as pivotal studies for this submission (refer to Section 3.2.1, 3.2.4 and 3.2.5)

3.2.3 Does the PK study provide supportive evidence for PK comparability between the proposed drug product and the listed drug?

Yes.

In Study EXS-P3-239, the PK of EE and LNG following single dose administration (chewed and swallowed with water) of EV402 (Batch LF09251A; identical to the to-be-marketed product) was compared to that of Reference (Lutera®) under fasting conditions. Plasma concentrations of EE tended to be higher following administration of EV402 compared to that of Reference, particularly in the absorption phase (Figure 3.2-1). However, the 90% CIs of GMRs of all major EE PK parameters, C_{max}, AUC_t, and AUC_{inf}, for pairwise comparison between EV402 and Reference were within the no effect boundary of 80-125% (Table 2.2-2). The PK profile of LNG appeared overlaid and the PK parameters were similar between EV402 and Reference (Figure 3.2-2 and Table 2.2-2). The 90% CIs of GMRs of the major LNG PK parameters for pairwise comparison were within the no effect boundary of 80-125% (Table 2.2-2). These findings demonstrated PK comparability between EV402 (chewed and swallowed with water) and Reference.

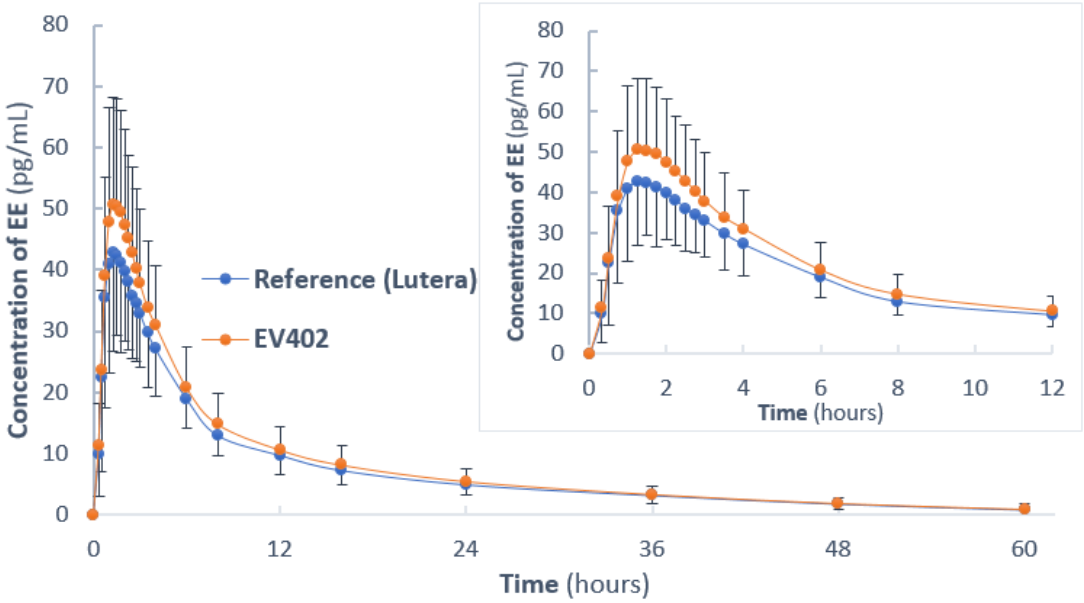


Figure 3.2-1. Mean (standard deviation) EE concentration-time profile following single dose administration of EV402 or Reference (Lutera) in healthy female subjects (n=32)**.** Inlet figure indicates the profile of EE up to 12 hours post-dose. (Reproduced by the Reviewer based on the raw data in the report of Study EXS-P3-239).

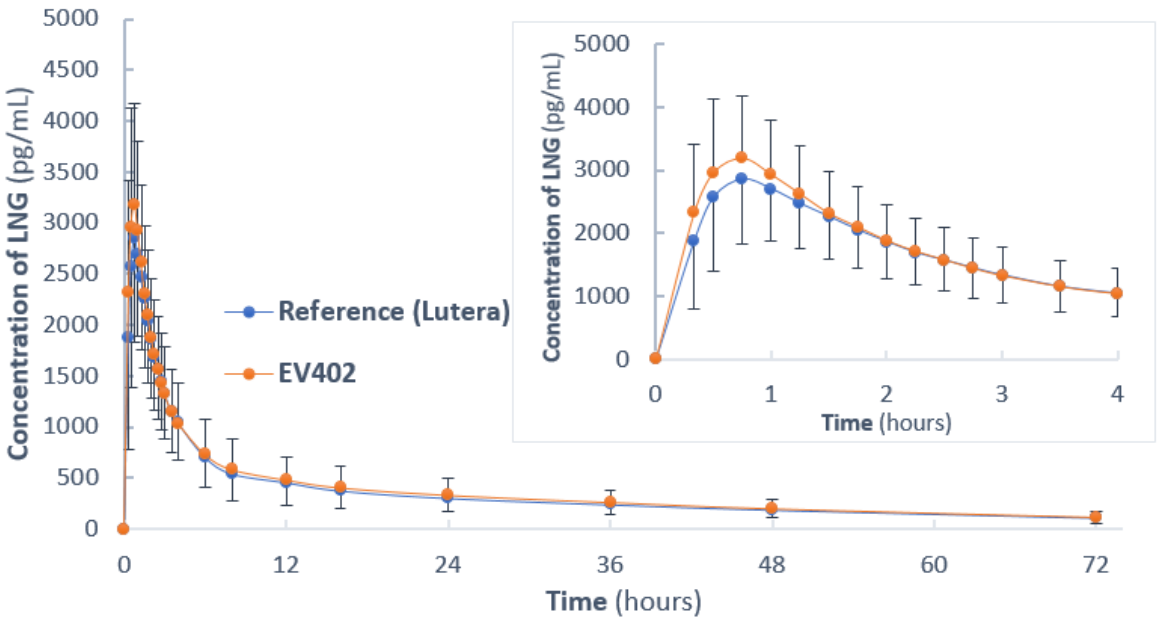


Figure 3.2-2. Mean (standard deviation) LNG concentration-time profile following single dose administration of EV402 or Reference (Lutera) in healthy female subjects (n=32)**.** Inlet figure indicates the profile of LNG up to 4 hours post-dose (Reproduced by the Reviewer based on the raw data in the report of Study EXS-P3-239).

3.2.4 Are there any clinically relevant findings in relation to administration method (swallowing with or without water) and what is the appropriate management strategy?

The effect of water intake on the PK of EE and LNG using the to-be-marketed product of EV402 was not studied. However, results from Study EXS-P3-821 suggested that the systemic exposure to EE may be significantly higher than that of Reference if EV402 is swallowed without water. To minimize the safety risk associated with the increased systemic exposure of EE when taking without consumption of water, EV402 is recommended to be chewed and then immediately swallowed with water.

In Study EXS-P3-821, the PK profile of EE and LNG following single dose administration of EV402 when chewed and swallowed with or without water was compared to that of Reference (Lutera®). The study used Batch LFD0415A which was the to-be-marketed formulation but there was (b) (4) compared to the to-be-marketed product. Plasma concentrations of EE tended to be higher following administration of EV402 (Batch LFD0415A) compared to that of Reference, especially in the absorption phase (Figure 4.2.2-1). Mean C_{max} and AUC values of EE were higher following administration of EV402 and this difference was enhanced when EV402 was swallowed without water intake (Table 4.2.2-1). The upper boundary of the 90% CIs of GMRs of all major EE PK parameters, C_{max}, AUC_t, and AUC_{inf}, for pairwise comparison between EV402 (Batch LFD0415A) when swallowed without water and Reference were above the bioequivalence range (i.e. 80-125%). In comparison, the 90% CI of GMRs of only C_{max} between EV402 (Batch LFD0415A) when swallowed with water and Reference was out of the range (Table 4.2.2-3). The PK profile of LNG appeared overlaid and the PK parameters were similar between EV402 (Batch LFD0415A) with or without water and Reference (Figure 4.2.2-1 and Table 4.2.2-2), respectively. The 90% CIs of GMRs of all major LNG PK parameters for pairwise comparison between EV402 and Reference were within the bioequivalence range (Table 4.2.2-4).

Based on the results from Study EXS-P3-821, it is anticipated that the systemic exposure to EE can be significantly increased if EV402 is swallowed without water compared to Reference. Results from the pivotal Study EXS-P3-239 demonstrated that the systemic exposure of EE and LNG from EV402 (Batch LF09251A: identical to the to-be-marketed product) was similar to that of Reference when EV402 was swallowed with water after chewing. Therefore, EV402 should be chewed and then immediately swallowed with water.

3.2.5 Are there any clinically relevant food-drug interactions and what is the appropriate management strategy?

The effect of food on the PK of EE and LNG using the to-be-marketed formulation of EV402 was not studied. However, results from Study EXS-P3-649 suggested that the systemic exposure to EE and LNG may be significantly lower than that of Reference if EV402 is administered with food. To minimize the risk of reduced efficacy associated with the decreased systemic exposure of EE when taking with food, EV402 is recommended to be taken on an empty stomach.

In Study EXS-P3-469, the PK of EE and LNG following single dose administration of the EE and LNG chewable tablet in the initial formulation (Formulation A) after a high-fat meal was compared to that at fasting. Systemic exposure of EE and LNG was significantly lower at the fed state, especially in the absorption phase (Figure 4.2.3-1). The C_{max} values for EE and LNG decreased by approximately 44% and 56%, respectively, at fed state; and the 90% CIs of GMRs for C_{max} pairwise comparison between the fed state and the fasting state were out of the bioequivalence range (Table 4.2.3-1, 4.2.3-2, 4.2.3-3 and 4.2.3-4). However, the 90% CIs of GMRs of the AUC values for EE and LNG for pairwise comparison between the fed state and the fasting state were within the bioequivalence range (Table 4.2.3-3 and 4.2.3-4). Based on the results from Study EXS-P3-649, it is anticipated that the systemic exposure of EE and LNG from EV402 could be reduced if the chewable tablet is swallowed after a high fat of meal. It is noted that in the approved label of the listed drug, Alesse®, neither information on food-drug interaction nor detailed instruction of drug administration in relation to food intake is available. Since results from the pivotal study demonstrated that the systemic exposure of EE and LNG was similar between EV402 (Batch LF09251A: identical to the to-be-marketed product) and Reference under fasted conditions, the Applicant's proposal of administering EV402 on empty stomach is acceptable.

4 APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The concentrations of EE and LNG in the completed comparative bioavailability studies (Studies EXP-P3-239, EXP-P3-821, and EHE-P4-469) were analyzed using validated Liquid Chromatography-tandem mass spectrometry/mass spectrometry (LC-MS/MS). Intra-run and inter-run precision and accuracy, specificity, carry-over, and matrix effects were fully evaluated in the LC-MS/MS assays and the recovery was also determined.

The review team requested inspections of the analytical and clinical sites ((b) (4) to Division of New Drug Bioequivalence Evaluation (DNDBE), Office of Study Integrity and Surveillance (OSIS) during filing review of the Applicant's initial submission of the NDA. DNDBE declined to conduct an on-site inspection and determined that an inspection was not warranted because both sites were recently inspected under other prior submissions (b) (4)). The final classification from the inspections indicated no action indicated (Memorandum from OSIS, DNDBE under NDA 209405 dated March 20, 2019).

The bioanalytical methods are summarized in Table 4.1-1.

Table 4.1-1. Bioanalytical methods for the measurement of EE and LNG

Analyte	Validation report	Method summary	Bioanalytical site
EE	EHO-V8-572(R22)	· 500 µL plasma using EDTA · Liquid-liquid phase extraction · Reverse phased HPLC with MS/MS detection · Internal standard: ethinyl estradiol-D4 · Assay range: 1 - 250 pg/mL	(b) (4)
LNG	LVE-V9-603 (R6)	· 500 µL plasma using EDTA · Solid phase extraction · Reverse phased HPLC with MS/MS detection · Internal standard: Levonorgestrel-D6 · Assay range: 50 - 15000 pg/mL	

The performance results of the validated bioanalytical method for each analyte are summarized in Table 4.1-2.

Table 4.1-2. The performance of the bioanalytical methods for measurement of EE and LNG

Analyte	Performance characteristics of quality control samples					Long term stability
	QC concentrations	Inter-run accuracy	Inter-run precision	Intra-run accuracy	Intra-run precision	
EE	1 (LLoQ), 3, 50, 125, and 195 pg/mL	95.0% - 100.9% (LLoQ = 97.6%)	3.6% -16.4% (LLoQ = 16.4%)	84.6% - 101.0% (LLoQ = 84.6%)	2.6% - 10.9% (LLoQ = 10.9%)	Up to 126 days at -20°C
LNG	50 (LLoQ), 150, 3000, 7500, and 11250 pg/mL	98.4% - 106.5% (LLoQ = 106.5%)	3.0% - 14.1% (LLoQ = 14.1%)	92.6% - 106.8% (LLoQ = 102.0%)	0.9% - 3.4% (LLoQ = 10.1%)	Up to 116 days at -20°C

LLoQ: Lower limit of quantification

The performance of the quality control determinations for the applied LC-MS/MS methods met the Agency's acceptance criteria (≤ 20% for precision [CV%] and within ±20% for accuracy at the LLoQ and ≤15% or within ±15% at all other concentrations). Assay performance for each individual PK study was

assessed using quality control samples and incurred sample reanalysis (ISR). The quality control samples obtained during the in-study validation met the acceptance criteria (%C.V. and % [bias] of the nominal value; ≤15.0% [LLoQ ≤20.0%]) for a successful analysis of the study samples. For the ISR evaluation, at least 10% of the total analyzable study samples for each analyte in each study were re-analyzed and compared to the original values. The assay reproducibility was demonstrated for greater than 90% of the samples reanalyzed (the percent difference criterion of ≤20.0%) for EE and LNG in each study (Table 4.1-3). The long-term stability evaluation per each validation method was sufficient to cover the sample storage time for each study (i.e. up to 126 days and 116 days at -20°C nominal for EE and LNG, respectively).

Table 4.1-3. Summary of the ISR evaluation in three PK studies

Analyte	Study EXP-P3-239	Study EXP-P3-821	Study EHE-P4-469
EE	225 samples were re-assayed as ISR and 224 samples (99.6%) met the percent difference criterion of ≤20.0%.	230 samples were re-assayed as ISR and 228 samples (99.1 %) met the percent difference criterion of ≤20.0%.	226 samples were re-assayed as ISR and 224 samples (99.1 %) met the percent difference criterion of ≤20.0%.
LNG	224 samples were re-assayed as ISR and 219 samples (98.2%) met the percent difference criterion of ≤20.0%.	242 samples were re-assayed as ISR and 227 samples (98.7 %) met the percent difference criterion of ≤20.0%.	222 samples were re-assayed as ISR and 217 samples (98.6%) met the percent difference criterion of ≤20.0%.

Overall, all bioanalytical methods applied for clinical PK sample were acceptable to support the PK characterization of EE and LNG in this submission.

4.2 Individual Study Reports

4.2.1 Study EXS-P3-239

Title: Single-dose crossover comparative bioavailability of EE/LNG 0.02 mg/0.1 mg chewable tablets compared to tablets in healthy female volunteers / fasting state

Objectives:

- Primary: To evaluate the relative bioavailability of the chewable tablets compared to the conventional tablet, following a single 0.02 mg/0.1 mg oral dose administration of EE/LNG under fasting conditions.
- Secondary: To determine the safety and tolerability of the test products compared to the reference formulation in healthy volunteers.

Study Design:

- A randomized, single dose, 3-period, 6-sequence, crossover design in 36 healthy female subjects
- Test drugs and administration method
  - Test 1: Formulation B (Batch LF09251A; To-be-marketed formulation product) was chewed (break tablet between teeth into small particles) and swallowed immediately with water (about 240 mL at ambient temperature) at fasting (i.e. after a 10-hour overnight fast)
  - Test 2: Formulation B (Batch LFD0556A) was chewed (break tablet between teeth into small particles) and swallowed immediately with water at fasting
  - Reference (Lutera) was swallowed whole with water at fasting
- PK samples: pre-dose and at 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48, 60 (for EE) and 72 (for LNG) hours
- Bioanalytical assay: the concentrations of EE and LNG in human plasma were determined using LC-MS/MS (refer to Section 4.1).

Results:

- Disposition of subjects: 36 subjects were randomized and 32 subjects completed the study (discontinuation: Subjects [redacted] (b) (6); 34 subjects received Test 1, Test 2 and Reference, respectively).
- PK and statistical results
  - A total of 32 subjects were analyzed and included in the PK and statistical analysis. Subject (b) (6) was included in the analysis of Test 1 (Period 2) and Reference (Period 1). Subject (b) (6) completed all three periods but was excluded from PK data collection due to protocol violations.
  - Concentration-time profiles of EE and LNG

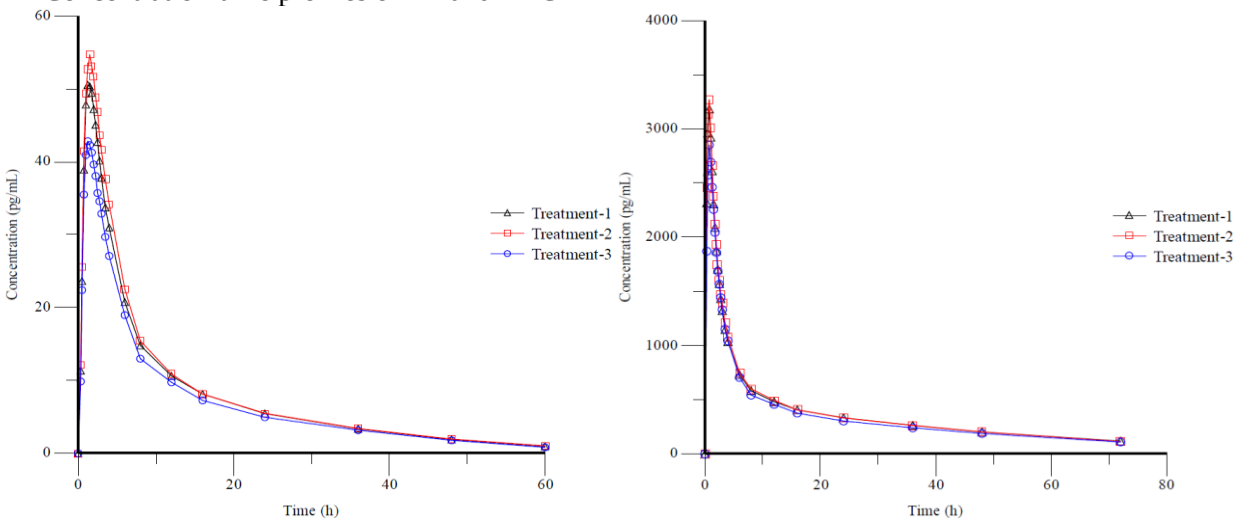


Figure 4.2.1-1. Mean EE and LNG concentration-time profiles following EV402 or Lutera (Treatment-1 = Formulation B (Batch LF09251A), n = 32; Treatment-2 = Formulation B (Batch LFD0556A), n = 31; Treatment-3 = Reference [Lutera], n =32).

Table 4.2.1-1. Summary of PK parameters of EE

Parameters	**Test 1 - EV402** Batch LF09251A with water (n=32)		**Test 2 - EV402** Batch LFD0556A with water (n=31)		**Reference** (n=32)	
	Mean	C.V. (%)	Mean	C.V. (%)	Mean	C.V. (%)
C_{max} (pg/mL)	53.218	33.9%	56.994	35.9%	46.237	38.0%
T_{max} (hours)[a]	1.50	(1.00-2.25)	1.75	(1.00-2.75)	1.27	(0.75-2.25)
AUC_t (pg·h/mL)	477.75	32.5%	502.37	31.6%	425.67	28.9%
AUC_{inf} (pg·h/mL)	515.51	31.0%	538.27	31.1%	460.77	27.9%
$T_{1/2}$ (hours)	16.421	25.0%	16.217	23.35	15.953	23.7%

[a]median (range)

Table 4.2.1-2. Summary of PK parameters of LNG

Parameters	**Test 1 - EV402** Batch LF09251A with water (n=32)[b]		**Test 2 - EV402** Batch LFD0556A with water (n=31)[c]		**Reference** (n=32)[b]	
	Mean	C.V. (%)	Mean	C.V. (%)	Mean	C.V. (%)
C_{max} (pg/mL)	3225.00	33.1%	3347.40	33.4%	3034.70	35.5%
T_{max} (hours)[a]	0.75	(0.50-1.00)	0.75	(0.50-1.00)	0.75	(0.50-4.00)
AUC_t (pg·h/mL)	27586.0	39.0%	27887.0	40.3%	25823.0	35.4%
AUC_{inf} (pg·h/mL)	34099.0	36.8%	34278.0	37.7%	32249.0	34.3%
$T_{1/2}$ (hours)	33.673	31.8%	32.167	34.2%	33.871	38.2%

[a]median (range); [b]n=30 and [c]n=29 for AUC_{inf} and $T_{1/2}$
The terminal phase of LNG could not be adequately estimated for two subjects ((b) (6) in the period for Reference and (b) (6) in the periods for Test 2 and Reference) because the criteria for estimation for elimination constant λ_Z were not met (The study protocol defined that the parameter λ_Z must be positive with a R^2 of at least 80% using at least three data points).

Table 4.2.1-3. Statistical results of PK parameters of EE

	EV402 Batch LF09251A	**EV402** Batch LFD0556A	**Reference**	**Statistics** GMR (90% CI)	
	Mean (n=32)	Mean (n=31)	Mean (n=32)	**Batch LF09251A vs Reference**	**Batch LFD0556A vs Reference**
C_{max} (pg/mL)	50.88	53.76	44.01	115.61 (110.32, 121.15)	122.14 (116.50, 128.06)
AUC_t (pg*hr/mL)	462.12	490.46	415.65	111.18 (107.00, 115.53)	118.00 (113.51, 122.66)
AUC_{inf} (pg*hr/mL)	501.54	527.51	451.28	111.14 (107.00, 115.43)	116.89 (112.50, 121.46)

Mean: geometric mean; GMR: geometric mean ratio; 90% CI (confidence interval)

Table 4.2.1-4. Statistical results of PK parameters of LNG

	EV402 Batch LF09251A	**EV402** Batch LFD0556A	**Reference**	**Statistics** GMR (90% CI)	
	Mean (n=32)	Mean (n=31)	Mean (n=32)	**Batch LF09251A vs Reference**	**Batch LFD0556A vs Reference**
C_{max} (pg/mL)	3026.1	3092.9	2794.9	108.27 (102.99, 113.83)	110.66 (105.21, 116.40)
AUC_t (pg*hr/mL)	25793.6	25771.4	24250.7	106.36 (102.05, 110.86)	106.27 (101.92, 110.81)
AUC_{inf} (pg*hr/mL)	32571.7[a]	32575.5[b]	31040.7[a]	104.93 (100.22, 109.87)	104.94 (100.17, 109.95)

Mean: geometric mean; GMR: geometric mean ratio; 90% CI (confidence interval); [a]n=30 and [b]n=29 for AUC_{inf}

Applicant's conclusion:

Comparative bioavailability assessment - Test-1 (Batch LF09251A) vs Reference

- For EE and LNG, the PK results demonstrate that the GMRs as well as the corresponding 90% CIs of C_{max}, AUC_t and AUC_{inf} were all within the 80-125% range.

Comparative bioavailability assessment - Test-2 (Batch LFD0556A) vs Reference

- For EE, the PK results demonstrate that the GMRs and corresponding 90% CIs were included within the range of 80% to 125% for AUC values, while the upper bound of the CI for C_{max} was 128.06%.
- For LNG, the PK results demonstrate that the GMRs and corresponding 90% CIs of C_{max}, AUC_t and AUC_{inf} were all included within the range of 80% to 125%.
- Overall, the drugs tested were generally safe and well tolerated by the subjects included in this study.

Reviewer's comments:

- *The study was a comparative PK study to assess whether there were significant differences in the PK of EE and LNG between EV402 using two different batches and Lutera® (Reference). The test products were chewed and swallowed with water whereas Reference was swallowed with water as intended. The study design (i.e. the sample size and statistical analyses) appears acceptable.*
- *This study collected PK samples for LNG for 72 hours post-dose which is less than three terminal elimination half-lives of LNG (approximately 36±13 hours; Alesse® Prescribing information) and thus may be inadequate to fully characterize its PK profile. In a response (dated September 27, 2019) to the Agency's Information Request, the Applicant stated that the sampling period should be sufficient to obtain a reliable estimation of the extent of absorption because*
  1) LNG has fast and nearly complete absorption;

2) The intra-individual variance of the primary PK endpoints was low.

3) The linear terminal elimination phase was reached at latest 24 hours post-dose, suggesting that within 24 hours post dose the drug product had completely moved through the gastrointestinal tract.

This Reviewer still believes that the sampling time up to 72 hours may be inadequate to characterize a full PK profile including absorption and elimination phases of LNG following oral administration. However, considering that the main purpose of this study was to compare the rate and extent of oral absorption between the test and reference products and LNG is rapidly and completely absorbed after oral administration (bioavailability = about 100%, Alesse® Prescribing information; and median T_{max} was 0.75 hour for both EV402 and reference drug), the sampling time up to 72 hours for LNG is acceptable.

- *This study used two batches of EV402, LF09251A and LFD0556A. There is a difference in manufacturing process between the two batches:* (b) (4) *for Batch LF09251A. Based on the pharmaceutical development report (3.2.P.2 Pharmaceutical Development), Batch LF09251A is identical to the proposed to-be-marketed product.*
- *While Subject* (b) (6) *completed all three periods, PK data of this subject was not included due to a violation of the drug administration procedure. Based on the study report, the subject appeared to chew and break Reference product although she was instructed to swallow the drug. Considering that administration method for each drug is critical in the comparative bioavailability assessment, excluding this subject is acceptable.*
- *The concentrations of EE tended to be higher following administration of both batches of EV402 compared to that of Reference, especially for the absorptive phase (Figure 4.2.1-1) and the C_{max} and AUC values of EE were higher for (Table 4.2.1-1). These results may be attributed to the difference in absorption pattern of EE between the two formulations and (or) administration methods (chewed and swallowed for EV402 vs swallowed whole for Reference).*
- *The 90% CIs of GMRs of all EE PK parameters for pairwise comparison between EV402 of Batch LF09251A (identical to the to-be-marketed product) and Reference were within the bioequivalence range. The upper bound of 90% CIs of GMRs of C_{max} for EV402 of Batch LFD0556A (i.e. 128.06%) was slightly above the bioequivalence range (Table 4.2.1-3).*
- *For both batches of EV402, the PK profiles of LNG appeared overlaid and the PK parameters were similar to that of Reference (Figure 4.2.1-1 and Table 4.2.1-2) and the 90% CIs of GMRs of the major LNG PK parameters, C_{max}, AUC_t, and AUC_{inf}, for pairwise comparison with Reference were within the bioequivalence range (Table 4.2.1-4).*
- *The Reviewer conducted independent PK and statistical analyses using the dataset. The reviewer's analysis results were consistent with those of the Applicant. In the Applicant's analysis, the AUC_{inf} of LNG in three periods of two subjects (Subject* (b) (6) *was not estimated based on the predefined criteria in the protocol. The Reviewer independently estimated the AUC_{inf} values in these periods and included them for the statistical analyses. The results were similar to those presented by the Applicant.*
- *Based on the results from this study, the proposed to-be-marketed product (Batch LF09251A) was bioequivalent to Reference when it was chewed and swallowed with water.*

4.2.2 Study EXS-P3-821

Title: Single-dose crossover comparative bioavailability under fasting-conditions of EE/LNG 0.02 mg/0.1 mg chewable tablets compared to tablets in healthy female volunteers

Objectives:

· Primary: To assess the relative bioavailability of the chewable tablet under different conditions (chewed with, and without water compared to the conventional tablet).

· Secondary: To determine the safety and tolerability of the EE/LNG chewable tablet formulation.

Study Design:

· A randomized, single dose, 3-period, 3-sequence, crossover design in 36 healthy female subjects

· Test drugs and administration method

- Test without water: Formulation B (Batch LFD0415A) was chewed thoroughly and then the saliva was swallowed without water at fasting (i.e. after a 10-hour overnight fast)
- Test with water: Formulation B (Batch LFD0415A) was chewed thoroughly and then the saliva was swallowed, followed by the consumption of about 240 mL of water at fasting
- Reference (Lutera): swallowed whole with about 240 mL of water at fasting

· PK samples: pre-dose and at 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48, 60 (for EE) and 72 (for LNG) hours

· Bioanalytical assay: the concentrations of EE and LNG in human plasma were determined using LC-MS/MS (refer to Section 4.1.).

Results:

· Disposition of subjects: 36 subjects were randomized and 31 subjects completed study (34 subjects received Test without water, 33 subjects received Test with water, and 33 subjects received Reference).

· PK and statistical results

- 33 subjects were analyzed and 32 subjects were included in the PK and statistical analyses for EE (Subject (b) (6): analyzed by an error); 33 subjects were analyzed and 30 subjects were included in the PK and statistical analyses for LNG (Subject (b) (6): analyzed by an error; Subjects (b) (6) and (b) (6) determined not reliable by the bioanalytical laboratory).
- Time-concentration profiles of EE and LNG

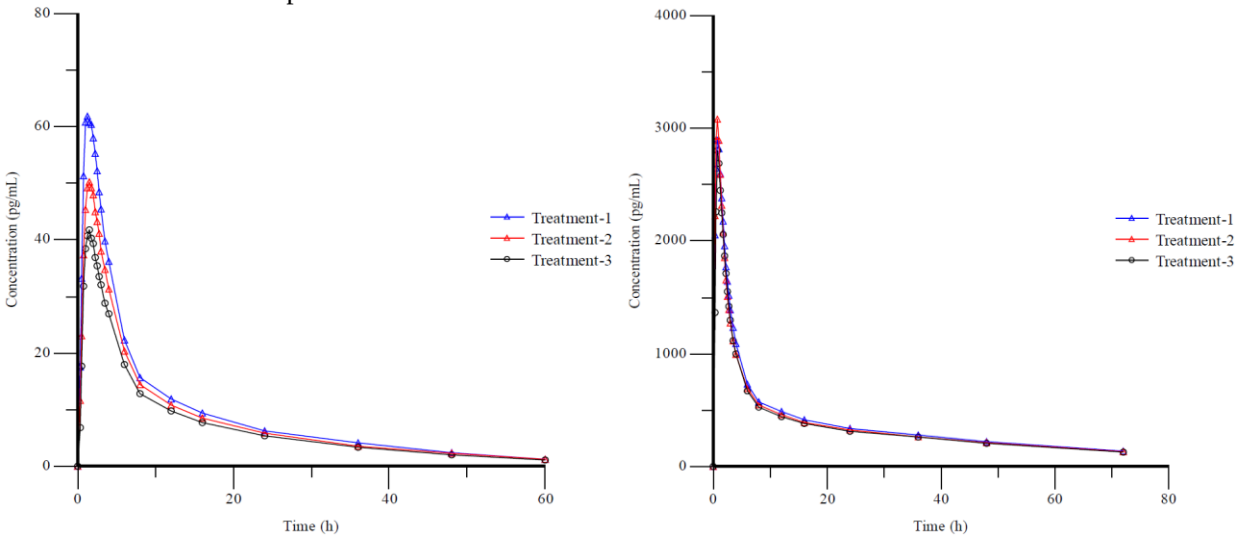


Figure 4.2.2-1. Mean EE and LNG concentration-time profile following EV402 or Lutera (Treatment-1 = Test without water, n = 32 for EE and 30 for LNG; Treatment-2 = Test with water, n = 31 for EE and 29 for LNG; Treatment-3 = Reference with water, n =32 for EE and 30 for LNG).

Table 4.2.2-1. Summary of PK parameters of EE

Parameters	EV402 without water (n=32) [b]		EV402 with water (n=31) [c]		Reference with water (n=32) [b]	
	Mean	C.V. (%)	Mean	C.V. (%)	Mean	C.V. (%)
C_{max} (pg/mL)	65.62	26.9%	53.86	26.7%	44.37	31.2%
T_{max} (hours)[a]	1.25	(1.00-2.25)	1.5	(1.25-2.50)	1.5	(1.00-2.25)
AUC_t (pg·h/mL)	560.35	29.3%	491.93	23.1%	431.24	30.7%
AUC_{inf} (pg·h/mL)	604.49	30.5%	529.93	23.1%	469.13	31.9%
$T_{1/2}$ (hours)	16	16.8%	16.56	19.8%	16.34	18.7%

[a]median (range), [b]n=31 and [c]n=30 for AUC_∞ and $T_{1/2}$

The terminal phase of EE could not be adequately estimated in the period of Reference for subject (b) (6) because the criteria for estimation for elimination constant λ_Z were not met (The parameter λ_Z must be positive with a R^2 of at least 80% using at least three data points).

Table 4.2.2-2. Summary of PK parameters of LNG

Parameters	EV402 without water (n=30)		EV402 with water (n=29)		Reference with water (n=30)	
	Mean	C.V. (%)	Mean	C.V. (%)	Mean	C.V. (%)
C_{max} (pg/mL)	2990.8	29.8%	3144.4	29.0%	2942.5	37.7%
T_{max} (hours)[a]	1.00	(0.50-1.75)	0.75	(0.50-1.50)	0.75	(0.50-2.25)
AUC_t (pg·h/mL)	28391.8	36.2%	27202.4	35.1%	26205.0	40.9%
AUC_{inf} (pg·h/mL)	36855.3	38.6%	35488.1	34.9%	34438.2	39.3%
$T_{1/2}$ (hours)	38.66	40.8%	40.06	44.2%	39.95	42.0%

[a]median (range)

Table 4.2.2-3. Statistical results of PK parameters of EE

	EV402 without water	EV402 with water	Reference		Statistics GMR (90% CI)	
	Mean (n)	Mean (n)	Mean (n)		Without water vs Reference	With water vs Reference
C_{max} (pg/mL)	63.94 (32)	52.52 (31)	42.71 (32)		149.70 (142.14, 157.67)	122.97 (116.70, 129.59)
AUC_t (pg*hr/mL)	541.67 (32)	481.18 (31)	415.58 (32)		130.34 (125.57, 135.29)	115.78 (111.50, 120.23)
AUC_{inf} (pg*hr/mL)	587.50 (31)	520.52 (30)	453.90 (31)		129.43 (124.52, 134.54)	114.68 (110.27, 119.26)

Mean: geometric mean; GMR: geometric mean ratio; 90% CI (confidence interval)

Table 4.2.2-4. Statistical results of PK parameters of LNG

	EV402 without water	EV402 with water	Reference		Statistics GMR (90% CI)	
	Mean (n=30)	Mean (n=29)	Mean (n=30)		Without water vs Reference	With water vs Reference
C_{max} (pg/mL)	2868.4	2982.8	2748.2		104.37 (98.50, 110.59)	108.54 (102.36, 115.08)
AUC_t (pg*hr/mL)	26812.0	25321.5	24470.6		109.57 (104.12, 115.31)	103.48 (98.27, 108.96)
AUC_{inf} (pg*hr/mL)	34561.0	32893.7	32268.6		107.10 (101.84, 112.64)	101.94 (96.87, 107.27)

Mean: geometric mean; GMR: geometric mean ratio; 90% CI (confidence interval)

Applicant's conclusion:

- Administration of the Test chewable tablet without water had greater C_{max} and AUC for EE when compared to the reference. When the Test formulation was administered with water, C_{max} and AUC for EE were similar to those of the reference product. The EE 90% CIs for AUC_t and AUC_{inf} were within the bioequivalence acceptance range, and only the upper limit of 90% CI for C_{max} was above 125.00%.

The C_{max} result is most likely related to the difference in formulations (chewable vs regular tablet), which probably resulted in an increased rate of absorption of the drug. A chewable tablet is not required to disintegrate prior to dissolution of the active ingredient and a portion of the drug can be absorbed through the oral mucosa, thus avoiding first pass metabolism.

- For LNG, comparable values of C_{max} and AUC were observed among the Test formulation administered without or with water and the reference. The 90% CIs between the chewable tablet under different conditions compared to the conventional tablet were all contained within the range of 80 and 125%. For both analytes, comparable values were observed for T_{max} and terminal elimination half-life for all treatments.
- Overall, the drugs tested were generally safe and well tolerated by the subjects.

Reviewer's comments:

- *This comparative PK study assessed whether there were significant differences in the PK of EE and LNG between EV402 under two medication conditions (chewed with or without water) and Lutera® (Reference). The overall study design (e.g. the sample size and statistical analyses) appears reasonable to assess the relative bioavailability of EE and LNG between the two products and the effect of water intake on the PK profile of EV402.*
- *This study used Batch LFD0415 for EV402. This batch has a different manufacturing process compared to the proposed to-be-marketed product in that* (b) (4) *for the to-be-marketed product.*
- *Two subjects* (b) (6) *) were excluded from the PK analysis for LNG due to the bioanalytical laboratory issue (an interference close to the internal standard peak).*
- *Plasma concentrations of EE tended to be higher when EV402 was chewed and swallowed with or without water compared to that of Reference, especially for the absorptive phase (Figure 4.2.2-1). The highest C_{max} and AUC values of EE were observed following administration of EV402 without water (Table 4.2.2-1). The 90% CIs of GMRs of AUC_t and AUC_{inf} for pairwise comparison demonstrated PK comparability between EV402 with water and Reference whereas the upper boundary of the 90% CI of C_{max} was slightly above the bioequivalence range. The 90% CIs of GMRs of major EE PK parameters, C_{max} and AUC values, between EV402 without water and Reference were out of the bioequivalence range (Table 4.2.2-3).*
- *The PK profiles of LNG appeared overlaid and PK parameters of LNG were similar for all three treatments (i.e. EV402 with and without water, and Reference) (Figure 4.2.2-1 and Table 4.2.2-2). The 90% CIs of GMRs of the major LNG parameters for pairwise comparison were all within the bioequivalence range (Table 4.2.2-4).*
- *C_{max} of EE following administration of EV402 with water was approximately 23% higher compared to Reference in this study. It is noted that the Batch LFD0415A used in this study had a different manufacturing process compared to the to-be-marketed product. In Study EXS-P3-239 using the final to-be-marketed formulation product for EV402 (Batch LF09251A), a slightly higher C_{max} of EE following administration EV402 with water was also observed when compared to Reference, but the 90% CIs of GMRs for pairwise comparison were within the bioequivalence range.*
- *The Reviewer conducted independent PK and statistical analyses using datasets submitted by the Applicant. The reviewer's analysis results were consistent with those of the Applicant. In the Applicant's analysis, the AUC_{inf} of EE in in the period of Reference for one subject (Subject* (b) (6) *) was not estimated based on the predefined criteria in the protocol. The Reviewer separately*

estimated the AUC_{inf} value in that period and included it for the statistical analysis. The results were similar to that provided by the Applicant.

- *Considering that the systemic exposure to EE was significantly higher when EV402 was taken without water compared to Reference, administration of EV402 with water is recommended.*

4.2.3 Study EXS-P3-469

Title: Single dose crossover comparative bioavailability under fasting conditions and food effect study of ethinyl estradiol/levonorgestrel 0.02 mg/0.1 mg chewable tablets compared to tablets in healthy female volunteers

Objectives:

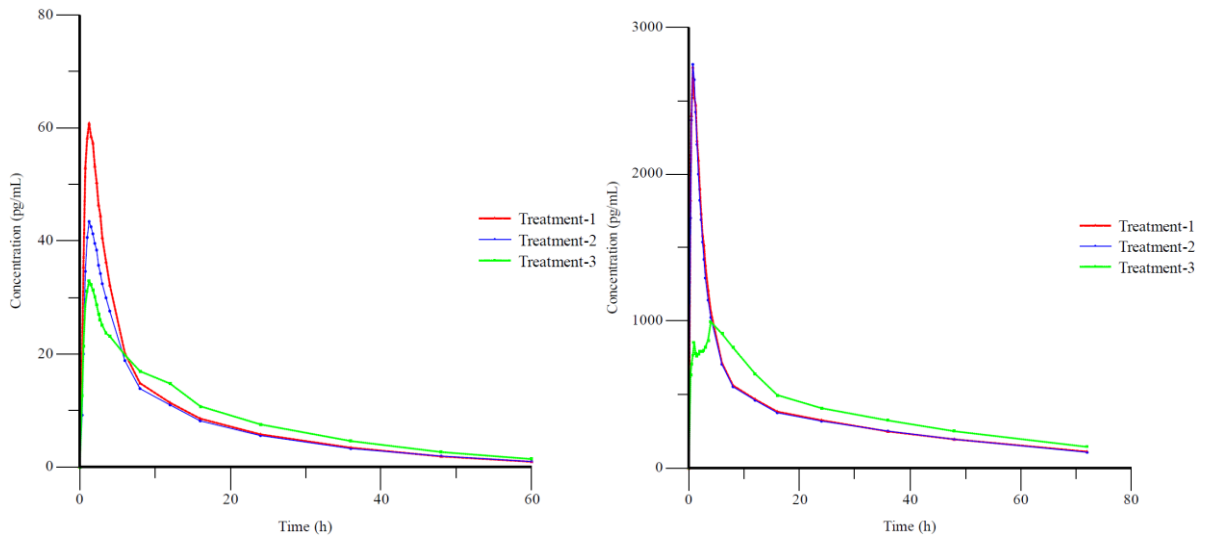
- Primary: To assess the relative bioavailability of the chewable tablet compared to the tablet following a single 0.02 mg/0.1 mg oral dose administration of EE/LNG when taken without food and to evaluate the food effect on the bioavailability of the chewable tablet following a single 0.02 mg/0.1 mg oral dose administration of EE/LNG when taken with and without food
- Secondary: To determine the safety and tolerability of EE/LNG 0.02/0.1 mg chewable tablets in normal healthy volunteers

Study Design:

- A randomized, single dose, 3-period, 6-sequence, crossover design in 36 healthy female subjects
- Test drugs and administration method
  - Test-fast: Formulation A (Batch LFD0293A, initial formulation) was chewed and swallowed without water at fasting and then followed by consumption of water
  - Reference: Lutera, fasted, swallowed with 240 mL of water
  - Test-fed: Formulation A (Batch LFD0293A) was chewed and swallowed without water at 30 minutes after the start of a high-fat, high-calorie breakfast and then followed by consumption of water.
- PK samples: predose and at 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48, 60 (for EE) and 72 (for LNG) hours
- Bioanalytical assay: the concentrations of EE and LNG in human plasma were determined using LC-MS/MS (refer to Section 4.1).

Results:

- Disposition of subjects: 36 subjects were randomized and 31 subjects completed the study (5 subjects, (b) (6), discontinued the study); 34 subjects received Test-fast, 33 subjects received Reference and 32 subjects received Test- fed.
- PK and statistical results
  - A total of 32 subjects were analyzed and included in the PK and statistical analysis for EE and LNG, respectively (Subject (b) (6) completed all periods but was excluded from the PK analysis of LNG after bioanalysis due to a positive pre-dose LNG concentration greater than 5% of the C_{max} value; Subject (b) (6) was included in the analysis of Test-fast [Period 1] and Reference [Period 2]).
  - Concentration-time profiles of EE and LNG



EE **LNG**

Figure 4.2.3-1. Mean EE and LNG concentration-time profiles following EV402 (Formulation A) or Lutera
(Treatment-1 = Test-fast, n = 32 for EE and 31 for LNG; Treatment-2 = Reference-fast, n = 32 for EE and 31 for LNG; Treatment-3 = Test fed, n=31 for EE and 30 for LNG).

Table 4.2.3-1. Summary of PK parameters of EE

Parameters	**Test-fast** (n=32)		**Reference** (n=32)		**Test-fed** (n=31)	
	Mean	C.V. (%)	Mean	C.V. (%)	Mean	C.V. (%)
C_{max} (pg/mL)	63.51	31.6	46.30	39.3	34.94	22.0
T_{max} (hours)[a]	1.25	(0.75 – 1.75)	1.38	(0.75 – 4.00)	1.25	(0.75 – 8.00)
AUC_t (pg·h/mL)	513.35	28.7	448.62	36.2	508.84	30.0
AUC_{inf} (pg·h/mL)	547.88	28.4	489.74	36.6	551.06	31.0
$T_{1/2}$ (hours)	15.40	18.5	16.63	30.5	15.53	22.6

[a]median (range)

Table 4.2.3-2. Summary of PK parameters of LNG

Parameters	**Test-fast** (n=31)		**Reference** (n=31)		**Test-fed** (n=30)	
	Mean	C.V. (%)	Mean	C.V. (%)	Mean	C.V. (%)
C_{max} (pg/mL)	2816.1	37.1	2882.8	43.6	1272.6	45.5
T_{max} (hours)[a]	0.75	(0.50 - 3.00)	0.75	(0.50 - 3.00)	4.00	(0.33 - 12.00)
AUC_{72} (pg·h/mL)	26518.8	39.5	25987.1	49.0	28201.4	42.8
AUC_{inf} (pg·h/mL)	32851.4	36.9	32444.2	45.9	36353.5	44.8
$T_{1/2}$ (hours)	34.94	31.1	35.15	39.8	35.57	41.2

[a]median (range)

Table 4.2.3-3. Statistical results of PK parameters of EE

	Test-fast	**Reference-fast**	**Test-fed**	**Statistics** (GMR [90% CI])	
	Mean (n=32)	Mean (n=32)	Mean (n=31)	**Test-fast vs Reference-fast**	**Test-fed vs fast**
C_{max} (pg/mL)	61.23	43.27	34.23	141.50 (132.22, 151.53)	55.91 (52.20, 59.88)
AUC_t (pg*hr/mL)	497.77	421.36	489.93	118.13 (112.89, 123.62)	98.42 (94.01, 103.05)
AUC_{inf} (pg*hr/mL)	531.63	460.20	528.77	115.52 (110.48, 120.80)	99.46 (95.07, 104.06)

Mean: geometric mean; GMR: geometric mean ratio; 90% CI (confidence interval)

Table 4.2.3-4. Statistical results of PK parameters of LNG

	Test-fast	**Reference-fast**	**Test-fed**	**Statistics** (GMR [90% CI])	
	Mean (n=31)	Mean (n=31)	Mean (n=30)	**Test-fast vs Reference-fast**	**Test-fed vs fast**
C_{max} (pg/mL)	2621.8	2632.7	1153.2	99.59 (89.52, 110.78)	43.99 (39.49, 49.00)
AUC_{72} (pg*hr/mL)	24589.4	23596.5	26072.8	104.21 (99.13, 109.55)	106.03 (100.79, 111.54)

AUC_{72}: AUC from 0 to 72 hours; Mean: geometric mean; GMR: geometric mean ratio; 90% CI (confidence interval)

Sponsor's conclusion:

- Based on these results, the Test product was not equivalent to the Reference product under fasting conditions because C_{max} of EE was 41.5% higher and the 90% CI of GMR was out of the no-effect boundaries of 80-125%.
- Overall, food significantly decreased peak values of EE and LNG for the Test product and also delayed the median time to peak for LNG for Test product (0.75 hours to 4.00 hours), but not the extent of absorption of either analyte.

Reviewer's comments:

- *The study was a comparative PK study to assess the bioavailability of EE and LNG using Formulation A (the initial formulation) in comparison to that of Lutera® (Reference). This study also evaluated the food effect on the PK of EE and LNG following administration of the chewable tablet. In addition, the test product was chewed and swallowed and then followed by water intake, which is different from the administration method in the other two studies, EXS-P3-239 (chewed and swallowed with water) and EXS-P3-821 (chewed and swallowed with or without water).*
- *Plasma concentrations of EE following administration (chewed and swallowed and then followed by water intake) of the initial formulation tended to be higher compared to that of Reference, especially for the absorptive phase (Figure 4.2.3-1). C_{max} and AUC values of EE were higher when the initial formulation product was chewed and swallowed at fasting compared to Reference (Table 4.2.3-1). While the 90% CI of the GMR for C_{max} of EE between the initial formulation (at fasting) and Reference was outside the range of 80% to 125%, the 90% CIs of its AUC values were within the range (Table 4.2.3-3).*
- *The PK profile of LNG appeared overlaid and the PK parameters of LNG were similar between EV402 and Reference at fasting (Figure 4.2.3-1 and Table 4.2.3-2). The 90% CIs of GMRs of the major LNG PK parameters for pairwise comparison were within the bioequivalence range (Table 4.2.3-4).*
- *A high-fat meal significantly decreased the C_{max} of EE and LNG by 44% and 56%, respectively, following administration of the initial formulation product but did not significantly affect the AUC values.*
- *Subject* (b) (6) *who had a positive pre-dose concentration (exceeding 5% of the corresponding C_{max}) in Period 2 was excluded from all statistics of the PK data. This exclusion criterion for the data analysis was described in the study protocol.*
- *While this study did not use the final to-be-marketed formulation product, the observed results in this study suggests that absorption profile of EE and LNG may be significantly affected when this chewable tablet is chewed and swallowed after a meal. It is noted that there are differences in the*

excipients between Formulation A and B (the to-be-market formulation) (Refer to 2.7.1 Summary of Biopharmaceutics Studies and Associated Analytical Methods).

4.3 References

· Alesse® Prescribing information

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/

JIHONG SHON
02/24/2020 05:14:47 PM

YANHUI LU
02/24/2020 06:30:03 PM