# Office of Clinical Pharmacology Review

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|---|---|
| **NDA or BLA Number** | 218718 |
| **Link to EDR** | \\CDSESUB1\evsprod\NDA218718\218718.enx |
| **Submission Date** | September 27, 2023 (SDN001) |
| **Submission Type** | Standard |
| **Brand Name** | FEMLYV™ |
| **Generic Name** | Norethindrone acetate and ethinyl estradiol |
| **Dosage Form and Strength** | Orally disintegrating tablets (ODTs); 24 ODTs each containing 1 mg norethindrone acetate and 20 mcg ethinyl estradiol and 4 inert ODTs |
| **Route of Administration** | Oral use |
| **Proposed Indication** | For use by females of reproductive potential to prevent pregnancy |
| **Applicant** | Millicent Puerto Rico LLC |
| **Associated IND** | IND 151441 |
| **OCP Review Team** | Dong Guo, Ph.D.; Yanhui Lu, Ph.D. |
| **OCP Final Signatory** | Yanhui Lu, Ph.D. |

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# 1. EXECUTIVE SUMMARY

FAMLYV™ (also referred to as MP0008 in this review) is a combined hormonal contraceptive for use by females of reproductive potential to prevent pregnancy. FEMLYV consists of 24 orally disintegrating tablets (ODTs) each containing 1 mg norethindrone acetate (NA) and 20 mcg ethinyl estradiol (EE), and 4 nonhormonal inert ODTs tablets. The proposed dosing regimen is take one ODT at the same time daily without regards to meals.

The Applicant is seeking approval through a 505(b)(2) regulatory pathway and has identified Minastrin® 24 Fe (24 active chewable tablets with NA 1 mg/EE 20 mcg plus 4 chewable tablets of nonhormonal tablets containing 75 mg ferrous fumarate, referred to as Minastrin tablets thereafter) as the listed drug (LD). The Applicant proposed to rely on the Agency's safety and efficacy findings of the LD.

The Applicant submitted reports of four clinical studies to support the approval of FAMLYV™: a pivotal relative bioavailability (BA) and food effect study, two supportive studies (a relative BA study and a food effect study), and an oral irritation study.

The pivotal relative BA study (MP0008-0004.0-PR) compared the systemic exposure of norethindrone (NE) and EE between the proposed product MP0008 (NA 1 mg and EE 20 mcg ODT) and the active tablet of Minastrin (NA 1 mg and EE 20 mcg) following a single dose administration under fasted condition in healthy premenopausal females. MP0008 was administered as proposed in the labeling (i.e., disintegrated in the mouth, swallowed, followed by 240 mL water) and the LD was administered using one of the recommended methods in the approved label (i.e., chewed, swallowed, followed by 240 mL water). The results demonstrated that Cmax and AUC of both NE and EE met the standard bioequivalence (BE) criteria. The study also demonstrated that administration of MP0008 with a high-fat meal reduced the absorption rate ($C_{max}$) of NE and EE (43% for NE and 47% for EE) and increased the extent (AUCs) of NE by 16% . Considering that the extent of $C_{max}$ reduction by food for the proposed product is similar to that for the LD (i.e., 51% reduction in Cmax for both NE and EE) and that the LD may be administered without regard to meals, the proposed product can be administered without regard to meal.

The Office of Study Integrity and Surveillance (OSIS) determined that inspections on the bioanalytical site and clinical site are not warranted because OSIS inspected the bioanalytical site in NON-RESPONSIVE under NDA NON-RESPONSIVE and the clinical site in December 2023 under NDA NON-RESPONSIVE OSIS concluded that data obtained from the pivotal relative BA and food effect study were reliable.

## 1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 218718 and finds this NDA acceptable from a clinical pharmacology perspective.

Key review issues with specific recommendations/comments are summarized in the table below:

| Review Issue | Recommendations and Comments |
|---|---|
| **General dosing instructions** | **Administration method:** The proposed drug achieved similar exposure parameters with the LD when disintegrated in the mouth, swallowed with saliva and followed by 240 mL water. The $C_{max}$ of EE was 42% higher when MP0008 disintegrated in the mouth and then swallowed without water compared to the LD. We recommend FEMLYV™ be administered with 240 mL water.<br>**Food effect:** A single-dose administration of MP0008 with high-fat food decreased the $C_{max}$ values of NE and EE by 43% and 47%, respectively. The magnitude of food effect on the exposure of NE and EE after MP0008 was administered with the proposed method is comparable to those in the LD label. Therefore, FAMLYV™ can be taken without regarding to meal. |
| **Other (Bridging to the listed drug, Minastrin)** | The exposure parameters between the proposed product, MP0008, and Minastrin met the standard BE criteria when MP0008 was administered with 240 mL water under fasting conditions in Study MP0008-0004.0-PR. |

## 1.2 Post-Marketing Requirements and Commitments

None.

# 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

## 2.1 Pharmacology and Clinical Pharmacokinetics (PK)

The pharmacokinetic profiles of NE and EE following a single dose of MP0008 (disintegrating in mouth, swallowed with saliva then followed by 240 mL water) are shown in Figure 1 and Figure 2, respectively, under fasting and fed conditions compared to that following a single dose of Minastrin under fasting conditions.

**Absorption:** After oral administration of a single dose of MP0008 (NA 1 mg/EE 20 mcg ODT) under fasting conditions, the $C_{max}$ of both NE and EE was attained at approximately 1.33 hours. High-fat/high-calorie food decreased the $C_{max}$ of NE and EE by 43% and 47%, respectively. High-fat food delayed the median $T_{max}$ of NE and EE approximately 2.67 hours and 0.33 hours, respectively.

**Distribution, Metabolism, and Excretion**: The Applicant proposed to rely on the FDA's previous clinical pharmacology findings of Minastrin tablets. The elimination half-lives of NE and EE following administration of the proposed product (MP0008) are approximately 10 hours and 18 hours, respectively.

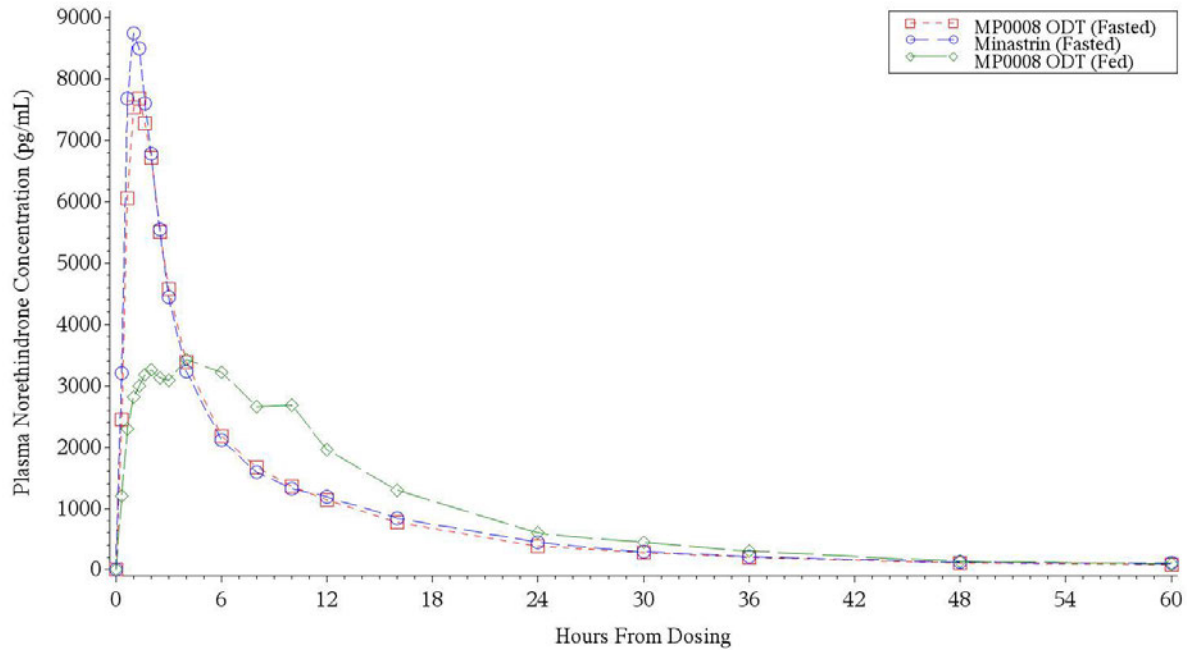


**Figure 1. Plasma Concentration-Time Profiles of Norethindrone in Healthy Female Subjects Following the Administration of MP0008 NA 1mg/EE 20 mcg ODT, Fasted and Fed (N=36), and Minastrin NA 1mg/EE 20 mcg Fasted (N = 36)**

*Source: Figure 11-1 Page 41 of the Study report for MP0008-0004.0-PR*

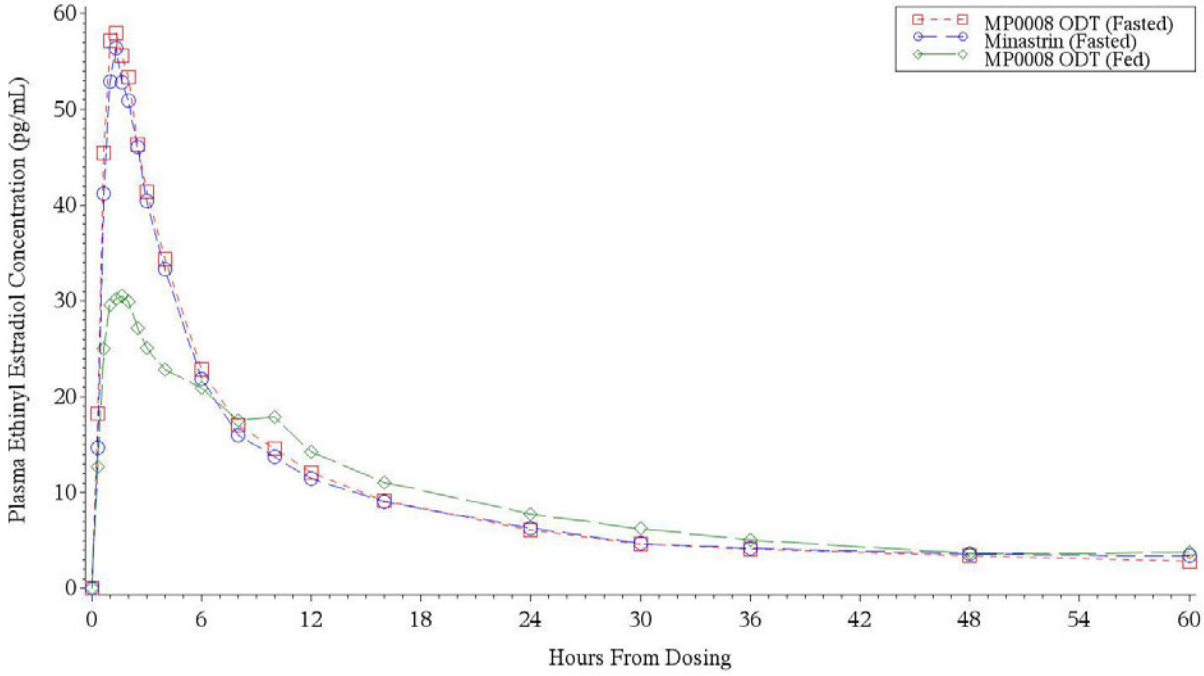


**Figure 2. Plasma Concentration-Time Profiles of Ethinyl Estradiol in Healthy Female Subjects Following the Administration of MP0008 NA 1mg/EE 20 mcg ODT, Fasted and Fed (N=36), and Minastrin NA 1mg/EE 20 mcg Fasted (N = 36)**

*Source: Figure 11-3 Page 47 of the Study report for MP0008-0004.0-PR*

## 2.2 Dosing and Therapeutic Individualization

### *2.2.1 General dosing*

Place one FEMLYV ODT on the tongue and allow to disintegrate and then follow with 8 oz. (240 mL) of water. Take at the same time daily without regards to meals. Take ODTs in the order directed on the blister pack.

### *2.2.2 Therapeutic individualization*

Not applicable.

## 2.3 Outstanding Issues

None.

## 2.4 Summary of Labeling Recommendations

Our labeling recommendations are as follows:

a. Subsection 8.6 Renal Impairment should be deleted because lack of such information is not appropriate for inclusion.
b. Replaced (b) (4) with "FEMLYV is contraindicated in females with hepatic impairment" in subsection 8.7 Hepatic Impairment to be consistent with earlier sections about Contraindications, Warnings and Precautions.
c. In subsection 12.3 Pharmacokinetics, removed (b) (4) Effect of food was reworded to make it clear that food intake doesn't have a clinically significant effect in the pharmacokinetics of FEMLYV.

# 3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

## 3.1 Overview of the Product and Regulatory Background

The Applicant has developed MP0008, an oral disintegrating tablet formulation as a contraceptive. MP0008 consists of 24 active tablets (green tablets), each containing NA 1 mg and EE 20 mcg, and 4 nonhormonal tablets (white tablets). The Applicant opened the IND on July 30, 2021 by submitting protocols of three phase 1 studies, aiming to establish a clinical bridge to Minastrin, an approved combined oral contraceptive (COC) containing 24 active tablets NA 1 mg and EE 20 mcg and 4 tablets of nonhormonal tablets containing iron.

After completing two studies (Study MP0008-0001.2-PR and Study MP0008-0002.1-PR), the Applicant requested a type C meeting with the FDA, seeking the Agency's agreement that the results of the completed studies could support a clinical bridge. The Agency didn't agree that the Applicant had demonstrated a clinical bridge for MP0008 because $C_{max}$ of EE after MP0008 was administered by disintegrating in the mouth and swallowing with saliva without water was higher than from the LD (Minastrin) (meeting minutes dated July 11, 2022). (b) (4) The FDA recommended that the Applicant reformulate the drug product if the Applicant continued to choose Minastrin as the LD.

The results of Study MP0008-0001.2-PR suggested that exposure parameters of NE and EE after MP0008 was swallowed whole with water were comparable to those of the LD. Therefore, instead of reformulating the drug product, the Applicant proposed a new comparative BA/BE Study MP0008-0004.1-PR to compare the exposure of NE and EE between the LD and MP0008 when MP0008 was administered by disintegrating in the mouth, swallow, and then follow with 240 mL of water.

## 3.2 General Pharmacology and Pharmacokinetic Characteristics

| | | | |
|---|---|---|---|
| **Pharmacology** | | | |
| **Mechanism of Action** | Lower the risk of becoming pregnant primarily by suppressing ovulation. | | |
| **Active Moieties** | Norethindrone and Ethinyl Estradiol | | |
| **General Information** | | | |
| **Bioanalysis** | A liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was used to determine norethindrone and ethinyl estradiol in human $K_2$-EDTA plasma. | | |
| **Drug exposure (Arithmatic mean (%CV))** | NE: $AUC_{0-t}$ (fasted): 50060 (48.2%) pg*h/mL,<br>$AUC_{0-t}$ (fed): 56550 (42.7%) pg*h/mL,<br>$AUC_{0-inf}$ (fasted): 51190 (49.4%) pg*h/mL,<br>$AUC_{0-inf}$ (fed): 57870 (43.9%) pg*h/mL,<br>$C_{max}$ (fasted): 8438 (33.5%) pg/mL,<br>$C_{max}$ (fed): 4849 (37.8%) pg/mL.<br>EE: $AUC_{0-t}$ (fasted): 505.1 (24.5%) pg*h/mL,<br>$AUC_{0-t}$ (fed): 488.0 (29.1%) pg*h/mL,<br>$AUC_{0-inf}$ (fasted): 595.6 (24.3%) pg*h/mL,<br>$AUC_{0-inf}$ (fed): 575.3 (27.0%) pg*h/mL,<br>$C_{max}$ (fasted): 62.8 (24.6%) pg/mL,<br>$C_{max}$ (fed): 33.8 (29.5%) pg/mL. | | |
| **Maximally tolerated dose or exposure** | Maximally tolerated dose was not established. | | |
| **Absorption** | | | |
| **Bioavailability** | The Applicant will rely on the FDA's previous clinical pharmacology findings of Minastrin® tablets. | | |
| **$T_{max}$ [Median (range)]** | NE: $T_{max}$ (fasted): 1.33 (0.66 – 2.50) h, $T_{max}$ (fed): 4.00 (0.67 – 10.01) h<br>EE: $T_{max}$ (fasted): 1.33 (0.67 – 2.03) h, $T_{max}$ (fed): 1.66 (0.67 – 6.01) h | | |
| **Food effect (Geometric least square mean ratio (%) of Fed/fasted [90% CI])** | **Active Moiety** | **$AUC_{0-inf}$** | **$C_{max}$** |
| | NE (N = 36) | 115. 8 (109.9 – 122.1) | 57.3 (53.7 – 61.2%) |
| | EE (N = 36) | 96.6 (92.4 – 101.0) | 53.3 (50.0 – 56.9%) |
| **Distribution** | | | |
| **Volume of distribution** | The Applicant will rely on the FDA's previous clinical pharmacology findings of Minastrin® tablets. | | |
| **Elimination** | | | |
| **Terminal elimination half-life (mean ± SD)** | NE: $T_{1/2}$ (fasted): 10.25 ± 2.67 h, $T_{1/2}$ (fed): 9.76 ± 2.49 h<br>EE: $T_{1/2}$ (fasted): 18.02 ± 6.03 h, $T_{1/2}$ (fed): 17.29 ± 4.93 h | | |
| **Metabolism and Excretion** | | | |
| **Primary metabolic and excretion pathway(s)** | The Applicant will rely on the FDA's previous clinical pharmacology finding of Minastrin® tablets. | | |

## 3.3 Clinical Pharmacology Review Questions

### *3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of safety and effectiveness?*

The relative bioavailability Study MP0008-0004.0-PR established BE between MP0008 and Minastrin® tablet, which established a PK-based bridge to rely on the Agency's findings of the LD from the clinical pharmacology's perspective.

Study MP0008-0004.0-PR was a an open-label, randomized, 3-period, 3-way cross-over comparative bioavailability study conducted in healthy female subjects. As shown in Table 1, Test (MP0008) to Reference (Minastrin® tablet) ratios of geometric means and corresponding 90% confidence intervals (CIs) for $C_{max}$, $AUC_{0-t}$ and $AUC_{0-inf}$ of NE and EE were all within the acceptance range of 80.00% to 125.00%, indicating that the MP0008 is bioequivalent to Minastrin under fasting condition.

**Table 1. Relative Bioavailability of MP0008 vs Minastrin Tablet Under Fasting Condition (Study MP0008-0004.0-PR)**

| Parameter | Least Squares Geometric Means | | % Test/Reference Ratio (90% CI) |
|---|---|---|---|
| | MP0008 [Test] N = 36 | Minastrin [Reference] N = 36 | |
| **Norethindrone** | | | |
| **$C_{max}$ (pg/mL)** | 8016 | 9205 | 87.08 (81.59 – 92.93) |
| **$AUC_{0-t}$ (pg•h/mL)** | 45100 | 47960 | 94.04 (90.02 – 98.24) |
| **$AUC_{0-inf}$ (pg•h/mL)** | 46030 | 49470 | 93.05 (88.27 – 98.09) |
| **$T_{max}$ (h)*** | 1.33 (0.66 - 2.50) | 1.01 (0.66 - 2.53) | N.A. |
| **Ethinyl Estradiol** | | | |
| **$C_{max}$ (pg/mL)** | 61.09 | 57.63 | 106.00 (99.26 – 113.20) |
| **$AUC_{0-t}$ (pg•h/mL)** | 491.1 | 467.0 | 105.15 (101.33 – 109.12) |
| **$AUC_{0-inf}$ (pg•h/mL)$** | 577.6 | 550.6 | 104.90 (100.27 – 109.75) |
| **$T_{max}$ (h)*** | 1.33 (0.67 – 2.03) | 1.33 (0.99 – 2.02) | N.A. |

*Source: Table 11-2,11-3, 11-5, 11-6 of Study report for MP0008-0004.0-PR.*
*Median (range) values are presented. $N = 35 for both test and reference product. N.A. = not applicable

### *3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?*

Yes, the dosing regimen proposed for MP0008 is the same as that of the LD, Minastrin® 24 Fe tablets.

### *3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?*

Yes, MP0008 is contraindicated in females who are known to have or develop liver tumors, benign or malignant, or hepatic impairment. Steroid hormones may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. This recommendation is the same as that of Minastrin® 24 Fe tablets.

### *3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?*

No.

High-fat food decreased the $C_{max}$ of NE and EE for MP0008 to a comparable magnitude as those for Minastrin. The LD can be administered without regarding to meal. Therefore, MP0008 can be taken without regarding to meal.

The Applicant assessed the effect of a high-fat meal on the pharmacokinetics of NE and EE in Study MP0008-0004.0-PR. High-fat food decreased the $C_{max}$ of NE and EE by 43% and 47%, respectively, and increased the AUC of NE by approximately 16% (Table 2). High-fat food delayed the $T_{max}$ of NE and EE approximately 2.67 hours and 0.33 hours, respectively. The food effect on the PK of NE and EE described in the label of the LD, Minastrin 24 Fe tablets, is "A single-dose administration of norethindrone acetate/ethinyl estradiol tablets with food decreased the maximum concentration of norethindrone by 51% and increased the extent of absorption by 15% and decreased the maximum concentration of ethinyl estradiol by 51% but not the extent of absorption". The magnitude of changes in PK parameters of NE and EE caused by food for the proposed product are comparable to that for the LD. Considering that the LD can be administrated without regarding to meal,the Applicant's proposal that MP0008 can be taken without regarding to meal is reasonable.

**Table 2. The Effect of Food Intake on the Pharmacokinetics of Norethindrone and Ethinyl Estradiol (Study MP0008-0004.0-PR)**

| Parameter | Least Squares Geometric Means | | % Test/Reference Ratio (90% CI) |
|---|---|---|---|
| | Fed [Test] (N=36) | Fasted [Reference] (N=36) | |
| **Norethindrone** | | | |
| **$C_{max}$ (pg/mL)** | 4596 | 8016 | 57.34 (53.73 – 61.19) |
| **$AUC_{0-t}$ (pg•h/mL)** | 52220 | 45100 | 115.79 (110.84 – 120.96) |
| **$AUC_{0-inf}$ (pg•h/mL)** | 53310 | 46030 | 115.82 (109.87 – 122.10) |
| **$T_{max}$ (h)*** | 4.00 (0.67 – 10.01) | 1.33 (0.66 - 2.50) | N.A. |
| **Ethinyl Estradiol** | | | |
| **$C_{max}$ (pg/mL)** | 32.57 | 61.09 | 53.32 (49.93 – 56.94) |
| **$AUC_{0-t}$ (pg•h/mL)** | 470.0 | 491.1 | 95.70 (92.22-99.32) |
| **$AUC_{0-inf}$ (pg•h/mL)$** | 557.8 | 577.6 | 96.57 (92.35 – 100.98) |
| **$T_{max}$ (h)*** | 1.66 (0.67 – 6.01) | 1.33 (0.67 – 2.03) | N.A. |

*Source: Table 11-2,11-4, 11-6, 11-7 of Study report for MP0008-0004.0-PR.*
**Median (range) values are presented. $N=35 for fasted condition. N.A. = not applicable*

### *3.3.5 Does pharmacokinetic data bridge the proposed to-be-marketed product to listed drug(s) or Phase 3 trial formulation?*

Yes, formulations of MP0008 tested in Study MP0008-0004.0-PR, Study MP0008-0002.1-PR and study MP0008-0001.2-PR are identical to the to-be-marketed product.

# 4. APPENDICES

## 4.1 Summary of Bioanalytical Method Validation and Performance

*Assays for NE and EE:*

LC-MS/MS methods were developed and validated for quantitative analysis of NE and EE in human plasma samples. Blood samples were collected in $K_2$EDTA tubes. The validation reports for each method and analytical study reports for pivotal Study MP0008-0004.0-PR, supportive study MP0008-0001.2-PR were submitted. The bioanalytical method validation data for NE and EE are summarized in Table 3 and Table 4, respectively. The established long-term storage stability (621 days for EE and 375 days for NE at -20°C) covered the sample storage time after sample collection (126 days at -20°C for study MP0008-0004.0-PR and 125 days at -20°C for study MP0008-0001.2-PR). The bioanalytical method validation results for NE and EE are acceptable.

**Table 3. Bioanalytical Method Validation for Norethindrone**

| Information Requested | Data |
|---|---|
| **Bioanalytical method validation report location** | N-X-BIO-21-004<br>Module 5.3.1.4 |
| **Analyte** | Norethindrone |
| **Internal standard (IS)** | [$^2$H6]norethindrone |
| **Method description** | Solid-phase; Reversed-phase HPLC with MS/MS detection |
| **Lower Limit of quantitation** | 25 pg/mL |
| **Average recovery of drug (%)** | 75.7% (range: 71.0% to 79.2% ) |
| **Average recovery of IS (%)** | 66.3% |
| **Standard curve concentrations** | 25 pg/mL to 25000 pg/mL. |
| **Quality Control (QC) concentrations** | 25 pg/mL(LLOQ QC), 75 pg/Ml (low QC), 12500 pg/mL (mid QC), 20000 pg/mL (high QC). |
| **QC Intraday precision range (%)** | 0.8% - 8.9% |
| **QC Intraday accuracy range (%)** | 100.6% - 112.2% |
| **QC Interday precision range (%)** | 1.6% - 6.7% |
| **QC Interday accuracy range (%)** | 99.2% - 109.6% |
| **Bench-top stability (hrs)** | 24 hours at ambient temperature |
| **Stock stability (days)** | 24 hours at ambient temperature;<br>up to 85 days for low to high QC at 5°C nominal;<br>up to 47 days for low to high QC at 5°C nominal. |
| **Autosampler stability (hrs)** | 179 hours at 10°C nominal. |
| **Freeze-thaw stability (cycles)** | 4 cycles |
| **Long-term storage stability (days)** | 375 days at -20°C nominal. |
| **Dilution integrity** | 200000 pg/mL diluted 10-fold. |
| **Selectivity** | No significant interference in the 10 blank matrix lots. |

*Source: Table 1 of validation report for N-X-bio-21-004 and N-X-bio-21-001_AMD01*

**Table 4. Bioanalytical Method Validation for Ethinyl Estradiol**

| Information Requested | Data |
|---|---|
| **Bioanalytical method validation report location** | N-X-BIO-21-004<br>Module 5.3.1.4 |
| **Analyte** | Ethinyl estradiol |
| **Internal standard (IS)** | [²H7]ethinyl estradiol |
| **Method description** | Solid-phase<br>Reversed-phase HPLC with MS/MS detection |
| **Limit of quantitation** | 2.5 pg/mL |
| **Average recovery of drug (%)** | 99.5% (range: 85.3% to111.2%) |
| **Average recovery of IS (%)** | 76.8 % |
| **Standard curve concentrations** | 2.5 pg/mL to 250 pg/mL. |
| **QC concentrations** | 2.5 pg/mL (LLOQ QC), 7.5 pg/mL (low QC), 125 pg/mL (mid QC), 200 pg/mL (high QC). |
| **QC Intraday precision range (%)** | 2.6% - 4.2% |
| **QC Intraday accuracy range (%)** | 94.0% - 103.6% |
| **QC Interday precision range (%)** | 3.1% - 8.0% |
| **QC Interday accuracy range (%)** | 97.0% - 101.0% |
| **Bench-top stability (hrs)** | 24 hours at ambient temperature |
| **Stock stability (days)** | 24 hours at ambient temperature;<br>up to 79 days for low to high QC at 5°C nominal;<br>up to 41 days for low to high QC at 5°C nominal. |
| **Processed stability (hrs)** | 179 hours at 10°C nominal. |
| **Freeze-thaw stability (cycles)** | 4 cycles |
| **Long-term storage stability (days)** | 621 days at -20°C nominal. |
| **Dilution integrity** | 2000 pg/mL diluted 10-fold. |
| **Selectivity** | No significant interference observed in the 6 blank matrix lots screened. |

*Source: Table 1 of validation report for N-X-bio-21-004 and N-X-bio-15-009_AMD01*

## 4.2 BA/BE Assessments

The Applicant conducted a pivotal comparative BA/BE study (Study MP0008-0004.0-PR), a supportive comparative BA/BE study (Study MP0008-0001.2-PR), and one pilot food effect study (Study MP0008-0002.1-PR) in healthy female subjects (Table 5).

The pivotal Study MP0008-0004.0-PR was conducted to establish a bridge between MP0008 and the LD, Minastrin tablet under fasting conditions and to evaluate the food effect on the pharmacokinetics of MP0008 when MP0008 was administered by disintegrating in the mouth, swallowing with saliva and followed by 240 mL water.

Study MP0008-0001.2-PR was a supportive study that compared the exposure of NE and EE between the LD and MP0008 when MP0008 disintegrated in the mouth and was swallowed without water , and whenMP0008 was swallowed whole with water. Because the administration method for MP0008 in this study was not the same as the proposed administration method for labeling, Study MP0008-0001.2-PR was reviewed as supportive evidence.

Study MP0008-0002.1-PR was a pilot food effect study that explored the food effect on the pharmacokinetics of NE and EE when MP0008 was administered by disintegrating in the mouth and swallowing with saliva without water. Also because the administration method for MP0008 in this study was not the same as the proposed administration method for labeling, Study MP0008-0002.1-PR was not fully reviewed.

**Table 5. List of Clinical Studies Submitted.**

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design | Test Product(s); Dosage Regimen; Route of Administration | N | Subjects | Duration of Treatment |
|---|---|---|---|---|---|---|---|
| BA/BE and food effect | MP0008-0004.0-PR | BE in terms of rate and extent of NE and EE absorption in fasting conditions between Test and Reference. Food Effect in terms of rate and extent of NE and EE absorption when Test was taken with and without food. | 3-treatment, 3-period, 6-sequence, crossover | Treatment A: MP0008 disintegrated in mouth, swallow with saliva, then follow with 240 mL water, after an overnight fast. Treatment B: Minastrin® tablet chewed, swallowed followed by 240 mL water after an overnight fast. Treatment C: MP0008 30 minutes after the start of a high-fat/high-calorie meal. | 36 | Healthy premenopausal female | Single dose |
| BA/BE | MP0008-0001.2-PR | BE in terms of rate and extent of NE and EE absorption in fasting conditions between Test and Reference. | 3-treatment, 3-period, 6-sequence, crossover | Treatment A: MP0008 disintegrated in mouth, swallow with saliva without water, after an overnight fast. Treatment B: Minastrin® tablet chewed, swallowed followed by 240 mL water after an overnight fast. Treatment C: MP0008 swallow whole, after an overnight fast. | 35 | Healthy premenopausal female | Single dose |
| Pilot food effect | MP0008-0002.1-PR | To compare rate and extent of sildenafil absorption between the test product administered by the supralingual and sublingual routes. | 2-treatment, 2-period, 2-sequence, crossover | Treatment A: MP0008 disintegrated in mouth, swallow with saliva without water, after overnight fast. Treatment B: MP0008 disintegrated in mouth, swallow with saliva without water after start of a high-fat/high-calorie meal | 23 | Healthy premenopausal female | Single dose |

*Source: Section 5.2 Tabular Listing of All Clinical Studies*

### *4.2.1 Study MP0008-0004.0-PR*

**Title**: An Open-Label, Randomized, 3-Period, 3-Way Crossover Study to Compare the Pharmacokinetics of Norethindrone (NE) and Ethinyl Estradiol (EE) Administered as an MP0008 Orally Disintegrating Tablet and Minastrin® 24 Fe Chewable Tablet and to Evaluate the Effect of a High-Fat/High-Calorie Meal on the Pharmacokinetics of NE and EE in Healthy Female Subjects

**Study Objectives**:

- To compare the single dose PK of NE and EE after administration of an MP0008 tablet and Minastrin® 24 (Minastrin) chewable tablet, under fasting conditions, in healthy adult female subjects.
- To evaluate the effect of a high-fat/high-calorie meal on the single dose PK of NE and EE administered as an MP0008 in healthy adult female subjects.

**Study design:**
This was a single-center, open-label, randomized, 3-period, 6-sequence, 3-way crossover, relative bioavailability study under fasting and fed conditions.
A single oral dose of one of the following 3 treatments was administered in each study period with a 7-day washout period according to the randomization scheme:

**Treatment A**: MP0008 NA 1 mg/EE 20 mcg ODT disintegrated in the mouth, swallowed by saliva and followed by 240 mL water under fasting condition

**Treatment B**: Minastrin NA 1 mg/EE 20 mcg chewable tablet chewed, swallowed and followed by 240 mL water under fasting condition.

**Treatment C**: MP0008 NA 1 mg/EE 20 mcg ODT disintegrated in the mouth, swallowed by saliva and followed by 240 mL water under fed condition (30 minutes after the start of a high-fat/high-calorie meal).

In each study period, 20 blood samples for PK measurements were collected prior to drug administration and at 0.333, 0.667, 1.00, 1.333, 1.667, 2.00, 2.5, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 30.00, 36.00, 48.00, 60.00 hours following drug administration. Blood samples were processed to plasma and analyzed for NE and EE using LC-MS/MS methods.

**Results**:

Comparative Bioavailability under fasting conditions (Treatment A vs Treatment B):
The plasma PK parameter values of NE and EE by treatment (N=36) are presented in Table 6 and Table 7, respectively. As shown in Table 1 (Section 3.3.1), the Test (MP0008) to Reference (Minastrin tablet) ratio of geometric means and corresponding 90% CIs for $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ of NE and EE were all within the acceptance range of 80.00% to 125.00%.

Food Effect Assessment (Treatment C vs Treatment A):
High-fat food decreased the $C_{max}$ of NE by 43%, increased the extent of absorption (AUC) of NE by 16%, and decreased the $C_{max}$ of EE by 47%. Food did not affect the extent of absorption of EE (Section 3.3.4, Table 2). High-fat food delayed the $T_{max}$ of NE and EE approximately 2.67 hours (from 1.33 hours to 4.00 hours) and 0.33 hours (from 1.33 hours to 1.66 hours), respectively.

**Table 6. Summary of Plasma Norethindrone Pharmacokinetic Parameters Following the Administration of MP0008, Fasted and Fed, and Minastrin Fasted (Study MP0008-0004.0-PR)**

| **Pharmacokinetic Parameters** | **Treatment A** (n=36) | **Treatment B** (n=36) | **Treatment C** (n=36) |
|---|---|---|---|
| $AUC_{0-t}$ (pg*hr/mL) | 45100 (48.7) | 47960 (43.3) | 52220 (41.6) |
| $AUC_{0-inf}$ (pg*hr/mL) | 46030 (48.9) | 49470 (46.6) | 53310 (42.1) |
| AUC%extrap (%) | 2.013 ± 1.7148 | 2.871 ± 5.4894 | 2.037 ± 1.8046 |
| $C_{max}$ (pg/mL) | 8016 (32.9) | 9205 (32.4) | 4596 (32.6) |
| $T_{max}$ (hr) | 1.332 (0.66, 2.50) | 1.008 (0.66, 2.53) | 4.001 (0.67, 10.01) |
| $K_{el}$ (1/hr) | 0.072 ± 0.018 | 0.075 ± 0.024 | 0.076 ± 0.020 |
| $t_{½}$ (hr) | 10.251 ± 2.6723 | 11.648 ± 11.6028 | 9.757 ± 2.4938 |
| CL/F (L/hr) | 21.07 ± 9.5596 | 19.31 ± 7.5211 | 17.74 ± 6.9016 |
| Vz/F (L) | 304.0 ± 138.05 | 281.5 ± 125.79 | 245.1 ± 104.08 |

Treatment A: MP0008 NA 1 mg/EE 20 mcg ODT, disintegrated in mouth swallowed with saliva and followed by 240 mL water after an overnight fast.
Treatment B: Minastrin NA 1 mg/EE 20 mcg chewable tablet, chewed, swallowed and followed by 240 mL water after an overnight fast.
Treatment C: MP0008 NA 1 mg/EE 20 mcg ODT, disintegrated in mouth swallowed with saliva and followed by 240 mL water 30 minutes after the start of a high-fat/high-calorie meal.
AUCs and Cmax values are presented as geometric mean and CV%. $T_{max}$ are presented as median (minimum, maximum).
Other parameters are presented as arithmetic mean ± SD.
Source: Table 11-2 page 44 of Study MP0008-0004.0-PR report.

**Table 7. Summary of Plasma Ethinyl Estradiol Pharmacokinetic Parameters Following the Administration of MP0008 Fasted and Fed, and Minastrin Fasted (Study MP0008-0004.0-PR)**

| Pharmacokinetic Parameters | Treatment A | Treatment B | Treatment C |
|---|---|---|---|
| $AUC_{0-t}$ (pg*hr/mL) | 491.1 (24.4) [n=36] | 467.0 (27.2) [n=36] | 470.0 (28.0) [n=36] |
| $AUC_{0-inf}$ (pg*hr/mL) | 579.7 (23.7) [n=35] | 552.5 (29.3) [n=35] | 557.8 (25.0) [n=36] |
| AUC%extrap (%) | 14.63 ± 5.08 [n=35] | 14.81 ± 7.77 [n=35] | 15.55 ± 5.63 [n=36] |
| $C_{max}$ (pg/mL) | 61.09 (24.4) [n=36] | 57.63 (20.8) [n=36] | 32.57 (26.9) [n=36] |
| $T_{max}$ (hr) | 1.333 (0.67, 2.03) [n=36] | 1.330 (0.99, 2.02) [n=36] | 1.663 (0.67, 6.01) [n=36] |
| $K_{el}$ (1/hr) | 0.042 ± 0.012 [n=35] | 0.048 ± 0.017 [n=35] | 0.043 ± 0.011 [n=36] |
| $t_{½}$ (hr) | 18.020 ± 6.0338 [n=35] | 17.420 ± 11.4916 [n=35] | 17.285 ± 4.9335 [n=36] |
| CL/F (L/hr) | 35.41 ± 8.1096 [n=35] | 37.63 ± 10.508 [n=35] | 36.89 ± 8.7790 [n=36] |
| Vz/F (L) | 896.9 ± 312.93 [n=35] | 860.2 ± 313.98 [n=35] | 901.6 ± 295.82 [n=36] |

Treatment A: MP0008 NA 1 mg/EE 20 mcg ODT, disintegrated in mouth swallowed with saliva and followed by 240 mL water after an overnight fast.
Treatment B: Minastrin NA 1 mg/EE 20 mcg chewable tablet, chewed, swallowed and followed by 240 mL water after an overnight fast.
Treatment C: MP0008 NA 1 mg/EE 20 mcg ODT, disintegrated in mouth swallowed with saliva and followed by 240 mL water 30 minutes after the start of a high-fat/high-calorie meal.
AUCs and Cmax values are presented as geometric mean and CV%.
$T_{max}$ are presented as median (minimum, maximum).
Other parameters are presented as arithmetic mean ± SD.
Source: Table 11-5 page 50 of Study MP0008-0004.0-PR report.

*Reviewer's Comments*

- *The Applicant's analysis excluded subject 3 treatment B and subject 11 treatment A for EE PK and statistical analysis since the λz interval could not be assigned. Slope-dependent parameters (t½, AUC0-inf, AUC%extrap, CL/F, and Vz/F) were missing for these two subjects.*
- *There was a numerical difference in the PK parameters between the Applicant's analysis and FDA reviewer's independent analysis due to exclusion of two EE $AUC_{0-inf}$ values in Applicant's analysis and using different algorithm on AUCs calculation but both analyses found that the exposure parameters ($C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$) for NE and EE of Test (MP0008) to Reference (Minastrin tablet) met BE criteria.*
- *High-fat food delayed the absorption of NE, decreased the rate of NE and EE,increased the extent of absorption of NE for MP0008.The magnitude of changes is similar to that of the reference product (Minastrin tablet). Minastrin tablet can be taken without regarding to meal. Therefore, it is reasonable to administer MP0008 without regarding to food.*

### *4.2.2 Study MP0008-0001.2-PR*

**Title**: An Open-Label, Randomized, 3-Way Crossover Study in Healthy Adult Female Subjects to Evaluate the Relative Bioavailability of Norethindrone Acetate (NA) and Ethinyl Estradiol (EE) Administered from an Orally Disintegrating Tablet (MP0008) With and Without Water and Minastrin® 24 Fe Tablet

**Study Objectives**:

- To compare the bioavailability of NE and EE from MP0008 administered without water to Minastrin in healthy adult female subjects..
- To evaluate the effect of water consumption on the bioavailability of NE and EE from MP0008 in healthy adult female subjects.

**Study design:**

This was a single-center, open-label, randomized, 3-way crossover relative bioavailability study under fasting conditions.

A single oral dose of one of the following 3 treatments was administered in each study period with a 7-day washout period according to the randomization scheme:

**Treatment A**: MP0008 NA 1 mg/EE 20 mcg ODT disintegrated in the mouth, swallowed by saliva without water under fasting condition.

**Treatment B**: MP0008 NA 1 mg/EE 20 mcg ODT swallowed whole with 240 mL water under fasting condition.

**Treatment C**: Minastrin NA 1 mg/EE 20 mcg tablet chewed, swallowed and followed by 240 mL water under fasting condition.

In each study period, 20 blood samples for pharmacokinetic measurements were collected prior to drug administration and at 0.333, 0.667, 1.00, 1.333, 1.667, 2.00, 2.5, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 30.00, 36.00, 48.00, 60.00 hours following drug administration. Blood samples were processed to plasma and analyzed for NE and EE using LC-MS/MS methods.

**Results**:

NE PK comparison (Table 8 to Table 11):

As summarized in Table 8, $C_{max}$ and AUCs of NE were similar following the administration of MP0008 (disintegrated in the mouth and swallow without water, treatment A), MP0008 (swallowed whole with water, treatment B), and Minastrin tablet (with water, treatment C). Likewise, median $T_{max}$ values ( approximately 1.3 hours) were similar among the 3 treatments.

**Table 8. Summary of Plasma Norethindrone Pharmacokinetic Parameters Following the Administration of MP0008 NA 1 mg/EE 20 mcg ODT, with and without water, and Minastrin NA 1mg/EE 20 mcg Fasted (Study MP0001-0001.2-PR)**

| **Pharmacokinetic Parameters** | **Treatment A (n=37)** | **Treatment B (n=39)** | **Treatment C (n=38)** |
|---|---|---|---|
| $AUC_{0-t}$ (pg*hr/mL) | 48000 (49.7) | 45460 (45.6) | 47000 (50.8) |
| $AUC_{0-inf}$ (pg*hr/mL) | 49050 (49.2) | 46340 (45.1) | 48060 (50.3) |
| AUC%extrap (%) | 2.135 ± 1.565 | 1.875 ± 1.472 | 2.192 ± 1.430 |
| $C_{max}$ (pg/mL) | 8809 (41.0) | 7694 (29.0) | 8377 (43.2) |
| $T_{max}$ (hr) | 1.332 (0.66, 2.52) | 1.333 (0.68, 4.00) | 1.328 (0.66, 4.00) |
| $K_{el}$ (1/hr) | 0.070 ± 0.019 | 0.071 ± 0.018 | 0.068 ± 0.015 |
| $t_{½}$ (hr) | 10.555 ± 2.732 | 10.358 ± 2.579 | 10.776 ± 2.566 |
| CL/F (L/hr) | 19.95 ± 10.407 | 20.87 ± 11.085 | 20.50 ± 11.381 |
| Vz/F (L) | 302.0 ± 191.37 | 318.8 ± 234.96 | 312.9 ± 169.10 |

Treatment A: MP0008 NA 1 mg/EE 20 mcg ODT disintegrated in the mouth, swallowed by saliva without water under fasting condition.
Treatment B: MP0008 NA 1 mg/EE 20 mcg ODT swallowed whole with 240 mL water under fasting condition.
Treatment C: Minastrin NA 1 mg/EE 20 mcg tablet chewed, swallowed and followed by 240 mL water under fasting condition.
AUCs and Cmax values are presented as geometric mean and CV%.
Tmax are presented as median (minimum, maximum).
Other parameters are presented as arithmetic mean ± SD.
Source: Table 11-2 page 44 of Study MP0008-0001.2-PR report.

**Table 9. Statistical Comparisons of Plasma Norethindrone Pharmacokinetic Parameters Following MP0008 Without Water Versus Minastrin (Study MP0008-0001.2-PR)**

| Parameter | Treatment A (Test) | | Treatment C (Reference) | | GMR(%) | 90% Confidence Interval |
|---|---|---|---|---|---|---|
| | Geometric Least Square Mean | n | Geometric Least Square Mean | n | | |
| $AUC_{0-t}$ (pg*hr/mL) | 48877 | 37 | 47618 | 38 | 102.64 | 97.81 - 107.72 |
| $AUC_{0-inf}$ (pg*hr/mL) | 49933 | 37 | 48660 | 38 | 102.62 | 97.85 - 107.61 |
| $C_{max}$ (pg/mL) | 8972 | 37 | 8531 | 38 | 105.17 | 98.42 - 112.39 |

Treatment A: MP0008 NA 1 mg/EE 20 mcg ODT disintegrated in the mouth, swallowed by saliva without water
Treatment C: Minastrin NA 1 mg/EE 20 mcgtablet chewed, swallowed and followed by 240 mL water
Source: Table 11-3 page 44 of Study MP0008-0001.2-PR report

**Table 10. Statistical Comparisons of Plasma Norethindrone Pharmacokinetic Parameters Following MP0008 Swallowed Whole With Water Versus MP0008 Disintegrated in the Mouth Swallowed Without Water (Study MP0008-0001.2-PR)**

| Parameter | Treatment B (Test) | | Treatment A (Reference) | | GMR(%) | 90% Confidence Interval |
|---|---|---|---|---|---|---|
| | Geometric Least Square Mean | n | Geometric Least Square Mean | n | | |
| $AUC_{0-t}$ (pg*hr/mL) | 46201 | 39 | 48877 | 37 | 94.52 | 90.15 - 99.11 |
| $AUC_{0-inf}$ (pg*hr/mL) | 47081 | 39 | 49933 | 37 | 94.29 | 89.99 - 98.79 |
| $C_{max}$ (pg/mL) | 7792 | 39 | 8972 | 37 | 86.95 | 81.36 - 92.70 |

Treatment A: MP0008 NA 1 mg/EE 20 mcg ODT disintegrated in the mouth, swallowed by saliva without water
Treatment B: MP0008 NA 1 mg/EE 20 mcg ODT swallowed whole with 240 mL water
Source: Table 11-4 page 46 of Study MP0008-0001.2-PR report

**Table 11. Statistical Comparisons of Plasma Norethindrone Pharmacokinetic Parameters Following MP0008 swallowed whole with water versus Minastrin (Study MP0008-0001.2-PR)**

| Parameter | Treatment B (Test) | | Treatment C (Reference) | | GMR(%) | 90% Confidence Interval |
|---|---|---|---|---|---|---|
| | Geometric Least Square Mean | n | Geometric Least Square Mean | n | | |
| $AUC_{0-t}$ (pg*hr/mL) | 46201 | 39 | 47618 | 38 | 97.02 | 93.53 – 100.65 |
| $AUC_{0-inf}$ (pg*hr/mL) | 47081 | 39 | 48660 | 38 | 96.75 | 93.32 – 100.31 |
| $C_{max}$ (pg/mL) | 7792 | 39 | 8531 | 38 | 91.34 | 86.85 – 96.07 |

Treatment B: MP0008 NA 1 mg/EE 20 mcg ODT swallowed whole with 240 mL water.
Treatment C: Minastrin NA 1 mg/EE 20 mcg tablet chewed, swallowed and followed by 240 mL water (reference)
Source: Reviewers' analysis using PK parameters generated by the Applicant

EE PK comparison (Table 12 to Table 15):

When MP0008 was administered by disintegrating in the mouth, swallowing with saliva without water, $C_{max}$ and AUCs of EE were 17% to 43% higher than those after Minastrin tablet was administered with water. The $C_{max}$ and AUCs of EE following the MP0008 swallowed whole with water was 18% to 38% lower compared to MP0008 administered without water.

**Table 12. Summary of Plasma Ethinyl Estradiol Pharmacokinetic Parameters Following the Administration of MP0008, Integrated in the Mouth Swallowed without Water and Swallowed Whole with Water, and Minastrin (Study MP0001-0001.2-PR)**

| Pharmacokinetic Parameters | Treatment A | Treatment B | Treatment C |
|---|---|---|---|
| $AUC_{0-t}$ (pg*hr/mL) | 603.0 (23.3) [n=37] | 474.7 (25.0) [n=39] | 502.3 (25.4) [n=38] |
| $AUC_{0-inf}$ (pg*hr/mL) | 690.5 (20.2) [n=37] | 574.2 (23.3) [n=38] | 596.8 (23.0) [n=37] |
| AUC%extrap (%) | 12.55 ± 4.37 [n=37] | 17.14 ± 6.68 [n=38] | 14.93 ± 5.50 [n=37] |
| $C_{max}$ (pg/mL) | 79.04 (24.2) [n=37] | 49.72 (28.8) [n=39] | 55.55 (25.7) [n=38] |
| $T_{max}$ (hr) | 1.325 (0.66, 3.22) [n=37] | 1.335 (0.67, 3.06) [n=39] | 1.336 (0.67, 2.50) [n=38] |
| $K_{el}$ (1/hr) | 0.043 ± 0.010 [n=37] | 0.040 ± 0.012 [n=38] | 0.042 ± 0.011 [n=37] |
| $t_{½}$ (hr) | 17.094 ± 4.563 [n=37] | 19.330 ± 6.632 [n=38] | 17.788 ± 5.136 [n=37] |
| CL/F (L/hr) | 29.55 ± 6.22 [n=37] | 35.74 ± 8.26 [n=38] | 34.34 ± 7.53 [n=37] |
| Vz/F (L) | 720.0 ± 204.05 [n=37] | 974.3 ± 336.01 [n=38] | 861.5 ± 261.28 [n=37] |

Treatment A: MP0008 NA 1 mg/EE 20 mcg ODT disintegrated in the mouth, swallowed by saliva without water under fasting condition
Treatment B: MP0008 NA 1 mg/EE 20 mcg ODT swallowed whole with 240 mL water under fasting condition.
Treatment C: Minastrin NA 1 mg/EE 20 mcg tablet chewed, swallowed and followed by 240 mL water under fasting condition.
AUCs and $C_{max}$ values are presented as geometric mean and CV%.
Tmax are presented as median (minimum, maximum).
Other parameters are presented as arithmetic mean ± SD.
Source: Table 11-5 page 51 of Study MP0008-0001.2-PR report.

**Table 13. Statistical Comparisons of Plasma Ethinyl Estradiol Pharmacokinetic Parameters Following MP0008 Disintegrated in the Mouth Swallowed Without Water Versus Minastrin (Study MP0008-0001.2-PR)**

| Parameter | Treatment A (Test) | | Treatment C (Reference) | | GMR(%) | 90% Confidence Interval |
|---|---|---|---|---|---|---|
| | Geometric Least Square Mean | n | Geometric Least Square Mean | n | | |
| $AUC_{0-t}$ (pg*hr/mL) | 614.90 | 37 | 507.92 | 38 | 121.06 | 116.71 - 125.57 |
| $AUC_{0-inf}$ (pg*hr/mL) | 703.30 | 37 | 598.60 | 37 | 117.49 | 113.11 - 122.04 |
| $C_{max}$ (pg/mL) | 80.12 | 37 | 56.12 | 38 | 142.77 | 135.13 - 150.83 |

Treatment A: MP0008 NA 1 mg/EE 20 mcg ODT disintegrated in the mouth, swallowed by saliva without water
Treatment C: Minastrin NA 1 mg/EE 20 mcg tablet chewed, swallowed and followed by 240 mL water
Source: Table 11-6 page 53 of Study MP0008-0001.2-PR report

**Table 14. Statistical Comparisons of Plasma Ethinyl Estradiol Pharmacokinetic Parameters Following MP0008 Swallowed Whole With Water Versus MP0008 Disintegrated in the Mouth Swallowed Without Water (Study MP0008-0001.2-PR)**

| Parameter | Treatment B (Test) | | Treatment A (Reference) | | GMR(%) | 90% Confidence Interval |
|---|---|---|---|---|---|---|
| | Geometric Least Square Mean | n | Geometric Least Square Mean | n | | |
| $AUC_{0-t}$ (pg*hr/mL) | 477.25 | 39 | 614.90 | 37 | 77.62 | 74.88 - 80.46 |
| $AUC_{0-inf}$ (pg*hr/mL) | 575.05 | 38 | 703.30 | 37 | 81.77 | 78.78 - 84.97 |
| $C_{max}$ (pg/mL) | 49.70 | 39 | 80.12 | 37 | 62.03 | 58.77 - 65.48 |

Treatment A: MP0008 NA 1 mg/EE 20 mcg ODT disintegrated in the mouth, swallowed by saliva without water
Treatment B: MP0008 NA 1 mg/EE 20 mcg ODT swallowed whole with 240 mL water
Source: Table 11-7 page 55 of Study MP0008-0001.2-PR report

**Table 15. Statistical Comparisons of Plasma Ethinyl Estradiol Pharmacokinetic Parameters Following MP0008 Swallowed Whole With Water Versus Minastrin (Study MP0008-0001.2-PR)**

| Parameter | Treatment B (Test) | | Treatment C (Reference) | | GMR(%) | 90% Confidence Interval |
|---|---|---|---|---|---|---|
| | Geometric Least Square Mean | n | Geometric Least Square Mean | n | | |
| $AUC_{0-t}$ (pg*hr/mL) | 477.25 | 39 | 507.92 | 38 | 93.96 | 90.66 - 97.39 |
| $AUC_{0-inf}$ (pg*hr/mL) | 575.05 | 38 | 598.60 | 37 | 96.07 | 92.53 - 99.74 |
| $C_{max}$ (pg/mL) | 49.70 | 39 | 56.12 | 38 | 88.56 | 83.92 - 93.46 |

Treatment B: MP0008 NA 1 mg/EE 20 mcg ODT swallowed whole with 240 mL water
Treatment C: Minastrin NA 1 mg/EE 20 mcg tablet chewed, swallowed and followed by 240 mL water (reference)
Source: Reviewers' analysis using PK parameters generated by the Applicant

*Reviewer's Comments*

*By comparing treatment B and treatment C, the NE and EE PK parameters after MP0008 swallowed whole with water were comparable to the LD (the BE criteria were met based on the Reviewers' analysis). We do not have an efficacy or safety concern if MP0008 is accidentally swallowed whole with water.*

### *4.2.3 Study MP0008-0002.1-PR*

**Title**: An Open-Label, Randomized, 2-Way Crossover Study in Healthy Adult Female Subjects to Evaluate the Effect of a High-Fat/High-Calorie Meal on Absorption of Norethindrone Acetate (NA) and Ethinyl Estradiol (EE) from an Orally Disintegrating Tablet (MP0008)

**Study Objectives**:

- To assess the effect of a high-fat/high-calorie meal on the single-dose pharmacokinetics (PK) of norethindrone (NE) and ethinyl estradiol (EE) administered as MP0008 in healthy adult female subjects.

**Study design:**

This was a single-center, open-label, randomized, 2-way crossover study to assess the effect of a high-

fat/high-calorie meal on the single dose PK of NE and EE administered as MP0008 in healthy adult female subjects.

A single oral dose of one of the following two treatments was administered in each study period with a 7-day washout period according to the randomization scheme:

**Treatment A**: MP0008 NA 1 mg/EE 20 mcg ODT disintegrated in the mouth, swallowed by saliva without water after an overnight fasting.

**Treatment B**: MP0008 NA 1 mg/EE 20 mcg ODT disintegrated in the mouth, swallowed by saliva without water at 30 minutes after the start of a high-fat/high-calorie meal.

In each study period, 20 blood samples for pharmacokinetic measurements were collected prior to drug administration and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, 48, 60 hours following drug administration. Blood samples were processed to plasma and analyzed for NE and EE using LC-MS/MS methods.

**Results**:

Food effect on NE PK when MP0008 administered without water (Table 16):
The mean AUCs of NE were similar while the mean $C_{max}$ of NE was 55% lower following administration of MP0008 1 mg/20 mcg ODT under fed condition compared to fasted condition. Median $T_{max}$ was delayed by food by approximately 1 hour (from 1.0 hour to 2.0 hours).

**Table 16. Summary of Plasma Norethindrone Pharmacokinetic Parameters Following the Administration of MP0008 without water, Fasted and Fed(Study MP0008-0002.1-PR)**

| Pharmacokinetic Parameters | Treatment A (Fasted) | Treatment B (Fed) |
|---|---|---|
| $AUC_{0-t}$ (pg*hr/mL) | 50410 (43.5) [n=23] | 55850 (37.0) [n=26] |
| $AUC_{0-inf}$ (pg*hr/mL) | 51550 (43.5) [n=23] | 57770 (39.9) [n=25] |
| AUC%extrap (%) | 1.550 (91.6) [n=23] | 1.596 (95.6) [n=25] |
| $C_{max}$ (pg/mL) | 9633 (33.0) [n=23] | 4367 (25.1) [n=26] |
| $T_{max}$ (hr) | 1.018 (0.66, 2.04) [n=23] | 2.000 (0.67, 10.00) [n=26] |
| $K_{el}$ (1/hr) | 0.073 ± 0.020 [n=23] | 0.077 ± 0.022 [n=25] |
| $t_{½}$ (hr) | 10.337 ± 3.344 [n=23] | 10.015 ± 4.410 [n=25] |
| CL/F (L/hr) | 18.43 ± 7.435 [n=23] | 16.25 ± 6.050 [n=25] |
| Vz/F (L) | 272.8 ± 146.52 [n=23] | 219.0 ± 75.193 [n=25] |

Treatment A: MP0008 NA 1 mg/EE 20 mcg ODT following an overnight fast
Treatment B: MP0008 NA 1 mg/EE 20 mcg ODT 30 minutes after the start of a high-fat/high-calorie meal
AUCs and $C_{max}$ values are presented as geometric mean (geometric CV%).
Tmax values are presented as median (minimum, maximum).
Other parameters are presented as arithmetic mean ± SD.
Source: Table 11-2 Page 39 of Study MP0008-0002.1-PR report

Food effect on EE PK when MP0008 administered without water (Table 17):
After the administration of MP0008 1 mg/20 mcg ODT under fed condition, the mean AUCs of EE were similar but mean $C_{max}$ was 34% lower compared to under fasted condition. Median $T_{max}$ was similar (both approximately 1.3 hours) following the administration under fasted and fed conditions.

**Table 17. Summary of Plasma Ethinyl Estradiol Pharmacokinetic Parameters Following the Administration of MP0008 without water, Fasted and Fed(Study MP0001-0002.1-PR)**

| Pharmacokinetic Parameters | Treatment A (Fast) | Treatment B (Fed) |
|---|---|---|
| $AUC_{0-t}$ (pg*hr/mL) | 671.5 (26.8) [n=23] | 603.9 (29.6) [n=26] |
| $AUC_{0-inf}$ (pg*hr/mL) | 755.2 (25.9) [n=22] | 672.5 (25.7) [n=23] |
| AUC%extrap (%) | 9.711 (23.7) [n=22] | 12.55 (31.9) [n=23] |
| $C_{max}$ (pg/mL) | 84.89 (27.9) [n=23] | 54.44 (28.4) [n=26] |
| $T_{max}$ (hr) | 1.334 (1.00, 2.04) [n=23] | 1.330 (0.67, 2.03) [n=26] |
| $K_{el}$ (1/hr) | 0.047 ± 0.010 [n=22] | 0.044 ± 0.012 [n=23] |
| $t_{½}$ (hr) | 15.506 ± 3.404 [n=22] | 17.120 ± 4.532 [n=23] |
| CL/F (L/hr) | 27.30 ± 6.89 [n=22] | 30.66 ± 7.79 [n=23] |
| Vz/F (L) | 590.0 ± 114.91 [n=22] | 735.7 ± 212.18 [n=23] |

Treatment A: MP0008 NA 1 mg/EE 20 mcg ODT following an overnight fast
Treatment B: MP0008 NA 1 mg/EE 20 mcg ODT 30 minutes after the start of a high-fat/high-calorie meal
AUCs and Cmax values are presented as geometric mean (geometric CV%).
Tmax values are presented as median (minimum, maximum).
Other parameters are presented as arithmetic mean ± SD.
Source: Table 11-5 Page 48 of Study MP0008-0002.1-PR report

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