CLINICAL REVIEW

Application Type	NDA
Application Number(s)	218718 (associated IND 151441)
Priority or Standard	Standard
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Division/Office	ORPURM/DUOG
Clinical Reviewer Names	Constance Glass, MD Ioanna Comstock, MD Gerald Willett, MD Audrey Gassman, MD
Review Completion Date	July 16, 2024
Established/Proper Name	Norethindrone Acetate (NA) and Ethinyl Estradiol (EE)
Trade Name	Femlyv
Applicant	Millicent Pharma Limited
Dosage Form	Oral Disintegrating Tablets (ODT)
Applicant Proposed Dosing Regimen	1 mg NA/20 mcg EE (24/4) • Take one orally disintegrating tablet (1 mg norethindrone acetate, 0.02 mg ethinyl estradiol) followed by 240 ml water at the same time every day for 24 days • Take one inert tablet (placebo) by mouth at the same time every day for 4 days • Take tablets in the order directed on the blister pack
Applicant Proposed Indication/Population	Prevention of pregnancy/Females of childbearing potential
Recommendation on Regulatory Action	Approval

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Glossary

AE	adverse event
ANOVA	analysis of variance
AR	adverse reaction
ATE	arterial thromboembolism
AUCinf	area under the plasma concentration-time curve from time 0 to infinity
BA	bioavailability
BE	bioequivalence
BMI	body mass index
BP	blood pressure
BRF	Benefit Risk Framework
BTB	breakthrough bleeding
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
Chem	chemistry
CI	confidence interval
Cmax	Maximum plasma concentration
Coag	coagulation
ConMeds	concomitant medication
COC	combination oral contraceptive
COVID-19	Coronavirus disease 2019
CRF	case report form
CRU	clinical research unit
CSR	clinical study report
DBP	diastolic blood pressure
DUOG	Division of Urology, Obstetrics, and Gynecology
ECG	electrocardiogram
eCTD	electronic common technical document
EE	ethinyl estradiol
EOS	end of study
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
Hem	hematology
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus

HR	heart rate
hr	hour
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IUS	intrauterine systems
ITT	intent to treat
kg	kilogram
kg/m^2	kilogram per meter square
LOCF	last observation carried forward
LSM	least-squares means
Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
mcg	microgram
mg	milligram
Minastrin	Minastrin 24 Fe
ml	milliliter
mITT	modified intent to treat
MPL	Millicent Pharma Limited
n	sample size
NA	norethindrone acetate
NE	norethindrone
NI	Northern Ireland
NDA	New Drug Application
ODT	orally disintegrating tablet
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORPURM	Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OSIS	Office of Study Integrity and Surveillance
OTC	over-the-counter
P	predose
PADER	Periodic Adverse Drug Experience Report
PD	pharmacodynamics
PI	Principal Investigator

PK	pharmacokinetics
PLLR	Pregnancy and Lactation Labeling Rule
PLR	Physician Labeling Rule
PMR	postmarketing requirement
POP	progestin-only pill
PR	protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
Preg	pregnancy
PRO	patient reported outcome
PSUR	Periodic Safety Update Report
QD	once daily
REMS	risk evaluation and mitigation strategy
RLD	reference listed drug
RR	respiratory rate
RRA	Remote Regulatory Assessment
S	screening
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment emergent adverse event
UA	urinalysis
UK	United Kingdom
US	United States
VTE	venous thromboembolism
WHO	World Health Organization

1. Executive Summary

1.1. Product Introduction

This application seeks approval for Femlyv, an orally disintegrating tablet (ODT) containing 1 mg norethindrone acetate (NA) and 0.02 mg ethinyl estradiol (EE). The Applicant refers to the product as MP0008. The proposed proprietary name for this product, Femlyv, has been submitted and accepted by the Agency.

Femlyv ODT is a monophasic combination oral contraceptive (COC) product containing NA (first generation progestin) and EE (estrogen) indicated for use by females of reproductive potential for the prevention of pregnancy. The orally disintegrating tablet represents a new dosage form. It will be provided in blister packs containing 28 tablets each (24 active tablets and 4 inactive tablets). This product should be taken once daily at the same time every day with 240 ml of water.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This application meets the regulatory requirement for substantial evidence of effectiveness based on the definition of bioequivalence per 21 CFR§320.1. Study MP0008-0004.0-PR demonstrates that the pharmacokinetics of Femlyv are within the bioequivalence margin when compared to an approved product, Minastrin 24 Fe. The clinical team assigned to this application recommends approval of Femlyv for the prevention of pregnancy.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The Femlyv orally disintegrating tablet (ODT) in this submission is the first ODT combination oral contraceptive to be considered for approval in the U.S. This new dosage form provides an additional contraceptive option for women who are unable to swallow a tablet or prefer a non-chewable option of COC. This product demonstrates bioequivalence to the cross-referenced drug - Minastrin 24 Fe chewable tablets. There were no serious adverse reactions or new safety concerns identified in the bioequivalence (BE), food effects and oral irritation studies for the orally disintegrating tablets. There were no new safety signals or increased risk for an adverse reaction identified in the post-approval safety reports of Minastrin 24 Fe chewable tablets. The benefit-risk assessment for this ODT product is similar to that of Minastrin 24 Fe chewable tablet and acceptable for approval. The Office of Clinical Pharmacology determined that Femlyv met the standard bioequivalence criteria when Femlyv was administered with 240 ml of water under fasting conditions in pivotal Study MP0008-0004.0-PR. The Division of Pharm/Tox for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/Specialty Medicine (DPT-RPURM/SM) determined from the nonclinical perspective this application is approvable. The Division of Medication Error Prevention and Analysis 2 (DMEPA 2) had no additional recommendations as Millicent Puerto Rico LLC (the Applicant) implemented all labeling recommendations. From all OPQ review disciplines, this application is recommended for approval. Agreed to labeling was reached with the Applicant.

No new safety signals for Femlyv or the reference drug Minastrin were identified in the four clinical pharmacology studies that assessed bioequivalence, food effects and oral irritation. There were no deaths or serious adverse events (SAEs) associated with these products and there were no clinically significant reports of oral irritation. The only SAE in the studies was a cannula-site cellulitis that was treated with antibiotics which was not related to drug use. There were no new safety signals in the 120-day safety report for Femlyv and in recent periodic adverse event reports for the reference product Minastrin.

In one of the four clinical pharmacology studies (Study 0001.2), 40% of participants experienced an adverse event of a headache after a single dose of Femlyv or Minastrin. Clinical review determined that half of these reported headaches did not appear to have a temporal correlation with intake of the single dose of either drug product. Of the 22 adverse events of headaches, 11 were not considered causally related. The remaining adverse events of headaches were distributed equally between Minastrin 24 Fe and Femlyv and no significant increases in blood pressure or associated migraine symptoms were associated with these events. After review, the temporally related headaches did not raise any new safety concerns with Femlyv. Other common adverse events, such as vaginal bleeding and dysmenorrhea, recorded in these studies, were consistent with the safety profile of other combination oral contraceptives.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Prevention of pregnancy (See section 2.1 for further information). Contraception can prevent unintended pregnancies that can have significant adverse health, social and economic effects on females and their partners. Effective contraception also reduces the number of pregnancy terminations and decreases the risk of maternal/fetal morbidity and mortality related to obstetric complications and childbirth.	Contraceptive options provide women with choices for their family planning needs.
Current Treatment Options	Current treatment options include: • Chewable combination oral contraceptive tablets • Combination oral contraceptive tablets to swallow (See Section 2.2 for further information)	Several combination oral contraceptives have been approved in the chewable dosage form. However, there are currently no approved orally disintegrating tablets. This dosage form may provide benefit to women who are unable to swallow tablets and/or prefer a non-chewable option.
Benefit	Bioequivalence is demonstrated (See Section 6.2 for further information) Combination oral contraceptives with norethindrone acetate and ethinyl estradiol have a long history of use and tolerability.	This product provides a bioequivalent ODT dosage form of norethindrone acetate 1 mg and ethinyl estradiol 0.02 mg chewable tablets (Minastrin 24 Fe). This ODT must be taken exactly as directed to ensure its safety and efficacy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	Combination oral contraceptives (COCs) as a general class have a number of safety issues that have been well recognized since their introduction in the 1960's. The use of COCs increases the risk of vascular events including: • Venous thromboembolic events (VTEs), such as deep vein thrombosis and pulmonary embolism • Cardiovascular events, such as myocardial infarction (especially in women > 35 years who smoke) • Cerebrovascular events, such as stroke (both ischemic and hemorrhagic types have been reported) The safety profile for Femlyv appeared similar to other COCs regarding common adverse reactions. There were no safety concerns identified in the bioequivalence, food effects and oral irritation studies. Review of Minastrin 24 Fe post-approval periodic adverse event reports (PADERS) and annual reports (AR) has not shown any new safety signals or increased risk for VTEs, ATEs, or cerebrovascular adverse events.	Labeling regarding thromboembolic disorders and other vascular problems for Femlyv will be similar to that of Minastrin 24 Fe. Routine postmarketing surveillance of voluntary reporting for VTEs and arterial thromboembolic events (ATEs) with Femlyv will be acceptable as this product contains the same drug substances and dosages of NA and EE as other approved COCs. With no new safety signals identified with the orally disintegrating tablets, the label for Femlyv will include adverse reaction percentages based on the much larger Minastrin 24 Fe database.

1.4. Patient Experience Data

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

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

2. Therapeutic Context

2.1. Analysis of Condition

Unintended pregnancies can infer significant health, social and economic hardship on females and their partners. Contraception reduces the number of unintended pregnancies and potential unsafe terminations, prevents pregnancy-related health risks for females, and reduces infant morbidity and mortality. Ensuring that females of reproductive potential continue to have access to various contraceptive methods and dose forms, including orally disintegrating tablets, provides significant public health benefits.

2.2. Analysis of Current Treatment Options

Various hormonal and non-hormonal options are available for prevention of pregnancy and include the following:

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

Femlyv contains norethindrone acetate (NA), a first- generation progestin with moderate androgenic activity. NA is a prodrug that is converted to norethindrone and is twice as potent with a longer half-life than norethindrone (NE). NE and NA are widely used for hormonal contraception and are available as either a progestin-only contraceptive or in combination hormonal contraceptive products with estrogen. Ethinyl estradiol is a derivative of estradiol and the estrogen included in almost all formulations of COCs. Both active ingredients have been used in COC and hormone therapy products in a variety of dose strengths for decades.

The contraceptive mechanism of action of COCs is primarily due to the progestin component and results from:

- Inhibition of follicular stimulation and ovulation by suppression of hypothalamic and pituitary secretions due to estrogen and progesterone feedback

- Progestins alteration of cervical mucus to inhibit sperm transport

There are numerous oral norethindrone acetate and ethinyl estradiol contraceptive products and generic options approved in the United States. This combination of oral NA plus EE contraceptive also offers additional options such as chewable tablets and gelatin capsules. The following table will provide an overview of the most pertinent products in this category.

Table 1: Norethindrone Acetate 1 mg and Ethinyl Estradiol 0.02 mg Oral Contraceptive Products Approved in the United States

Product NDA number	Year of Approval	Dosage form; Route of Administration	NA/EE Regimen
Loestrin Fe 1/20 017354	1973	Tablets; Oral	21 days active tablets Inactive tabs x 7 days containing Fe fumarate
Loestrin 24 Fe 021871	2006	Tablets; Oral	24 days active tablets Inactive tabs x 4 days containing Fe fumarate
Taytulla® 204426	2013	Gelatin capsule; Oral	24 active capsules 4 inactive capsules containing Fe fumarate
Minastrin Fe 203667	2013	Chewable tablets; Oral	24 chewable tablets 4 inactive chewable tablets containing Fe fumarate

Fe = iron supplement
Source: Drugs@FDA

This product would represent the only orally disintegrating combination product approved and marketed in the United States.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The reference product, Minastrin 24 Fe (NDA 203667), was approved in the U.S. on May 8, 2013 via the 505(b)(2) regulatory pathway with a clinical bridge to the NE and EE components of the reference listed drug (RLD), Loestrin 24 Fe (NDA 021871).

On April 6, 2023, Minastrin 24 Fe was withdrawn from the market as a business decision, not related to safety or effectiveness. The Safety/effectiveness (S/E) determination was based on the review of Annual Reports and Periodic Adverse Drug Experience Reports (PADER) from May 8, 2018 through May 7, 2023. No new safety issues had been identified. The bioequivalence study was completed prior to Minastrin 24 Fe being withdrawn from the market.

Currently, there are 14 available 24/4 continuous oral contraceptives (COCs) containing 1 mg norethindrone acetate (NA) and 20 mcg ethinyl estradiol (EE). Table 2 lists all presently available COCs with corresponding NDA or ANDA numbers.

Table 2: Currently available 24/4 Continuous Oral Contraceptives (COCs) containing 1 mg NA/0.02 mg EE

COC Tablets or Capsules	ANDA Number
Aurovela 24 Fe	207504
Blisovi 24 Fe	091398
Finzala (chewable)	210087
Gemmily	213317
Gildess 24 Fe	090293
Hailey 24 Fe	204847
Larin 24 Fe	202994
Merzee	212706
Mibelas 24 Fe (chewable)	206287
Norethindrone acetate and ethinyl estradiol and ferrous fumarate	090938
Norethindrone acetate and ethinyl estradiol and ferrous fumarate	210369
Norethindrone acetate and ethinyl estradiol and ferrous fumarate	209609
Norethindrone acetate and ethinyl estradiol and ferrous fumarate	213418
Oshih	216558
COC Capsule	**NDA Number**
Taytulla	204426

Fe= iron supplement
Source: Drugs@FDA

3.2. Summary of Presubmission/Submission Regulatory Activity

The design and conduct of pharmacokinetic studies and oral tolerability studies as well as pre-NDA submission written responses discussed with the Agency occurred under PIND 151441.

3.3. Foreign Regulatory Actions and Marketing History

There are no foreign regulatory actions on this ODT product or foreign development under a different name. The cross-referenced product, Minastrin 24 Fe, was recently withdrawn from the U.S. market. There have been no regulatory actions for safety concerns regarding Minastrin 24 Fe use.

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

4.1. Office of Scientific Investigations (OSI)

The Office of Study Integrity and Surveillance (OSIS) determined that an on-site inspection was not warranted at this time because OSIS conducted a Remote Regulatory Assessment (RRA) for the site in NON-RESPONSIVE The RRA was conducted under the following Submission: NDA NON-RESPONSIVE NON-RESPONSIVE OSIS concluded that the data from the site that provided results from the BE study was reliable.

4.2. Product Quality

The reader is referred to the Quality review dated June 12, 2024 for further information.

4.3. Clinical Microbiology

The reader is referred to the Quality review dated June 12, 2024 for further information.

4.4. Nonclinical Pharmacology/Toxicology

The primary Pharmacology/Toxicology reviewer, Edna Albuquerque, found that the application for Femlyv did not raise any toxicological concerns and recommended approval.

The prescription labeling was reviewed by the nonclinical review team and determined to be acceptable. The reader is referred to the Pharmacology/Toxicology review dated June 5, 2024 for further information.

4.5. Clinical Pharmacology

The Clinical Pharmacology reviewer, Dong Guo, has determined that Femlyv meets the bioequivalence criteria for approval.

The prescription labeling was reviewed by the clinical pharmacology review team and determined to be acceptable. The reader is referred to the Clinical Pharmacology review dated May 29, 2024 for further information.

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Review

Not applicable

5. Sources of Clinical Data and Review Strategy

5.1.Table of Clinical Studies

Table 3 summarizes the clinical studies submitted in support of this application.

Table 3: Listing of Clinical Studies

Trial Identity # Centers Country	Trial Design	Regimen/ schedule/ route	Study Endpoints	Study Population
MP0008-0001.2-PR/CA33502 Single Center UK (NI)	Comparative BA/BE Randomized Non-blinded Single dose 6-sequence 3-treatment 3-period Crossover Fasting ODT without water vs ODT swallowed whole with water vs RLD	**Treatment A** = Femlyv ODT without water **Treatment B** = Femlyv ODT swallowed whole followed by 240 ml water **Treatment C** = Minastrin chewed, swallowed, and followed by 240 ml water	Pharmacokinetics	Healthy premenopausal female volunteers Age 19-45 40 enrolled 35 completed
MP0008-0002.1-PR/CA33511 Single Center UK (NI)	Comparative BA Randomized Non-blinded Single dose 2-sequence 2-treatment 2-period Crossover Food effect study	**Reference** = Femlyv ODT fasting without water **Test** = Femlyv ODT fed without water	Pharmacokinetics	Healthy premenopausal female volunteers Age 19-45 26 enrolled 23 completed
MP0008-0004.0-PR/CA38951 Single Center UK (NI)	Comparative BA/BE Randomized Non-blinded Single dose 6-sequence 3-treatment 3-period Crossover Femlyv ODT fasting vs Femlyv ODT fed vs RLD	**Treatment A** = Femlyv ODT fasting followed by 240 ml water **Treatment B** = Minastrin 24 Fe chewed, swallowed, and followed by 240 ml water **Treatment C**= Femlyv ODT fed	Pharmacokinetics	Healthy premenopausal female volunteers Age 24-45 36 enrolled 36 completed

MP0008-0003.4-PR/CA33717 Single Center USA	Oral irritation safety/tolerability Open label 1-period ODT formulation only Multiple-dose treatment 28 days	Femlyv ODT once daily in the morning for 24 consecutive days of active tablet followed by 4 consecutive days of inactive tablet	Oral irritation and inflammation Adverse events	Healthy premenopausal female volunteers Age 20-45 55 enrolled 55 completed

BA = bioavailability; BE = bioequivalence; ODT = orally disintegrating tablet; RLD= reference listed drug; UK = United Kingdom; NI = Northern Ireland; Femlyv ODT = orally disintegrating tablet containing norethindrone acetate 1 mg/ethinyl estradiol 20 mcg; Minastrin = Minastrin 24 Fe chewable tablet (active) containing norethindrone acetate 1 mg/ethinyl estradiol 20 mcg
Source: MP0008-NA and EE ODT, 2.5 Clinical Overview, Page 5/13.

Clinical Review Comment: In the remainder of the review the studies identified in the above table will be referred to as Studies 0001.2, 0002.1, 0003.4, and 0004.0.

5.2. Review Strategy

The clinical review for this NDA application containing a new dosage formulation of an approved combined oral contraceptive product focused on the following:

- The results of the oral irritation study (Study 0003.4)
- All adverse event data collected for the four trials in this submission
- The four-month safety update submitted on February 13, 2024
- Postmarketing safety review of Minastrin 24 Fe conducted by the clinical reviewer

Clinical Review Comment: All clinical studies performed with Femlyv were completed at the time of the original application submission on September 27, 2023. There were no ongoing clinical studies. No additional safety information was included in the 120-day safety report dated February 13, 2024. In addition, an integrated summary of effectiveness (ISE) and integrated summary of safety (ISS) were not required for this application as data to support a bridge to the approved Minastrin 24 Fe product was obtained solely from clinical pharmacology trials.

6. Review of Relevant Individual Trials (Studies 0001.2, 0002.1 & 0004.0) Used to Support Efficacy

6.1. Study 0001.2

6.1.1. Study Design

Overview and Objective

This open-label, randomized, 6-sequence, 3-treatment (Treatment A, Treatment B, and reference product), 3-period crossover study compared the bioavailability of Femlyv ODT without water (Treatment A) and Femlyv ODT swallowed whole with water (Treatment B) with the approved reference product, Minastrin® 24 Fe chewable tablet (Treatment C).

The secondary objective was to evaluate the effect of water consumption on the bioavailability of NE and EE from Femlyv in healthy adult female subjects.

Trial Design

Clinical Review Comment: Refer to the Clinical Pharmacology review of Study 0001.2 for more specific information regarding trial design (e.g., study site, demographics, treatment sequencing, statistical methods, pharmacokinetic results) dated May 29, 2024. No clinical issues were identified with the design or conduct of this study.

Entry Criteria

Key inclusion criteria included the following:

1. Healthy female volunteers between 18 and 45 years, inclusive
2. Non-smoker or ex-smoker of nicotine containing products for at least 3 months
3. Body mass index (BMI) 19 - 29.9 kg/m^2, inclusive
4. Females that have undergone sterilization procedures ≥ 6 months prior to first dosing
5. Willingness to use one of the following non-hormonal methods of contraception form prior to first dosing and until 28 days after discharge from the CRU
    a. Abstinence
    b. Barrier method (e.g., condom, diaphragm)
    c. Non-hormonal IUD placed for at least 3 months prior to the first dosing
    d. Negative test for selected drugs of abuse at the screening visit (did not include alcohol) and on Day-1 of Period 1 (included alcohol)

Key exclusion criteria included the following:

1. Pregnant or lactating
2. Contraindication for the use of combined hormonal contraceptives, such as,
    a. History of thromboembolic disorders
    b. Breast cancer or undiagnosed breast nodules
    c. Cerebral vascular or coronary artery disease
    d. Known or suspected clotting disorders
    e. Undiagnosed vaginal bleeding
    f. Hypertension (SBP>140 mmHg, DBP>90 mmHg, or DBP>95 mmHg at screening

visit)

3. History of migraines or severe headaches during previous estrogen therapy
4. Use of oral hormonal contraceptive (containing an estrogen and/or progestin) or any form of hormone contraception 28 days prior to Day-1 of study
5. Use of medroxyprogesterone acetate contraceptive injection (DMPA) within 1 year prior to Day-1 of study
6. Use of any substances known to be CYP3A enzyme inducers or inhibitors.
7. Use of alcohol containing foods or beverages within 72 hours prior to Day-1 of Period-1
8. Use caffeine containing foods or beverages within 24 hours prior to Day-1 of Period -1
9. Consumption of grapefruit or Seville orange containing foods or beverages within 14 days prior to Day-1 of Period-1 of study.

Clinical Review Comment: The entry criteria are acceptable from a clinical standpoint.

Study 0001.2-PR Schedule of Study Events

Study Safety Procedures:

- Medical history and physical examination at Baseline (within 28 days prior to first dosing)
- Vital signs, ECG, serum laboratory screening, and serum pregnancy testing at baseline and end of study or early termination from study.
- Urine drug screen and cotinine testing at baseline
- Urine drug and alcohol screen on Admission to Clinical Research Unit (Day-1 of each Period)
- Seven-day washout phase prior to initiating the subsequent Period.

Clinical Review Comment: The study safety procedures are acceptable from a clinical standpoint.

6.1.2. Study Results

Compliance with Good Clinical Practices

An attestation to conducting the study in compliance with Good Clinical Practice (GCP) guidelines was submitted with this application.

Financial Disclosure

The investigators who participated in Study 0001.2 certified to not having a financial interest related to the outcome of this study.

Patient Disposition

Of the 40 participants enrolled and randomized to one of the six sequences, 35 participants completed the study. The reasons for discontinuation include:

- 2 subjects discontinued due to adverse events.
    - IV catheter site pain that progressed to cellulitis and resulted in hospitalization for intravenous antibiotics.
    - Premenstrual syndrome with reports of feeling emotional and stressed on Day 8 of Period 2. On day 10 and the participant discontinued the study. Upon follow-up, the participants symptoms resolved within 10 days after discontinuing the study.
- 1 subject was discontinued after a failed drug/alcohol screen at check-in for Period-3
- 2 subjects withdrew for personal reasons.

In total, 40 subjects completed at least one 1 period of the study and received at least one dose of the investigational drug. Thirty- seven (37) subjects received at least one dose of the investigational drug ODT without water and 39 subjects received the investigational drug to swallow whole with water. Thirty-five (35) subjects received all 3 doses of study drug per the protocol. Data from the 40 subjects enrolled were included in the pharmacokinetic analysis.

Protocol Violations/Deviations

There were 5 subjects that ended the water restriction in Treatment A earlier than one hour. An additional sensitivity PK analysis excluded these subjects as a subgroup analysis.

Table of Demographic Characteristics

The demographic characteristics of the primary efficacy (pharmacokinetic analysis) population for Study 0001.2 are shown in Table 4.

Table 4: Study 0001.2 Demographic Characteristics of Primary Efficacy Analysis

Demographic Parameters	Subject Data (n = 40)
Age	
Mean years (SD)	32.6 (6.71)
Median (years)	33.5
Min, max (years)	19, 45
Race, n (%)	
White	36 (90%)
Black or African American	3 (8%)
Asian	1 (3%)
Ethnicity, n (%)	
Hispanic or Latino	1 (3%)
Not Hispanic or Latino	39 (98%)
Body Mass Index (kg/m2)	
Mean (SD)	24.4 (2.9)
Median	24.3
Min, max	19.6, 29.8

Source: Study MP0008-0001.2-PR/CA33502, Study Report Body, Table 14.1.3, page 72.

Other Baseline Characteristics (e.g., ethnicity, disease characteristics)

Treatment groups were clinically similar in baseline characteristics.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Subjects were monitored for treatment compliance via directly observed treatment administration. Subjects were confined to the clinical research facility for at least 60 hours post drug administration. The oral cavity was inspected after drug administration to ensure complete consumption of the administered drugs. Treatment compliance issues occurred in 5 subjects that desired water within one hour of the dosing in Treatment A group.

Concomitant medications were administered to 14 study subjects for various indications. The majority of concomitant medications administered during this study was related to the adverse event of headache in 11 study subjects. For additional discussion regarding safety analyses of these adverse events of headaches, refer to section 8. One patient received intravenous antibiotics for the treatment of cellulitis from the intravenous cannula site.

Clinical Review Comment:
In this trial, headache was the most common adverse event and on initial review, the number of events of headaches appeared to be increased as compared to other clinical trials with oral contraceptives. The clinical reviewer performed additional safety analyses to assess whether

these events were causally related to the administration of Femlyv or related to intake of Minastrin 24 Fe or due to other etiologies. The study site administered a single dose of paracetamol to resolve the adverse event of headache when reported as "moderate" in severity by the participant. See section 8 for further discussion of the adverse event of headaches.

Cannula site pain was directly related to use of indwelling intravenous cannulas that were placed and not the drug substance or product. Outside of the single patient with cellulitis, the numbers of intravenous cannula adverse events were small, and none were considered by the Applicant or the clinical reviewer to be related to Femlyv.

Efficacy Results – Primary Endpoint

The primary endpoint was related to bioequivalence through evaluation of Cmax and AUC of the progestin to the reference Minastrin 24 Fe. Refer to Study 0004.0 for the determination of the bioequivalence of EE to the reference Minastrin 24 Fe.

Data Quality and Integrity

Data quality and integrity issues were not identified by the Applicant or by OSIS.

Efficacy Results – Secondary and other relevant endpoints

The Applicant conducted the bioequivalence study to assess a single oral dose of Femlyv ODT with and without water intake. Use of this dose was tolerated by the study population without clinically significant changes in vital signs, laboratory abnormalities, physical examinations, or ECG findings. No differences in bioequivalence of the progestin were identified when used with or without water intake.

The reader is referred to the Clinical Pharmacology review dated May 29, 2024 for the dose/dose response, durability of response, and persistence of effect for further information.

Additional Analyses Conducted on the Individual Trial

There were no additional analyses conducted in this trial.

6.2. Study 0002.1

6.2.1. Study Design

Overview and Objective

This randomized, single-center, balanced, single dose, non-blinded, 2-treatment, 2-period, crossover study to assess the effect of a high-fat/high-calorie meal (Treatment B) on the bioavailability of Femlyv following an overnight fast (Treatment A).

Trial Design

In general, the overall aspects of the study design were identical to Study 0001.2 (see Section 6.1.1) including: inclusion criteria, diagnostic criteria, procedures and schedule, dietary restrictions, as well as handling of subject completion, discontinuation, or withdrawal.

Key changes that were added to the exclusion criteria from Study 0001.2

- Hypersensitivity, idiosyncratic reaction, or intolerance to estrogens, progestogens, or other hormonal agents or to any component of the formulations or the high-fat meal (e.g., lactose intolerance).

Clinical Review Comment: Refer to the Clinical Pharmacology review of Study 0002.1 dated May 29, 2024 for additional review and comments regarding trial design (e.g., study site, demographics, treatment sequencing) and pharmacokinetic results.

Study Endpoints

The primary endpoints were the pharmacokinetic (PK) parameters of norethindrone (NE) and ethinyl estradiol (EE) after high-fat/high-calorie meal. The PK parameters of interest included $C_{max,}$ AUC0-t and AUC0-inf for NE and EE.

Protocol Amendments

No protocol amendments of clinical significance were submitted.

6.2.2. Study Results

Compliance with Good Clinical Practices

An attestation to conducting the study in compliance with Good Clinical Practice (GCP) guidelines was submitted in this application.

Financial Disclosures

The investigators who participated in Study 0002.1 certified to not having a financial interest related to the outcome of this study.

Patient Disposition

Of the 26 study participants who were enrolled and subsequently randomized, 23 completed the study per protocol and received all doses of study drug. All 26 subjects received at least one dose of the study drug.

Protocol Violations/Deviations

There were three subjects discontinued from the study, two for testing positive for COVID-19 and one with COVID-19 exposure. There were no significant protocol deviations that affected the bioavailability analysis of the study population.

Clinical Review Comment: The conduct of this study and the efficacy and safety of the study do not appear to have been substantially impacted by discontinuations resulting from COVID-19 infections.

Table of Demographic Characteristics

The demographic characteristics of the subjects enrolled in Study MP0002.1 are shown in Table 5.

Table 5: Study 0002.1 Demographic Characteristics of Pharmacokinetics Analysis Population

Demographic Parameters	Subject Data (n = 26)
Age	
Mean years (SD)	33.5 (7.51)
Median (years)	33.0
Min, max (years)	19, 45
Race, n (%)	
White	24 (92%)
Asian	2 (8%)
Ethnicity, n (%)	
Not Hispanic or Latino	26 (100%)
Body Mass Index (kg/m2)	
Mean (SD)	24.1 (2.62)
Median	23.2
Min, max	20.7, 29.3

Source: Study MP0008-0002.1-PR/CA33511, Study Report Body, Page 34/189

Other Baseline Characteristics (e.g., ethnicity, disease characteristics)

Treatment groups were clinically similar in baseline characteristics.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Subjects were monitored for treatment compliance via directly observed treatment administration. Subjects were confined to the clinical research facility for at least 36 hours post drug administration. The oral cavity was inspected after drug administration to ensure thorough consumption of the administered drug. Treatment compliance issues were not reported.

A single dose of a concomitant medication (paracetamol) was administered to two study subjects with a headache in Treatment Period A (administration of Femlyv following an overnight fast).

Efficacy Results-Primary Endpoint

Intake of a high-fat diet by the participants decreased the C_{max} of NE and EE and were comparable to results from the reference drug Minastrin 24 Fe. This study showed bioequivalence for the progestin. See Study 0004.0 for bioequivalence of EE. The C_{max} of EE was 42% higher when Femlyv was disintegrated in the mouth and then swallowed without water compared to the reference drug. Femlyv is recommended to be administered with 240 ml water. The clinical pharmacology reviewer concluded that there were no differences between Femlev and Minastrin 24 Fe when a high fat diet was consumed.

Data Quality and Integrity

Data quality and integrity issues were not identified by the Applicant or OSIS.

Efficacy Results – Secondary and other relevant endpoints

Overall, the investigational product was tolerated by the study population during the fasting and fed treatment conditions without clinically significant laboratory abnormalities, vital signs, physical examination, or ECG findings.

6.3. Study 0004.0

6.3.1 Study Design

Overview and Objective

This randomized, single-center, balanced, single-dose, non-blinded, 3-treatment, 3-period, 6-sequence, crossover study evaluated the effect of food on the bioavailability of Femlyv ODT under fasting conditions (Treatment A) with Minastrin 24 Fe (RLD) chewable tablets under fasting conditions (Treatment B) and with Femlyv ODT under fed conditions (Treatment C).

Trial Design

Clinical Review Comment: Refer to the Clinical Pharmacology review of Study 0004.0 dated May 29, 2024 for more specific discussion regarding trial design (e.g., study site, demographics, treatment sequencing, statistical analysis plan) and the pharmacokinetic results.

In general, the overall aspects of the study design were identical to Study 0001.2 (see Section 6.1.1) including: diagnostic criteria, procedures and schedule, dietary restrictions, as well as handling of subject completion, discontinuation, or withdrawal. However, there were modifications to the inclusion and exclusion criteria that included the following:

Key changes added to the inclusion criteria when compared to those in Study 0001.2

- Body Mass Index (BMI) 18.0- 30.0 kg/m_2, inclusive
- History and presence of regular menstrual cycles with a usual length of 21 to 35 days and a variability of ±3 days; (subjects who were recently postpartum or post-abortion must have had at least 2 regular menstrual cycles).

Key changes added to the exclusion criteria when compared to those in Study 0001.2

- Hypersensitivity, idiosyncratic reaction, or intolerance to estrogens, progestogens, or other hormonal agents or to any component of the formulations or the high-fat meal (e.g., lactose intolerance).
- Was lactose intolerant.

Study Endpoints

The primary endpoints were the pharmacokinetic (PK) parameters of Femlyv for the bioequivalence evaluation. The PK parameters of interest included $C_{max,}$ AUC0-t and AUC0-inf of NE and EE for the analysis of the bioequivalence of Femlyv ODT fasting versus RLD and Femlyv ODT fed versus Femlyv ODT fasting.

Secondary endpoints included the tolerability to the test product, adverse events, clinical laboratory test results, and physical examination findings.

Protocol Amendments

No protocol amendments were submitted that required clinical review.

6.3.2. Study Results

Compliance with Good Clinical Practices

An attestation to conducting the study in compliance with Good Clinical Practice (GCP) guidelines was submitted in this application.

Financial Disclosure

The investigators who participated in Study 0004.0 certified to not having a financial interest related to the outcome of this study.

Patient Disposition

Of the 36 study participants who were enrolled and subsequently randomized, all 36 completed the study per protocol and received all doses of study drug.

Protocol Violations/Deviations

There were no disruptions in the study or discontinuations due to COVID-19 pandemic. There were no significant protocol deviations that affected the bioavailability analysis of the study population or the study conduct.

Table of Demographic Characteristics

The demographic characteristics of the subjects enrolled in Study MP0004.0 are shown in Table 6.

Table 6: Study 0004.0 Demographic Characteristics of Pharmacokinetics Analysis Population

Demographic Parameters	Subject Data (n = 36)
Age	
Mean years (SD)	33.5 (6.23)
Median (years)	32.5
Min, max (years)	24, 45
Race, n (%)	
White	34 (94%)
Black or African American	2 (6%)
Ethnicity, n (%)	
Hispanic or Latino	1 (3%)
Not Hispanic or Latino	35 (97%)
Body Mass Index (kg/m_2)	
Mean (SD)	24.5 (2.9)
Median	24.0
Min, max	19.4, 29.9

Source: Study MP0008-0004.0-PR/CA38951, Study Report Body, Page 38

Other Baseline Characteristics (e.g., ethnicity, disease characteristics)

Treatment groups were clinically similar in baseline characteristics.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Subjects were monitored for treatment compliance via directly observed treatment administration. Subjects were confined to the clinical research facility for at least 36 hours post drug administration. The oral cavity was inspected after drug administration to ensure thorough consumption of the administered drug. Treatment compliance issues were not reported.

Concomitant medications were administered to 1 study subject with a headache in two different periods. One with the reference drug Minastrin (Treatment B) and 30 minutes after high fat/high calorie meal with Femlyv ODT (Treatment C).

Efficacy Results-Primary Endpoint

The high- fat diet decreased the C_{max} of NE and EE comparable to the reference drug. Considering the results of this study, the clinical and clinical pharmacology reviewers concur that Femlyv can be taken without regards to meals and no limitation with respect to food intake is needed in labeling.

Data Quality and Integrity

Data quality and integrity issues were not identified.

Efficacy Results – Secondary and other relevant endpoints

Overall, the investigational product was tolerated by the study population during the fasting and fed treatment conditions without clinically significant laboratory abnormalities, vital signs, physical examination, or ECG findings.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Efficacy of Femlyv is supported by the four pharmacokinetic studies demonstrating bioequivalence to the RLD, which formed a bridge to the approved product, Minastrin 24 Fe. The reader is referred to the Clinical Pharmacology review for further information and conclusions on the results of the bioequivalence studies.

Clinical Review Comment:
Efficacy data results from these studies were not combined as these trials were designed to demonstrate a bioequivalence bridge to the approved product, Minastrin 24 Fe.

7.1.1. Primary Endpoints

The primary endpoints of the pharmacokinetic studies evaluating Femlyv included the PK parameters of NE and EE are as stated in Section 6.

The reader is referred to the Clinical Pharmacology review for further information.

7.1.2. Secondary and Other Endpoints

The secondary safety endpoints from bioequivalence and food studies were combined with results from the oral irritation study (Study 0003.4). Refer to Section 8 for a clinical discussion of the integrated safety results.

7.1.3. Subpopulations

An analysis of subpopulations is not applicable to the review of this application.

7.1.4. Dose and Dose-Response

An analysis of subpopulations is not applicable to the review of this application.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

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

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Although the study populations were demographically less diverse that the target population in the U.S., the studied population was sufficient to provide a bridge to support the efficacy of Femlyv.

7.2.2. Other Relevant Benefits

Although there are chewable combination oral contraceptive pills available in the U.S., there are no other approved oral disintegrating tablets (ODT) COCs. The ease of dosing with an ODT formulation may benefit those who have difficulty swallowing pills or do not desire to chew a tablet.

7.3. Integrated Assessment of Effectiveness

The reader is referred to the Clinical Pharmacology review dated May 29, 2024 for further information.

8. Review of Safety

8.1. Safety Review Approach

The clinical safety review of Femlyv consisted of the analysis of all adverse events in the safety population of the three pharmacokinetic studies and the oral irritation study. All participants in the safety population received at least one dose of Femlyv ODT. The Applicant submitted individual adverse event datasets for each of the three pharmacokinetic studies and the oral irritation study. Integration of key safety findings from all four studies is presented in Section 8.4. Recent PADERS from the reference drug Minastrin 24 Fe were also reviewed along with relevant literature and no unlabeled or unreported adverse events were identified. In addition, a review of the Applicant's 120-day safety update was conducted by the clinical reviewer. No

additional safety information was included in the 120-day safety report dated February 13, 2024. This was acceptable to the clinical review team as all clinical studies performed with Femlyv were completed at the time of the original application submission on September 27, 2023 and there is no overseas marketing of this ODT product.

8.2. Review of the Safety Database

8.2.1 Overall Exposure

The development program for Femlyv included the following three Phase I pharmacokinetic studies:

- Study 0001.2 (Bioavailability and Bioequivalence)
- Study 0002.1 (Bioavailability)
- Study 0004.0 (Bioavailability and Bioequivalence)

Additionally, the Applicant conducted an oral irritation study (Study 0003.4). The number of participants in the safety population for these four clinical pharmacology studies are shown in Table 7.

Table 7: Safety Population for the Four Femlyv Studies

Safety Database for Femlyv N[1]= 157		
Femlyv Studies	Femlyv [2] Safety Population	Reference[3] Safety Population
0001.2	40	38
0002.1	26	-
0003.4	55	-
0004.0	36	36
Total	157	74

[1] N is the sum of all subjects exposed to at least one investigational study product in the development program.
[2] Three pharmacokinetic studies and one oral irritation study included administration of the to-be-marketed orally disintegrating product, Femlyv
[3] Reference (Minastrin 24 Fe chewable tablets) administered in two pharmacokinetic studies
Sources: Study synopses from the four studies

In the two pharmacokinetic studies that evaluated bioequivalence participants were scheduled to receive a single dose of investigational product or reference drug during each of three treatment periods. In the pharmacokinetic 2-way crossover study evaluating the effect of a high-fat/high-calorie meal, participants were scheduled to receive single doses of the investigational product at two time periods. Only subjects in the oral irritation study received

multiple consecutive doses. In this study, subjects received 24 consecutive days of the investigational product.

Clinical Review Comment:
The number of subjects exposed to at least one dose of Femlyv was sufficient to provide pharmacokinetic and safety data to bridge to the approved Minastrin 24 Fe product. For the oral irritation assessments, the assessment timeframe up to 24-days was adequate to assess the oral irritation potential of the investigational product given the half-life of the progestin and estrogen components of Femlyv.

8.2.2 Relevant characteristics of the safety population:

The demographic makeup of the safety population in the four Femlyv clinical pharmacology studies are shown in the following table:

Table 8: Safety Demographics for the Four Femlyv Studies

MP0008 Studies	Median Age (SD)	Median BMI (SD)
0001.2 CA33502	33.5 (6.7)	24.3 (2.9)
0002.1 CA33511	33.0 (7.5)	23.2 (2.6)
0003.4 CA33717	33.0 (6.6)	27.1 (3.9)
0004.0 CA38951	32.5 (6.2)	23.9 (2.9)

Source: Demographic in the Summary of Clinical Safety (Pages 6, 13, 17 & 24)

Clinical Review Comment:
Aside from the slightly increased BMI in Study 0003.4, the median age and median BMI were comparable between the test (Femlyv) and reference (Minastrin 24 Fe) products across these pharmacokinetic studies. For a pharmacokinetic study, the mean ages and BMIs and ranges of these baseline characteristics were clinically similar which is acceptable for pharmacokinetic studies.

8.2.3 Adequacy of the safety database:

The safety database comprised of clinical pharmacology studies that demonstrated a bridge to an approved product along with relevant postmarketing data provides an adequate safety database that supports bridging the risks of the approved product Minastrin 24 Fe to that of Femlyv. The database for the clinical pharmacology studies consisted of healthy females of child-bearing potential which is acceptable as this product is intended for use in that population.

8.3 Adequacy of Applicant's Clinical Safety Assessments

8.3.1 Issues Regarding Data Integrity and Submission Quality

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

8.3.2 Categorization of Adverse Events

Adverse events were categorized appropriately. Definitions of serious adverse events and treatment-emergent adverse events were acceptable and appropriate. Adverse event follow-up, categorization, and causality assessment were adequately described prior to study initiation.

8.3.3 Routine Clinical Tests

Safety measures defined by the protocol, which included medical supervision, physical examination (including oral cavity examination), vital signs, 12-lead electrocardiogram (ECG), clinical laboratory tests and adverse events (AEs) monitoring were adequate to ensure subjects' safety.

Clinical Review Comment: Categorization of adverse events and safety testing performed by the Applicant are acceptable.

8.4 Safety Results

8.4.1 Deaths

No deaths occurred in the four developmental studies for Femlyv.

8.4.2 Serious Adverse Events

One subject in Study 0001.2 had an intravenous (IV) catheter site cellulitis requiring hospitalization for intravenous antibiotics. The Applicant and the clinical reviewer agree that this SAE was not related to use of the investigational product. There were no serious adverse events causally related to administration of the investigational drug product.

8.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

Two subjects in Study 0001.2 did not complete the study participation due to adverse events. Two subjects in Study 0002.1 discontinued the study early due testing positive for COVID-19 infection and one subject discontinued due to COVID-19 exposure. There were no subject discontinuations in Study 0004.0 or in the oral irritation study, Study 0003.4. Table 10 summarizes subject discontinuations due to adverse events.

Table 9: Summary of Subject Discontinuations due to Adverse Events

Participant Number	Adverse Event	Relationship to Drug	Timing of Product Received
(b) (6) (Study 0001.2)	IV cannula cellulitis requiring hospitalization and intravenous antibiotics	Not drug-related	Day 2 of Period 2, 1.5 days following Femlyv without water
(b) (6) (Study 0001.2)	Premenstrual syndrome	Not drug-related	Day 9 of Period 2, 8 days following Femlyv without water
(b) (6) (Study 0002.1)	Positive COVID-19	Not drug related	Period 1, 10 days following Femlyv fed state
(b) (6) (Study 0002.1)	Positive COVID-19	Not drug related	Prior to check in for Period 2, 6 days following Femlyv fed state

Source: Summary of Clinical Safety (Pages 8 & 15)

Clinical Review Comment:
The clinical reviewers concur with the Applicant that these adverse events were not related to the investigational product. Two positive COVID-19 participants were also identified in Study 0004, but there is no evidence that they discontinued early or that the COVID-19 infection affected their individual results or the overall study results.

8.4.4 Significant Adverse Events

There were no clinically significant adverse events reported in any of the four pharmacokinetic studies.

8.4.5 Treatment Emergent Adverse Events and Adverse Reactions

The most frequently reported adverse events were headache, nausea, and menstrual irregularities. All TEAEs were classified as mild or moderate severity. Table 10 illustrates the frequency of adverse reactions in the safety population (i.e., all subjects receiving at least one dose of Femlyv ODT in Studies 0001.2, 0002.1, 0004.0 and 0003.4).

Table 10: Treatment Emergent Adverse Events (≥5% in any study) – Safety Population (MedDRA V24.1)

Adverse Event n (%)	Study 0001.2 N=40[1]	Study 0002.1 N=26[2]	Study 0004.0 N=36[3]	Study 0003.4 N=55[4]	Total N = 157
Any adverse event	29 (73%)	11 (42%)	11 (31%)	31 (56%)	82 (52%)
Headache	16 (40%)	5 (19%)	3 (8%)	8 (15%)	31 (20%)
Nausea	3 (8%)	3 (12%)	2 (6%)	6 (11%)	14 (9%)
Vaginal hemorrhage	1 (3%)	0 (0%)	0 (0%)	6 (11%)	7 (4%)
Dizziness	6 (15%)	0 (0%)	1 (3%)	0 (0%)	6 (3.8%)
Menstrual disorder	2 (5%)	0 (0%)	0 (0%)	5 (9%)	5 (3.2%)
Dry mouth	0 (0%)	0 (0%)	0 (0%)	4 (7%)	4 (2.5%)
COVID-19 positive	2 (5%)	2 (8%)	2 (6%)	0 (0%)	4 (2.5%)
Vomiting	0 (0%)	2 (8%)	1 (3%)	0 (0%)	3 (1.9%)
Dysmenorrhea	3 (8%)	0 (0%)	0 (0%)	1 (2%)	2 (1%)
Oropharyngeal pain	2 (5%)	1 (4%)	0 (0%)	0 (0%)	3 (2%)
Photophobia	0 (0%)	2 (8%)	0 (0%)	0 (0%)	2 (1%)
Fatigue	0 (0%)	2 (8%)	0 (0%)	0 (0%)	2 (1%)

[1] = Overall events in Study 0001.2 includes all treatment groups (A, B & C)
[2] = Overall events in Study 0002.1 includes both treatment groups (A&B)
[3] = Overall events in Study 0004.0 includes all treatment groups (A,B & C)
[4] = Overall events in Study 0003.4 are derived from one multidose (24 day) regimen
Source: Summary of Clinical Safety: Study 0001 Table 2, page 9; Study 0002 Table 4, page 14; Study 0004 Table 6, page 20; Study 0003 Table 8, page 27

Clinical Review Comment:
The treatment emergent adverse events as shown in the preceding table indicate no new safety signals. Evaluation of the separate treatment groups within Studies 0001.2 and 0004.0 (which include the reference product Minastrin 24 Fe) show no safety concerns between the two formulations. The most frequent adverse events identified in these four submitted studies (headache, nausea, and menstrual irregularities) are known AEs associated with hormonal contraceptive use. An information request was sent to the Applicant on February 28, 2024 to

provide narratives for subjects who experienced dental or oropharyngeal related adverse reactions and vaginal hemorrhage. See Section 8.5 for further information.

In Study 0001.2, the rate of adverse events of headaches after Femlyv or Minastrin 24 Fe appeared to be clinically increased as compared to other clinical pharmacology studies that have assessed combined oral contraceptives. Additional clinical review was performed, and the following were noted:

1) ***None of the headaches were considered serious, severe, or classified as a migraine.***
2) ***None of the headaches were associated with clinically significant increases in blood pressure.***
3) ***None of these headaches required medical intervention beyond a single dose of paracetamol.***

16 study subjects (40%) participating in Study 0001.2 reported 22 adverse events of headaches after a single dose of either Femlyv or Minastrin 24 Fe administration (e.g., 15 adverse events after Femlyv intake and 7 after Minastrin 24 Fe intake). Upon further review, only 11/22 (50%) adverse events of headaches in 7 subjects were considered temporally related (i.e., those reported to have occurred during the initial half-lives of Femlyv and Minastrin 24 Fe). Of note, the adverse events of headaches that were temporally related to drug intake were evenly distributed between Femlyv and Minastrin 24 Fe [e.g., 6 adverse events after Femlyv intake (54.5%) and 5 adverse events after Minastrin 24 Fe intake (45.5%)]. 3 of the 5 subjects who reported temporally related headaches after Femlyv administration also reported having temporally related headaches with Minastrin 24 Fe.

In comparison, 8 study subjects (15%) participating in Study 0003.4 each reported a single headache during a multidose 24-day regimen of Femlyv administration. 6/8 (75%) adverse events of headaches were considered temporally related to the active drug (e.g., 2 occurred on Day 28 during the inactive tablet intake period). The time to onset of the adverse event of headache in these subjects ranged from Day 1 to Day 21 of continued use. No subject experienced a second headache with continued use of the product.

As the headaches that required intervention with paracetamol were considered of clinical importance, an analysis of those adverse events and whether the event was temporally related to single or continued use of Femlyv or Minastrin 24 Fe was performed. Table 11 summarizes the adverse events of headaches that were temporally related to either single dose administration of Femlyv or Minastrin 24 Fe during Study 0001.2 or temporally related to a multidose use of Femlyv for a 24 day regimen during Study 0003.4.

Table 11: Adverse Events of Headaches Reported in Study 0001.2 and Study 0003.4

	Study 0001.2 [1] N (%)		***Study 0003.4 [2] N (%)***
Subjects reporting adverse events of headaches	***16 (40%)***		***8 (15%)***
Total adverse events of headaches	***22***		***8***
	Femlyv	***Minastrin 24 Fe***	***-***
Adverse events of headaches after Femlyv or Minastrin administration	***15 (68.2%)***	***7 (31.8%)***	
Temporally related headaches	***6 (54.5%)***	***5 (45.5%)***	***6 (75%)***
Temporally related headaches requiring paracetamol	***6 (100%)***	***3 (60%)***	***3 (50%)***

[1] = Overall events in Study 0001.2 includes all treatment groups (A, B & C)
[2] = Overall events in Study 0003.4 are derived from one multidose (24 day) regimen
Source: Clinical reviewer analysis

In Study 0001.2, all 6 (100%) adverse events of headaches that were possibly causally related to Femlyv use were treated with a single dose of paracetamol. In comparison, there were 3/5 (60%) adverse events of headaches that were possibly causally related to Minastrin use that were treated with paracetamol. However, 2 of the 3 subjects receiving paracetamol for a headache occurring after Minastrin administration also required paracetamol for treatment of a headache after Femlyv administration. There was no increased risk for the adverse event of headache noted with a multidose use of Femlyv during Study 0003.4. Given that the safety profile of Minastrin also includes headaches and that none of these were serious or severe, these headaches do not appear to represent a new safety signal or trend.

8.4.6 Laboratory Findings

Significant laboratory findings aside from the Covid-19 positive tests were not reported or identified by the clinical reviewer.

8.4.7 Vital Signs

Significant vital sign findings were not reported and no issues were identified with vital signs by the clinical reviewer.

8.4.8 Electrocardiograms (ECGs)

Two single episodes of sinus tachycardia occurred in two subjects in two separate Studies (Study 0002.1 and Study 0004.0). Resolution occurred in both events and the subjects

completed the studies without further incident. No subject experienced tachycardia in the multiple dose study.

Clinical Review Comment: Although tachycardia is listed in Section 6.2 (Postmarketing Experience) of the reference drug Minastrin 24 Fe, it has not been commonly reported with use of hormonal birth control and has not been identified as causally related to use of hormonal contraception or Minastrin 24 Fe. As this event is already labeled in the postmarketing section of Minastrin 24 Fe and it is not possible to determine causality or frequency from the small subject numbers in clinical pharmacology studies, no further labeling or analyses of tachycardia is needed.

8.4.9 QT

QT prolongation studies were not required for this hormonal contraceptive.

8.4.10 Immunogenicity

Immunogenicity studies were not required as this is not a peptide or biologic product.

8.5 Analysis of Submission-Specific Safety Issue

8.5.1 Adverse Events Oropharyngeal Pain, Toothache, and Vaginal Hemorrhage

The adverse events of "oropharyngeal pain" or "toothache" were reported in a total of four subjects (two in RLD Treatment group) and seven subjects reported "vaginal hemorrhage" in the safety population. An information request was sent to the applicant on February 28, 2024, to provide case narratives for the subjects who experienced these adverse events for an in-depth review. Further investigation of oral pain concerns with an ODT formulation along with an in-depth review of "vaginal hemorrhage" was warranted as this event predominantly occurred in the multiple dose study. Table 12 summarizes the details of these adverse events.

Table 12: Summary of Subjects Experiencing Adverse Events Oropharyngeal Pain, Toothache and Vaginal Hemorrhage

Subject ID	Adverse Event	Causality Assessment	Additional details	Product received
Study 0001.2				
(b) (6)	Vaginal hemorrhage:	1.Unrelated	1.Mild symptoms; resolved	1.Femlyv without water

	1. Spotting 2. Vaginal bleeding	2.Unlikely Related	2.Vaginal bleeding with clots; resolved after 1.5 days	2.Minastrin (RLD)
(b) (6)	Oropharyngeal pain (sore throat)	Unrelated	+COVID-19; resolved	Femlyv without water
	Toothache	Unrelated	Mild symptoms; resolved	Femlyv without water
	Oropharyngeal pain (sore throat)	Unrelated	Mild symptoms; resolved	Minastrin (RLD)
Study 0002.1				
(b) (6)	Oropharyngeal pain (sore throat)	Unrelated	Associated symptoms of lower respiratory infection resolved with antibiotics	Femlyv with food
Study 0004.0				
(b) (6)	Oropharyngeal pain (sore throat)	Unrelated	Mild symptoms of upper respiratory infection; resolved	Minastrin (RLD)
Study 0003.4				
(b) (6)	Vaginal hemorrhage (vaginal spotting); menstrual disorder (early menses)	Possibly related	Mild symptoms; resolved	Femlyv (Day 20)
	Vaginal hemorrhage (vaginal spotting)	Possibly related	Mild symptoms; resolved	Day 28; Femlyv completed Day 24
	Vaginal hemorrhage (vaginal spotting)	Possibly related	Mild symptoms; resolved	Femlyv (Day 12)
	1. Vaginal hemorrhage (vaginal bleeding) 2.Dysmenorrhea (menstrual cramps)	Possibly related	Mild symptoms; resolved	1. and 2. Femlyv (Day13)
	Vaginal hemorrhage (vaginal bleeding)	Possibly related	Mild symptoms; resolved	Femlyv (Day 10)
	1.Vaginal hemorrhage (vaginal spotting) 2.Menstrual	1.Possibly related 2.Possibly	1.Mild symptoms; resolved 2.Mild symptoms; resolved	1.Femlyv (Day 14) 2.Day 27; Femlyv completed on Day

	disorder (irregular period)	Related		24

Source: Clinical reviewer analysis

It is important to note that the adverse event of vaginal hemorrhage is a preferred term and does not infer that a hemorrhage requiring medical intervention. Rather, this term refers to a group of gynecologic disorders that range from vaginal spotting to vaginal bleeding. The following are the case narratives provided by the Applicant for the subjects experiencing oropharyngeal pain, toothache, and vaginal hemorrhage related adverse reactions taking Femlyv:

Study 0001.2

- **Subject (b) (6) (vaginal hemorrhage):**
  Four days after receiving single dose of Femlyv without water the patient experienced vaginal spotting which resolved in two days. The patient also experienced vaginal bleeding between menses with clots six days after receiving a single dose of the reference drug, Minastrin, which resolved in one day. These adverse events were considered unrelated and "unlikely related" to the study drug.

  Clinical Review comment:
  We disagree with the Applicant's assessment of causality of the adverse event of vaginal hemorrhage (spotting and bleeding) in this subject. The vaginal hemorrhage was noted to be reported as mild symptoms of spotting with Femlyv and vaginal bleeding with Minastrin. A single dose of a COC is unlikely to cause clinically significant spotting or bleeding but could be related to irregular spotting or bleeding. There was no reference to which day in the subject's menstrual cycle that the study drug or reference drug were given during each Treatment Period. This adverse reaction resolved without further treatment.

- **Subject (b) (6) (oropharyngeal pain):**
  Twelve hours after receiving a single dose of Femlyv without water, the subject developed a sore throat (oropharyngeal pain). The following day, the subject tested positive for COVID-19. The oropharyngeal pain resolved in two days without treatment and COVID-19 resolved in seven days. The adverse event was considered to be "unrelated" to the study drug.

  Clinical Review Comment:
  We agree with the Applicant's assessment of causality of the adverse event of oropharyngeal pain in this subject. As the oropharyngeal pain could be a symptom of COVID-19, the pain is unlikely related to the study drug as there was no indication that the

tablet did not appropriately resolve or caused a significant oropharyngeal ulcer or issue. There is no evidence that any formulation of oral contraceptive tablets results in significant oropharyngeal irritation unless the tablet is not swallowed or taken as directed.

- **Subject (b) (6) (toothache):**
  Nine days after receiving a single dose of Femlyv without water, the subject experienced a toothache that resolved within 3 hours without treatment. This adverse event was considered "unrelated" to the study drug.

  Clinical Review comment:
  We agree with the Applicant's assessment of causality of the adverse event of toothache in this subject. The toothache is unlikely related to a single dose of the drug product as the subject developed symptoms well after the drug was administered.

Study 0002.1

- **Subject (b) (6) (oropharyngeal pain):**
  Twenty-eight days after receiving single dose of Femlyv with food, the subject developed oropharyngeal pain (sore throat). This was associated with cough, chest pain and respiratory chest infection. She received antibiotics and the oropharyngeal pain resolved in 1.3 days. This adverse event was considered to be "unrelated" to the study drug.

  Clinical Review comment:
  We agree with the Applicant's assessment of causality of the adverse event of oropharyngeal pain in this subject. The oropharyngeal pain is unlikely related to a single dose of the study drug as the subject developed symptoms well after the drug was administered.

Study 0003.4

- **Subject (b) (6) (vaginal hemorrhage):**
  On day 20, two hours after taking daily Femlyv, the subject began vaginal spotting (vaginal hemorrhage). The following day, on day 21 the subject reported vaginal bleeding (menstrual disorder) with early menses. On day 22 the subject heavier bleeding lasting 1 day. All bleeding resolved on Day 26, two days after completing the investigational study and drug. These adverse events were considered "possibly related" to the study drug.

  Clinical Review comment:

We agree with the Applicant's assessment of causality of the adverse event of vaginal hemorrhage in this subject. Early menstrual bleeding (bleeding toward the end of the active pills of a COC pack) can be a normal finding with the first or second COC pack. Bleeding usually improves with continued COC use. The bleeding was likely related to study drug, but the event was not severe orserious and resolved without medical intervention.

- **Subject (b) (6) (vaginal hemorrhage):**
  Four days after receiving the last dose of Femlyv, on day 28, the subject developed 6 hours of vaginal spotting (vaginal hemorrhage). The subject had been on a COC six days prior to her first dose of Femlyv. This adverse event was considered "possibly related" to the study drug.

  Clinical Review comment:
  We agree with the Applicant's assessment of causality of the adverse event of vaginal hemorrhage(spotting) in this subject. This was likely a withdrawal bleed related to the study drug and no medical intervention was needed.

- **Subject (b) (6) (vaginal hemorrhage):**
  Prior to receiving her Day 12 dose, the subject experienced vaginal spotting (vaginal hemorrhage) with a 5-day duration and the subject continued the study drug per protocol. This adverse event was considered "possibly related" to the study drug.

  Clinical Review comment:
  We agree with the Applicant's assessment of causality of the adverse event of vaginal hemorrhage (spotting) in this subject. The patient developed breakthrough bleeding (BTB). This can be a normal finding when beginning a COC and is likely related to the study drug. No medical intervention was needed.

- **Subject (b) (6) (vaginal hemorrhage):**
  On Day 13, the subject experience vaginal bleeding (vaginal hemorrhage) and dysmenorrhea (menstrual cramps). Dysmenorrhea resolved on Day 19 and the vaginal bleeding on Day 25 of the study. Both adverse events were considered "possibly related" to the investigational drug.

  Clinical Review comment:
  We agree with the Applicant's assessment of causality of the adverse event of vaginal hemorrhage (bleeding) in this subject. The subject developed BTB and dysmenorrhea. Both events can persist until the end of the COC pack. These gynecologic adverse events

were likely related to study drug but were not serious or significant and resolved without medical intervention.

- **Subject (b) (6) (vaginal hemorrhage)**
  On Day 10, the patient developed vaginal bleeding (vaginal hemorrhage). The bleeding resolved by Day 24 of the study. This adverse event was considered "possibly related" to the study drug.

  Clinical Review comment:
  We agree with the Applicant's assessment of causality of the adverse event of vaginal hemorrhage (bleeding) in this subject. The subject developed BTB which continued for the remainder of the study and can be a normal finding the first month of taking a COC. This event was likely related to the study drug and the event resolved without medical intervention.

- **Subject (b) (6) (vaginal hemorrhage)**
  On Day 14, the subject developed a single episode of vaginal spotting (vaginal hemorrhage). Three days after the last dose, Day 27, the subject experienced an irregular period (menstrual disorder) with a duration of one day. This event was considered "possibly related" to study drug.

  Clinical Review comment:
  We agree with the Applicant's assessment of causality of the adverse event of vaginal hemorrhage (spotting and bleeding) in this subject. The subject experienced a single episode of BTB and a withdrawal bleed with a duration of 1 day. Both events were likely related to the study drug but were not considered serious, clinically significant and resolved without medical intervention.

<u>Clinical Review Summary of the Adverse Reactions related to Gynecologic conditions:</u>

Vaginal spotting, vaginal bleeding (termed vaginal hemorrhage by the Applicant) and dysmenorrhea were noted predominately in the multiple dose study. After review of these case report narratives, these adverse reactions were all reported as known labeled adverse reactions associated with COC use. The adverse reactions related to Femlyv and oropharyngeal pain did not appear to be related to use of the study drug, but likely to other participant issues. The safety profile of Femlyv based on the adverse event reporting and review of the adverse reactions does not appear to be clinically different from that of the approved product, Minastrin 24 Fe and labeling will reflect the risk profile obtained from Minastrin 24 Fe.

8.6 Safety Analyses by Demographic Subgroups

Not applicable.

8.7 Specific Safety Studies/Clinical Trials

8.7.1 Study 0003.4

8.7.1.1 Study Design

Overview and Objective

This Phase 1 multiple-dose, uncontrolled, one-period study determined the oral irritation potential following daily use of Femlyv oral disintegrating tablet (ODT).

The primary objective was to determine the potential for oral irritation of Femlyv ODT following daily use of the active formulation over a 24-day treatment period. The secondary objective was to evaluate the safety and tolerability of Femlyv ODT.

Trial Design

Study 0003.4 was an open-label, multiple-dose, one-period study involving 55 healthy nonpregnant female volunteers at a single-center located in Tempe, Arizona. The investigational product was administered by qualified personnel at the clinical research center in the morning on Days 1, 3, and 10. The investigational product was self-administered by the study subjects Days 2, 4 through 9, and 11 through 24.

Key inclusion criteria included the following:

1. Healthy female volunteers between 18 and 45 years, inclusive
2. Regular cyclic menses with a length of 21 to 35 days (subjects who were recently postpartum or post-abortion must have had at least 2 regular menstrual cycles)
3. Non-smoker or ex-smoker for at least 3 months
4. Body mass index (BMI) 18 -35 kg/m_2, inclusive
5. Willingness to use one of the following non-hormonal methods of contraception prior to the first dosing and throughout the study:
    a. Abstinence
    b. Non-hormonal IUD in place for at least 3 months prior to first dosing
    c. Barrier method (e.g., condom, diaphragm) with spermicide
    d. Permanent sterilization
6. Willingness to switch to the investigational drug from oral, intravaginal, or transdermal contraceptives from Day 1 through Day 29 of study.

Key exclusion criteria included the following:

1. Pregnant or lactating
2. Perimenopausal or postmenopausal
3. Visible disease or condition of the oral mucosa at the screening or baseline visit which will interfere with the oral irritation evaluation.
4. Contraindication for the use of hormonal contraceptive, such as
    a. History of thrombophlebitis or thromboembolic disorders
    b. Known or suspected clotting disorders
    c. Cerebral vascular or coronary artery disease
    d. Known or suspected carcinoma of the breast
5. History of steroid-dependent malignancy, including malignant melanoma
6. Use of progestational implants, progestin, estrogen or estrogen/progestational injectable drug therapy within 9 months of enrollment
7. Use of hormonal intrauterine system within 3 months of enrollment
8. Dentures which reduce oral contact with the investigational product
9. Known or history of migraines
10. Use of any substances to be strong inhibitors or strong inducers of CYP3A enzymes
11. COVID-19 vaccination within 14 days prior to Day 1.
12. Concomitant use of hormonal contraceptives beyond day prior to investigational drug.

The test drug was administered by qualified staff personnel at the clinical research center in the mornings on Days 1, 3 (+/-1) and 10 (+/-2) under direct supervision. Subjects were instructed to place the tablet on the tongue and allow the tablet to dissolve in the mouth and swallow with saliva. Water was not used. The subjects were instructed to not swallow whole, crush, split, or chew the ODT investigational drug. Dates and times of the drug product administration were recorded. Study subjects were required to complete a daily dosing diary with the date and time of the doses that were administered at home and to keep the same dosing schedule from Day 1, (+/- 1 hour). When the subjects were out of the clinical research unit, follow-up phone calls, e-mails, and/or text messages were performed, approximately every 2 days, to assist and verify subjects' compliance with treatment and questioned about the occurrence of adverse events.

Oral soft-tissue examinations were performed at screening visit, baseline (pre-dose) and 30 ± 5 minutes post dosing at each clinic visit. The condition of the lips, buccal mucosa, labial mucosa, sublingual mucosa, attached gingivae, tongue, hard/soft palate, uvula, and oropharynx were rated as normal (Score 0) or abnormal (Scores 1-3). The oral soft tissues were examined for irritation/inflammation and/or infection. Any abnormalities were described, and the examiner indicated whether the abnormality was attributable to the study product.

Irritation/inflammation of each area was scored using the following scale:

Score	Irritation/inflammation characterization
0	Normal
1	Erythema plus slight edema
2	Moderate edema and /or edema (i.e., beginning of tissue breakdown or slough
3	Severe irritation/inflammation (i.e., definite blistering, ulceration, or epithelial slough)

Source: Study Report Body CA33717 page 26/126

Figure 1 illustrates schedule of study events.

Figure 1: Study 0003.4 Schedule of Study Events

Study Procedures [a]	S [b]	Study Days										FU [c]
Days →		-1	1			2	3 (± 1)	4-9	10 (± 2)	11-24	25 (± 2)	29 (± 2)
Hours →			Baseline/P [d]	0	0.5							
Administrative Procedures												
Informed Consent	X											
Inclusion/Exclusion Criteria	X		X									
Medical History	X											
Safety Evaluations												
Full Physical Examination [e]	X											
Abbreviated Physical Examination [e]												X
Pelvic Examination [e]	X											
PAP Smear, HPV, Gonorrhea, and Chlamydia Test	X											
Height	X											
Weight	X	X [f]										
12-Lead Safety ECG	X	X [f]										X
Vital Signs (HR, BP, RR, and T)	X		X				X [g]		X [g]		X [g]	X
Hem, Serum Chem [h], Coag, and UA	X	X [f]										X
Serum Preg Test	X		X									X
Urine Drug Screen	X		X									
Urine Alcohol Screen			X									
Cotinine Test	X											
HIV/Hepatitis Screen	X											
AE Monitoring	X		X					X				
ConMeds Monitoring	X		X					X				
Study Drug Dosing and Irritancy Assessment												
Oral Soft-Tissue Examination [i]	X		X		X [j]		X [j]		X [j]		X [j]	X
MP0008 Dosing at CRU				X			X		X			
MP0008 Dosing Out-of-CRU [k]						X		X		X		
Other Procedures												
Confinement in the CRU			X									
Visit and Return Visits	X	X					X		X		X	X

a For details on Procedures, refer to Section 13 of the protocol (Appendix 16.1.1).
b Within 28 days prior to the first dosing. Upon successful completion of the screening procedures, eligible subjects who were not currently users of oral contraceptives were asked to schedule a baseline visit at the CRU on the first day (or within 7 days after the start) of their next menstrual cycle. Oral contraceptive users were asked to schedule the baseline Visit 5 (±2) days (if they had been using a 24-day product) or 8 (±2) days (if they had been using a 21-day product), after their last scheduled dose of the active formulation of their usual product.
c All subjects who received at least one dose of study drug (including subjects who terminated the study early) returned to the CRU on Day 29 (±2 days) or
5 (±2) days after the last dose of study drug, for follow-up procedures and to determine if any AE had occurred since the last study visit.
d Subjects visited the CRU on Day -1, and were admitted to the CRU on Day 1, at the time indicated by the CRU. Subjects may have been admitted earlier than Day 1 for COVID-19 testing not related to study protocol as per CRU requirements.
e Symptom-driven physical/pelvic examinations may have been performed at other times, at the PI's or designee's discretion.
f Performed on Day -1 if the screening examination was more than 48 hours prior to Day 1.
g Performed prior to dosing. If Day 25 procedures were performed on Day 23 or Day 24, procedures were performed prior to dosing.
h Samples for serum chemistry were obtained after a fast of at least 8 hours, however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to when the serum chemistry sample was taken.
i At screening and at all post-baseline examinations, oral soft-tissue examination was performed by the PI or designee. At baseline the oral soft-tissue examination was performed by a qualified professional.
j Performed 30 (±5) minutes postdose. If Day 25 procedures were performed on Day 23 or Day 24, procedures were performed 30 (±5) minutes postdose.
k Prior to release from the CRU, subjects received a properly labeled container with the appropriate MP0008 doses which was to be self-administered by subjects out-of-CRU. Subjects were instructed to self-administer the study drug approximately at the same time they received their first dose at the CRU (±1 hour of dosing time on Day 1). Subjects were given diaries to record the time of their self-administered doses, whether the dose was accompanied or not by food or fluid, and any missed doses. Subjects returned the container/blister pack(s) (empty or not) and their diary at the next visit. Out-of-CRU dosing was monitored via attempted phone calls, e-mails, or text messages where subjects were reminded to take their medication and queried about the occurrence of AEs.
Abbreviations: AE = Adverse event(s), BP = Blood pressure, Chem = Chemistry, Coag = Coagulation, ConMeds = Concomitant medication, COVID-19 = Coronavirus disease 2019, CRU = Clinical research unit, ECG = Electrocardiogram, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HPV = Human papillomavirus, HR = Heart rate, P = Predose, PAP = Papanicolaou, PI = Principal Investigator, Preg = Pregnancy, RR = Respiratory rate, S = Screening, T = Temperature, and UA = Urinalysis.
Source: Study MP0008-0003.4-PR/CA33717, Study Report Body, Table 9-1, page 22.

The clinical protocol restricted the use of the following:

1. Use of tobacco products was not allowed within 3 months prior to screening until the end of the study.
2. Abstinence from consumption of alcohol for 24 hours prior to Days 1 (+/- 1 day, 3 (+/-1 day), and 10 (+/- 2 days), and on Day 25 (+/- 2 days).
3. Avoidance of strenuous physical exercise which could cause muscle aches or injury from the screening visit until completion of the study.

Subjects withdrawn or dropped out after randomization could not be replaced.

Study Endpoints

The primary endpoint was the assessment of oral irritation/inflammation of the soft tissue in the oral cavity.

The secondary endpoints included adverse events, clinical laboratory test results, and physical examination findings.

Statistical Analysis Plan

Continuous variables were summarized with the following descriptive statistics: n (number of subjects), arithmetic mean, standard deviation (SD), and minimum, median, and maximum values. Categorical data were summarized with frequencies and percentages.

Protocol Amendments

No significant protocol amendments were submitted that required clinical review.

8.7.1.2 Study Results

Compliance with Good Clinical Practices

An attestation to conducting the study in compliance with Good Clinical Practice (GCP) guidelines was submitted in this application.

Financial Disclosure

The investigators who participated in Study 0003.4 certified to not having a financial interest related to the outcome of this study.

Patient Disposition

Of the 55 study participants who were enrolled and subsequently randomized, 55 completed the study. Although, one subject missed eight doses in error. No subjects prematurely discontinued study participation.

All subjects enrolled in the study received at least one dose of the investigational product and underwent oral irritation/inflammation assessments. They constitute both the Safety Analysis population as well as the Oral Irritation/Inflammation population.

Protocol Violations/Deviations

There were no significant protocol violations or deviations reported.

Table of Demographic Characteristics

The demographic characteristics of the safety analysis population for Study 0003.4 are shown in Table 13.

Table 13: Study 0003.4 - Demographic Characteristics of the Safety Analysis Population

Demographic Parameters	Subject Data (n= 55)
Age	
Mean years (SD)	33.6, (6.55)
Median (years)	33
Min, max (years)	20, 45
Race, n (%)	
White	49 (89%)
Black or African American	4 (7%)
American Indian or Alaska native	1 (2%)
Native Hawaiian or Pacific Islander	1 (2%)
Ethnicity	
Hispanic or Latino	44 (80%)
Not Hispanic or Latino	11 (20%)
Body Mass Index (kg/m^2)	
Mean (SD)	27.1 (3.93)
Median	27.1
Min, max	18.1, 34.98

Source: Study MP0008-0003.4-PR/CA33717, Study Report Body, Table 11-1, page 29.

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

Treatment groups were similar in baseline characteristics.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Subjects were monitored for treatment compliance via directly observed product administration at the clinical research site in the morning on Days 1, 3, 10, and 25. Dates and times of the drug product administration were recorded.

Study subjects were required to complete a daily dosing diary with the date and time of the doses that were administered at home. Monitoring via phone calls, e-mails, and/or text messages was performed to verify the subjects' compliance with treatment.

Concomitant medications were administered to 7 study subjects. Table 14 summarizes the information regarding concomitant medications.

Table 14: Study 0003.4 - Concomitant Medications Administered to Study Subjects

Study Subject Number	Investigational product	Concomitant drug names(s)	Indication
(b) (6)	Active	Paracetamol	Viral syndrome
	Active	Paracetamol	Mid lower back pain
	Active	Penicillin VK	Streptococcal pharyngitis
	Active	Paracetamol	Frontal headache
	Active	Paracetamol	Temporal headache
	Active	Dextromethorphan hydrobromide and guaifenesin (Vicks cough syrup) Acyclovir topical	Cough Cold sore
	Active	Paracetamol	Headache

Source: Study 0003, Appendix 16.2.5.5. Prior and Concomitant Medications.

Efficacy Results – Primary Endpoint

There were no efficacy determinations in Study 0003.4.

Data Quality and Integrity

Data quality and integrity issues were not identified by the Applicant or the clinical reviewer.

Efficacy Results – Secondary and other relevant endpoints

Following administration of Femlyv ODT, oral abnormalities were seen in only 6 out of the 55 subjects. No irritation/inflammation score > 1 (erythema plus slight edema) was identified. There were no discontinuations of the investigational drug due to oral irritation adverse events and resolution of any oral irritation occurred with continued use.

The Applicant concluded that there were no issues identified with the oral tolerance of Femlyv

Clinical Review comment:
Although 2 subjects had erythema on Day 3, the areas of erythema in these subjects were not similar in location within the oral cavity or the overall surface area of erythema noted. The oral abnormality in each subject resolved with continued use and the inflammation was not severe that the subjects discontinued the investigational product. Overall, the investigational product was well tolerated by the study subjects and without significant potential for oral irritation or inflammation with continued use for 24 consecutive days.

The clinical reviewers concur with the Applicant that the results of the clinical oral irritation study do not show any oral tolerability issues that would preclude approval.

8.8 Additional Safety Explorations

8.8.1 Human Carcinogenicity or Tumor Development

Not applicable.

8.8.2 Human Reproduction and Pregnancy

Not applicable.

8.8.3 Pediatrics and Assessment of Effects on Growth

An agreed initial pediatric study plan iPSP is in place. Additional pediatric clinical studies are not planned or needed.

8.9 Safety in the Postmarket Setting

8.9.1 Safety Concerns Identified Through Postmarket Experience

The risks associated with hormonal contraceptives are well-known and consistent with CHC class safety labeling. There is extensive postmarketing experience with COCs containing 1 mg NA/0.02 mg EE and class labeling will be applied to this new ODT formulation. No new concerning safety signals or trends have emerged from assessment of the postmarketing experience.

In addition, recent PADERs for the reference drug (Minastrin 24 Fe) were reviewed by this clinical review team and at the time of the S/E determination. Safety data from these PADERS did not demonstrate any new safety signals or trends that required additional safety labeling changes.

8.9.2 Expectations on Safety in the Postmarket Setting

There is no reason to suspect that Femlyv would have any other additional safety concerns that differ from Minastrin®24 Fe chewable tablets.

8.9.3 Additional Safety Issues From Other Disciplines

Not applicable.

8.10 Integrated Assessment of Safety

A safety evaluation for each individual study, 0001.2, 0002.1, 0004.0, 0003.4 was performed. An integrated safety analysis was performed combining the four studies. Significant safety issues did not arise in the pharmacokinetic or oral tolerability studies of this product. Adverse event frequencies in the study population were comparable to adverse event frequencies in the reference product. The risk of serious adverse events is not expected to differ from the risk of

these events in the cross-referenced product.

Overall, the safety of Femlyv has been demonstrated through bioequivalence to the approved Minastrin 24 Fe product and supported by the postmarketing safety profile identified in the 120-day safety update, PADERs and postmarketing safety experience with hormonal contraceptives.

9 Advisory Committee Meeting and Other External Consultation

Not applicable for this new formulation of an approved combined oral contraceptive product.

10 Labeling Recommendations

10.1 Prescription Drug Labeling

Labeling recommendations have been made to align product labeling with that of the cross-referenced product, the current FDA's guidance for industry: "Labeling for Combined Hormonal Contraceptives," and knowledge of drug class effects. Drug labeling negotiations with the Applicant included the following changes to align with current class labeling:

- Highlights of Prescribing Information
- Indications and Usage
- Dosage and Administration
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Drug Interactions
- Use in Specific Populations
- Overdosage

10.2 Nonprescription Drug Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

A Risk Evaluation and Mitigation Strategy was not required for this product. Given the favorable safety profile of this drug, there are no additional risk management strategies required beyond the recommended labeling and routine postmarketing adverse event review.

12 Postmarketing Requirements and Commitments

Not required for this NDA application submission.

13 Appendices

13.1 References

There are no clinically related references submitted that negatively impact approval of Femlyv ODT. The clinical review team for this application assessed the published literature and did not identify any recent medical literature that negatively impacts approval.

13.2 Financial Disclosure

There were no financial disclosures to report.

Covered Clinical Study (Name and/or Number): MP0008-0001.2-PR/CA33502; MP0008-0002.1-PR/CA33511; MP0008-0004.0-PR/CA38951; MP0008-0004.0-PR/CA33717

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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

/s/

CONSTANCE I GLASS
07/17/2024 09:48:07 AM

IOANNA A COMSTOCK
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GERALD D WILLETT
07/17/2024 10:52:35 AM

AUDREY L GASSMAN
07/17/2024 02:03:15 PM