CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216285Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	216285
Priority or Standard	Standard
Submit Date(s)	August 30, 2021
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Division/Office	ORPURM/DUOG
Reviewer Name(s)	Ioanna Comstock, MD
Review Completion Date	May 23, 2022
Established/Proper Name	Drospirenone Chewable Tablets
(Proposed) Trade Name	Pending
Applicant	Exeltis USA, Inc.
Dosage Form(s)	Chewable tablets
Applicant Proposed Dosing Regimen(s)	Drospirenone 3.5 mg chewable tablets once daily for 24 days followed by one inactive chewable tablet once daily for 4 days
Applicant Proposed Indication(s)/Population(s)	Prevention of pregnancy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Females of childbearing potential

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Glossary

AE	adverse event
AR	adverse reaction
ATE	arterial thromboembolism
BA	bioavailability
BE	bioequivalence
BMI	body mass index
BRF	Benefit Risk Framework
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHC	combination hormonal contraception
COA	clinical outcome assessment
COC	combination oral contraception
DRSP	drospirenone
DSUR	Development Safety Update Report
DUOG	Division of Urology, Obstetrics, and Gynecology
ECG	electrocardiogram
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GCP	good clinical practice
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IUS	intrauterine systems
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
OPQ	Office of Pharmaceutical Quality
ORPURM	Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OSIS	Office of Study Integrity and Surveillance
PADER	Periodic Adverse Drug Experience Report
PD	pharmacodynamics
PK	pharmacokinetics
PLLR	Pregnancy and Lactation Labeling Rule
PLR	Physician Labeling Rule
PMR	postmarketing requirement
POP	progestin-only pill
PREA	Pediatric Research Equity Act

PRO	patient reported outcome
PT	preferred term
REMS	risk evaluation and mitigation strategy
RLD	reference listed drug
SAE	serious adverse event
TEAE	treatment emergent adverse event
VTE	venous thromboembolism

1. Executive Summary

1.1. Product Introduction

This application seeks approval for drospirenone (DRSP) 3.5 mg chewable tablets. The Applicant refers to the product as drospirenone 3.5 mg chewable tablets and that designation will be used in this review. The proposed proprietary names for this product that have been submitted thus far have not been accepted by the Agency. The Sponsor refers to the proposed product by its established name, Drospirenone Chewable Tablets, until a proprietary name can be agreed upon after NDA approval.

Drospirenone 3.5 mg chewable tablets is a progestin-only contraceptive product indicated for use by females of reproductive potential for the prevention of pregnancy. The chewable tablets 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.

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 BLCL-DRS-FDA-04 demonstrates the pharmacokinetics of drospirenone 3.5 mg chewable tablets are within the bioequivalence margin. I recommend approval of drospirenone 3.5 mg chewable tablets for prevention of pregnancy.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The drospirenone 3.5 mg chewable tablet in this submission is the first chewable progestin-only pill to be considered for approval. This new dosage form provides an additional contraceptive option for women who prefer or require a chewable tablet. The product demonstrates bioequivalence to the cross-referenced drug – drospirenone 4 mg tablets (Slynd®). There were no safety concerns identified in the bioequivalence, food effects and oral irritation studies for the chewable tablet. There were no new safety signals or increased risk for an adverse reaction identified in the post-approval safety reports of Slynd. The benefit-risk assessment for this chewable product is similar to that of the Slynd swallowed tablet and acceptable for approval.

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: • Drospirenone-containing contraceptive tablets (combination and progestin-only products) • Chewable combination oral contraceptive tablets (See Section 2.2 for further information)	Several combination oral contraceptives have been approved in chewable dosage form. However, there are currently no approved progestin-only chewable tablets. This dosage form may provide benefit to women who prefer not to or are unable to swallow tablets and/or for whom progestin-only contraception is sought/ recommended.

Benefit	Bioequivalence is demonstrated (See Section 6.1 for further information) Progestin-only pills may be preferred in certain patient populations as the estrogen component in combination oral contraceptive pills confers additional risk to users.	This product provides a bioequivalent chewable dosage form of drospirenone 4 mg tablets (Slynd). This chewable tablet must be taken exactly as directed to ensure its safety and efficacy.
Risk and Risk Management	Combination oral contraceptives containing drospirenone and ethinyl estradiol may be associated with a higher risk of venous thromboembolism (VTE) than those containing other progestins. It is unknown whether the risk of VTE is increased with drospirenone alone. • Thromboembolic events: No cases of VTE or arterial thromboembolism (ATE) were reported in the developmental studies of the reference listed drug (Slynd) or drospirenone 3.5 mg chewable tablets. The progestin drospirenone has anti-mineralocorticoid activity, including the potential for hyperkalemia in high-risk females. • Hyperkalemia: There were four cases of mild hyperkalemia during the clinical development of drospirenone 3.5 mg chewable tablets. All cases involved mild potassium elevations and/or isolated increases that resolved spontaneously while still on study medication. None were associated with clinically significant adverse reactions or evidence of electrocardiogram (ECG) changes. Some progestin-only products have been associated with clinically significant bone loss due to a chronic hypoestrogenic state.	Labeling regarding thromboembolic disorders for the chewable dosage form will be similar to that of Slynd. Routine postmarketing surveillance of voluntary reporting for VTEs and ATEs with the DRSP chewable POP will be acceptable. With no new safety signals identified with the chewable tablets the label for DRSP 3.5 will include adverse reaction percentages based on the much larger Slynd database. The current restrictions regarding the potential for hyperkalemia that are present in the labeling for DRSP-containing products should be maintained in the product label for the DRSP chewable tablet.

	• Bone mineral density: The postmarketing bone mineral density study of Slynd is currently underway for adults and adolescents (see Section 12 for specifics and the plan for the chewable dosage form) There were no safety concerns identified in the bioequivalence, food effects and oral irritation studies. Review of Slynd post-approval periodic adverse event reports (PADERS) has not shown any new safety signals or increased risk for VTEs, ATEs, or hyperkalemic adverse events.	

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.			

In the two pharmacokinetic studies (Studies BLCL-DRS-FDA-04 and BLCL-DRS-FDA-06), an assessment of the subjects' acceptability of the proposed product's taste and easiness of chewing was performed. This analysis of the subjects' sensory experience with chewing the proposed drug product was not done in consultation with the Division of Clinical Outcome Assessment (DCOA) and is considered exploratory in regard to labeling. The reader is referred to Sections 6.1.1 and 6.2.1 for further information regarding these analyses.

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, including chewable 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)
    - Implant
    - Injectable
    - Hormone releasing intrauterine systems (IUS)
- Non-hormone releasing intrauterine systems
- Sterilization methods
- Barrier methods and spermicidal agents
- Natural-planning methods
- Abstinence

DRSP is a fourth-generation progestin derived from the aldosterone antagonist spironolactone, a potassium-sparing diuretic used to treat hypertension. The contraceptive mechanism of action for DRSP is inhibition of follicular stimulation and ovulation by the suppression of luteinizing hormone. Another possible contraceptive mechanism of action for progestins as a class is alteration of the cervical mucus to inhibit sperm transport.

There are six DRSP-containing contraceptive products approved in the United States which include five combination oral contraceptives and one progestin-only pill (POP).
The following table provides an overview of these products:

Table 1. Drospirenone-Containing Contraceptive Products Approved in the United States

Product NDA number(s)	Year of Approval	DRSP	Estrogen	Regimen	Indication(s)
Yasmin® 21098	2001	3 mg	0.03 mg EE	DRSP/EE x 21 days Inactive tabs x 7 days*	Prevention of pregnancy
Yaz® 21676 21873 22045	2006 2006 2007	3 mg	0.02 mg EE	DRSP/EE x 24 days Inactive tabs x 4 days*	1. Prevention of pregnancy 2. PMDD 3. Moderate acne
Safyral® 22574	2010	3 mg	0.03 mg EE	DRSP/EE/FS x 21 days FS tabs x 7 days*	1. Prevention of pregnancy 2. Raise folate levels
Beyaz® 22532	2010	3 mg	0.02 mg EE	DRSP/EE/FS x 24 days FS tabs x 4 days*	1. Prevention of pregnancy 2. PMDD 3. Moderate acne 4. Raise folate levels
Slynd® 211367	2019	4 mg	N/A	DRSP x 24 days Inactive tabs x 4 days*	Prevention of pregnancy
Nextstellis 214154	2021	3 mg	14.2 mg E4	DRSP/estetrol x 24 days Inactive tabs x 4 days*	Prevention of pregnancy

DRSP = drospirenone; EE = ethinyl estradiol; FS = folate supplement (levomefolate calcium); PMDD = premenstrual dysphoric disorder, E4 = estetrol
*placebo tablets
Sources: Drugs@FDA, Adapted from Slynd® NDA 211367 Multidisciplinary Review

This product would represent the only chewable drospirenone-containing POP approved and marketed in the United States.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The reference product, Slynd® (NDA 211367), containing (b) (4) 4 mg DRSP, was approved in the US in May 2019 via the 505(b)(2) regulatory pathway with a clinical bridge to the drospirenone component of the reference listed drug YAZ (DRSP 3 mg/ethinyl estradiol 0.02 mg) (NDA 021676). Slynd is approved and marketed in 48 countries (including countries in Europe, Middle East, Australia, Latin America, and the US) as a progestin-only pill for the prevention of pregnancy.

The Applicant has developed a new formulation of a chewable tablet dosage form containing 3.5 mg of DRSP. The Applicant conducted a relative bioavailability (BA) study (BLCL-DRS-FDA-04) comparing the proposed 3.5 mg DRSP chewable tablet to the cross-referenced product, Slynd, after single oral administration that demonstrated bioequivalence to Slynd. Therefore, the bioequivalence of the 3.5 mg DRSP chewable tablet to the listed drug YAZ, is supported by the pivotal BA study included in this NDA 216285 application.

This product serves as an alternative contraceptive option for females who may have difficulty swallowing whole tablets. DRSP 3.5 mg chewable tablets is to be taken daily for 24 days followed by a placebo tablet taken daily for 4 days.

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 with the Division occurred under PIND 146207.

3.3. Foreign Regulatory Actions and Marketing History

There are no relevant foreign regulatory actions on this chewable product. The cross-referenced product, Slynd, is approved and marketed worldwide. There have been no regulatory actions taken in any country for safety concerns regarding Slynd 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 an analytical inspection and a clinical inspection had been conducted within the surveillance interval (June 2019 and August 2019, respectively). The final classification for the inspection was No Action Indicated (NAI).

4.2. Product Quality

The reader is referred to the Quality review and to Dr. Willett's CDTL review for further information.

4.3. Clinical Microbiology

The reader is referred to the Quality review and to Dr. Willett's CDTL review for further information.

4.4. Nonclinical Pharmacology/Toxicology

The primary Pharmacology/Toxicology reviewer, Dr. Andrea Benedict, PhD found that the application for drospirenone 3.5 mg chewable tablets did not raise any toxicological concerns and recommended approval.

The reader is referred to the Pharmacology/Toxicology review and to Dr. Willett's CDTL review for further information.

4.5. Clinical Pharmacology

The Clinical Pharmacology team has determined that drospirenone 3.5 mg chewable tablets meets the bioequivalence criteria for approval. Dr. Mohammad (Ahsan) Akbar, PhD stated in his primary review:

> *The Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology (DCEP) has reviewed the clinical pharmacology information submitted for NDA 216285 (DRSP 3.5 mg chewable tablets). We find that the current application is acceptable for approval from the clinical pharmacology standpoints.*

The reader is referred to the Clinical Pharmacology review and to Dr. Willett's CDTL review for further information.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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

Table 2: Listing of Clinical Studies

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	Subject DSP	Study Population	No. of Centers and Countries
Studies to Support Efficacy and Safety							
2020-FLE1-SLINC-PK-04 (BLCL-DRS-FDA-04)	Comparative BA/BE Randomized Open-label Laboratory-blinded Single-dose 6-sequence 3-treatment 3-period Crossover Chewable vs RLD Fasting only	**Test-1** = DRSP 4 mg chewable tablet, chewed thoroughly then swallowed without water **Test-2** = DRSP 3.5 mg chewable tablet, chewed thoroughly then swallowed without water **Reference** = Slynd® tablet swallowed whole with water	Pharmacokinetics	Single-dose 14-day washout	48 ENR 10 DC 39 AN	Healthy female volunteers Age 18-40	Single-center Portugal
2020-FLE1-SLINC-PK-06 (BLCL-DRS-FDA-06)	Comparative BA Randomized Open-label Laboratory-blinded 2-sequence 2-treatment 2-period Crossover	**Test** = 10 hr fast; high fat/high calorie meal; wait 30 minutes then DRSP 3.5 mg chewable tablet, chewed thoroughly then swallowed without water	Pharmacokinetics	Single-dose 14-day washout	22 ENR 3 DC 19 AN	Healthy female volunteers Age 18-40	Single-center Portugal

	Chewable vs RLD Fasting/Fed	**Reference** = 10 hr fast; DRSP 3.5 mg chewable tablet, chewed thoroughly and swallowed without water					
Studies to Support Safety							
2020-FLE1-SLINC-CE-07 (BLCL-DRS-FDA-07)	Oral irritation Safety/tolerability Open-label 1-period Chewable formulation only	DRSP 3.5 mg chewable tablet once daily in the morning for 24 consecutive days of active tablet followed by 4 consecutive days of inactive tablet	Oral irritation and abrasion Adverse events	Multiple-dose treatment 28 days	40 ENR 0 DC 40 AN	Healthy female volunteers Age 18-45	Single-center Portugal

DRSP = drospirenone; BA = bioavailability; BE = bioequivalence; RLD= reference listed drug; DSP = disposition; ENR = enrolled; DC = discontinued after first dosing; AN = analyzed; Slynd® = drospirenone 4 mg tablet

5.2. Review Strategy

The clinical review for this application entailed the comprehensive review of the following:

- The oral irritation study [Study 2020-FLE1-SLINC-CE-07 (BLCL-DRS-FDA-07)]
- All adverse event data collected for the three pivotal trials in this submission
- The four-month safety update submitted with the application
- Current references and global postmarketing data

An integrated summary of effectiveness (ISE) and integrated summary of safety (ISS) were not required for this application.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. 2020-FLE1-SLINC-PK-04 (BLCL-DRS-FDA-04)

6.1.1. Study Design

Overview and Objective

This laboratory-blinded, randomized, 6-sequence, 3-treatment (Test-1, Test-2, and reference products), 3-period crossover study compared the bioavailability of drospirenone 4 mg chewable tablets (Test-1) and drospirenone 3.5 mg chewable tablets (Test-2) with the approved reference product, Slynd®.

The secondary objectives were 1) to assess the subjects' sensory experience to the test products and 2) to evaluate the safety and tolerability of the test products.

Trial Design

Study BLCL-DRS-FDA-04 was a single-dose, open-label, laboratory-blinded, randomized, crossover study involving 48 healthy nonpregnant female volunteers at a single-center located in Porto, Portugal. Subjects were confined at the clinical research facility for at least 11 hours prior to drug administration and for a minimum of 24 hours post drug administration. Subjects received each of the three treatments for three treatment periods. Subjects were randomly assigned to one of six sequences. Doses of investigational products were administered after an overnight fasting of at least 10 hours and separated by a washout interval of 14 days.

Figure 1 illustrates the 6-sequence, 3-treatment, 3-period crossover study design.

Figure 1: BLCL-DRS-FDA-04 Study Sequences

Sequence	Period 1	Period 2	Period 3
1 (n=8)	Reference	Test-1	Test-2
2 (n=8)	Test-1	Test-2	Reference
3 (n=8)	Test-2	Reference	Test-1
4 (n=8)	Test-2	Test-1	Reference
5 (n=8)	Reference	Test-2	Test-1
6 (n=8)	Test-1	Reference	Test-2

Test-1 = DRSP 4 mg chewable tablets (test drug from batch LFD0745/LFD0745A)
Test-2 = DRSP 3.5 mg chewable tablets (test drug from batch LFD0748/LFD0748A)
Reference = Slynd® 4 mg tablets
Source: Study BLCL-DRS-FDA-04, Study Report Body, 8.3.4. Assignment of Subjects to Treatment Sequences

Key inclusion criteria included the following:

1. Healthy female volunteers between 18 and 40 years, inclusive
2. Previous use of hormonal contraceptives without complications
3. Body mass index (BMI) 18.0 - 30.0 kg/m_2, inclusive
4. Non-smoker or ex-smoker for at least 3 months
5. Regular cyclic menses or reporting regular cyclic menses prior to use of hormonal contraception
6. Willingness to use one of the following non-hormonal methods of contraception from at least 14 days prior to admission for Period 1 until the end of the study
    a. Abstinence
    b. Non-hormonal IUD
    c. Condom, cap, diaphragm, or sponge with spermicide
    d. Permanent sterilization

Key exclusion criteria included the following:

1. Pregnant or lactating
2. Perimenopausal or menopausal
3. Contraindication for the use of hormonal contraceptives, 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
    e. Known or suspected progestin sensitive cancer
    f. Abnormal genital bleeding or endometrial hyperplasia
    g. Known or suspected tumors of the liver and pituitary
4. Serum potassium above the upper limit of normal range or conditions predisposing to hyperkalemia

5. Use of combined (estrogen and progestin containing) hormonal contraceptives (e.g., oral, intravaginal, transdermal) or progestin-only pills within 14 days prior to enrollment
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. Difficulty in chewing or swallowing tablets or capsules

After an overnight 10-hour fast, subjects received a single dose of one of the investigational products (Test-1 and Test-2) or RLD in each treatment period under direct supervision. Subjects receiving either test drug were instructed to chew the tablet thoroughly and then swallow immediately without water. Subjects receiving the reference drug were instructed to swallow the tablet whole with 240 mL of water. After dosing, the oral cavity was examined to ensure the entire chewed fragments were swallowed. If fragments remained in the oral cavity, the subject was instructed to swallow them.

The subjects' acceptability of the test products was assessed and recorded within 5 minutes after the administration of each dose of the test products. The following characteristics were rated using a 5-item Likert scale:

- Assessment of acceptability of taste, mouthfeel and aftertaste with Likert scale ranging from 1 = liked to 2 = disliked
- Assessment of ease of thoroughly chewing the tablet and ease of swallowing (in case it is inadvertently swallowed) with Likert scale ranging from 1 = very easy to 5 = very difficult.

Subjects had blood samples drawn at baseline and then at pre-determined intervals after study drug administration. A 14-day washout period followed Periods 1 and 2. Figure 2 illustrates the schedule of study events.

Figure 2: BLCL-DRS-FDA-04 Schedule of Study Events

		Each Study Period			
Assessments	**Screening**	**Admission**	**Confinement[1]**	**Ambulatory[2]**	**End of study**
Written informed consent[3]	X				
Verification of eligibility criteria	X	X			
Demographic data	X				
Body height and weight	X				
Medical history	X				
Medical history update[4]		X			
Vital Signs[5]	X	X	X		X
Physical examination	X				
Physical examination update[4]		X			
Oral cavity examination	X	X	X[6]		X
Acceptability assessment (Test products, only)			X[7]		
12-lead ECG	X			X[8]	X
Clinical laboratory tests[9]	X	X		X	X
SARS-CoV-2 test		X[10]			
Pregnancy test in all females[11]	X	X			X
Drugs-of-abuse and ethanol screen	X	X			
Administration of investigational product[12]			X		
Blood sampling for drug assays[13]			X	X	
Adverse events monitoring	X	X	X	X	X

[1] From at least 11 hours before dosing to at least 24 hours post dose.
[2] Ambulatory visits at 36, 48 and 72 hours post dose.
[3] The latest version of ICF must have been signed by the subject before any study-related procedure.
[4] Clinically relevant changes were reported as adverse events.

[5] Vital signs were recorded at screening, admission, 6 and 24 hours post dose, and at the end of study or early discontinuation of subjects administered at least one dose of investigational product. Vital signs included blood pressure, pulse, and body temperature.
[6] Oral cavity examinations were performed in the test product periods at pre-dose and at approximately 30 minutes and 2 hours post dose.
[7] Subject's acceptability assessment of test products was assessed within 5 minutes post dose.
[8] At approximately 72 hours post dose.
[9] Clinical laboratory tests included hematology, general biochemistry, and coagulation studies.
[10] SARS-CoV-2 polymerase chain reaction (PCR) test was performed prior to admission to each study period.
[11] A serum pregnancy test was performed at screening and at the end of study. A urine pregnancy test was performed at admission to each study period.
[12] Investigational products were administrated in the morning, orally, after an overnight fasting of at least 10 hours. Test-1 (DRSP 4 mg chewable tablets) and Test-2 (DRSP 3.5 mg chewable tablets) products were chewed and swallowed without water; Reference product (Slynd®) was swallowed with 240 mL of water.
[13] Blood samples (4 mL each) for the determination of drospirenone plasma concentrations were collected at pre-dose; and at 0:15; 0:30, 0:45, 1:00, 1:15, 1:30, 1:45, 2:00, 2:30, 3:00, 4:00, 6:00, 8:00, 12:00, 16:00, 24:00, 36:00, 48:00 and 72:00 hours:minutes post dose.
Source: Study BLCL-DRS-FDA-04, Study Report Body**,** Table A

The clinical protocol restricted the use of the following medications:

1. Combined hormonal contraceptives (e.g., oral, intravaginal, transdermal) or progestin-only pills for 14 days prior to admission for Period 1 until the end of the study (i.e., until the last blood sample collection for pharmacokinetic assessment was obtained).
2. Any prescription medication, over-the-counter products, vitamins, food supplements, or herbal supplements for 14 days prior to admission for Period 1 until the end of the study.

The protocol further restricted the use of the following:

1. Meals and snacks served from admission to the study period until 24 hours post dose were standardized and identical in composition for all study subjects. Subjects began fasting for at least 10 hours prior to drug administration and continued fasting for at least four hours post drug administration.
2. Except for water given with the reference product (240 mL of room temperature water), no fluids were allowed from 1 hour before drug administration until 1-hour post-dose. Water was provided *ad libitum* at all other times.
3. Seville oranges, pomelo, pomegranate, starfruit, or grapefruit products were to be avoided for seven days prior to admission for Period 1 until the end of the study.
4. Chewing gum was not allowed during confinement in each study period.
5. Any methylxanthines-containing food or beverages (e.g., tea, coffee, cola, sodas, or chocolate) were not served to subjects during confinement at the clinical research facility.
6. Abstinence from consumption of alcohol for 24 hours prior to admission until the last blood sample collection for pharmacokinetic assessment in each study period.
7. Use of tobacco products was not allowed within 3 months prior to screening until the end of the study.
8. Avoidance of strenuous physical exercise within 48 hours prior to blood collection for clinical laboratory tests.

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

Study Endpoints

The primary endpoints were the pharmacokinetic parameters of drospirenone for the bioequivalence evaluation. The PK parameters of interest included C_{max} and AUC_{0-72} of drospirenone for the analysis of bioequivalence of DRSP 4 mg chewable tablets versus RLD and DRSP 3.5 mg chewable tablets versus RLD.

The secondary endpoints included assessment of the subjects' sensory experience to the test products, adverse events, clinical laboratory test results, and physical examination findings.

Statistical Analysis Plan

Analysis of Variance (ANOVA) was used to determine bioequivalence for each comparison of interest. The fixed effects added to the ANOVA model were: 1) treatment received, 2) the period during which treatment was given, and 3) the sequence in which treatment was given. Subject nested within sequence was added as a random effect. The Test-to-Reference geometric least-square means ratio (GMR) and the corresponding 90% confidence interval were calculated for each comparison of interest.

Protocol Amendments

No significant protocol amendments were submitted.

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 in this application.

Financial Disclosure

The investigators who participated in Study BLCL-DRS-FDA-04 certified to not having a financial interest related to the outcome of this study.

Patient Disposition

Of the 48 study participants who were enrolled and subsequently randomized, 38 completed the study. 10 subjects prematurely discontinued study participation. The reasons for discontinuation include the following:

- 5 subjects discontinued due to adverse events.
  - 1 with urinary tract infection
  - 1 with tonsillitis,
  - 1 with fever syndrome
  - 2 with dental infections
- 3 subjects were discontinued due to failure to meet admission criteria for the remaining treatment period(s).
- 1 subject was removed because of the physician's decision to not continue treatment.
- 1 subject withdrew for personal reasons.

In total, 48 subjects received at least one dose of the investigational products and constituted the safety population. 46 subjects received at least one dose of a test (chewable) product and constituted the acceptability analysis population. 39 subjects had evaluable pharmacokinetic

data on at least one test period and the reference period and constituted the pharmacokinetic analysis population.

Table 3 summarizes subject disposition.

Table 3: BLCL-DRS-FDA-04 Study Subject Disposition

Disposition	Number of Subjects
Subjects Randomized (n)	48
Subjects Completing Period 1 (n)	47
Subjects Completing Period 2 (n)	41
Subjects Completing Period 3 (n)	38
Subjects Discontinued After First Dosing	10
Reasons for Study Discontinuation [n (%)]	
Adverse Event	5 (10)
Failure to Meet Admission Criteria	3 (6)
Physician Decision	1 (2)
Withdrawal by Subject	1 (2)

Source: Study BLCL-DRS-FDA-04, Study Report Body, Table C

Protocol Violations/Deviations

There were no significant protocol violations or deviations reported.

Table of Demographic Characteristics

The demographic characteristics of the primary efficacy (pharmacokinetic analysis) population for Study BLCL-DRS-FDA-04 are shown in Table 4.

Table 4: BLCL-DRS-FDA-04 Demographic Characteristics of Primary Efficacy Population

Demographic Parameters	Subject Data (n = 39)
Age	
Mean years (SD)	28.5 (5.6)
Median (years)	27.0
Min, max (years)	20, 39
Race, n (%)	
White	30 (76.9)
Black or African American	4 (10.3)
American Indian or Alaska Native	1 (2.6)
Multiple	4 (10.3)
Region	
United States	0 (0)
Rest of the World	
Europe (Portugal)	39 (100)
Body Mass Index (kg/m2)	
Mean (SD)	24.5 (3.0)
Median	24.8
Min, max	19.0, 30.0

Source: Study BLCL-DRS-FDA-04, Study Report Body, Table D

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

Treatment groups were similar in baseline characteristics.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Subjects were monitored for treatment compliance via directly observed treatment administration. Subjects were confined to the clinical research facility for at least 11 hours preceding drug administration until 24 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 14 study subjects for various indications. Table 5 summarizes the information regarding concomitant medications.

Table 5: BLCL-DRS-FDA-04 Concomitant Medications Administered to Study Subjects

Study subject ID	Investigational product	Concomitant drug name(s)	Indication
(b) (6)	Test-1	Fosfomycin Ibuprofen	Urinary tract infection
	Test-1	Benzathine benzylpenicillin Paracetamol	Tonsillitis Fever
	Test-1	Paracetamol	Headache Fever
	Reference Test-1	Paracetamol Paracetamol	Dysmenorrhea Headache
	Test-1	Amoxicillin Ibuprofen Paracetamol Clotrimazole	Tooth infection Vaginal candidiasis
	Test-1	Ibuprofen	Odontalgia
	Test-1	Domperidone Paracetamol	Nausea Headache
	Test-1	Paracetamol	Migraine
	Test-1	Loratadine	Allergic rhinitis
	Test-1	Amoxicillin and beta-lactamase inhibitor Ibuprofen Tramadol Paracetamol	Tooth infection
	Test-1	Domperidone Paracetamol	Nausea

Source: Study BLCL-DRS-FDA-04, Appendix 16.2.4.4. Concomitant Medications

Reviewer comment:
Although all but one concomitant medication was given after administration of the Test-1 product (drospirenone 4 mg chewable tablets), the number of adverse events requiring additional medication is too small to draw any conclusions regarding the AE profile differences between any of the investigational products.

Efficacy Results – Primary Endpoint

The reader is referred to the Clinical Pharmacology review for the analysis and discussion of the primary efficacy endpoint.

Data Quality and Integrity

Data quality and integrity issues were not identified.

Efficacy Results – Secondary and other relevant endpoints

Table 6 summarizes the assessment of the subjects' sensory experience to the Test-1 product (drospirenone 4 mg chewable tablets).

Table 6: BLCL-DRS-FDA-04 Subjects' Acceptability Assessment of Test-1

Likert Scale score	Taste [n (%)]	Mouthfeel [n (%)]	Aftertaste [n (%)]	Easiness of chewing [n (%)]
1	25 (54.3)	21 (45.7)	19 (41.3)	23 (50.0)
2	12 (26.1)	8 (17.4)	9 (19.6)	20 (43.5)
3	8 (17.4)	13 (28.3)	14 (30.4)	2 (4.3)
4	1 (2.2)	3 (6.5)	2 (4.3)	1 (2.2)
5	0 (0.0)	1 (2.2)	2 (4.3)	0 (0.0)

Test-1 = drospirenone 4 mg chewable tablets
46 subjects participated in the acceptability assessment of Test-1
Taste/Mouthfeel/Aftertaste: 1= Like, 2= Slightly like, 3= Neither like nor dislike, 4= Slightly dislike, 5= Dislike
Chewing: 1= Very easy, 2= Easy, 3= Neither easy nor difficult, 4= Difficult, 5= Very difficult
Source: Study BLCL-DRS-FDA-04, Study Report Body, Table M

Table 7 summarizes the assessment of the subjects' sensory experience to the Test-2 product (drospirenone 3.5 mg chewable tablets).

Table 7: BLCL-DRS-FDA-04 Subjects' Acceptability Assessment of Test-2

Likert Scale score	Taste [n (%)]	Mouthfeel [n (%)]	Aftertaste [n (%)]	Easiness of chewing [n (%)]
1	22 (53.7)	15 (36.6)	15 (36.6)	21 (51.2)
2	10 (24.4)	7 (17.1)	10 (24.4)	17 (41.5)
3	8 (19.5)	15 (36.6)	12 (29.3)	3 (7.3)
4	1 (2.4)	3 (7.3)	1 (2.4)	0 (0.0)
5	0 (0.0)	1 (2.4)	3 (7.3)	0 (0.0)

Test-2 = drospirenone 3.5 mg chewable tablets
41 subjects participated in the acceptability assessment of Test-2
Taste/Mouthfeel/Aftertaste: 1= Like, 2= Slightly like, 3= Neither like nor dislike, 4= Slightly dislike, 5= Dislike
Chewing: 1= Very easy, 2= Easy, 3= Neither easy nor difficult, 4= Difficult, 5= Very difficult
Source: Study BLCL-DRS-FDA-04, Study Report Body, Table N

Reviewer comment:
Overall, the two test products were well accepted by the study subjects and were found to be easily chewed.

Dose/Dose Response

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

Durability of Response

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

Persistence of Effect

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

Additional Analyses Conducted on the Individual Trial

There were no additional analyses conducted in this trial.

6.2. 2020-FLE1-SLINC-PK-06 (BLCL-DRS-FDA-06)

6.2.1. Study Design

Overview and Objective

This laboratory-blinded, randomized, 2-sequence, 2-treatment (investigational product administered in fasting and fed conditions), 2-period crossover study evaluated the effect of food on the bioavailability of drospirenone 3.5 mg chewable tablets.

The secondary objectives were 1) to assess the subjects' sensory experience to drospirenone 3.5 mg chewable tablets and 2) to evaluate the safety and tolerability of the product.

Trial Design

Study BLCL-DRS-FDA-06 was a single-dose, open-label, laboratory-blinded, randomized, crossover study involving 22 healthy nonpregnant female volunteers at a single-center located in Porto, Portugal. Subjects were confined at the clinical research facility for at least 11 hours prior to drug administration and for a minimum of 24 hours post drug administration. Subjects received each of the two treatments for two treatment periods. Subjects were randomly assigned to one of two sequences. Doses of investigational products were separated by a washout interval of 14 days.

DRSP 3.5 mg chewable tablets were administered as follows:

- Fasting treatment (reference): after an overnight fast of at least 10 hours, the investigational product was thoroughly chewed and swallowed without water.

- Fed treatment (test): after an overnight fast of at least 10 hours, subjects had a standard high-fat and high-calorie meal. The investigational product was thoroughly chewed and swallowed without water approximately 30 minutes after the start of the meal.

Figure 3 illustrates the 2-sequence, 2-treatment, 2-period crossover study design.

Figure 3: BLCL-DRS-FDA-06 Study Sequences

Sequence	Period 1	Period 2
1 (n=11)	Test	Reference
2 (n=11)	Reference	Test

Reference = DRSP 3.5 mg chewable tablets (test drug from batch LFD0748/LFD0748A) chewed and swallowed without water after an overnight fast of at least 10 hours.
Test = DRSP 3.5 mg chewable tablets (test drug from batch LFD0748/LFD0748A) chewed and swallowed without water 30 minutes after a standard high-fat, high-calorie meal.
Source: Study BLCL-DRS-FDA-06, Study Report Body, 8.3.4. Assignment of Subjects to Treatment Sequences

All other aspects of the study design were identical to Study BLCL-DRS-FDA-04 (see Section 6.1.1) including: diagnostic criteria, inclusion and exclusion criteria, procedures and schedule, dietary restrictions, as well as handling of subject completion, discontinuation, or withdrawal.

Study Endpoints

The primary endpoints were the pharmacokinetic parameters of drospirenone for the food effect assessment including C_{max} and AUC_{0-72} of drospirenone.

The secondary endpoints included assessment of the subjects' sensory experience to the test product, adverse events, clinical laboratory test results, and physical examination findings.

Statistical Analysis Plan

The statistical analysis plan was identical to Study BLCL-DRS-FDA-04 (see Section 6.1.1). Lack of food effect was inferred if the 90% CI for the Test-to-Reference GMR of the *ln*-transformed parameters C_{max} and AUC_{0-72} were all within the 80.00% to 125.00% acceptance interval.

Protocol Amendments

No significant protocol amendments 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 Disclosure

The investigators who participated in Study BLCL-DRS-FDA-06 certified to not having a financial interest related to the outcome of this study.

Patient Disposition

Of the 22 study participants who were enrolled and subsequently randomized, 19 completed the study. 3 subjects prematurely discontinued study participation. The reasons for discontinuation include the following:

- 1 subject discontinued due to an adverse event (urinary tract infection).
- 2 subjects withdrew for personal reasons.

In total, 22 subjects received at least one dose of the investigational product and constituted the safety population and the acceptability analysis population. 19 subjects had evaluable pharmacokinetic data on both the test period and the reference period and constituted the pharmacokinetic analysis population.

Table 8 summarizes subject disposition.

Table 8: BLCL-DRS-FDA-06 Study Subject Disposition

Disposition	Number of Subjects
Subjects Randomized (n)	22
Subjects Completing Period 1 (n)	22
Subjects Completing Period 2 (n)	19
Subjects Discontinued After First Dosing	3
Reasons for Study Discontinuation [n (%)]	
Adverse Event	1 (4.5)
Withdrawal by Subject	2 (9.0)

Source: Study BLCL-DRS-FDA-04, Study Report Body, Table C

Protocol Violations/Deviations

There were no significant protocol violations or deviations reported.

Table of Demographic Characteristics

The demographic characteristics of the pharmacokinetic analysis population for Study BLCL-DRS-FDA-06 are shown in Table 9.

Table 9: BLCL-DRS-FDA-06 Demographic Characteristics of Pharmacokinetic Analysis Population

Demographic Parameters	Subject Data (n = 19)
Age	
Mean years (SD)	27.5 (4.5)
Median (years)	28.0
Min, max (years)	20, 38
Race, n (%)	
White	13 (68.4)
Black or African American	3 (15.8)
Multiple	3 (15.8)
Region	
United States	0 (0)
Rest of the World	
Europe (Portugal)	19 (100)
Body Mass Index (kg/m2)	
Mean (SD)	23.1 (2.6)
Median	22.8
Min, max	18.5, 28.6

Source: Study BLCL-DRS-FDA-06, Study Report Body, Table D

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

Treatment groups were similar in baseline characteristics.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Subjects were monitored for treatment compliance via directly observed treatment administration. Subjects were confined to the clinical research facility for at least 11 hours preceding drug administration until 24 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 3 study subjects. Table 10 summarizes the information regarding concomitant medications.

Table 10: BLCL-DRS-FDA-06 Concomitant Medications Administered to Study Subjects

Study subject ID	Investigational product	Concomitant drug name(s)	Indication
(b) (6)	Reference	Paracetamol	Headache
	Test	Paracetamol	Headache
	Reference	Paracetamol	Headache
	Reference	Fosfomycin	Urinary tract infection

Source: Study BLCL-DRS-FDA-06, Appendix 16.2.4.4. Concomitant Medications

Efficacy Results – Primary Endpoint

The reader is referred to the Clinical Pharmacology review for the analysis and discussion of the food effect endpoint.

Data Quality and Integrity

Data quality and integrity issues were not identified.

Efficacy Results – Secondary and other relevant endpoints

Table 11 summarizes the assessment of the subjects' sensory experience to DRSP 3.5 mg chewable tablets following an overnight fast.

Table 11: BLCL-DRS-FDA-06 Subjects' Acceptability Assessment – Reference Treatment

Likert Scale score	Taste [n (%)]	Mouthfeel [n (%)]	Aftertaste [n (%)]	Easiness of chewing [n (%)]
1	11 (50.0)	7 (31.8)	10 (45.5)	8 (36.4)
2	3 (13.6)	7 (31.8)	4 (18.2)	10 (45.5)
3	6 (27.3)	5 (22.7)	6 (27.3)	2 (9.1)
4	2 (9.1)	1 (4.5)	1 (4.5)	1 (4.5)
5	0 (0.0)	2 (9.1)	1 (4.5)	1 (4.5)

Reference treatment = administration of DRSP 3.5 mg chewable tablet after a 10-hour overnight fast.
22 subjects participated in the acceptability assessment after the reference treatment.
Taste/Mouthfeel/Aftertaste: 1= Like, 2= Slightly like, 3= Neither like nor dislike, 4= Slightly dislike, 5= Dislike
Chewing: 1= Very easy, 2= Easy, 3= Neither easy nor difficult, 4= Difficult, 5= Very difficult
Source: Study BLCL-DRS-FDA-06, Study Report Body, Table L

Table 12 summarizes the assessment of the subjects' sensory experience to DRSP 3.5 mg chewable tablets following a high-fat and high-calorie meal.

Table 12: BLCL-DRS-FDA-06 Subjects' Acceptability Assessment – Test Treatment

Likert Scale score	Taste [n (%)]	Mouthfeel [n (%)]	Aftertaste [n (%)]	Easiness of chewing [n (%)]
1	11 (57.9)	8 (42.1)	8 (42.1)	6 (31.6)
2	3 (15.8)	2 (10.5)	4 (21.1)	9 (47.4)
3	4 (21.1)	8 (42.1)	4 (21.1)	3 (15.8)
4	1 (5.3)	1 (5.3)	3 (15.8)	1 (5.3)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Test treatment = administration of DRSP 3.5 mg chewable tablet 30 minutes after the consumption of a high-fat and high-calorie meal.
19 subjects participated in the acceptability assessment after the test treatment.
Taste/Mouthfeel/Aftertaste: 1= Like, 2= Slightly like, 3= Neither like nor dislike, 4= Slightly dislike, 5= Dislike
Chewing: 1= Very easy, 2= Easy, 3= Neither easy nor difficult, 4= Difficult, 5= Very difficult
Source: Study BLCL-DRS-FDA-06, Study Report Body, Table K

Reviewer comment:
Overall, the investigational product was well accepted by the study subjects and was found to be easily chewed during the fasting and fed treatment conditions.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Efficacy of drospirenone 3.5 mg chewable tablets is supported by a single pharmacokinetic study demonstrating bioequivalence. Therefore, assessment of efficacy across clinical trials is not applicable to the review of this application.

7.1.1. Primary Endpoints

The primary endpoints of the pharmacokinetic studies evaluating DRSP 3.5 mg chewable tablets included the pharmacokinetic parameters of drospirenone 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 endpoints included assessment of the subjects' sensory experience to the test product, adverse events, clinical laboratory test results, and physical examination findings as stated in Section 6.

Reviewer Comment:
The secondary endpoints were used in combination with results from the oral irritation study [Study 2020-FLE1-SLINC-CE-07 (BLCL-DRS-FDA-07] to support the safety and tolerability of DRSP 3.5 mg chewable tablets.

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 dose and dose-response 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 than the target population in the US, this is unlikely to significantly impact the efficacy of DRSP 3.5 mg chewable tablets.

7.2.2. Other Relevant Benefits

Progestin-only pills may be preferred in certain, high-risk patient populations as the estrogen component in combination oral contraceptive pills confers additional risk to users. While there are chewable COCs available in the US, there are no approved chewable POPs. The chewable formulation of drospirenone may benefit those desiring or requiring a POP to avoid estrogen exposure and who have difficulty swallowing pills.

7.3. Integrated Assessment of Effectiveness

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

8. Review of Safety

8.1. Safety Review Approach

The safety review of DRSP 3.5 mg chewable tablets consisted of analysis of all adverse events in the safety population, i.e., all subjects who received at least one dose of DRSP 3.5 mg chewable tablets. The Applicant submitted individual adverse event datasets for each of the two pharmacokinetics studies and the oral tolerability and safety study as agreed upon by the Agency in the pre-NDA meeting. This reviewer integrated the adverse event data from all three studies (see Section 5.1 for list of studies).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The development program for drospirenone chewable tablets included two pharmacokinetic studies (BLCL-DRS-FDA-01 and BLCL-DRS-FDA-03) in which the Applicant evaluated the relative bioavailability of an earlier investigational product, drospirenone 4 mg chewable tablets. The pharmacokinetic results of these studies showed that DRSP 4 mg chewable tablets were not bioequivalent to the cross-referenced product (Slynd).

In Studies BLCL-DRS-FDA-01 and BLCL-DRS-FDA-03, seventy subjects were exposed to the earlier investigational product. Four subjects did not complete the studies due to adverse events. Two subjects were withdrawn due to Influenza, one due to tonsillitis (not drug-related), and one due to rash and angioedema (likely drug-related). There were no serious adverse events or deaths reported in the earlier studies with DRSP 4 mg chewable tablets.

The Applicant conducted further studies with the to-be-marketed product, DRSP 3.5 mg chewable tablets. The safety analysis for this application included all study subjects exposed to at least one dose of DRSP 3.5 mg chewable tablets. Two pharmacokinetic studies and one oral tolerability and safety study contributed to the analysis. Overall exposure to DRSP 3.5 mg chewable tablets consisted of 103 healthy volunteers. All subjects were exposed to at least one dose of the investigational product. Forty-one subjects were exposed to the reference product. Overall exposure was adequate for evaluation. Table 13 summarizes the safety population.

Table 13: Safety Population

Safety Database for Drospirenone 3.5 mg Chewable Tablets Individuals exposed to any treatment in this development program for the indication under review N[1]= 149			
Clinical Trial Groups	Drospirenone 3.5 mg chewable tablets[2]	Drospirenone 4 mg chewable tablets[3]	Reference[4]
Healthy volunteers	103	46	41
All trials conducted for this indication[3]	3	1	1

[1] N is the sum of all subjects exposed to any investigational product in the development program
[2] Two pharmacokinetic studies (BLCL-DRS-FDA-04 and BLCL-DRS-FDA-06) and one oral irritation study (BLCL-DRS-FDA-07) included administration of the to-be-marketed product, DRSP 3.5 mg chewable tablets
[3] One pharmacokinetic study (BLCL-DRS-FDA-04) included administration of DRSP 4 mg chewable tablets
[4] Reference (Slynd 4 mg oral tablets) administered in one pharmacokinetic study (BLCL-DRS-FDA-04)

Subjects in the pharmacokinetic studies received a single dose of study product or reference during each of three treatment periods. Only subjects in the oral irritation study received multiple consecutive doses. In this study, subjects received 24 consecutive days of active chewable tablets, followed immediately by 4 consecutive days of placebo tablets as per intended real-world product use. The duration of exposure is adequate to assess oral irritation potential of the study product. Table 14 summarizes duration of exposure to the study product.

Table 14: Duration of Exposure to Drospirenone 3.5 mg Chewable Tablets

	Single dose[1]	Multiple doses[2]	All subjects exposed
Number of subjects (N)	63	40	103

[1] Pharmacokinetic studies only (BLCL-DRS-FDA-04 and BLCL-DRS-FDA-06)
[2] One 28-day cycle (24 consecutive days of active chewable tablets, followed by 4 consecutive days of placebo tablets) in the oral irritation study (BLCL-DRS-FDA-07)

8.2.2. Relevant characteristics of the safety population:

Study subjects had a mean BMI ≤ 25 kg/m^2. However, approximately one-third of study participants in the pivotal trial for the cross-referenced product, Slynd, were obese (BMI ≥ 30 mg/m^2) and the Pearl Index was not affected by BMI. Given its bioequivalence to the cross-referenced product, there is no reason to suspect that a drospirenone chewable tablet would have decreased effectiveness in an obese population.

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

8.2.3. Adequacy of the safety database:

The safety database adequately represents the frequency of adverse events related to DRSP 3.5 mg chewable tablets. Significant differences from the target population are not expected. The database consisted of healthy females of child-bearing potential. This is consistent with studies evaluating tolerability and safety of a new dosage form or formulation of existing contraceptive products.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

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

8.3.2. Categorization of Adverse Events

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

8.4. Safety Results

8.4.1. Deaths

No deaths occurred.

8.4.2. Serious Adverse Events

No serious adverse events occurred.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Five subjects in Study BLCL-DRS-FDA-04 and one subject in Study BLCL-DRS-FDA-06 did not complete study participation due to adverse events. There were no subject discontinuations in the oral irritation study, Study BLCL-DRS-FDA-07. Table 15 summarizes subject discontinuations due to adverse events.

Table 15: Summary of Subject Discontinuations due to Adverse Events

Subject ID	Adverse Event	Relationship to Drug[1]	Product received
(b) (6)	Urinary tract infection	Not drug-related	DRSP 4 mg chewable tablets
	Tonsillitis	Not drug-related	DRSP 4 mg chewable tablets
	Fever syndrome	Drug-related	DRSP 4 mg chewable tablets
	Dental infection	Drug-related	DRSP 4 mg chewable tablets
	Dental infection	Not drug-related	DRSP 4 mg chewable tablets
	Urinary tract infection	Not drug-related	DRSP 3.5 mg chewable tablets

[1] The classification of whether or not an adverse event was considered drug-related represents that which was determined by the investigator.

Reviewer Comment:
An information request was sent to the Applicant on March 4, 2022 to provide narratives for subjects who experienced dental- or infection-related adverse reactions. See Section 8.5 for further information.

8.4.4. Significant Adverse Events

There were no significant adverse events reported.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most frequently reported adverse events were headache and menstrual irregularities. All TEAEs were classified as mild or moderate severity. Table 16 illustrates the frequency of adverse reactions in the safety population (i.e., all subjects receiving at least one dose of DRSP 3.5 mg chewable tablets in Studies BLCL-DRS-FDA-04, BLCL-DRS-FDA-06 and BLCL-DRS-FDA-07).

Table 16: Frequency of Adverse Reactions – Safety Population

Adverse Reaction	FDA-04 N=41	FDA-06 N=22	FDA-07 N=40	Total N = 103 N (%)
Any adverse reaction	15	12	26	53 (51.4%)
Headache	7	9	4	20 (19.4%)
Menstruation irregular[2]	0	1	15	16 (15.5%)
Abdominal pain[1]	3	1	1	5 (4.9%)
Nausea	2	1	2	5 (4.9%)
Acne	1	1	3	5 (4.9%)
Dysmenorrhea	0	1	2	3 (2.9%)
Breast pain	1	0	1	2 (1.9%)
Migraine	0	0	2	2 (1.9%)
Major depression	1	0	0	1 (1%)
Odontalgia	0	0	1	1 (1%)

[1] Includes MedDRA preferred terms (PT) abdominal discomfort and abdominal pain and abdominal pain upper
[2] Includes MedDRA PT menstruation irregular and metrorrhagia and menorrhagia

The adverse event profile of DRSP 3.5 mg chewable tablets is similar to that of the cross-referenced product Slynd as shown in Table 17. There are no unexpected adverse reactions or new safety signals associated with the chewable dosage form.

Table 17: Frequency of Adverse Reactions in Subjects Receiving Slynd in Four Pooled Studies

Adverse Reaction	Total N = 2598 N (%)
Any adverse reaction	627 (24.1%)
Acne	98 (3.8%)
Metrorrhagia	72 (2.8%)
Headache	71 (2.7%)
Breast pain	57 (2.2%)
Weight increased	50 (1.9%)
Dysmenorrhea	49 (1.9%)
Nausea	47 (1.8%)
Vaginal hemorrhage	45 (1.7%)
Libido decreased	33 (1.3%)
Breast tenderness	31 (1.2%)
Menstruation irregular	30 (1.2%)

Source: Slynd FDA-approved labeling, Section 6 *Adverse Reactions*

8.4.6. Laboratory Findings

DRSP is a fourth-generation progestogen and is an analogue of the aldosterone antagonist spironolactone. As such, DRSP possesses anti-mineralocorticoid activity so that there is a potential for subjects to develop hyperkalemia.

Four subjects had hyperkalemia during participation in the clinical development studies of DRSP 3.5mg chewable tablets. All four subjects had mild potassium elevations that were not considered clinically relevant by the investigators. Three subjects had isolated increases that returned to normal while still on study medication. None of the subjects had clinical signs/symptoms of hyperkalemia or evidence of electrocardiogram (ECG) changes. Table 18 summarizes the time course of these hyperkalemic events.

Table 18: Time Course of Potassium Elevations in Safety Population

Subject Number	Protocol Phase	Actual Date	Potassium (mmol/L)[1]
Study BLCL-DRS-FDA-04			
(b) (6)	Screening	(b) (6)	4.0
	Period 1: Admission		4.2
	Period 1: Ambulatory		3.8
	Period 2: Admission		5.0
	Period 2: Ambulatory		4.1
	Period 3: Admission		**5.3**
	End of Study		4.4
	Screening		4.3
	Period 1: Admission		4.5
	Period 1: Ambulatory		4.5
	Period 2: Admission		**5.2**
	Period 2: Ambulatory		4.4
	Period 3: Admission		4.1
	End of Study		4.2
Study BLCL-DRS-FDA-06			
(b) (6)	Screening	(b) (6)	4.4
	Period 1: Admission		4.3
	Period 1: Ambulatory		4.7
	Period 2: Admission		**5.4**
	End of Study		4.7
Study BLCL-DRS-FDA-07			
(b) (6)	Screening	(b) (6)	4.6
	Day 1		**5.3**
	End of Study		**5.4**

[1] Normal range of potassium is 3.5 – 5.1 mmol/L

Reviewer comment:
Subject (b) (6) had elevated potassium levels that were not considered clinically relevant by the investigator. No associated AEs were reported for this subject during study participation and the ECG performed at screening and at the end-of-study visit did not show any abnormalities. No further serum potassium levels were obtained upon completion of the subject's participation in the oral irritation trial.

8.4.7. Vital Signs

Significant vital sign findings were not reported.

8.4.8. Electrocardiograms (ECGs)

Abnormal ECG findings were not reported.

8.4.9. QT

QT prolongation studies were not required.

8.4.10. Immunogenicity

Immunogenicity studies were not required.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Adverse Events Odontalgia, Dental Infection and Fever Syndrome

The adverse events "odontalgia" and "dental infection" were reported in four subjects in the safety population. Additionally, one subject was identified as having "fever syndrome" with a reasonable possibility of relatedness to the study product. Given that the adverse events "odontalgia", "dental infection" and "fever syndrome" were reported more frequently than would be anticipated in these studies, an in-depth review was warranted. An information request was sent to the Applicant on March 4, 2022 to provide narratives for subjects who experienced dental- or infection-related adverse reactions. Table 19 summarizes the details of these adverse events.

Table 19: Summary of Subjects Experiencing Adverse Events Odontalgia, Dental Infection and Fever Syndrome

Subject ID	Adverse Event	Causality Assessment	Additional details	Product received
Study FDA-BLCL-DRS-FDA-04				
(b) (6)	Fever syndrome	Reasonably possible	resolved, mild	DRSP 4 mg chewable tablets
	Dental infection	Reasonably possible	resolved, mild	DRSP 4 mg chewable tablets
	Odontalgia	Not reasonably possible	resolved, mild	DRSP 4 mg chewable tablets
	Dental infection	Not reasonably possible		DRSP 4 mg chewable tablets
Study FDA-BLCL-DRS-FDA-07				
(b) (6)	Odontalgia	Not reasonably possible		DRSP 3.5 mg chewable tablets

The following are the case narratives for the subjects experiencing dental- or infection-related adverse reactions:

- **Subject** (b) (6) received a single dose of drospirenone 4 mg chewable tablets and was subsequently withdrawn from the study by the investigator for "fever syndrome". Additional details clarified that the subject experienced symptoms consistent with a viral infection including fever (Tmax 38.0 ºC) and dry cough that resolved 48-72 hours after initial presentation. A SARS-CoV-2 PCR test was performed and was negative. These events occurred approximately 6 hours after study drug administration; therefore, the relationship of the adverse event to study drug was considered "reasonably possible".

  Reviewer Comment:
  I disagree with the Applicant's assessment of causality of the adverse event of fever syndrome in this subject as it is unlikely related to a single dose of the drug product.

- **Subject** (b) (6) received a single dose of drospirenone 4 mg oral tablets (reference drug) in Period 1 without difficulty and received a single dose of drospirenone 4 mg chewable tablets in Period 2. The subject complained of odontalgia approximately 19

  hours post dose that persisted for 72 hours despite treatment with acetaminophen and ibuprofen. The investigator prescribed amoxicillin for presumed "dental infection" and withdrew the subject from the study. During a follow-up phone call, the subject reported that she had undergone a dental extraction. The relationship of the adverse event to study drug was considered "reasonably possible".

  Reviewer Comment:
  I disagree with the Applicant's assessment of causality of the adverse event of dental infection in this subject. While chewing the drug product may have exacerbated a pre-existing dental issue, the dental infection is unlikely related to a single dose of the drug product.

- **Subject** (b) (6) received a single dose of drospirenone 4 mg chewable tablets in Period 1. She remained asymptomatic at her scheduled ambulatory visits at 36-hours, 48-hours and 72-hours post-dose. The subject reported a single episode of odontalgia that occurred approximately 96 hours post drug product dose and resolved with one dose of ibuprofen. The subject was withdrawn from the study at admission to Period 2 due to a positive drugs-of-abuse test. The relationship of the adverse event to study drug was considered "not reasonably possible".

  Reviewer Comment:
  I agree with the Applicant's assessment of causality of the adverse event of odontalgia in this subject.

- **Subject** (b) (6) received a single dose of drospirenone 4 mg chewable tablets in Period 1. The subject reported in a follow up phone call that she experienced a dental infection four days after study drug administration. The subject was prescribed amoxicillin/clavulanic acid for presumed "dental infection" and was withdrawn from the study. The relationship of the adverse event to study drug was considered "not reasonably possible".

  Reviewer Comment:
  I agree with the Applicant's assessment of causality of the adverse event of dental infection in this subject.

- **Subject** (b) (6) was enrolled in the oral irritation study and completed the entire treatment period of drospirenone 3.5 mg chewable tablets once daily for 24 days followed by one inactive chewable tablet daily for 4 consecutive days. On the 15th day

of treatment with active tablets, the subject experienced odontalgia for which she was prescribed ibuprofen. The subject endorsed use of ibuprofen for 2 days and underwent an evaluation with a dentist. The subject's odontalgia resolved after undergoing a

dental procedure that included removal of a previous dental cavity amalgram filling performed in (b) (6) and subsequent esthetic restoration. There was no evidence of oral irration/inflammation or abrasion on any of the scheduled pre- and post-dose oral cavity assessments during the entire treatment period. The relationship of the adverse event to study drug was considered "not reasonably possible".

Reviewer Comment:
I agree with the Applicant's assessment of causality of the adverse event of odontalgia in this subject.

Four cases above were associated with use of drospirenone 4 mg chewable tablets during Study BLCL-DRS-FDA-04 and therefore not applicable to the proposed to-be-marketed drug product in this application. The TEAE in a subject taking drospirenone 3.5 mg chewable tablets did not appear to have a "reasonably possible" association with the study drug. I conclude that there is no evidence of a new safety signal regarding odontalgia and/or dental infection associated with drospirenone 3.5 mg chewable tablets.

8.6. Safety Analyses by Demographic Subgroups

Not applicable.

8.7. Specific Safety Studies/Clinical Trials

8.7.1. Study 2020-FLE1-SLINC-CE-07 (BLCL-DRS-FDA-07)

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 drospirenone chewable tablets.

The primary objective was to determine the potential for oral irritation of drospirenone 3.5 mg chewable tablets following daily use of the active formulation for 24 days then daily use of the inactive (placebo) formulation for an additional 4 days. The secondary objective was to evaluate the safety and tolerability of DRSP 3.5 mg chewable tablets.

Trial Design

Study BLCL-DRS-FDA-07 was an open-label, multiple-dose, uncontrolled, one-period study involving 40 healthy nonpregnant female volunteers at a single-center located in Porto, Portugal. The investigational product was administered by qualified personnel at the clinical research center in the morning on Days 1, 3, 8, 24, and 28. The investigational product was self-administered by the study subjects in the morning on Days 2, 4 to 7, 9 to 23, and 25 to 27.

Key inclusion criteria included the following:

1. Healthy female volunteers between 18 and 40 years, inclusive
2. Previous use of hormonal contraceptives without complications
3. Body mass index (BMI) 18.0 - 30.0 kg/m_2, inclusive
4. Non-smoker or ex-smoker for at least 3 months
5. Regular cyclic menses or reporting regular cyclic menses prior to use of hormonal contraception
6. Willingness to use one of the following non-hormonal methods of contraception from at least 14 days prior to admission for Period 1 until the end of the study
    a. Abstinence
    b. Non-hormonal IUD
    c. Condom, cap, diaphragm, or sponge with spermicide
    d. Permanent sterilization

Key exclusion criteria included the following:

1. Pregnant or lactating
2. Perimenopausal or menopausal
3. Contraindication for the use of hormonal contraceptives, 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
    e. Known or suspected progestin sensitive cancer
    f. Abnormal genital bleeding or endometrial hyperplasia
    g. Known or suspected tumors of the liver and pituitary
4. Serum potassium above the upper limit of normal range or conditions predisposing to hyperkalemia
5. Use of combined (estrogen and progestin containing) hormonal contraceptives (e.g., oral, intravaginal, transdermal) or progestin-only pills within 14 days prior to enrollment
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. Difficulty in chewing or swallowing tablets or capsules
9. Dentures which reduce oral contact with the investigational product
10. Any visible disease of the oral mucosa (e.g., a score greater than "1" on the oral soft-tissue examination) which will interfere with the oral irritation evaluation.

The test drug was administered by qualified staff personnel at the clinical research center in the mornings on Days 1, 3, 8, 24, and 28 under direct supervision. Subjects were instructed to chew the tablet thoroughly and then swallow immediately without water. 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. Follow-up phone calls were performed on Days 4, 6, 10, 12, 14, 16, 18, 20, 22, and 26 to verify the subjects' compliance with treatment.

Oral soft-tissue examinations were performed at baseline (screening visit) and at 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 or abnormal. The oral soft tissues were examined for irritation/inflammation and abrasions. 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
0.5	Slight erythema, no edema
1	Erythema plus slight edema
2	Moderate erythema and/or edema (e.g., beginning of tissue breakdown or slough)
3	Severe irritation/inflammation (e.g., definite blistering, ulceration or epithelial slough)

Abrasions were defined as a depressed lesion, which is limited to the epithelium and does not extend through the epithelium to the dermis. If present, abrasions were reported as adverse events. The location of the abrasion(s) was specified, and the severity of each abrasion was scored using the following scale:

Score	Abrasion characterization
0	None
1	Mild (causing no limitation of usual oral activities; the subject may experience slight discomfort)
2	Moderate (causing some limitation of usual oral activities; the subject may experience annoying discomfort)
3	Severe (causing inability to carry out usual oral activities; the subject may experience intolerable discomfort or pain)

Figure 4 illustrates the schedule of study events.

Figure 4: BLCL-DRS-FDA-07 Schedule of Study Events

		Treatment Period			
Assessments	**Screening[1]**	**Day 1 Visit (Admission)**	**Day 3, 8 and 24 visits[2]**	**Follow-up Calls[3]**	**Day 28 Visit[4] (End of study)**
Written informed consent[5]	X				
Verification of eligibility criteria	X	X			
Demographic data	X				
Body height and weight	X				
Medical history	X				
Vital Signs[6]	X	X	X		X
Physical examination	X				
Oral soft tissue examination[7]	X	X	X		X
12-lead ECG	X				X
Clinical laboratory tests[8]	X	X			X
SARS-CoV-2 test		X[9]			
Pregnancy test in all females[10]	X	X			X
Drugs-of-abuse and ethanol screen	X	X			
Dispensing the investigational product[11]		X			
Treatment compliance verification				X	
Adverse events monitoring	X	X	X	X	X

[1] Screening procedures occurred within 28 days prior to admission (Day 1).
[2] Ambulatory visits in the morning on Days 1, 3, 8, 24, and 28.
[3] A follow-up call took place on Days 4, 6, 10, 12, 14, 16, 18, 20, 22 and 26.
[4] Or early discontinuation in subjects who were administered at least 1 dose of investigational product.
[5] The latest version of ICF was signed by the subject before any study-related procedure.
[6] Vital signs were recorded at screening, admission and each ambulatory visit. Vital signs included blood pressure, pulse rate and body temperature. Vital signs on Days 1, 3, 8, 24 and 28 were recorded at pre-dose.

[7] Oral examination was performed at pre-dose and 30 minutes after dosing on Days 1, 3, 8, 24, and 28.
[8] Clinical laboratory tests included hematology, general biochemistry, and coagulation studies.
[9] SARS-CoV-2 PCR test was performed prior to admission to treatment period.
[10] The pregnancy test was performed in serum at screening and end of study, and in urine at admission (Day 1).
[11] Investigational products were administrated in the morning by the site staff on Days 1, 3, 8, 24 and 28 and were self-administered by the subject on the remaining days of the treatment period.
Source: Study BLCL-DRS-FDA-07, Study Report Body, Table A

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 Day 1 Visit.
3. Abstinence from consumption of any food or beverages containing poppy seeds within 48 hours prior to Day 1 Visit because it could render a false positive during drugs-of-abuse test.
4. Avoidance of strenuous physical exercise within 48 hours prior to blood collection for clinical laboratory tests.

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.

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 BLCL-DRS-FDA-07 certified to not having a financial interest related to the outcome of this study.

Patient Disposition

Of the 40 study participants who were enrolled and subsequently randomized, 40 completed the study. 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 and abrasion assessments. They constitute both the Safety Analysis population as well as the Oral Irritation/Inflammation and Abrasion Analysis 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 BLCL-DRS-FDA-07 are shown in Table 20.

Table 20: BLCL-DRS-FDA-07 Demographic Characteristics of the Safety Analysis Population

Demographic Parameters	Subject Data (n = 40)
Age	
Mean years (SD)	29.7 (5.0)
Median (years)	29.0
Min, max (years)	20, 40
Race, n (%)	
White	36 (90.0)
Black or African American	2 (5.0)
Multiple	2 (5.0)
Region	
United States	0 (0)
Rest of the World	
Europe (Portugal)	40 (100)
Body Mass Index (kg/m2)	
Mean (SD)	23.2 (2.3)
Median	23.1
Min, max	18.7, 28.7

Source: Study BLCL-DRS-FDA-07, Study Report Body, Table D

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, 8, 24, and 28. 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. Follow-up phone calls were performed on Days 4, 6, 10, 12, 14, 16, 18, 20, 22, and 26 to verify the subjects' compliance with treatment.

Concomitant medications were administered to 8 study subjects. Table 21 summarizes the information regarding concomitant medications.

Table 21: BLCL-DRS-FDA-07 Concomitant Medications Administered to Study Subjects

Study subject ID	Investigational product	Concomitant drug name(s)	Indication
(b) (6)	Active	Fluconazole	Vaginal candidiasis
	Active	Acyclovir	Herpes labialis
	Active	Econazole cream Econazole suppository	Vaginal candidiasis
	Active	Paracetamol	Backache
	Active	Antiemetics Ibuprofen Paracetamol Metamizole sodium	Nausea Headache*
	Active	Ibuprofen	Odontolgia
	Active	Betamethasone cream	Acne
	Active	Paracetamol	Dysmenorrhea

*Study subject (b) (6) experienced headache on four separate occasions during the administration of active tablets for which she received concomitant medications.
Source: Study BLCL-DRS-FDA-07, Appendix 16.2.3.4. Concomitant Medications

Efficacy Results – Primary Endpoint

There were no efficacy determinations in this study.

Data Quality and Integrity

Data quality and integrity issues were not identified.

Efficacy Results – Secondary and other relevant endpoints

Following administration of the drospirenone 3.5 mg chewable active and inactive tablets, none

of the 40 subjects had evidence of irritation at the examination of the attached gingivae, buccal mucosa, hard/soft palate, labial mucosa, oropharynx, sublingual mucosa, tongue or uvula. Only one (2.5%) subject (study subject ID (b) (6) showed slight erythema without edema on the lips at the Day 8 pre-dose oral irritation assessment (active tablet). This was reported as a TEAE ("Herpes virus infection").

No evidence of abrasion within the oral cavity was found in any subject following administration of the drospirenone 3.5 mg chewable active and inactive tablets.

Reviewer comment:
Overall, the investigational product was well tolerated by the study subjects and did not show a potential for oral irritation/inflammation or abrasion when chewed and swallowed for 28 consecutive days.

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 is in place. A Postmarketing Requirement assessing bone mineral density change after chronic use of DRSP 3.5mg chewable tablets in adult and adolescent females is planned by the Division. The plan to include DRSP 3.5 mg chewable tablets in the PMR assessing the impact on BMD in adolescents was discussed with the PeRC committee on May 3, 2022. The PeRC committee supported the inclusion of DRSP 3.5mg chewable tablets in the existing PMR for Slynd. See Section 12 for further information.

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

Not applicable.

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. Epidemiological studies have not indicated an association between progestin-only preparations and an increased risk of myocardial infarction, cerebral

thromboembolism, or venous thromboembolism. However, combined oral contraceptives containing drospirenone and ethinyl estradiol may be associated with a higher risk of venous thromboembolism (VTE) than those containing some other progestins in combination with ethinyl estradiol. It is unknown whether the risk of VTE is increased with drospirenone alone.

An extensive review of global postmarketing data included in the Applicant's submissions of Periodic Adverse Drug Experience Reports, Annual Reports and Development Safety Update Reports for Slynd did not raise any safety signals regarding an increased risk of VTE with chronic use of drospirenone-only products.

An Information Request Letter was sent to the Applicant on January 13, 2022 requesting the calculation of the cumulative incidence of VTE worldwide in female users since the approval of Slynd in May 2019. In response to this IR, the Applicant performed a cumulative search of the pharmacovigilance (PV) database and identified 17 cases of VTE. Based on the total world-wide patient exposure in the postmarketing period estimated to be 423,248.74 patient years, the spontaneous reporting incidence of VTEs was calculated as 0.4 per 10,000 patient years. This estimate does not raise any new safety concerns.

The Division of Pharmacovigilance II (DPV II) in the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing cases of adverse events identified in the FDA Adverse Event Reporting System (FAERS) database and published in the medical literature with the use of Slynd for contraception. Four cases reporting hypersensitivity reactions were identified in FAERS. The reported reactions included rash, urticaria, and pruritis. Two of the cases required administration of intravenous corticosteroids to help mitigate the reaction. All four narratives provided details to support Slynd use as the most likely causal factor (e.g., time-to-onset after Slynd use, resolution after discontinuation of drug, and no reported confounding factors). The current Slynd label does not communicate the risk of hypersensitivity reactions and recommendations for including this in the label has been communicated to the Applicant (see Section 10.1.1).

8.9.2. Expectations on Safety in the Postmarket Setting

There is no reason to suspect that a drospirenone chewable tablet would have any other additional safety concerns that differ from a drospirenone tablet that is swallowed.

8.9.3. Additional Safety Issues From Other Disciplines

Not applicable.

8.10. Integrated Assessment of Safety

Significant safety issues did not arise in pharmacokinetic or oral tolerability studies of this

product. Adverse event frequencies in the study population were comparable to adverse event frequencies in the reference product. The risk of serious adverse events is not expected to differ from the risk of these events in the cross-referenced product.

Overall, the safety of drospirenone 3.5mg chewable tablets has been demonstrated.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

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

Product labeling updates for this drug implement Physician Labeling Rule (PLR) as well as Pregnancy and Lactation Labeling Rule (PLLR) requirements. Additionally, changes to the Dosing and Administration (Section 2) and Patient Counseling (Section 17) were recommended to convey the ability to administer this product with or without water and food. Changes to Adverse Reactions (Section 6) have been recommended to reflect the identification of the risk of hypersensitivity reactions associated with use of the cross-referenced product as mentioned in Section 8.9.1 above.

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

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

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

12. Postmarketing Requirements and Commitments

Drospirenone is a progestin that acts by inhibiting the production of gonadotropin-releasing hormone, thereby decreasing gonadotropin secretion and estradiol production. This hypoestrogenic state may lead to bone loss. Bone loss over time can significantly increase the risk of fracture as females age and has been identified as a safety concern with use of other progestin-only contraceptives.

Although the clinical trial for Slynd did not identify differences in bone metabolic parameters, these values are not sufficient to assess bone safety. The long-term effects of chronic drospirenone use on bone mineral density (BMD) in adult and adolescent females are unknown. A Postmarketing Requirement (PMR) assessing BMD changes in adults and adolescents taking Slynd (drospirenone) compared to users of non-hormonal contraceptive methods was required in the Slynd approval letter (NDA 211367, PMR 3631-1). The primary objective of this trial is to determine the mean percentage change in BMD of the lumbar spine as measured by DXA at 6 and 12 months.

This new PMR (PMR 4287-1) will evaluate the effect of Slynd (drospirenone) and drospirenone 3.5 mg chewable tablets on BMD in adults and adolescents and compare BMD to females using non-hormonal contraception. Updates to the milestones initially set for PMR 3631-1 were proposed by the Applicant to allow adequate time for recruitment of subjects using the chewable dosage form and collection/analysis of data. The following timetable includes the scheduled milestones for PMR 4287-1 that were agreed upon by the Division and the Applicant:

- Draft Protocol Submission: 08/2022
- Final Protocol Submission: 10/2022
- Trial Completion: 07/2026
- Final Report Submission: 10/2026

13. Appendices

13.1. References

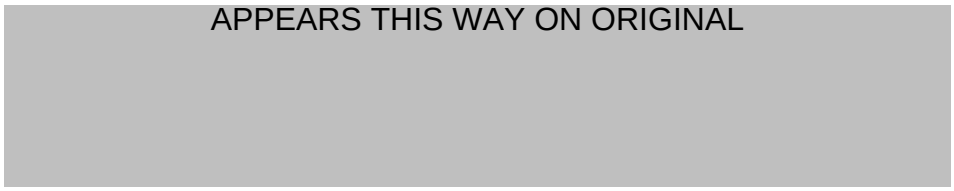
There are no clinically related references in this submission that negatively impact approval of drospirenone 3.5 mg chewable tablets. This reviewer is not aware of any recent medical literature that negatively impacts approval.

13.2. Financial Disclosure

There were no financial disclosures to report.

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 12		
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)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