NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	211367
Priority or Standard	Standard
Submit Date(s)	July 27, 2018
Received Date(s)	July 27, 2018
PDUFA Goal Date	May 27, 2019
Division/Office	Division of Bone Reproductive and Urologic Products (DBRUP)/Office of Drug Evaluation III (ODE III)
Review Completion Date	May 24, 2019
Established Name	Drospirenone (DRSP)
Research Name	LF111
(Proposed) Trade Name	Slynd
Pharmacologic Class	Progestin
Applicant	Exeltis USA Inc.
Formulation(s)	Oral tablets
Dosing Regimen	One 4-mg oral DRSP tablet daily for 24 consecutive days followed by one inert tablet daily for 4 consecutive days
Indication/Population	Prevention of pregnancy in females of reproductive potential
Recommendation on Regulatory Action	Approval

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Managers	Jennifer Dao Jennifer Mercier
Nonclinical Reviewer	Andrea L. Benedict, Ph.D.
Nonclinical Team Leader	Mukesh Summan, Ph.D., DABT
Office of Clinical Pharmacology Reviewer(s)	Da Zhang, Ph.D., Hongshan Li, Ph.D.
Office of Clinical Pharmacology Team Leader(s)	Jingyu Yu, Ph.D., Doanh Tran, Ph.D.
Clinical Reviewer	Ronald J. Orleans, M.D.
Clinical Team Leader	Gerald Willett, M.D.
Biostatistics Reviewer	Yun Tang, Ph.D.
Biostatistics Team Leader	Mahboob Sobhan, Ph.D.
Cross-Disciplinary Team Leader	Gerald Willett, M.D.
Deputy Division Director (DBRUP)	Audrey Gassman, M.D.

Additional Reviewers of Application

OPQ	Soumya Mitra, Ph.D. Hamid R. Shafiei, Ph.D. Mark R. Seggel, Ph.D. CMC Lead
OPDP	Lynn Panholzer, Pharm.D.
DMPP	Karen Dowdy
OSI	Roy Blay, Ph.D.
OSE/DMEPA	Celeste Karpow, Pharm.D., MPH Briana Rider, Pharm.D.
OSE/DRISK	Laura A. Zendel

CMC = chemistry, manufacturing, and controls
OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management

Reviewers Team and Signature Approvals

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Biostatistics	Yun Tang	OB/3	7, 8 ☒ Authored ☐ Approved ☐ Acknowledged
Reviewer	**Signature:** Mahboob Sobhan -S Digitally signed by Mahboob Sobhan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mahboob Sobhan -S, 0.9.2342.19200300.100.1.1=1300084769 Date: 2019.05.23 11:09:27 -04'00'		For
Biostatistics	Mahboob Sobhan	OB/3	7, 8 ☐ Authored ☒ Approved ☐ Acknowledged
Team Lead	**Signature:** Mahboob Sobhan -S Digitally signed by Mahboob Sobhan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mahboob Sobhan -S, 0.9.2342.19200300.100.1.1=1300084769 Date: 2019.05.23 11:09:57 -04'00'		
Biostatistics	Laura Lee Johnson	OB/3	7, 8 ☐ Authored ☒ Approved ☐ Acknowledged
Division Director	**Signature:** Laura L. Johnson -S Digitally signed by Laura L. Johnson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011413414, cn=Laura L. Johnson -S Date: 2019.05.23 11:10:53 -04'00'		
Clinical Pharmacology	Da Zhang	OCP/DCPIII	6 ☒ Authored ☐ Approved ☐ Acknowledged
Reviewer	**Signature:** Da Zhang -S Digital y signed by Da Zhang S DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Da Zhang S 0 9 2342 19200300 100 1 1=0012242580 Date: 2019 05 23 13 42 11 04'00'		
Clinical Pharmacology	Hongshan Li	OCP/DPM	6 ☒ Authored ☒ Approved ☐ Acknowledged
Reviewer	**Signature:** Doanh C. Tran -S Digitally signed by Doanh C. Tran -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Doanh C. Tran -S, 0.9.2342.19200300.100.1.1=1300378169 Date: 2019.05.23 14:50:29 -04'00'		Signing for H. Li
Clinical Pharmacology	Jingyu Yu	OCP/DPM	6 ☐ Authored ☒ Approved ☐ Acknowledged
Team Lead	**Signature:** Jingyu Yu -S Digitally signed by Jingyu Yu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jingyu Yu -S, 0.9.2342.19200300.100.1.1=2000794699 Date: 2019.05.23 11:53:04 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology	Doanh Tran	OCP/DCPIII	6 ☐ Authored ☒ Approved ☐ Acknowledged
Team Lead	**Signature:** Doanh C. Tran -S Digitally signed by Doanh C. Tran -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Doanh C. Tran -S, 0.9.2342.19200300.100.1.1=1300378169 Date: 2019.05.23 11:00:15 -04'00'		
Pharmacology and Toxicology	Andrea L. Benedict, Ph.D.	OND/ODE3/DBRUP	5 ☒ Authored ☐ Approved ☐ Acknowledged
Reviewer	**Signature:** Andrea L. Benedict -S Digitally signed by Andrea L. Benedict -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001432019, cn=Andrea L. Benedict -S Date: 2019.05.23 11:04:35 -04'00'		
Pharmacology and Toxicology	Mukesh Summan, Ph.D., DABT	OND/ODE3/DBRUP	5 ☐ Authored ☒ Approved ☐ Acknowledged
Supervisor	**Signature:** Mukesh Summan -S Digitally signed by Mukesh Summan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mukesh Summan -S, 0.9.2342.19200300.100.1.1=2000337340 Date: 2019.05.23 11:32:36 -04'00'		
Clinical	Ronald Orleans, M.D.	OND/ODE3/DBRUP	7,8 ☒ Authored ☒ Approved ☐ Acknowledged
Primary Reviewer	**Signature:**		
Clinical	Gerald Willett, M.D.	OND/ODE3/DBRUP	1,2,3 ☒ Authored ☒ Approved ☐ Acknowledged
Cross-Disciplinary Team Lead	**Signature:**		
Clinical	Audrey Gassman, M.D.	OND/ODE3/DBRUP	Enter sections. ☐ Authored ☒ Approved ☐ Acknowledged
Deputy Director	**Signature:**		

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
ASCUS	atypical squamous cells of undetermined significance
ATE	arterial thromboembolic event
BA	bioavailability
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CLCr	creatinine clearance
CMC	chemistry, manufacturing, and controls
COC	combination oral contraceptive
DSG	desogestrel
DRSP	drospirenone
ECG	electrocardiogram
EE	ethinyl estradiol
FDA	Food and Drug Administration
GCP	good clinical practice
IND	Investigational New Drug
IRB	institutional review board
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
LF111	(b) (4) drospirenone 4 mg
MedDRA	Medical Dictionary for Regulatory Activities
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	Pearl Index
PK	pharmacokinetics
POP	progestin-only pill
SAE	serious adverse event
SPA	Special Protocol Assessment
TEAE	treatment emergent adverse event
VTE	venous thromboembolic event

1. Executive Summary

1.1. Product Introduction

General and Efficacy Introduction

Exeltis USA Inc. seeks approval of LF111 [redacted] (b) (4) drospirenone [DRSP] 4 mg) under section 505 (b)(2) for pregnancy prevention. LF111 will be used primarily to describe the proposed product in this review. Each 28-day cycle consists of the oral administration of one active tablet for 24 consecutive days followed by one inert tablet for 4 consecutive days.

DRSP is a fourth-generation progestin derived from the aldosterone antagonist spironolactone, a potassium-sparing diuretic used to treat hypertension.

The anti-gonadotropic contraceptive mechanism of action for DRSP lies in its ability to inhibit 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. Inhibition of ovulation is easier to demonstrate as a mechanism of action since cervical mucus changes (e.g., the Insler Score) alone do not evaluate functional sperm alterations or changes in sperm transport. However, since progestin products do not consistently inhibit ovulation, the alteration of cervical mucus is considered an important secondary mechanism of action.

The Applicant has developed a [redacted] (b) (4) oral formulation of DRSP 4 mg as a progestin-only pill (POP) in distinction to the currently approved DRSP-containing combination oral contraceptives (shown in Table 1 below)

There are five DRSP-containing hormonal products approved in the United States which include four originator combination oral contraceptives and one originator menopausal product. Pertinent information on these products are shown in the following table:

Table 1. Drospirenone-Containing Originator Hormonal Products Approved in United States

Product NDA #(s) Approval Yr	DRSP	EE	Regimen (one tablet, orally/day)	Notes
Yasmin® 21-098 2001	3 mg	30 µg	DRSP/EE x 21 days Inert tabs x 7 days*	Indication = prevent pregnancy
Yaz® 21-676 21-873 both in 2006 22-045 2007	3 mg	20 µg	DRSP/EE x 24 days Inert tabs x 4 days*	Indications = prevent pregnancy, PMDD, moderate acne
Safyral®* 22-574 2010	3 mg	30 µg	DRSP/EE/FS x 21 days FS x 7 days**	Indications = prevent pregnancy, raise folate levels
Beyaz®* 22-532 2010	3 mg	20 µg	DRSP/EE/FS x 24 days FS x 4 days**	Indications = prevent pregnancy, PMDD, moderate acne, raise folate levels
Angeliq® 21-355 2005	0.25 mg 0.5 mg	0.5 mg 1.0 mg	Both dosage strengths orally one per day	Indications = vasomotor symptoms, vulvar and vaginal atrophy

DRSP = drospirenone; EE = ethinyl estradiol; FS = folate supplement (levomefolate calcium); PMDD = premenstrual dysphoric disorder; E2 = estradiol; Yr = year
*placebo tablets
** Also contains folate supplement
Source: Drugs @ FDA

Of note, there is another DRSP-containing combination oral contraceptive approved and marketed in Europe (Yasminelle®), which has the same dosage as Yaz® but is taken in a 21/7 regimen.

Safety introduction

Anti-estrogenic effects from progestin-only products are mainly considered as adverse events rather than clinical benefit. These adverse events may be manifested in vasomotor symptoms and bone loss. The anti-estrogenic effects vary among the different progestins. The effect of LF111 as an anti-estrogen is most clinically concerning with respect to bone loss.. The available information on this anti-estrogen effect will be discussed further in this review in Section 8.2.5.

Anti-mineralocorticoid safety issues that relate to DRSP use include the possibility of hyperkalemia. Extensive study has been performed in the DRSP-containing combination contraceptives (particularly Yasmin® and Yaz®) for this safety concern. The initial safety timeline (Table 2) for DRSP regarding evaluation of hyperkalemia includes the following:

Table 2. Timeline Regarding Hyperkalemia Assessment for DRSP-Containing COCs

May 14, 1999	New NDA Submitted for Yasmin®
Mar 17, 2000 & Jul 10, 2000	Applicant (Berlex) was sent an approvable letter on each of these dates. The Division sought additional safety data in regard to hyperkalemia. Berlex provided additional information from four studies and committed to phase IV activities to evaluate adverse outcomes that might be a consequence of hyperkalemia.
May 11, 2001	Yasmin® was approved. Office Director's memo described the overall effects on serum potassium as small, making risk for hyperkalemia slight.
Oct 17, 2003	New NDA submitted for Yaz®
Nov 17, 2004	Yaz® receives an approvable action. The Division requested evidence that the 24/4-day dosing regimen provided a clinical benefit over a 21/7-day dosing regimen. The primary clinical reviewer (Dr. Willett) found that many of the potassium elevations in subjects taking Yaz® to be mild and often associated with hemolysis or delayed transport. No evidence of hyperkalemia-related symptoms was noted at the time of these elevations.
Aug 8, 2006	The primary medical officer (Dr. Furlong) reviewed the final study results for a postmarketing study that included a safety analysis for hyperkalemia. She noted: "The Ingenix Study did not detect any safety concerns that differentiate Yasmin® from other oral contraceptives."
Mar 16, 2006	Yaz® is approved

DRSP = drospirenone; COC = combination oral contraceptive

As noted in the preceding table, symptomatic hyperkalemia was not a major safety issue in the development of DRSP-containing COCs. As noted in greater detail in Section 8.2.5. hyperkalemia was evaluated in greater detail since the dosage of DRSP was increased above that used in COCs.

Thromboembolic adverse events have been evaluated for DRSP-containing COCs in postmarketing epidemiologic studies. A major safety concern for these products is that of venous thromboembolic events (VTEs). These were initially identified following marketing of Yasmin® via spontaneous reporting. There have been numerous large epidemiologic studies of different designs performed since these reports surfaced. The studies have found divergent results when comparing VTEs in patients taking DRSP-containing COCs compared to events occurring in patients taking COCs containing levonorgestrel and some other progestins. The labels for these DRSP-containing products present the epidemiologic results in tabular and/or forest plot form. The present labeling safety message derived from the epidemiologic findings is that DRSP-containing COCs may be associated with a higher risk of venous thromboembolism than COCs containing the progestin levonorgestrel or some other progestins. Given that the absolute risk of VTEs for a given patient is relatively small and the limited safety data of the risk on this progestin-only product, a VTE warning will be carried over into the drospirenone only product labeling. Thromboembolic adverse events for this DRSP POP will be discussed in Section 8.2.5.

1.2. Conclusions on the Substantial Evidence of Effectiveness

LF111 (DRSP 4 mg) is proposed as a progestin-only oral contraceptive in females of reproductive potential. The Applicant's evidence of efficacy primarily is derived from their one-year, multicenter, open-label, U.S. phase 3 trial CF111/303. The Pearl Index (PI), which is based on the number of on-treatment pregnancies in evaluable cycles (cycles with sexual activity and absence of back-up contraception), was utilized as the primary endpoint in non-breastfeeding

women ≤35 years at entry. The Applicant's calculation of the PI was 2.9 (95% confidence interval (CI): 1.5, 5.1) based on 12 on-treatment pregnancies. The FDA reviewers however identified five additional on-treatment pregnancies, including two well-documented cases from two study sites that were closed for protocol violations by the Applicant. The FDA reviewers' PI assessment was 4.0 (95% CI: 2.3, 6.4). Although this PI is higher than that seen with some recent COCs assessed in the United States, we find this rate acceptable for the oral progestin-only subclass of contraceptives which historically have had somewhat higher PIs.

The Applicant did conduct two additional studies in Europe (CF111/301 and CF111/302). The Pearl Index and efficacy data from in these European studies were not part of the primary analysis and the results are not included in the label because the information is not generally applicable to the US population. However, the results from these European studies did not raise additional concern about the U.S. findings.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Although there are many hormonal contraceptive options presently on the market, it is important to provide women with more contraceptive options. The drospirenone (DRSP) product in consideration in this submission is the first progestin-only pill (POP) to be considered for approval in many years and the first one to propose a 24 (active tablets)/4 (placebo tablets)-day regimen with a (b) (4) formulation of DRSP. Although progestin-only products historically have appeared to have a more favorable safety profile and have been used in breast feeding women, their downside has been the need to take them at the same time each day and the continuous daily use which can lead to increased unscheduled bleeding/spotting resulting in tolerance and non-compliance with these products.

The Applicant provided an adequate number of evaluable cycles in a U.S.-based population to assess efficacy. The Pearl Index of 4.0 (95% CI: 2.3, 6.4) is acceptable for approval for an oral progestin-only contraceptive. Subgroup analysis did not suggest that subjects with a higher body mass index had a greater risk for pregnancy.

The United States has had nearly 18 years' worth of marketing experience with DRSP in four originator combination oral contraceptives and one product for menopausal symptoms. Due to its anti-mineralocorticoid effect and potential for hyperkalemia the DRSP products were thoroughly investigated for this complication prior to approval and in postmarketing safety evaluations. Symptomatic hyperkalemia was not found to be a significant safety concern for this product. There were no subjects in the LF111 development studies reported with symptomatic hyperkalemia or potassium associated electrocardiographic alterations. 14/2598 subjects (0.5%) had persistent hyperkalemia and 2/2598 subjects (0.1%) were withdrawn from study medication based on laboratory testing demonstrating increased potassium. As a result of these results, LF111 labeling will have the same safety labeling regarding potassium that is present in the DRSP-containing combination products.

There were no venous or arterial thromboembolic events (VTEs or ATEs) in the LF111 development studies. The possibility of DRSP-containing combined oral contraceptives (COCs) having a higher risk of thromboembolic events as compared to levonorgestrel-containing COCs has been debated in the epidemiologic literature. Although there were no thromboembolic events in the clinical trial, identification of these thromboembolic events in a clinical trial database is difficult given that these are uncommon events in healthy population. As the risk of thromboembolic events may be increased with real world use in a population that may have more health issues, the warning on thromboembolic risk will remain in product labeling. At this time, given the lack of thromboembolic

events in the clinical trial, a dedicated postmarketing study for VTE is not recommended for LF111 at this time but the risk will be monitored through evaluation of postmarketing adverse reactions. If a new safety signal or trend is identified with use of this DRSP product, a large postmarketing observational trial to evaluate the risk of thromboembolic events will be warranted.

The laboratory results pertaining to bone metabolism biomarkers did not raise any specific concerns. However, bone biomarkers are very limited in their ability to detect bone loss in this population. Therefore, The Applicant will conduct a postmarketing bone mineral density study in adults and adolescents and included a proposed synopsis and milestones in this submission.

No deaths were reported in any of the developmental trials. There were no significant or new unexpected safety signals in the evaluation of serious adverse events, discontinuations due to adverse events or treatment emergent adverse events/reactions.

Based on the risk-benefit profile, approval of LF111 is recommended for the prevention of pregnancy in women of reproductive potential. It is acceptable to conduct the bone mineral density study in the postmarketing period. Longer term use will be needed to determine whether this risk will require labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Unintended pregnancy continues to represent a significant reproductive health problem in the United States. Although the increase in longer acting contraceptive methods has improved the situation, the continuing development of newer safe and effective products in all forms of contraception is important.	Development of new safe and effective contraception options are crucial for women's health. The development of a progestin-only oral contraceptive with more convenient dosing and provision of a withdrawal period may provide women with additional options in a contraceptive subclass that historically has shown less adverse reactions.
Current Treatment Options	Norethindrone 0.35 mg, one tablet daily (at the same time)	Presently there are only two brands of oral progestin-only pills (both with the same dose of norethindrone). They are taken continuously at the same time each day.
Benefit	In consideration of the contraceptive subclass (progestin-only) and safety profile, the Pearl Index is acceptable for product approval.	Efficacy findings support approval of LF111 for prevention of pregnancy in females of reproductive potential. Inclusion of scheduled and unscheduled

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		bleeding data that may impact patient tolerance and compliance with use will be included in the label. Unlike products with an estrogen component, women who smoke may use this product even if they are over 35 years of age
Risk and Risk Management	Hyperkalemia and thromboembolic disorders were the safety issues of special interest that were the focus of the reviewers in this submission because of the known safety profile with use of DRSP in combination with estrogen. Hyperkalemia: There was no evidence that the hyperkalemia was associated with clinically significant adverse reactions or electrocardiographic changes in any subject. Thromboembolic events: No VTEs or ATEs were reported in the developmental studies of LF111. Bone loss: Progestin only products have been associated with clinically significant bone loss. Surrogate biomarkers for bone metabolism (bone alkaline phosphatase and cross-linked C-terminal telopeptides) were evaluated in Study CF111/302 and no safety signals or trends were identified in this data. However, evaluation of bone marker data is insufficient to adequately capture the risk of bone loss with long term use of DRSP.	The current labeling restrictions regarding the potential for hyperkalemia that are present in the COCs containing DRSP should be maintained in the product label for the DRSP POP. Routine postmarketing surveillance of voluntary reporting is acceptable for VTEs and ATEs with the DRSP POP. A postmarketing required study of the effect of this DRSP POP on bone mineral density will be conducted according to agreed milestones.

1.4. Patient Experience Data

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

X	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			
			X	Patient reported outcome (PRO)	e-diary information regarding bleeding utilized for safety Section 8.2.4
			□	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			
	□	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 was not submitted in the application, but was considered in this review.				

2. Therapeutic Context

2.1. Analysis of Condition

Products designed to prevent pregnancy encompass the following array of drugs, devices, and drug/device combinations that are approved and marketed in the US.

Drug only

- COCs
- POPs (see Section 2.2)
- Medroxyprogesterone acetate injections
- Spermicides

Device only

- Male and female condoms
- Diaphragm and cervical cap
- Intratubal device

Drug/device

- Hormonal and copper intrauterine devices
- Hormonal vaginal ring
- Hormonal implants
- Hormonal patches

2.2. Analysis of Current Treatment Options

POPs are oral contraceptive products that do not contain estrogen.

Previously approved POPs in the US have only utilized a continuous active pill regimen. These POP products have known issues with compliance and tolerance as a result of the increased rate of unscheduled bleeding as compared to combined oral contraceptives with estrogen. In addition, the current POPs also have to be taken daily in a narrow time window that places an additional burden on women who use these products.

- *Currently approved oral POPs for contraception include Micronor® and Nor-QD®. Both products were approved in 1973 and both contain norethindrone 0.35 mg in tablets taken daily. There are no pill-free intervals with these products. Although the innovator products are no longer available, a generic been approved in the US. Some additional information for the approved innovator POPs is found in Table 3.*

Table 3. Approved Progestin-Only Pills in United States

Product(s) Name Year Approved	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Ortho Micronor® (norethindrone) 1973 Nor-QD® (norethindrone) 1973	Norethindrone 0.35 mg One tablet every day at the same time	Labels state if used perfectly the first-year failure rate is 0.5%. However typical failure rate is estimated to be closer to 5%	The labeling safety information mentions that ovarian cysts are more common in POP users than most other birth control methods. The most common side effect for POPs is a change in menstrual bleeding. In general POPs have less adverse events than COCs.

POP = progestin-only pill; COC = combination oral contraceptive; QD = once daily

- *It is not possible to compare the efficacy of products approved in the 1970s with current contraceptives, such as DRSP, as the current US population is heavier, has a lower rate of smoking and is different demographically.*
- [redacted] (b) (4)

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Exeltis USA (the Applicant) is submitting NDA 211367 in support of a [redacted] (b) (4) DRSP 4 mg (LF111) as a POP to be taken daily for 24 days followed by a placebo tablet taken daily for 4 days for the indication of prevention of pregnancy. The U.S. development program for LF111 for contraception was carried out under investigational new drug (IND) 111347. Exeltis USA submitted a statement of right of reference. This statement includes the names (and former names) of other aligned companies in the Insud Pharma group (formerly Chemo Espana S.L.). These companies include Chemo Research S.L., Laboratorios Leon Farma S.A., Exeltis France (formerly Chemo France) and Exeltis USA (formerly Everett Laboratories).

3.2. Summary of Presubmission/Submission Regulatory Activity

Regulatory History

Key Interactions

September 9, 2013: EOP-Phase 2 Meeting with CHEMO France

Dose Selection

- The Division noted that the multiple-dose pharmacokinetic (PK) study (CF111/103A) showed a lower systemic exposure of DRSP from LF111 compared to Yaz®, with relative bioavailability of 77.8% for AUC and 66.8% for C_{max}. The results of pharmacodynamics studies demonstrated that LF111 at 4-mg dose and 24/4 regimen appeared to be adequate in suppressing ovulation.
- The Applicant noted that the 3-mg micronized DRSP dose (approved in various COCs) or a lower dose of LF111 might not provide sufficient contraceptive efficacy for women with high body mass index (BMI) or women who do not comply exactly with the dose regimen and proposed studying the 4 mg regime.

Inclusion Criteria

- The Applicant was encouraged to enroll subjects <18 years of age and to remove the upper age limit.

Safety

- The plan to study 20 subjects with at least 12 completing the one-year evaluation was considered acceptable for the endometrial safety study.
- The proposal to define scheduled bleeding as any bleeding beginning on day 25 to day 28±1 day and continuing up to 8 consecutive days was acceptable. Unscheduled bleeding should be defined as any bleeding outside this window.

February 12, 2014: Protocol for Study CF111/303 was submitted for a Special Protocol Assessment

- The protocol for phase 3 U.S. Study CF111/303 was initially submitted to the Division on February 12, 2014 for a Special Protocol Assessment (SPA). The Division found that "the design and planned analysis of your study did not adequately address the objectives necessary to support a regulatory submission" and issued a "SPECIAL PROTOCOL ASSESSMENT-NO AGREEMENT" letter dated March 28, 2014.

March 28, 2014: Special Protocol Assessment (No Agreement)

Efficacy

- The Division requested approximately 5,000 evaluable cycles coming from U.S. women.
- "On drug" pregnancies should be defined as all conceptions that occur from the initiation of study drug (Day1) through 7 days after the final tablet is taken. If a clear relation to dosing cannot be determined, the pregnancy will be considered as "on-drug."
- The efficacy cohort should consist of subjects who are ≤35 years at the time of enrollment. Subjects who turn 36 during the course of the study should not be censored from the efficacy cohort.

Safety

- The following bleeding definitions were advised:
  - Light = less than usual menses
  - Moderate = like usual menses
  - Heavy = more than usual menses
- We recommended that a minimum of 200 women >35 years of age be enrolled in the phase 3 trials to study safety in this age group. At least 100 of these women (50%) should be enrolled in the U.S. trial.

May 29, 2014: Applicant Response

- The Applicant notified the Division that they would not need to submit the protocol for another SPA. They believed that they addressed all the Division's responses as listed in the in the SPA No Agreement Letter dated March 28, 2014. In accordance with Division recommendations, the pivotal study protocol was revised and submitted as IND 111347 (SN 0005).

    - *The Division agreed that the submitted protocol was generally acceptable.*

March 4, 2015: Advice Letter

- The Division agreed that the Applicant's post approval study of BMD in women of all ages, including pediatric users, was acceptable.
    - The study should provide comparator-controlled data on changes in bone mineral density.
    - Analysis of BMD data should be stratified by age to account for the differences in bone metabolism among adolescents. Specifically, adolescent girls should be accruing BMD, so plateauing of BMD in this population may indicate an adverse effect.
    - If adverse effects on BMD are demonstrated following one-year of treatment, subjects should be followed to determine the time off-treatment required for resolution of this effect.

December 19, 2017: Pre-NDA Meeting

- The Division agreed that the data from the U.S. trial (CF111/303) when combined with the data from the European development program would be sufficient for review of a 505(b)(2) NDA. It was noted that the U.S. study included over 5000 cycles and included an adequate proportion of obese subjects.
- If the product is approved, a postmarketing BMD study will be required.
- For the Integrated Summary of Effectiveness, data from the phase 3 trial conducted in the U.S. (Protocol CF111/303) should not be pooled with the European studies. Also, data from Protocol CF111/304, conducted on adolescent subjects, will not be pooled for efficacy.
- Three different Medical Dictionary for Regulatory Activities (MedDRA) dictionaries were used for the phase 3 protocols CF111/301, CF111/302, and CF111/303: MedDRA v15, v16, and v17, respectively. The Applicant agreed to align all data sets with the MedDRA v17.0 dictionary.

February 18, 2019: Division's Information Request Regarding Hyperkalemia

On February 11, 2019 the Division requested the following:

- Provide all potassium results from subjects who had potassium levels > than 5.3 mmol/L (also include information on hemolytic specimens, delay in testing and pertinent concomitant medications).

- Provide any adverse events that occurred at the time of potassium elevation and/or electrocardiogram results.

    - *The Applicant responded to this request on February 18, 2019. Hyperkalemia is discussed in Sections 8.2.4 and 8.2.5. Individual subject results can be found in the Appendix.*

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

4.1. Office of Scientific Investigations

Office of Scientific Investigations (OSI) inspections were performed at the following clinical study sites for the pivotal U.S. Study CF111/303. The inspections were done to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects were protected:

- Study site 108: Charles Eubank, Jr. M.D., Corpus Christi, TX 78414 (76 subjects)
- Study site 124: Robert Feldman, M.D., Miami, FL 33143 (40 subjects)
- Study site 122: Samuel Lederman, M.D., Lake Worth, FL 33416 (90 subjects)

All the above sites received a No Action Indicated (NAI) designation. The OSI reviewer, Roy Blay, Ph.D., concluded that based on the results of these inspections, the study (Protocol CF111/303) appears to have been conducted adequately, and that the data generated by these sites appear acceptable in support of the study indication.

4.2. Product Quality

Drospirenone is a synthetic progestin structurally related to spironolactone. The chemistry, manufacturing and controls for drospirenone drug substance are documented in (b) (4) Type II Drug Master File (DMF) (b) (4) The drug substance meets the requirements of the USP monograph for drospirenone including related substances and residual solvents.

In addition to the USP monograph requirements, the NDA drug substance specification includes requirements for Specific Surface Area (SSA) and Particle Size Distribution (PSD). PSD and SSA are critical to performance of the drug product and directly impact product dissolution.

The data provided in the DMF and in the NDA have been found adequate to support the use of the active pharmaceutical ingredient (API) in the manufacture of the drug product.

Drospirenone tablets are dispensed in a blister card containing 24 white, immediate-release active tablets and 4 green, inert tablets. The active tablets contain 4 mg drospirenone, which accounts for (b) (4) % w/w of the total formulation. Inactive ingredients include microcrystalline cellulose, lactose, colloidal silicon dioxide, and magnesium stearate. All excipients are of USP/NF compendial grade. There is no source of elemental iron in the product.

The inert placebo tablets contain lactose monohydrate, corn starch, povidone (b) (4), colloidal silicon dioxide, and magnesium stearate. All components of the placebo tablet comply with USP/NF or with the requirements of 21 CFR 82.102. (b) (4)

Because of the low dose (only 4 mg drospirenone), the low drug load in the tablets ([(b) (4)]% w/w) and the low aqueous solubility of drospirenone, a well-controlled manufacturing process is critical to ensuring that the drug product has the requisite content uniformity and performance (i.e., dissolution). Sufficient information was submitted to demonstrate that adequate manufacturing process parameters (e.g., for [(b) (4)], tablet coating) and in-process controls have been established to consistently produce drug product with the desired strength, quality and performance.

The drug product regulatory specification includes test to provide further assurance that drospirenone tablets will have the requisite the identity, strength, quality, purity, and bioavailability. Of note is the dissolution test which includes sampling at 15 minutes and at 3 hours. Such a two-tiered approach is particularly useful for ensuring that immediate-release tablets with a low solubility active ingredient perform adequately. The acceptance criteria were established based on dissolution test results from clinical batches. The acceptance criterion for total degradation products in the tablets was revised from not more than (NMT) [(b) (4)]% to NMT [(b) (4)]% at the request of the nonclinical review team. Individual related substances are controlled at NMT[(b) (4)]%.

Long-term and accelerated stability studies support a 36-month expiration dating period for drug product stored at 25°C and packaged in the commercial aluminum foil / PVC-PVdC blisters.

All facilities associated with the manufacture, testing and packaging of the drug substance and the drug product have acceptable CGMP status. The Office of Process and Facilities issued an overall manufacturing inspection recommendation of APPROVE on March 8, 2019.

The applicant has claimed a categorical exclusion from the environmental assessment (EA) requirements in accordance with 21 CFR Part 25.31(b) and provided supporting data. The CDER EA Team reviewed the data and concluded that the results were indicative of no environmental impact, and thus support the applicant's categorical exclusion.

Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product. The application is therefore recommended for approval from the drug substance, drug product, manufacturing process, facilities and biopharmaceutics perspectives. Labeling negotiations are now complete and acceptable to CMC.

4.3. Clinical Microbiology

Not Applicable

4.4. Devices and Companion Diagnostic Issues

Not Applicable

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

NDA 211367 is a 505(b)(2) application for LF111 ((b) (4) DRSP 4 mg) with reference to Yaz® as the listed drug product. The Applicant refers to the Agency's previous findings of safety and efficacy for the nonclinical pharmacology, pharmacokinetics, and toxicology of the DRSP component of Yaz® (NDA 21676), (b) (4) Yaz® is approved as a combination of DRSP (3 mg) and ethinyl estradiol (0.02 mg). The listed drug is a combined oral contraceptive.

The Applicant has not conducted any new nonclinical pharmacology or toxicology studies with LF111. No additional nonclinical studies were required or requested by the Division to support an NDA application, pending an adequate scientific bridge was established through clinical comparative pharmacokinetic studies of LF111 to the U.S. comparator Yaz®.

The scientific bridge between LF111 and Yaz® is provided by a comparative clinical bioavailability (BA) study (CF111/103A). In this study, the Applicant demonstrated that the DRSP exposure following administration of multiple doses of LF111 ((b) (4) DRSP 4 mg) was less than or comparable to the reference drug (Yaz®). Therefore, an adequate scientific bridge has been established to the listed drug Yaz®. Reliance on the Agency's prior determination of safety of DRSP in Yaz® to support the nonclinical sections of the NDA, as reflected in the approved listed drug labeling, is appropriate. (b) (4)

In conclusion, there are no nonclinical concerns and Pharmacology/Toxicology supports the approval of LF111 (b) (4) DRSP 4 mg for the indication of prevention of pregnancy in women under NDA 211367.

5.2. Referenced NDAs, BLAs, DMFs

NDA 21676: Yaz® (Bayer HealthCare Pharmaceuticals Inc.; Approval Date: March 16, 2006).

5.3. Pharmacology

No new nonclinical pharmacology studies were conducted with LF111 for this 505(b)(2) submission.

Primary Pharmacology

Drospirenone is a spironolactone analogue with anti-mineralocorticoid activity.

The contraceptive action of DRSP is attributed to its suppression of gonadotropins which inhibits ovulation.

Safety Pharmacology

No new nonclinical safety pharmacology studies were conducted with LF111 for this 505(b)(2) submission.

5.4. ADME/PK

No new nonclinical pharmacokinetic/ADME/toxicokinetic studies were conducted with LF111 for this 505(b)(2) submission.

5.5. Toxicology

5.5.1. General Toxicology

The Applicant did not conduct any new nonclinical toxicology studies.

5.5.2. Genetic Toxicology

The Applicant did not conduct any new genetic toxicology studies with LF111 for this 505(b)(2) submission.

A complete battery of genetic toxicology studies has been conducted under the referenced NDA with DRSP in vitro and in vivo, and no evidence of mutagenic activity was observed.

5.5.3. Carcinogenicity

The Applicant did not conduct any new nonclinical carcinogenicity studies with LF111.

As reflected for the DRSP component in the current Yaz® approved drug product labeling, in a 24-month oral carcinogenicity study in mice with doses up to 10 mg/kg/day DRSP, equating to two times the maximum clinical exposure (based on AUC), there was an increase in carcinomas of the harderian gland in the high-dose DRSP group. In a similar study in rats given doses up to 10 mg/kg/day DRSP, 10 times the maximum clinical exposure (based on AUC), there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the high-dose DRSP group.

5.5.4. Reproductive and Developmental Toxicology

No new reproductive or developmental toxicology studies were conducted with LF111.

5.5.5. Other Toxicology Studies

None.

6. Clinical Pharmacology

6.1. Executive Summary

Drospirenone (DRSP), a progestogen, has a pharmacological profile similar to progesterone and possesses anti-mineralocorticoid and antiandrogenic activity. In combination with ethinyl estradiol (EE) and 17β estradiol (E2), DRSP has been extensively studied in the preclinical and clinical setting; micronized DRSP 3 mg in combination with EE 30 or 20 µg, from 21 days to 24 days, is registered for use in the prevention of pregnancy as an oral contraceptive (Yasmin®, Jasminelle®, Yaz®) in Europe and the United States. The purpose of this New Drug Application (NDA) is to obtain the approval of LF111 (a progestin-only pill (POP)) for the prevention of pregnancy in women who elect to use an oral contraceptive. LF111 contains 24 tablets of 4 mg DRSP and four inert (placebo) tablets. Each 28-day cycle includes oral administration of one active tablet for 24 consecutive days followed by one inert tablet for 4 consecutive days.

6.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 211367 and recommend approval of this NDA. The key review issues with specific recommendations/ comments are summarized in the table below:

Table 4. Clinical Pharmacology Issues and Recommendations

Review Issue	Recommendations and Comments
Supportive evidence of effectiveness	Three pivotal phase 3 studies (Studies CF111/301, CF111/302, CF111/303) demonstrated the safety and efficacy of LF111 for the proposed indication of prevention of pregnancy.
General dosing instructions	One tablet once daily every day for 28 days, with or without food; one white active tablet containing 4 mg DRSP for 24 consecutive days, followed by one green inert placebo tablet for 4 consecutive days.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Contraindication in women with liver tumors, benign or malignant, or liver disease. Contraindication in women with renal impairment. Use a back-up or alternative method of contraception when enzyme inducers are used with LF111.
Label	Refer to Section 11 for the review team's recommendations.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed product (LF111) was used for clinical trials CF111/103A, CF111/103C, CF111/106, CF111/107, all pharmacodynamic studies and the pivotal phase 3 trials.
Other (specify)	None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

LF111 is a progestin-only pill containing DRSP, which prevents pregnancy primarily through suppressing ovulation.

Pharmacokinetics of LF111

Table 5 provides a summary of the clinical pharmacology characteristics of LF111.

Table 5. Pharmacokinetics Summary of LF111

Pharmacokinetic Characteristic	Drug Information
Absorption	Maximum concentrations of DRSP in plasma of about 29 ng/ml are reached at about 2 to 6 hours after single ingestion. During a treatment cycle, maximum steady-state concentrations of DRSP in serum of about 42 ng/ml are reached after about 10 days of treatment. Plasma DRSP levels (AUC) accumulate by a factor of about 2 as a consequence of the ratio of terminal half-life and dosing interval. Concomitant ingestion of food has no influence on the extent of absorption of DRSP.
Distribution	After daily administration of LF111 tablets, the average DRSP concentration in breast milk over 24-hour period was 5.60±4.51 ng/mL. Based on this concentration, the estimated average infant daily dosages for an exclusively breastfed infant is 840 ng/kg/day. Other distribution properties for DRSP are supported by the label for the listed drug Yaz®.
Metabolism	The Applicant did not conduct studies to characterize the metabolism of LF111. The metabolism properties for DRSP are supported by the label for the listed drug Yaz®.
Excretion	DRSP serum concentrations are characterized by a terminal disposition phase half-life of approximately 30 hours after both single and multiple dose regimens.

AUC = area under the concentration-time curve; DRSP = drospirenone

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

One tablet once daily every day for 28 days, with or without food; one white active tablet containing 4 mg DRSP for 24 consecutive days, followed by one green inert placebo tablet for 4 consecutive days.

Therapeutic Individualization

Hepatic Impairment*:* LF111 is contraindicated in patients with hepatic disease.

The Applicant did not conduct dedicated studies with LF111 in patients with hepatic impairment. Based on the Yaz® label, the mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. DRSP has not been studied in women with severe hepatic impairment. The proposed contraindication in patients with hepatic disease is consistent with the label for the listed drug Yaz®.

Renal Impairment: LF111 is contraindicated in patients with renal impairment.

The Applicant did not conduct dedicated studies with LF111 in patients with renal impairment. Based on the Yaz® label, the effect of renal impairment on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effect of DRSP on serum potassium concentrations were investigated

in three separate groups of female subjects (n=28, age 30 to 65). All subjects were on a low potassium diet. During the study, seven subjects continued the use of potassium-sparing drugs for the treatment of their underlying illness. On the 14th day (steady-state) of DRSP treatment, the serum DRSP concentrations in the group with creatinine clearance (CLcr) of 50 to 79 mL/min were comparable to those in the control group with CLcr ≥80 mL/min. The serum DRSP concentrations were on average 37% higher in the group with CLcr of 30 to 49 mL/min compared to those in the control group. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium-sparing drugs during the study, mean serum potassium concentrations increased by up to 0.33 mEq/L. The proposed contraindication in patients with renal impairment is consistent with the label for the listed drug Yaz®.

Drug-drug interaction

No drug-drug interaction studies were conducted with LF111. Based on the Yaz® label, the patient should use a back-up or alternative method of contraception when enzyme inducers are used with LF111.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Table 6. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of action	LF111 lowers the risk of becoming pregnant primarily through suppressing ovulation.
Active moieties	DRSP
QT prolongation	ECG assessments were stable at multiple oral dose of 4 mg DRSP [Studies CF111/201 A and CF111/302]
General information	
Bioanalysis	DRSP concentrations in the plasma and milk were measured using validated high-performance liquid chromatography (HPLC) methods.
Healthy vs. patients	The target population of LF111 are healthy pre-menopausal women.
Drug exposure at steady state (Mean ± SD)	DRSP $AUC_{(0\text{-}Tau)}$ and C_{max} (Mean ± SD) at steady state were 586.2±146.6 ng*h/mL and 42.3±11.2 ng/mL, respectively. [Study CF111/103 A]
Minimal effective dose or exposure	Phase 3 studies assessed the efficacy (Pearl Index) of LF111 4 mg in a regimen 24 /4 placebo. See Pharmacodynamics (phase 2 studies) section below.
Maximally tolerated dose or exposure	Maximally tolerated dose has not been established.
Pharmacodynamics	LF111 demonstrated ovulation inhibition despite two delayed intakes of 24 hours scheduled on day 5 and day 13 in one cycle [Study CF111/201A] and four delayed intakes of 24 hours scheduled on days 3, 6, 11, and 22 in one cycle [Study CF111/205].

Dose proportionality	LF111 PK data were available only at 4-mg dose level. Thus, dose proportionality was not assessed.
Accumulation	Plasma DRSP levels (AUC) accumulate by a factor of about 2. [Study CF111/103 A]
Variability	At steady state, the values of inter-subject variability (CV%) of DRSP for C_{max} and $AUC_{(0\text{-}Tau)}$ were 26.3% and 25.0%, respectively. [Study CF111/103 A]
Absorption	
Bioavailability	The absolute bioavailability of LF111 in humans was not assessed.
T_{max} (Median)	3.5 hours [Study CF111/103 A]
Food effect	Concomitant ingestion of food had no influence on the AUC of DRSP, whereas the C_{max} increased by about 30%. [Study CF111/106]
Distribution	
Volume of distribution	Based on the label for the listed drug Yaz®, the volume of distribution of orally administered DRSP is 4 L/kg.
Plasma protein binding	Based on the label for the listed drug Yaz®, DRSP does not bind to SHBG or corticosteroid binding globulin (CBG) but is about 97% bound to other serum proteins.
Elimination	
Terminal elimination half-life (mean ± SD)	After single dose: 27.93±8.43 hours; After multiple dose: 28.95±6.83 hours [Study CF111/103 A]
Metabolism	
Primary metabolic pathway(s)	Based on the label for the listed drug Yaz®, DRSP is extensively metabolized after oral administration. The two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate, formed by reduction and subsequent sulfation. These metabolites were shown not to be pharmacologically active. DRSP is also subject to oxidative metabolism catalyzed by CYP3A4.
Excretion	
Primary excretion pathways (% dose) ±SD	Based on the label for the listed drug Yaz®, excretion of DRSP was nearly complete after 10 days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces.
In vitro interaction liability (drug as perpetrator)	
Inhibition/induction of metabolism	Based on the label for the listed drug Yaz®, in vitro studies and in vivo interaction studies in female volunteers using omeprazole, simvastatin and midazolam as marker substrate, an interaction of drospirenone with the metabolism of other active substances is unlikely.

AUC = area under the concentration-time curve; CV% = percent of coefficient of variation; CYP = cytochrome P450; DSRP = drospirenone; ECG = electrocardiogram; SD = standard deviation.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The clinical pharmacology information that provides supportive evidence of effectiveness includes: (1) Suppression of ovulation and (2) effective ovulation inhibition despite delayed intakes.

Suppression of ovulation

The Applicant conducted a pharmacodynamic study (CF111/202) to assess the ovulation inhibition potential of LF111 as reflected by the ovarian activity (follicular growth, estradiol, and progesterone serum concentrations). In this study, the use of DRSP 4 mg in a regimen 24/4

placebo over two treatment cycles, LF111 was effective regarding suppression of ovarian activity. The rate of subjects without ovulation for LF111 was 100% for first cycle and 96.3% for the second cycle. The vast majority of subjects in the treatment group had Hoogland Scores ≤4, corresponding to ovulation inhibition, and the Landgren Scores were always negative. In Study CF111/203, there were no significant differences regarding ovulation inhibition as assessed using Hoogland score between LF111 (DRSP 4.0 mg 24/4) compared to DRSP (2.8 mg 28/0) regimen. The LF111 (DRSP 4.0 mg 24/4) treatment included a higher DRSP dose (4.0-mg tablet), but there was a hormone-free interval of 4 days at the end of each treatment cycle, with which subjects tended to have fewer unscheduled bleeding or spotting days.

Effective ovulation inhibition despite delayed intakes

In Study CF111/201A, ovulation inhibition with DRSP 4 mg (24/4 regimen) was reported in 100% of subjects despite delaying two pills (days 5 and 13) for 24 hours in one cycle. Ovulation returned in the first cycle after the last pill intake in 17 out of 20 subjects. Study CF111/204 demonstrated that ovulation inhibition with DRSP 4 mg (24/4 regimen) is maintained despite four scheduled 24-hour delays in pill intake at days 3, 6, 11, and 22 of a 28-day cycle.

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

Yes, the proposed dosing regimen appears appropriate for suppression of ovulation. In addition, for safety consideration, the Applicant conducted Study CF111/103C to compare the relative bioavailability of DRSP 4 mg tablets to the listed drug Yaz®. The results showed that the AUC and C_{max} were about 20% higher than Yaz® after single dose administration. However, based on lower drug accumulation for DRSP 4 mg tablets (C_{max} accumulation of 1.5 and AUC accumulation of 1.9 [Study CF111/103A]) compared to Yaz® (C_{max} accumulation of about 1.8 and AUC accumulation of about 2.8 [Yaz® label]), it is expected that the C_{max} and AUC for DRSP 4 mg tablets would be similar to or lower than Yaz® at steady state. This conclusion is further supported by data from Study CF111/103A, where the AUC and C_{max} of the 4 mg DRSP tablet were 77.8% and 66.8%, respectively, after multiple dose administration of a Yaz product marketed in the European Union.

The effect of LF111 on electrocardiogram (ECG) was investigated in Study CF111/201A and CF111/302, in which ECG demonstrated to be stable during the study. No abnormal values were detected at inclusion and end-of-study visits. No clinically relevant mean change over time was detected for weight, systolic and diastolic blood pressure, and heart rate.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Yes. Comments for each specific subpopulation are provided below.

Renal Impairment

The Applicant did not conduct dedicated studies with LF111 in patients with renal impairment. Based on the Yaz® label, in subjects with creatinine clearance (CLcr) of 50 to 79 mL/min, serum DRSP levels were comparable to those in a control group with CLcr ≥80 mL/min. In subjects with CLcr of 30 to 49 mL/min, serum DRSP concentrations were on average 37% higher than those in the control group. Even though in this study DRSP treatment did not show any clinically significant effect on serum potassium concentration, patients with renal impairment in general is predisposed to have a higher risk to develop hyperkalemia. Therefore, the review team recommends LF111 be contraindicated in patients with renal impairment, which is consistent with recommendations in the drug label for Yaz®.

Hepatic Impairment

The Applicant did not conduct dedicated studies with LF111 in patients with hepatic impairment. Based on the Yaz® label, the mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. According to the Yaz® label, DRSP has anti-mineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, including patients with liver impairment. In addition, the increased DRSP exposure could lead to a higher potential for hyperkalemia in patients with liver impairment. Therefore, the review team recommends LF111 be contraindicated in patients with hepatic impairment, which is consistent with recommendations in the drug label for Yaz®.

Body Weight and Body Mass Index

The Applicant conducted a population PK analysis to assess the effect of body weight on the PK of DRSP (phase III Study CF111/303). Based on the results from the population PK analysis, body weight was identified as statistically significant covariate affecting on DRSP drug exposure (Table 7). Changing body weight from the median value 73 kg to the 5^{th} percentile value 51kg or to the 95% percentile value 118 kg caused a moderate change in DRSP drug exposure of 22.2% and -23.6%, respectively. Illustratively, subjects with a body weight ≤51 kg (the lightest 5% of the phase III population) or ≥118 kg (the heaviest 5%) would experience a median individual exposure of 870.6 and 471.9 ng*h/mL, respectively. However, the pivotal phase III Study CF111/303 indicated there was no significant difference in Pearl Index (PI, the primary efficacy endpoint) by BMI subgroups. The overall PI (95% CI) for women with a BMI <30 kg/m^2 was 4.2 (2.2, 7.4) compared to 3.5 (1.1, 8.1) for women with a BMI ≥30 kg/m^2 (Table 8).

With these results, the review team does not recommend a body-weight based dose adjustment.

Table 7. DRSP Exposure Statistics in Final Population PK Model With Covariate Body Weight (CF111/303)

		$AUC_{0\text{-}24,ss}$ (ng·h/mL)		
Category	N	5th Percentile	Median	95th Percentile
All	1263	391.7	661.3	1239
BW (kg)				
≤ 51	72	514.5	870.6	1521
(51 - 118)	1123	403.5	659.2	1224
≥ 118	68	294.1	471.9	926.2

DRSP = drospirenone; BW = body weight
Source: Clinical Trial Report CF111/303, Section 16.1.13. Table 1.0:2

Table 8. Overall Pearl Index by BMI Subgroups in Women Aged ≤ 35 years (CF111/303)

BMI Subgroup	N	On-Treatment Pregnancies	Evaluable Cycles	Pearl Index (95% CI)
<30 kg/m^2	621	12	3681	4.2 (2.2, 7.4)
≥30 kg/m^2	332	5	1866	3.5 (1.1, 8.1)

BMI = body mass index; CI = confidence interval
Source: Clinical Reviewer's Analysis

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

Food effect

Based on Study CF111/106, there is no clinically relevant food effect on the extent of absorption of DRSP and a slight increase in C_{max}. The single dose administration of LF111 taken after a standard high-fat breakfast has a relative bioavailability [90% CI] of 107.99% [104.72-111.36%] for $AUC_{(0\text{-}72h)}$ and 129.35% [118.58-141.10%] for C_{max}.

The review team recommends that LF111 can be administered with or without food.

Drug-drug interactions

No studies were conducted to address the drug-drug interaction potential for LF111. The drug-drug interaction recommendations were made based on the Yaz® label and are shown below.

Effect of other drugs on DRSP

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the systemic concentrations of DRSP and potentially diminish the effectiveness of DRSP or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of DRSP include efavirenz, phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between DRSP and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Therefore, the review team recommends counseling women to use an alternative non-hormonal method

of contraception or a back-up method when enzyme inducers are used with DRSP, and to continue back-up non-hormonal contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

In a clinical drug-drug interaction study conducted in premenopausal women, once daily co-administration of DRSP 3 mg/EE 0.02 mg containing tablets with strong CYP3A4 inhibitor, ketoconazole 200 mg twice daily for 10 days, resulted in a moderate increase of DRSP systemic exposure.

Influence of DRSP on other medicinal products

Based on in vitro studies and in vivo interaction studies in female volunteers using omeprazole, simvastatin and midazolam as marker substrate, an interaction of DRSP with the metabolism of other active substances is unlikely and no labeling was necessary.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant's tabular listing of clinical studies included 12 phase 1 studies. Most of these studies evaluated bioavailability. One study evaluated transfer in breast milk. Of the six phase 2 studies in the listing, four evaluated ovulation inhibition. One of the ovulation inhibition studies also assessed cervical mucus effects. Another phase 2 study was intended to assess tolerability compared to norethindrone but was prematurely interrupted due to political turmoil in Tunisia. The last phase 2 study listed was a 12-month open label study in Bulgaria that evaluated endometrial safety.

The four phase 3 clinical studies are summarized in Table 9.

Table 9. Phase 3 Clinical Trials

Study ID Study sites	Design	Doses/ Duration	Objectives	Subjects/ Arm Entered/ Completed	Age (Yrs) Mean Median (Range)	Pearl Index[a]
CF111/301 -41 Centers in Europe (Czech Republic, Germany, Hungary, Poland & Romania)	Prospective, multicenter, open label	DRSP 4 mg 24/4 regimen 13 cycles	Efficacy & safety	Screened: 824 Treated: 713 Treatment cycles: 7638 Completed: 515 (72.2%)	28.7 28.0 (18-46)	Overall PI* (95% CI) 0.71 (0.15, 2.06)
CF111/302 -73 Centers in Europe (Austria, Czech Republic, Germany, Hungary, Poland, Romania, Slovakia & Spain)	Prospective, multicenter, comparative, randomized, double-blind, double-dummy	DRSP 4 mg 24/4 regimen 9 cycles DSG 0.075 mg 9 cycles	Efficacy & safety	Screened: 1365 Randomized: -872 for DRSP -341 for DSG Treated: -858 for DRSP -332 for DSG Treatment cycles: -6691 for DRSP -2487 for DSG Completed: -688 for DRSP (80.2%) 250 for DSG (75.1%)	DRSP 28.9 28.0 (18-45) DSG 28.9 28.0 (18-44)	Overall PI** (95% CI) DRSP: 0.9715 (0.3154, 2.2671) DSG: 0.5227 (0.0132, 2.9124)
CF111/303 -41 Centers in the U.S. (b)	Prospective, multicenter, open label	DRSP 4 mg 24/4 once daily for 13 cycles	Efficacy, safety & PK	For 39 centers^ Screened: 1552 Treated: 1006 Treatment cycles: 5337 -Completed: 352 (35.0%)	27.5 27.0 (18-51)	Evaluable cycles PI*** (95% CI) 2.9^ (1.5, 5.1)
CF111/304 9 Centers In Europe (Germany, Finland, Sweden & Ukraine)	Prospective, multicenter, open label, female adolescents (age 12-17)	DRSP 4 mg	Safety	Screened: 111 Treated: 102 Completed 6 cycles: 89 of 102 (87.3%) Completed 13 cycles: 74 of 85 (87.1%)	16.1 16.0 (14-17)	PI not assessed but no pregnancy reported

DRSP = drospirenone (b) (4) DSG = desogestrel; PI = Pearl Index; CI = confidence interval; PK = pharmacokinetics
[a] The Pearl Index numbers are the Applicant's
[b] Two sites of the 41 (104 and 120) were closed for non-compliance to federal regulations
^ Excluding sites 104 and 120
* Based on three on-treatment pregnancies in 5530 cycles without back-up contraception and with sexual activity in the ≤35-year age group
** Defined as all pregnancies that occurred during the study excluding any that occurred after premature termination of the study drug in women ≤35 years of age.
*** Based on 12 confirmed on-treatment pregnancies identified by the Applicant in evaluable cycles in non-breastfeeding women aged ≤35 years (at time of enrollment)
Sources: Section 5.2 Tabular listing of clinical studies; Integrated Summary of Effectiveness page 17 of 88 and individual study reports

- *The Division has agreed that single arm, non-comparative studies for this indication are acceptable provided there are sufficient subjects studied for an adequate duration.*

- *Safety data from the two excluded sites (104 and 120) are included separately in this review.*
- *The total number of treatment cycles for DRSP 4 mg in Studies CF111/301, CF111/302 and CF111/303 is 19,666. This is acceptable for safety.*
- *The Agency did not agree with the number of on-treatment pregnancies in CF111/303 (see efficacy review). The desogestrel efficacy data listed in this Applicant derived table was not reviewed or considered in the efficacy review.*

Phase 1 and phase 2 studies used to support safety are discussed in the Review of Safety Section 8.2.

7.2. Review Strategy

Review of efficacy data will focus primarily on phase 3 U.S. Study CF111/303. Labeling information regarding pregnancy rate (the primary efficacy endpoints) will only be derived from this US study. Other efficacy data obtained from studies Europe will be considered as supportive. Review of safety data will encompass all the phase 3 clinical studies completed in the United States and Europe.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The pivotal clinical trial in this submission was Study CF111/303 which was the only phase 3 study conducted in the United States. This 13-cycle study (cycle =28 days) included over 5000 evaluable cycles for non-breastfeeding subjects aged ≤35 years at the time of trial enrollment. Evaluable cycles were defined as exposure cycles with intercourse at least once per cycle and without back-up contraception. At least 200 women completed one year of treatment.

- *It is important to mention at the beginning of this section that two study centers (104 and 120) out of 41 in Study CF111/303 were closed due to non-compliance. This clinical review of Study CF111/303 will have a separately marked section that discusses these two closed centers (Section 8.1.2). All the other data presented will be solely from the other 39 study centers.*

8.1.1. A Pivotal, Multicenter, Non-Comparative Trial on the Contraceptive Efficacy, Safety, Tolerability and Pharmacokinetics of LF111 (Drospirenone 4.0 mg) During 13 Cycles (Study CF111/303)

Trial Design

Study CF111/303 was a prospective, multicenter, open-label, non-controlled trial in female subjects, age 15 and above, who presented to the clinic seeking contraception. There was no upper age limit as long as the subject was considered premenopausal. In addition, breastfeeding women were also allowed to participate, though not included in the efficacy determinations.

The trial included women who:

- Never used hormonal contraceptives before (naïve users)
- Had used hormonal contraceptives more than 3 months prior to signing consent (previous users)
- Had used hormonal contraceptives in the 3 months before consent and who had at least one complete menstrual cycle before enrollment (also previous users)
- Directly switched from another hormonal method (switchers)

Naïve users and previous users started the study drug on the first day of their period. Switchers started study drug the day following the last active pill of the previous hormonal contraceptive. From day 1 to day 24 of each medication cycle, one white active tablet was swallowed whole at the same time every day. From day 25 to day 28, one green inert tablet was taken at the same time every day. LF111 was taken without regard to food.

Study Objectives

The primary objective of this study was to demonstrate the contraceptive efficacy of LF111. The secondary objectives were to demonstrate the safety and tolerability of LF111 and assess the pharmacokinetics (PK) of LF111.

Key Inclusion Criteria

1. Sexually active, postmenarcheal (15 to 17 years), and premenopausal female subjects (>18 years) at risk of pregnancy
2. Regular cycles during the last 6 months before consent/assent when not using hormonal contraception
3. For non-breastfeeding women who were pregnant in the last 6 months, at least three completed menstrual cycles after delivery
4. Breastfeeding women could be included 6 weeks after delivery irrespective of menstrual cycles postdelivery
5. At screening, maximum systolic blood pressure (median value of three values) ≤159 mm Hg and diastolic blood pressure (median value of three values) ≤99 mm Hg

Key Exclusion Criteria

1. Pregnancy
2. History of infertility
3. Abnormal finding on pelvic, breast or ultrasound examination that in the investigator's opinion contraindicated participation in the trial
4. Known polycystic ovary syndrome
5. Unexplained amenorrhea
6. Abnormal Papanicolaou (Pap) smear is atypical squamous cells of undetermined significance (ASCUS) positive for high-risk human papillomavirus or higher; subjects with ASCUS who were negative for high-risk human papillomavirus could enroll

7. Known contraindications or hypersensitivity to DRSP including:
    - Renal insufficiency
    - Adrenal insufficiency
    - Hepatic dysfunction
    - Venous thrombophlebitis or thromboembolic disorders
    - Cerebral-vascular or coronary-artery disease
    - Valvular heart disease with thrombogenic complications
    - Diabetes with vascular involvement
    - Headaches with focal neurological symptoms
    - Major surgery with prolonged immobilization
    - Known or suspected carcinoma of the breast
    - Known or suspected sex-steroid sensitive malignancies
    - Undiagnosed abnormal genital bleeding
    - Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use or liver tumor (benign or malignant) or active clinically significant liver disease
8. Uncontrolled thyroid disorders and other uncontrolled concomitant diseases
9. Known inherited or acquired predisposition to venous or arterial thromboembolism (e.g., factor V Leiden, prothrombin mutation, anti-phospholipid antibodies)
10. Known or suspected HIV and/or hepatitis infection at screening
11. Received a dose of depot medroxyprogesterone acetate (DMPA) during the 10 months prior to consent/assent, or received any combination injectable contraceptive during the 6 months prior to consent/assent
12. Long-term treatment of any medication that might interfere with the efficacy of hormonal contraceptives Prohibited medications included:
    - Anticonvulsants (e.g., phenytoin, carbamazepine, oxcarbazepine, topiramate, felbamate, primidone)
    - Barbiturates
    - Rifampin
    - Bosentan
    - Griseofulvin
    - St. John's wort
13. Progestin-releasing intrauterine device or contraceptive implant received or in place within the last 2 months prior to consent/assent
14. Evidence or history of clinically significant psychiatric illness or suicide risk

Dose Selection

(b) (4) initially explored a 3-mg dose of (b) (4) DRSP by comparing it to Jasminelle® (3 mg micronized DRSP and 0.02 mg ethinyl estradiol), a combined oral contraceptive (21/7 regimen) approved in Europe. They found that the lower bound of the AUC (234.72 ng*h/mL) was not included in the range of AUC of Jasminelle® (337.80 to 527.81ng*h/mL), which suggested that the risk of pregnancy might be greater at the lower

ranges. Based on the results of this study (CF111/101), the Applicant predicted that a dose of (b) (4) 4 mg DRSP would provide a mean AUC that would be included in the range of the AUC of Jasminelle®.

Based on these data, the Applicant pursued a PK study with 4 mg of (b) (4) DRSP (CF111/102). In a study comparing LF111 and Jasminelle® (Study CF111/102), the Applicant showed that the extent of absorption of (b) (4) 4 mg DRSP is similar to the 3 mg of micronized DRSP in Jasminelle® based on $AUC_{(0-72hr)}$. The rate of absorption is slower compared to Jasminelle® as indicated by a decreased C_{max} and delayed T_{max}.

Ovulation Inhibition, Pharmacokinetic Analysis and Mode of Action

See Section 6 of this review.

Study Schedule

The trial consisted of a screening visit (visit 1a), study drug dispensation visit (visit 1b), 13 28-day treatment cycles (visit 2 to visit 6/early discontinuation visit) and a follow-up visit 10 to 14 days after the last DRSP intake.

For a detailed list of procedures performed at each study visit, see Appendix 1 (Schedule of Study Procedures) at the end of this review. Visit summaries with key procedures (bulleted) are included below:

Visit 1a (screening)

- Informed consent
- Screening procedures
- Serum pregnancy test
- Adverse events and concomitant medications/devices (at all visits)

Visit 1b (scheduled when lab tests available)

- Subject eligibility confirmed
- Study drug provided
- Electronic diary provided
- Urine pregnancy test

Visit 2 (day 20±2 of medication cycle 1)

- Serum potassium was evaluated in subjects who took medications that may increase serum potassium (angiotensin-converting-enzyme inhibitors, angiotensin–II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, and aldosterone
  antagonists).
- Urine pregnancy test (dipstick) was performed.
- Pharmacokinetic blood sampling was done.
- The e-diary was reviewed.

- Dispense dipstick urine pregnancy tests (for cycles 2 through 3) were given to the subject and the subject was taught how to perform a urine dipstick pregnancy test at home at the beginning of each new medication cycle. Additional urine pregnancy tests were provided to the subjects at later visits

Visits 3 through 6

- Urine pregnancy test (dipstick) was performed.
- Dipstick urine pregnancy tests (for cycles 4 through 6) were dispensed to the subject and the subject was taught to perform a urine dipstick pregnancy test at home at the beginning of each new medication cycle.

Visit 7 (follow-up visit, 10 to 14 days after visit 6)

- Urine pregnancy test (dipstick) was performed.
- Subject queried regarding menstrual cycle

Electronic Diary

From day 1 of cycle 1 (i.e., the start of LF111 intake) to visit 6, the subject recorded in the e-diary her vaginal bleeding patterns, concomitant contraceptive use including emergency contraception, intake of a tablet from the blister pack or forgotten intake of LF111, as well as confirmation of sexual activity for each medication cycle. Diary entries were recorded weekly. On day 9 of each cycle, the subject was asked if she experienced any AEs (yes/no). She was contacted on day 10 by the site staff to collect information on any adverse events that have occurred.

Efficacy Analyses

The primary endpoint (Pearl Index) and other analyses are described in Section 8.1.2.

Vaginal Bleeding Assessment

From day 1 of cycle 1 to visit 6/early discontinuation visit, subjects recorded any vaginal bleeding and/or spotting in their e-diary. Documentation included:

- Scheduled bleeding (dates, intensity per day)
- Spotting (dates)
- Unscheduled bleeding (dates, intensity per day)

Vaginal bleeding definitions are listed below:

1. Light bleeding = Less than usual menses
2. Moderate bleeding = Similar to usual menses
3. Heavy bleeding = More than usual menses
4. Spotting = No protection (including panty liners) needed
5. Episode of bleeding/spotting = Bleeding/spotting bounded on either end by 2 days of no bleeding or spotting

6. Scheduled bleeding = Any bleeding or spotting that occurred during hormone-free intervals (days 25 to 28±1 day). Bleeding/spotting that starts during this period and continues for up to 8 consecutive days is considered scheduled bleeding
7. Unscheduled bleeding = Bleeding/spotting outside the time window defined for scheduled bleedings. If any unscheduled bleeding occurred, the intake of the study drug was to be continued if possible

Instructions for Missed Tablets

- If the subject is less than 24 hours late in taking any tablet, the missed tablet should be taken as soon as it is remembered, and the next tablet should be taken at the usual time.
- If the subject is more than 24 hours late taking a white active tablet, then she should take the tablet as soon as she remembers and then take the next one on time, even if that means taking up to two tablets at the same time. In this case (more than 24 hours late) she should use a barrier method of contraception for the next 7 days if she has sexual intercourse.
- In the event of a "severe GI disturbance" (diarrhea or vomiting) or if vomiting occurs within 3 to 4 hours after tablet-taking, a barrier method of contraception should be used for the next 7 days if she has sexual intercourse.

In case of forgotten tablets, the investigator advised the subject to re-enter the medication cycle correctly, so that each medication cycle had a length of 28 days. In case of more consecutive forgotten tablets, the forgotten tablets were to remain in the package and the subject was to continue with the tablet appropriate for the respective day. Taking two tablets in one day was considered acceptable. The intake of a tablet, forgotten intake of a tablet and the use of concomitant contraceptives had to be recorded in the e-diary.

Prohibited Medications

The concomitant use of the following medications and contraceptive devices were not permitted during the trial:

- Estrogens
- Progestogens (including for the treatment of spotting or unscheduled bleeding)
- Human chorionic gonadotropin
- Barrier contraceptive methods except occasional use for safety reasons; e.g., to reduce risk of infection, or in case of gastro-intestinal disorders, vomiting or missed tablet
- Spermicides, excepting occasional contraceptive back-up use in case of gastro-intestinal disorders, vomiting or missed tablet
- Emergency contraception
- Intrauterine devices

Protocol Amendments

Key protocol amendments for Study CF111/303 related to:

- Conditions which permitted barrier contraception
- Allowance of breastfeeding women to enroll
- Instructions for subjects >24 hours late taking their study medication
- Definition of "on-drug" pregnancy and evaluable cycles
- Utilization of ultrasounds for conception dating

    - *Most of these protocol changes were based of the Division's Advice Letter dated January 6, 2015. Overall, the enrolled population and study design were acceptable to the Division.*

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attests that the pivotal phase 3 clinical trial was conducted in compliance with Good Clinical Practice (GCP). See the following section regarding study site exclusions.

Study Site Exclusions

The Applicant excluded two sites (104 and 120) due to serious breaches of FDA regulations, International Conference on Harmonization, GCP, and trial protocol requirements. The Division requested additional information on these subjects (narratives and case report forms). The Applicant responded to this request on Nov 21, 2018. Summary information from these two sites is presented below.

Site 104

Of the 24 enrolled subjects at site 104, two completed the trial, eight did not start treatment, and 14 discontinued prematurely (one of whom became pregnant). There were no deaths or serious adverse events reported from this study center.

There were approximately 77 protocol violations at site 104. Significant issues at this site included lack of subject oversight and data quality, including blank worksheets, incomplete drug accountability forms, unsigned checklists/forms, missing relationships to study drug of adverse events (AEs), direct data entry without available source, significant e-diary noncompliance of subjects, missing consent forms, no certified letters for lost to follow-up subjects, and erroneous reporting to the institutional review board (IRB). The Applicant closed this site and decided that data of this site had to be excluded from statistical safety and efficacy analyses due to serious non-compliance.

Site 120

Of the 39 enrolled subjects at site 120, eight completed the trial, 16 did not start treatment, and 15 discontinued prematurely (one of whom became pregnant). Of the 15 subjects who

discontinued prematurely, six had compliance issues with their e-diary. There were no deaths or serious adverse events reported from this study center.

There were approximately 48 protocol violations at site 120. For this site, serious non-compliance with federal regulations (including regulatory documentation issues), IRB policy (including failures to follow IRB reporting requirements), GCP and protocol requirements (including research procedures conducted by study personnel without the appropriate certifications) was reported. The IRB determined that the collected data should be excluded because the accuracy of data could not be confirmed. The Applicant closed this site and excluded data of this site from statistical safety and efficacy analyses due to serious non-compliance.

- *During the study, one subject from site 104 (Subject (b) (6)) and one subject from site 120 (Subject (b) (6)) had well-documented on-drug pregnancies. The Division included these two pregnancies in the efficacy analysis.*
- *Treatment-emergent adverse events for sites 104 and 120 are listed in Appendix 4: TEAEs, Sites 104 and 120 of this review. No new safety signals were noted at these sites.*

Patient Disposition

A total of 1,552 subjects were enrolled at 39 centers in the United States. There were 546 screening failures. Of these, 1,006 (64.8%) received at least one dose of DRSP (safety set). In the safety set, a total of 352 (35.0%) subjects completed the trial, and 654 (65.0%) subjects prematurely discontinued the trial. Table 10 summarizes the subject disposition information in Study CF111/303. The most common reasons for study discontinuation were lost to follow up (26.7%), withdrawal of consent (15.4%), and adverse event (11.2%).

Table 10. Summary of Subjects' Disposition: Study CF111/303

Disposition	**(N=1006)** n (%)**
Completed study	352 (35.0)
Discontinued study	654 (65.0)
Reasons for discontinuation*	
Adverse event	113 (11.2)
Withdrawal of consent	155 (15.4)
At the request of the Applicant	20 (2.0)
Exclusion criterion	16 (1.6)
Investigator's opinion	7 (0.7)
Lost to follow-up	269 (26.7)
Major protocol deviations	1 (0.1)
Other	53 (5.3)
Pregnancy	15 (1.5)
Wish for pregnancy	5 (0.5)

Source: CF111/303 study report page 84 of 1623
** Sites 104 and 120 not included

- *Subject overall discontinuation rate in Study CF111/303 was 65.0%, which is notably higher than the anticipated discontinuation rate of 45% in the study protocol. This overall rate is also higher compared to European trials*

conducted by the Applicant. Although this rate is somewhat higher than recent contraceptive trials in the U.S. and/or Canada this is the first large scale pivotal progestin-only study in many years and therefore there is no current comparator. Given that there are other choices for contraception, from a clinical perspective, this rate may reflect what will occur during real world use of this product in the US. Despite the high withdrawal rate in Study CF111/303, 5,547 evaluable cycles were obtained for primary efficacy analysis. Per the agreement between FDA and the Applicant, this number of evaluable cycles is considered sufficient for evaluating the efficacy of DRSP.

Protocol Violations/Deviations

The Clinical and Statistical team decided that protocol deviations were categorized according to their impact on the evaluable cycles and number of pregnancies used for the final primary efficacy analysis. A total of 953 subjects of the Final Efficacy Analysis Set had a total of 6,806 cycles, of which 6,075 were classified as the exposure cycles per the Applicant's definition of exposure cycle. From the 6,075 exposure cycles, a total of 528 cycles were excluded due to protocol deviations, resulting in 5,547 evaluable cycles. These protocol deviations leading to cycle exclusion from the primary efficacy analysis are summarized in Table 11. The main reason for exclusion was not qualifying for exposure cycles (731 cycles, 10.7%), followed up by cycles with intercourse with additional contraception (257 cycles, 3.8%), cycles with no intercourse (152 cycles, 2.2%), and cycles having missing answer about intercourse (118 cycles, 1.7%). No pregnancies were excluded due to protocol deviations.

Table 11. Deviations Leading to Cycles Exclusion From Analyses (Study CF111/303: Final Efficacy Analysis Set)

	DRSP 4.0 mg (N=953) n (%)
Total number of cycles	6806 (100.0)
Total number of exposure cycles	6075 (89.3)
Total number of evaluable cycles	5547 (81.5)
Reason for exclusion from evaluable cycles:	
Non-exposure cycles	731 (10.7)
Cycles with intercourse with additional contraception	257 (3.8)
Cycles with NO intercourse	152 (2.2)
Cycle has missing answer about intercourse	118 (1.7)
Applicant request	1 (<0.01)

N = number of subjects in final efficacy analysis set; n = number of cycles with data available; % = percentage based on total number of cycles; DSRP = drospirenone.
Source: Reviewer's calculation.

Demographic and Baseline Characteristics

The demographic and other baseline information for safety population are presented in Table 12.

Table 12. Demographics and Baseline Characteristics of Subjects in Study CF111/303 (Safety Set)

Characteristic	Statistic	Safety Set (N=1006*)
Age group		
≤35 years	n (%)	928 (92.2)
>35 years	n (%)	78 (7.8)
Ethnicity		
Hispanic or Latino	n (%)	229 (22.8)
Not Hispanic or Latino	n (%)	777 (77.2)
Race		
American Indian or Alaska Native	n (%)	13 (1.3)
Asian	n (%)	20 (2.0)
Black or African American	n (%)	358 (35.6)
Native Hawaiian or other Pacific Islander	n (%)	5 (0.5)
White	n (%)	571 (56.8)
Other	n (%)	39 (3.9)
Highest level of education		
No high school diploma	n (%)	36 (3.6)
High school diploma or equivalent	n (%)	235 (23.4)
Some college	n (%)	412 (41.0)
College degree or higher	n (%)	323 (32.1)
Weight group		
<Median weight of safety set	n (%)	483 (48.0)
≥Median weight of safety set	n (%)	523 (52.0)
BMI group		
BMI <30kg/m^2	n (%)	652 (64.8)
BMI ≥30kg/m^2	n (%)	354 (35.2)
Blood pressure group		
SBP<130 mmHg and DBP<85 mmHg	n (%)	887 (88.2)
SBP≥130 mmHg and DBP≥85 mmHg	n (%)	119 (11.8)
Breastfeeding status		
Breastfeeding	n (%)	11 (1.0)
Non-breastfeeding	n (%)	995 (98.9)

* Sites 104 and 120 not included
BMI = body mass index, SD = standard deviation, SBP = systolic blood pressure, DBP = diastolic blood pressure
Percentage was based on N
All 1006 subjects were sexually active. The median age was 28.0 years (range 18 to 51). The median BMI was 27.1 kg/m^2 (range 15.8 to 68.0)
Source: CF111/303 study report page 89 of 1623

The hormonal contraceptive user characteristics are shown in Table 13.

Table 13. Pill User Characteristics in Study CF111/303 (Safety Set)

Pill User Category	Statistic	Safety Set (N=1006*)
Naive user	n (%)	209 (20.8)
Previous user without hormonal contraceptives		
≥3 months	n (%)	463 (46.0)
Progestin-only method(s)	n (%)	7 (0.7)
Combination hormonal contraception only	n (%)	10 (1.0)
Uncategorized	n (%)	446 (44.3)
<3 months	n (%)	70 (7.0)
Progestin-only method(s)	n (%)	3 (0.3)
Combination hormonal contraception only	n (%)	19 (1.9)
Uncategorized	n (%)	48 (4.8)
Switcher	n (%)	264 (26.2)

* Excludes sites 104 and 120

Percentage was based on N
Source: CF111/303 study report page 90 of 1623

Previous users without hormonal contraception for 3 months or more comprised the highest proportion followed by switchers.

Table 14. Substance Use in Study CF111/303 (Safety Set)

Substance Use Category	Statistic	Safety Set (N=1006*)
Smoking status		
Non-smoker (without smoking history)	n (%)	675 (67.1)
Current smoker	n (%)	182 (18.1)
Ex-smoker	n (%)	147 (14.6)
Nicotine replacement therapy	n (%)	2 (0.2)
Smoking duration for current smokers	n	182
	Mean (SD)	8.8 (6.4)
	Median	8.0
	Min/Max	0/31
Cigarettes per day for current smokers	n	181
	Mean (SD)	6.1 (5.3)
	Median	5.0
	Min/Max	1/20
Pack years for current smokers	n	181
	Mean (SD)	3.2 (4.1)
	Median	1.5
	Min/Max	0/20
Non-smoking duration for ex-smokers (years)	n	147
	Mean (SD)	3.7 (4.9)
	Median	2.0
	Min/Max	0/29
Alcohol status		
Abstainer	n (%)	343 (34.1)
Moderate drinker	n (%)	663 (65.9)
Excessive drinker	n (%)	0

* Excludes sites 104 and 120
Source: CF111/303 study report page 91 of 1623

The majority of trial subjects (67.1%) reported being non-smokers. Current smokers comprised 18.1% with a mean smoking duration of 8.8 years and a mean number of 6.1 cigarettes per day.

- *In the European Study 301, the majority of trial subjects (69.1%) reported being non-smokers. Current smokers comprised 25.5% of study subjects with a mean number of 9.4 cigarettes smoked per day.*
- *In the European Study 302, the majority of trial subjects on DRSP 4 mg (67.0%) were nonsmokers. Current smokers comprised 27.6% of this group with a mean number of 8.3 cigarettes smoked per day.*
- *We usually see a higher percentage of current smokers in European studies, but in these phase 3 studies, percentages of smokers were similar to the U.S. Study 303.*

Treatment Compliance, Concomitant Medications, and Use of Additional Contraceptives

Efficacy Analysis – Primary Endpoint

Analysis sets:

- Safety Set consisted of all subjects who received at least one dose of study drug
- Full Analysis Set consisted of all subjects who received at least one dose of study drug and who were not pregnant at the date of first study drug intake
- Modified Full Analysis Set consisted of all non-breastfeeding subjects who received at least one dose of study drug and who were not pregnant at the date of first study drug intake

An on-drug pregnancy was defined as all conceptions that occurred from day 1 (the initiation of study medication) through 7 days after the final tablet (active or placebo) was taken.

Evaluable cycles were defined as exposure cycles with intercourse without back-up contraceptive at least once per cycle based on electronic diary.

Also, a cycle was defined as evaluable if:

- A subject became pregnant during the cycle regardless if back-up contraception was used or not and regardless if the subject was breastfeeding or not.
- A subject did not answer the question in the e-diary about intercourse or answered "I had NO sexual intercourse at all" but became pregnant at the respective cycle.

A cycle was defined as non-evaluable if the subject did not become pregnant and:

- Had sexual intercourse and used an additional contraception (e.g. condoms)
- Had NO sexual intercourse at all
- Cycle had missing e-diary answer about intercourse

Efficacy Results – Primary Endpoint

In Study CF111/303, the primary efficacy endpoint was the Pearl Index (PI) based on the on-treatment pregnancies and evaluable cycles in women aged 35 years or younger at the time of trial enrollment. The PI was defined as the number of pregnancies per 100 woman-years of exposure.

In the original NDA submission, the Applicant calculated the PI based on 12 confirmed pregnancies excluding sites 104 and 120. In response to the Division's information request, the Applicant submitted the primary efficacy results based on 14 pregnancies including sites 104 and 120. Upon detailed review of the submitted pregnancy data, the clinical reviewer identified three additional pregnancies for a total of 17 confirmed on-treatment pregnancies for Study CF111/303. These three additional confirmed on-treatment pregnancies included:

- Subjects (b) (6): their pregnancies were categorized as suspected, non-confirmed pregnancies by the Applicant.

The above three subjects were excluded from the Applicant's efficacy analysis; however, the clinical reviewer determined that an on-drug pregnancy could not be ruled out so that these additional pregnancies should be counted in the efficacy analysis. The findings of additional three pregnancies were communicated to the Applicant through email on December 20, 2018.

Table 15 below list all subjects in Study 303 who had a positive pregnancy test. The 18 pregnancies deemed on-treatment (1 breastfeeding, 17 non-breastfeeding) by the reviewers are noted with a superscripted "a" in the leftmost column.

Table 15. Subjects With a Positive Pregnancy Test, Study CF111/303 (N=24)

#	Subject #	Age (Yrs) BMI Race	User Type	Drug Start Date	Last Active Pill	Date of Positive Urine Preg. Test	Concept. Date (Cycle)	On/Off Drug Per Applicant	On/Off Drug Per Medical Reviewer Notes
1[a]	(b) (6)	23 <30 B	PR	(b) (6)	(b) (6)	-9/23/15	Unknown -Non-compliant	On	On -Elective abortion
2[a]		23 <30 B	SW	(b) (6) x74 days	(b) (6)	-7/26/16 -TVS on 8/2/16= 5wks	7/15/16 (cycle 2)	On	On
3		18 <30 Cauc.	New	(b) (6) x20 days	(b) (6)	-8/29/16 -TVS on 8/30/16= 6wks 3d	7/30/16	Off	Off -Elective abortion
4[a]		22 ≥30 B	PR	(b) (6) x349 days	(b) (6)	-10/31/15 -TVS on 11/10/15=6wks 4d	10/29/15 (cycle 13)	On	On -Elective abortion
5[a]		28 <30 B	SW	(b) (6)	(b) (6) (Unsure)	-12/9/16 -Subject reported + urine and serum test	Unknown (Lost to f/u)	Off	On (Cannot be ruled out)
6		32 ≥30 Cauc.	PR	(b) (6) x364 days	(b) (6)	-Faintly + 7/21/15. -F/U serum tests neg.	None	Not pregnant	Not pregnant
7		29 <30 Cauc.	PR	(b) (6) x310 days	(b) (6)	-11/17/15 Serum neg. -TVS on 11/17/15 neg.	None	Not pregnant	Not pregnant
8		21 <30 Cauc.	SW	(b) (6) x18 days	(b) (6)	-7/7/16 -TVS on 7/7/16= 5wks 2d	6/14/16	Off	Off
9[a]		26 <30 Cauc.	New	(b) (6)		-9/15/16 & 9/16/16 -TVS not done	8/21/16 (cycle 4)	Elective. Abortion (b) (6) Insuff. Inform.	On (Cannot be ruled out)

#	Subject #	Age (Yrs) BMI Race	User Type	Drug Start Date	Last Active Pill	Date of Positive Urine Preg. Test	Concept. Date (Cycle)	On/Off Drug Per Applicant	On/Off Drug Per Medical Reviewer Notes
10[a]	(b) (6)	33 ≥30 B	PR	(b) (6)	(b) (6)	-4/28/15 -TVS on 5/12/15= 5wks 6d	4/15/15 (cycle 1)	On	On
11[a]		26 <30 Cauc.	SW		Unsure	-10/28/16 -TVS on 10/28/16= 7wks 1d	9/22/16 (cycle 3)	On	On -Elective abortion
12[a]		25 ≥30 B	PR		(b) (6)	-4/10/17 -TVS on 4/11/17= 6wks 2d	3/12/17 (cycle 8)	On	On
13[a]		18 <30 Cauc.	PR			-8/10/15 -TVS on 8/26/15= 6wks 1d	7/27/15 (cycle 3)	On	On
14[a]		35 <30 Cauc.	New			-3/10/15	2/9/15 (cycle 3)	On	On -Ectopic
15		33 ≥30 B	SW		(Neg urine test on (b) (6))	-2/23/15 -Subject reported, -Not confirmed. -Negative serum test 3/11/15.		Not pregnant	Not pregnant
16[a]		29 ≥30 B	PR		(b) (6)	-6/17/15	5/?/15 -Non-compliant (cycle 1)	On	On
17[a]		30 <30 B	PR			-12/17/15 -TVS on 12/23/15= 6 wks 6 d	11/21/15 (cycle 9)	On	On
18[a]		24 <30 B	PR			-Subject Reported + urine test on 10/15/15	Unknown	Insuff. Inform.	On (Cannot be ruled out)
19[a]		33 <30 Cauc.	New			-5/11/16 -TVS on 5/12/16= 4 wks 4 d	4/8/16 (cycle 6)	On	On
20[a]		22 ≥30 B	New	(?)		-1/2/16	12/2/15 (cycle 2)	On	On

#	Subject #	Age (Yrs) BMI Race	User Type	Drug Start Date	Last Active Pill	Date of Positive Urine Preg. Test	Concept. Date (Cycle)	On/Off Drug Per Applicant	On/Off Drug Per Medical Reviewer Notes
21	129105	(b) (6)	PR		(b) (6)	-7/11/15 -serum neg. 7/14/15 -urine neg. 7/30/15	None (False positive urine)	Not pregnant	Not pregnant
22[a]	130108		New			-7/10/15	6/24/15 (cycle 3)	On	On -Spont. abortion
23[a]	131137		New			-8/25/16	8/7/16 (cycle 13)	On	On -Elective abortion
24[a]	136107		PR	x115 days		-2/6/17 -TVS on 2/23/17= 6 wks 5 d	1/7/17 (cycle 4)	On	On -Breast Feeding -IUGR -Not included in PI calc.

BMI = body mass index defined as kg/m^2; PR = previous user (at least 3 calendar months break after the administration of another hormonal contraceptive); SW = switcher (direct switch from another hormonal contraceptive to the study drug with no break in administration); B = black; Cauc. = Caucasian; TVS = transvaginal sonography; F/U = follow-up; PI = Pearl Index; IUGR = intrauterine growth restriction
[a] Pregnancy deemed on-treatment
* Subjects from sites 104 and 120 were not included in the Applicant's analysis
New (naïve) user: First administration of a hormonal contraceptive

- *The Division calculates the worst-case approach and count as on-drug pregnancies any conceptions for which a clear relation to dosing cannot be determined (e.g., subjects do not record date of last intake, or estimated date of conception is not determined). If there is any possibility that a pregnancy occurred on-drug, it was counted as such.*
- *The Division determined that a total of 17 on-drug pregnancies occurred during Study 303. The 18th subject who conceived on LF111 (Subject (b) (6)) was breastfeeding so was not included in the PI calculation which prespecified only non-lactating women be included in labeling.*

Table 16 presents the PI results for DRSP in the primary efficacy population. The primary efficacy analysis population included 953 subjects. Based on the 17 pregnancies and 5,547 evaluable cycles from 953 subjects, the PI calculated by the Agency is 4.0 (95% CI: 2.3, 6.4), which is higher than the PI reported by the Applicant. The Applicant reported a PI of 3.3 (95% CI: 1.8, 5.5) using 14 pregnancies and 5,546 evaluable cycles from 953 subjects.

Table 16. Pearl Index Based on Evaluable Cycles in Women Aged ≤35 Years (Primary Efficacy Set in Study CF111/303)

	N	On-Treatment Pregnancies	Evaluable Cycles	Pearl Index (95% CI)
FDA	953	17	5547	4.0 (2.3, 6.4)
Applicant	953	14	5546	3.3 (1.8, 5.5)

Note: 95% CI was based on the Poisson distr bution
FDA = U.S. Food and Drug Administration; CI = confidence interval
Source: Reviewer's analysis, Table 15.2.1.1.1_PH.1 in response to information request by FDA (October 15, 2018).

The cumulative pregnancy rates based on the life table method were also calculated for the primary efficacy population. The Agency's estimated cumulative pregnancy rate in women ≤35 years at one year was 3.7% (95% CI: 1.7, 5.5) (Table 17). The Applicant did not provide life table analysis results for the primary efficacy endpoint based on 14 pregnancies.

Table 17. Life Table Analysis of Pregnancy Based on Evaluable Cycles in Women Aged ≤35 Years (Primary Efficacy Set in Study CF111/303)

	N	On-Treatment Pregnancies	Evaluable Cycles	Cumulative Pregnancy Rate (95% CI) (%)
FDA	953	17	5547	3.7 (1.7, 5.5)

FDA = U.S. Food and Drug Administration; CI = confidence interval
Source: Reviewer's analysis.

- *The FDA uses the worst case scenario for labeling contraceptive products. Therefore, the FDA's PI calculation was used in labeling.*
- *The lifetable analysis that showed a cumulative pregnancy rate of 3.7% (95% CI: 1.7, 5.5) at one year is comparable to the PI of 4.0 (95% CI: 2.3, 6.4Subgroup Analyses*

The PI and cumulative pregnancy rates (life table analysis) were also calculated for subgroups of race (white versus black versus other) and BMI (<30 kg/m^2 versus ≥30kg/m^2). As shown in Table 18, there were numerical differences in the PIs across different race and BMI groups. The PI was notably higher for blacks compared to whites: 7.0 versus 2.8. The failure rate in women with BMI ≥30kg/m^2 is unexpectedly lower compared to women with BMI <30 kg/m^2: 3.5 versus 4.2. Similar to the overall analysis, the life table analyses results were also comparable to the PI results for subgroups.

Table 18. Pearl Index and Life Table Analysis Based on Evaluable Cycles in Women Aged ≤35 Years by Subgroup (Primary Efficacy Set in Study CF111/303).

	N	On-Treatment Pregnancies	Evaluable Cycles	Pearl Index (95% CI)	Cumulative Pregnancy Rate (95% CI) (%)
BMI					
<30kg/m^2	621	12	3681	4.2 (2.2, 7.4)	4.0 (1.5, 6.5)
≥30kg/m^2	332	5	1866	3.5 (1.1, 8.1)	3.0 (0.1, 5.8)
Race					
Black	367	10	1870	7.0 (3.3, 12.8)	6.2 (2.0, 10.3)
White	508	7	3243	2.8 (1.1, 5.8)	2.6 (0.5, 4.7)
Other	78	0	434	–	–

BMI = body mass index; CI = confidence interval
Source: Reviewer's analysis

- *Subjects with higher BMIs had a PI lower than that of the lower BMI group. The number of pregnancies in the high BMI subgroup relative to the low BMI subgroup was 5 versus 12.*
- *Although subgroup analyses are important considerations for contraceptive use, none of these exploratory analyses revealed new concerns or that would limit labeling for this product.*

Pharmacokinetic Endpoints

In this trial, DRSP plasma samples were collected in the first and sixth cycle (visits 2 and 4; two samples per visit; each cycle is 28 days), resulting in a total of four samples per subject.

- *From a clinical perspective, the DRSP pharmacokinetic data provided insight into the effect of the covariate body weight on drug exposure, and in the correlation between the number of bleeding days for that cycle and drug exposure. Changing the body weight from the median 73kg to 51kg or 118kg causes a moderate change in exposure of 22.2% or -23.6%, respectively. Each additional day of bleeding correlates to 0.8% drop in exposure.*
- *Further discussion of the PK data can be found in the Clinical Pharmacology review.*

Integrated Review of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

Not Applicable

8.1.4. Integrated Assessment of Effectiveness

Not Applicable

8.2. Review of Safety

8.2.1. Safety Review Approach

The clinical safety of LF111 is obtained from data derived from 19 clinical studies:

- Four phase 3 studies: (CF111/301, CF111/302, CF111/303, and CF111/304 in adolescents)
- Six phase 2 studies: (CF111/201A, CF111/201B, CF111/202, CF111/203, CF111/204, and CF111/205)
- Nine phase 1 studies: (CF111/101A, CF111/101B, CF111/102, CF111/103A, CF111/103C, CF111/104, CF111/105, CF111/106, and CF111/107)
    - *The Applicant often described Study 205 (endometrial safety) along with phase 3 studies in the Summary of Clinical Safety, but Study 205 is listed as phase 2 in the Tabular Listing.*

8.2.2. Review of the Safety Database

Phase 3 Studies

Three phase 3 studies (CF111/301, CF111/302 and CF111/303) were designed to demonstrate the efficacy, safety, and tolerability of LF111. Studies CF111/301 and CF111/303 were single-arm studies. Study CF111/302 was an active control, double-blind, double dummy, randomized study. CF111/304 was designed to assess the safety and tolerability of LF111 in adolescents.

- *The active control used in Study 302 was Cerazette® (desogestrel 0.075 mg). Cerazette® is a non-US approved POP.*
- *Summary details of the phase 3 studies are presented in tabular form in Section 7.1.*

The safety population (Safety Set) consisted of all subjects who received at least one dose of study drug and were not pregnant at enrollment.

Safety was assessed by the incidence, type, severity and seriousness of adverse events, clinical assessments, vital signs, and laboratory parameters. Tolerability was assessed by vaginal bleeding pattern. Venous thromboembolism and hyperkalemia were considered AEs of special interest.

- *The Division and the Applicant agreed (Pre-NDA Meeting Minutes - December 19, 2017), that data from the phase 3 studies in adults would be integrated with respect to safety based on the similarity in study design and population across these studies.*
- *Safety data from the phase 3 study in adolescents was not integrated with the other phase 3 studies.*
- *Safety data from the two excluded sites (104 & 120) in Study 303 were not included in the safety review. As noted in the reviewer summary of these sites in Section 8.1.1 there were no deaths or serious adverse events (SAEs) reported.*

Phase 2 Studies

A total of six phase 2 studies were submitted for review (see Table 19 below).

Table 19. Phase 2 Clinical Studies

Study Number (Country/Countries)	Study Objective(s)	Study Design	Duration (Cycles)	Safety Population
CF111/201A -Tunisia -1 site -Jul 2010 to Oct 2010	PD/OI and safety	Open-label multiple-dose study in healthy females of childbearing potential, age 20–30 yrs	2 cycles of 28 days each, with delayed 24-hour intakes on days 5 and 13 of the second cycle	LF111* 20
CF111/201B -Tunisia -1 site, -early termination due to political instability	Tolerability and safety	Open-label, randomized study in healthy females at risk for pregnancy, age 20–35 yrs, BMI <30 kg/m^2	LF111 or norethindrone 0.35 mg for 3 cycles of 28 days each	LF111* n=10 or norethindrone n=10
CF111/202 -Germany -1 site -Feb 2012 to Sept 2012	PD/OI, Insler Score and safety	Open-label, randomized, multiple-dose study in healthy females at risk for pregnancy, age 18–35 yrs	LF111 or desogestrel 0.075 for 2 cycles of 28 days each	LF111* n=32 or desogestrel n=32
CF111/203 -Germany -1 site -Oct 2011 to Apr 2012	PD/OI and safety	Open-label, randomized, multiple-dose study in healthy females at risk of pregnancy, age 18–35 yrs	LF111 or DRSP 2.8 mg for 2 cycles of 28 days each	LF111* N=27 or DRSP 2.8 mg n=25
CF111/204 -Germany -1 site -Jun 2013 to Mar 2014	PD/OI and safety	Open-label, multiple-dose study in healthy females at risk for pregnancy ages age 18–35 yrs	2 cycles of 28 days each, with delayed 24-hour intake on 4 study days in cycle 1 or in cycle 2	LF111* 127
CF111/205 Bulgaria -1 site Oct 2013 to Apr 2015	Endometrial safety	Open-label	13 cycles	LF111 21

* LF111 = active DRSP 4 mg for 24 days followed by placebo for 4 days
PD/OI = pharmacodynamics/ovulation inhibition; DRSP = drospirenone
Source: Adapted from Summary of Clinical Safety; page 7 and Section 5.2

- *The phase 1 and phase 2 studies used a variety of study design elements (e.g., use of a comparator or different doses, durations of dosing and age ranges of subjects) and analysis tools (e.g., different Medical Dictionary for Regulatory Activities [MedDRA] dictionary versions), so it was agreed not to integrate these data. Since the comparator is not a US approved product, no evaluation of the comparator data was performed.*

Phase 1 Studies

Table 20 presents the phase 1 studies used to support safety.

Table 20. Phase 1 Studies Used to Support Safety

Study Number	Duration (Cycles)	# Subjects
DRSP 3 mg		
CF111/101A (BA) Turkey	Single dose	14
CF111/101B (BA) Turkey	Single dose	14
DRSP 4 mg		
CF111/102 (BA) Turkey	Single dose	10
CF111/103A (BA) Bulgaria	Single and repeat doses (1+12 days)	24
CF111/103C (BA under fed conditions) Canada	Single dose	32
CF111/104 (PK) France	Single dose	8
CF111/105 (BA) Bulgaria	Single dose	14
CF111/106 (Food effect) Bulgaria	Single dose	24
CF111/107 (Transfer in milk) Latvia	Repeated doses	12

DRSP = drospirenone; BA = bioavailability; PK = pharmacokinetics

Relevant Characteristics of the Safety Population

Subject Disposition - Adult Studies

For studies CF111/301, CF111/302, CF111/303 and CF111/205, data from a total of 3,434 adult subjects was pooled for analysis and is presented in Table 21. Of these subjects, 1,572 subjects (60.5%) completed and 1,026 subjects (39.5%) prematurely discontinued from the study in which they were enrolled. Completion rates were similar across studies CF111/301, 302 and 205 (72.2%, 80.2% and 81.0%, respectively).

Study CF111/303 had a lower completion rate (35.0%). The most frequently specified reasons for study discontinuation in CF111/303 were loss to follow-up (26.8%), withdrawal of consent (15.4%) and AEs (11.2%). Across all phase 3 studies in adults, the most frequently specified reasons for discontinuation were loss to follow-up (11.3%), withdrawal of consent (11.2%) and AEs (10.9%).

Table 21. Subject Disposition: Studies CF111/301, CF111/302, CF111/303, and CF111/205

Subject Disposition	CF111/301	CF111/302	CF111/303	CF111/205	Total
Enrolled Subjects	**824**	**1024**	**1552**	**34**	**3434**
Safety set, n (%)	713 (86.5)	858 (83.8)	1006* (64.8)	21 (61.8)	2598 (75.7)
Completed, n (%)	515 (72.2)	688 (80.2)	352 (35.0)	17 (81.0)	1572 (60.5)
PrDisc, n (%)	198 (27.8)	170 (19.8)	654 (65.0)	4 (19.0)	1026 (39.5)
Reason for discontinuation, n (%) N = safety set					
	N=713	N=858	N=1006	N=21	N=2598
Subject request (withdrawal of consent)	78 (10.9)	57 (6.6)	155 (15.4)	2 (9.5)	292 (11.2)
Applicant request	1 (0.1)	0	27 (2.7)	0	28 (1.1)
Major protocol violations	1 (0.1)	5 (0.6)	1 (0.1)	0	7 (0.3)
Pregnancy	2 (0.3)	4 (0.5)	15 (1.5)	0	21 (0.8)
Wish for pregnancy	2 (0.3)	4 (0.5)	5 (0.5)	0	11 (0.4)
Ineligibility	4 (0.6)	5 (0.6)	16 (1.6)	0	25 (1.0)
Adverse event	88 (12.3)	82 (9.6)	113 (11.2)	1 (4.8)	284 (10.9)
Lost to follow-up	10 (1.4)	12 (1.4)	270 (26.8)	1 (4.8)	293 (11.3)
Other	12 (1.7)	1 (0.1)	52 (5.2)	0	65 (2.5)

PrDisc = premature discontinuation
*Excluding sites 104 and 120
Source: Summary of Clinical Safety, Page 15, Table 2

- *The number of subjects studied with evaluable data is acceptable from a safety perspective.*
- *A total of 284 subjects (10.9%) experienced a treatment emergent adverse event (TEAE) causing discontinuation from the study.*
- *The number of subjects with withdrawal of consent and lost to follow-up were much greater in the U.S. study compared to the European studies. The percentage of subjects discontinuing due to an adverse event is comparable between the U.S. and European trials.*

Subject Disposition: Adolescent Study (CF111/304)

A total of 102 subjects were enrolled in the adolescent study. Disposition data is presented below. Overall, 89 subjects (87.3%) completed the core phase of the study. Of these, 85 subjects (83.3%) entered the extension phase of the study.

Thirteen (12.7%) and 11 (12.9%) subjects discontinued prematurely from the core and extension phases, respectively. Completion rates were similar between the study's core and extension phases (87.3% and 87.1%, respectively). The most frequent reason for premature discontinuation in adolescents was non-serious AEs (core phase 8.8% and extension phase 3.5%).

Table 22. Subject Disposition: Phase 3 Study in Adolescents (Safety Set)

	DRSP 4 mg	
Disposition	**Core Phase n (%)**	**Extension Phase n (%)**
Subjects who entered core phase	102 (100)	-
Subjects who entered extension phase	-	85 (83.3)
Subjects who completed respective phase	89 (87.3)	74 (87.1)
Subjects who prematurely terminated the trial in respective phase	13 (12.7)	11 (12.9)
Primary reason for premature trial termination in respective phase		
At subject's own request	2 (2.0)	2 (2.4)
Major protocol deviations	-	1 (1.2)
Pregnancy	-	-
Wish for pregnancy	-	-
Adverse event: nonserious	9 (8.8)	3 (3.5)
Adverse event: serious	0	0
Other reasons		
Non-compliance	1 (1.0)	1 (1.2)
Lost to follow-up	1 (1.0)	2 (2.4)
Moved abroad	-	1 (1.2)
Study drug gap	-	1 (1.2)

DRSP = drospirenone
Source: Summary of Clinical Safety, Page 16, Table 3

Extent of Exposure – Adult Studies

Table 23 presents pooled exposure data (by days). Across all subjects in these studies, the overall mean duration of treatment was 236.1 days (range: 197.3 to 304.1 days across studies). Most subjects (82.3%) received treatment for at least 84 days, and 63.5% of subjects received treatment for at least 252 days.

Table 23. Extent of Exposure: Studies CF111/301, CF111/302, CF111/303, and CF111/205 (Safety Set)

Exposure	**CF111/301 DRSP 4 mg N=713**	**CF111/302 DRSP 4 mg N=858**	**CF111/303 DRSP 4 mg N=1006***	**CF111/205 DRSP 4 mg N=21**	**Total DRSP 4 mg N=2598**
Treatment duration (days)					
Mean (SD)	304.1 (107.9)	222.7 (65.79)	197.3 (144.4)	328.1 (82.42)	236.1 (121.4)
Median	364.0	252.0	168.0	364.0	252.0
Min, Max	1, 393	3, 276	1, 411	107, 381	1, 411
Cumulative treatment, n (%)					
≥28 days	698 (97.9)	835 (97.3)	839 (83.4)	21 (100.0)	2393 (92.1)
≥84 days	655 (91.9)	787 (91.7)	674 (67.0)	21 (100.0)	2137 (82.3)
≥252 days	539 (75.6)	673 (78.4)	420 (41.7)	17 (81.0)	1649 (63.5)

* Excluding sites 104 and 120
SD = standard deviation
Source: Summary of Clinical Safety, Page 17, Table 4

- *The total number of treatment cycles for Studies CF111/301, CF111/302 and CF111/303 (19,666) was previously noted to be acceptable for safety in Section 7.1 of this review.*

Extent of Exposure – Adolescent Study

Table 24 presents exposure data (by days) in the adolescent study. In this study the planned duration of treatment was 13 28-day cycles (including the extension phase). Across all subjects in this study, the overall mean duration of treatment was 312.3 days. Most subjects (82.4%) received treatment for at least 224 days, and 66.7% of subjects received treatment for at least 364 days.

Table 24. Extent of Exposure: Phase 3 Study in Adolescents (Safety Set)

Parameter	DRSP 4 mg (N=102)
Treatment duration (days)	
Mean (SD)	312.3 (99.71)
Median	364.0
Min, max	27, 384
Cumulative overall treatment duration, n (%)	
Any	102 (100)
≥28 days	101 (99.0)
≥224 days	84 (82.4)
≥364 days	68 (66.7)

SD = standard deviation
Source: Summary of Clinical Safety, Page 18, Table 5

Demographics – Adult Studies

Table 25 presents pooled demographic data for studies CF111/301, CF111/302, CF111/303 and CF111/205. The mean subject age was 28.3 years and was similar across the individual studies. Most subjects were ≤35 years old (84.6%) and Caucasian (83.1%). Except for a higher percentage of black or African American subjects in Study CF111/303 (35.6%) than the other studies, racial composition was similar across the populations of each study. The mean BMI across all studies was 25.15 kg/m^2, and most subjects (83.6%) had a BMI less than 30 kg/m^2. Consistent with its objectives, the mean BMI (28.6 kg/m^2) and percentage of subjects with a BMI ≥30 kg/m^2 (35.2%) were higher in Study CF111/303 than in the other studies (ranges: 22.69 to 23.00 kg/m^2 and 3.5% to 5.8%, respectively).

Table 25. Demographics: Studies CF111/301, CF111/302, CF111/303, and CF111/205 (Safety Set)

Characteristic	CF111/301 DRSP 4 mg N=713	CF111/302 DRSP 4 mg N=858	CF111/303 DRSP 4 mg N=1006**	CF111/205 DRSP 4 mg N=21	Total DRSP 4 mg N=2598
Age (years)					
Mean (SD)	28.7 (7.07)	28.9 (7.12)	27.5 (5.94)	29.0 (5.84)	28.3 (6.69)
Median	28.0	28.0	27.0	29.0	27.0
Min, max	18, 46	18, 45	18, 51	19, 36	18, 51
Age group, n (%)					
≤35 years	569 (79.8)	682 (79.5)	928 (92.2)	18 (85.7)	2197
>35 years	144 (20.2)	176 (20.5)	78 (7.8)	3 (14.3)	401 (15.4)
Race, n (%)					
Caucasian	710 (99.6)	856 (99.8)	571 (56.8)	21 (100.0)	2158 (83.1)
Black	1 (0.1)	2 (0.2)	358 (35.6)	0	361 (13.9)
Asian	1 (0.1)	0	20 (2.0)	0	21 (0.8)
Other*	1 (0.1)	0	57 (5.7)	0	58 (2.2)
BMI (kg/m^2)					
Mean (SD)	23.00 (3.781)	22.96 (3.537)	28.61 (7.632)	22.69 (4.034)	25.15 (6.184)
Median	22.40	22.30	27.05	22.10	23.50
Min, max	16.2, 38.3	16.6, 41	15.8, 68	17.1, 32	15.8, 68
BMI group, n (%)					
<30 kg/m^2	672 (94.2)	828 (96.5)	652 (64.8)	20 (95.2)	2172 (83.6)
≥30 kg/m^2	41 (5.8)	30 (3.5)	354 (35.2)	1 (4.8)	426 (16.4)

SD = standard deviation; BMI = body mass index; DRSP = drospirenone
* For Study CF111/303, the category of "Other" in the Race included subjects who were "American Indian or Alaska Native", "Native Hawaiian or Other Pacific Islander" or "Other"
** Excluding sites 104 and 120
Source: Summary of Clinical Safety, Page 20, Table 6

- *Subject demographics for the pivotal Study CF111/303 are similar to that reported in other contraceptive studies and also discussed in the efficacy section of this review.*

Demographics – Adolescent Study

For the phase 3 study in adolescents, selected demographic data are presented in Table 26. The mean subject age was 16.1 years. Most subjects (97.1%) were Caucasian, and the mean BMI was 21.47 kg/m^2. Most subjects were either currently in intermediate secondary school (32.4%) or high school (48.0%).

Table 26. Demographics: Phase 3 Study in Adolescents (Safety Set)

Parameter	DRSP 4 mg (N=102)
Age (years)	
Mean (SD)	16.1 (0.89)
Median	16.0
Min, Max	14, 17
Race, n (%)	
Caucasian	99 (97.1)
Other	3 (2.9)
BMI (kg/m^2)	
Mean (SD)	21.47 (2.661)
Min, Max	17.8, 29.1

DRSP = drospirenone; SD = standard deviation; BMI = body mass index
Source: Summary of Clinical Safety, Page 21, Table 7

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The quality of the submission was acceptable for review.

Categorization of Adverse Events

Safety data were summarized for the Safety Set, which consisted of all subjects who received at least one dose of LF111.

For each individual study, AEs were coded to the version of MedDRA that was current at the time of study completion. For the purposes of pooling, AEs in the integrated phase 3 studies in adults were recoded to MedDRA Version 17.0.

Treatment emergent adverse events (TEAEs) were defined as adverse events (AEs) which started at or after the first intake of trial medication and include those events which started prior to the first intake of trial medication but which worsened after the first intake. Adverse events starting after the last intake of trial medication but within the follow-up were also regarded as treatment-emergent.

Treatment-related TEAEs (also called adverse drug reactions) in the phase 3 studies were defined as any TEAEs considered at least possibly related to the LF111.

Routine Clinical Tests

The routine clinical testing obtained in this NDA was acceptable for the evaluation of progestin-only hormonal contraceptive products.

8.2.4. Safety Results

8.2.4.1. Deaths

No deaths occurred in any subject participating in the LF111 development program.

8.2.4.2. Serious Adverse Events

8.2.4.2.1. Adult Studies

Table 27 presents SAEs reported in >1 subject in the major safety and efficacy trials in adults.

Table 27. Serious Adverse Events Reported in >1 Subject: Studies CF111/301, CF111/302, CF111/303, and CF111/205 (Safety Set)

	CF111/301 DRSP 4 mg N=713 n (%)	CF111/302 DRSP 4 mg N=858 n (%)	CF111/303 DRSP 4 mg N=1006* n (%)	CF111/205 DRSP 4 mg N=21 n (%)	Total DRSP 4 mg N=2598 n (%)
Subjects with ≥1 SAE	10 (1.4)	20 (2.3)	17 (1.7)	2 (9.5)	49 (1.9)
Hyperkalemia	0	1 (0.1)	5 (0.5)	0	6 (0.2)
Appendicitis	0	3 (0.3)	1 (0.1)	0	4 (0.2)
Abortion induced	0	3 (0.3)	0	0	3 (0.1)
Abortion spontaneous	0	1 (0.1)	1 (0.1)	0	2 (0.1)
Breast prosthesis implantation	2 (0.3)	0	0	0	2 (0.1)
Cervical dysplasia	0	2 (0.2)	0	0	2 (0.1)
Cholelithiasis	1 (0.1)	0	1 (0.1)	0	2 (0.1)
Fibroadenoma of breast	0	2 (0.2)	0	0	2 (0.1)
Pyelonephritis	1 (0.1)	0	1 (0.1)	0	2 (0.1)

DRSP = drospirenone; SAE = serious adverse event
*Excluding sites 104 and 120
Source: Summary of Clinical Safety, Page 70, Table 28; Integrated Summary of Safety (ISS), Page 2292, Table 14.3.3.1

- *As noted in the following discussion of hyperkalemia as an SAE, the Applicant's determination of six cases as SAEs was not justified. None required hospitalization or for that matter were even symptomatic. The narratives for these six subjects are provided in the subsequent section of the review. A broader discussion of hyperkalemia is present in Section 8.2.5.*
- *Cervical dysplasia is usually managed on an outpatient basis. The case report forms do not indicate that the two subjects listed as SAEs were hospitalized.*
- *A table listing all individual SAEs is provided as Appendix 2.*

Hyperkalemia as an SAE

Short narratives of subjects with hyperkalemia listed as serious adverse events are presented below. Of note, all potassium units listed below are mmol/L. The reference range for potassium for all these subjects was 3.5 to 5.3 mmol/L.

Study CF111-302

Subject (b) (6)

The subject was a 19-year-old Caucasian female who started study drug on (b) (6) and stopped on (b) (6) On (b) (6) she was found to have serum potassium of 5.7. The investigator confirmed that the subject had no clinical signs of hyperkalemia. The ECG performed on the same day was without pathological findings. Potassium was repeated on (b) (6) and found to be 4.0 which was a normal value.

Study CF111-303

Subject (b) (6)

This 27-year-old white female was noted to have elevated potassium of 5.5 on (b) (6) (day 249). She was asymptomatic with no history of renal disease. A retest on (b) (6) revealed a potassium of 5.5 again. She stopped study drug on (b) (6). On (b) (6) her serum potassium was in the normal range at 5.1.

Subject (b) (6)

This 29-year-old white female had severe pyelonephritis on (b) (6). She was diagnosed with sepsis and hypokalemia. Serum potassium levels during the trial were normal. Study drug was discontinued on (b) (6). She was found to have hyperkalemia (5.4) on (b) (6) approximately 2.5 months after discontinuing study drug.

Subject (b) (6)

A 33-year-old black female who had a pretreatment serum potassium of 5.3 on (b) (6). She started study drug on (b) (6) Serum potassium levels were normal until (b) (6) at which time her serum potassium was 5.5. She stopped study drug on (b) (6), at which time her potassium was 5.4.

Subject (b) (6)

This 29-year-old white female had hyperkalemia (5.6) on (b) (6) (day 81 of treatment). The test was repeated on (b) (6) at 5.8 and (b) (6) at 5.9. Treatment was stopped on (b) (6). Potassium returned to normal at 4.9 on (b) (6) .

Subject (b) (6)

This 22-year-old American Indian was reported to have hyperkalemia (5.7) on (b) (6) , which was 1 day after the last study drug was taken on (b) (6). Repeated serum potassium on (b) (6) was 4.8.

- *There was one additional SAE of "increased potassium." (Subject (b) (6) in Study CF111-302 was a 36-year-old Caucasian female who started study drug on (b) (6). On (b) (6) her potassium was elevated at 5.9). No signs or symptoms related to this were observed. On (b) (6), her potassium was 5.8. On (b) (6), she was asymptomatic, had a normal EKG and her potassium was 4.6. She stopped taking the study drug on (b) (6)*
- *Although the hyperkalemia/increased potassium is not considered a SAE in these particular seven subjects, DRSP is related to the occurrence of hyperkalemia (see Section 8.2.5).*

8.2.4.2.2. Possible Relation to Study Drug

Study CF111-205

Subject (b) (6) (uterine myomas)

A 36-year-old Caucasian female started the treatment with study medication on (b) (6) and ended the treatment on (b) (6). The initial ultrasound endometrial examination from (b) (6) recorded an endometrial thickness of 11 mm and one area suspected for fibroma on the posterior wall. On (b) (6) (visit 7), multiple myomas ranging from 2 cm to 4.8 cm were recorded.

- *Generally, progestin-only contraceptives do not appear to cause growth of uterine fibroids however the data are unclear. Therefore, it is uncertain whether DRSP stimulated the fibroid growth in this subject.*

Study CF111-301

Subject (b) (6) (cholelithiasis)

This 30-year-old woman with a history of obesity since 2004 started to take DRSP 4.0 mg on (b) (6). On (b) (6) the subject was admitted to the hospital due to cholelithiasis. Laparoscopic cholecystectomy was performed on the next day. There were no complications during the post-operative period. On (b) (6), the subject was considered as recovered and was discharged from the hospital.

- *Some studies have demonstrated a small but statistically significant increase in the risk of gall bladder disease associated with desogestrel, drospirenone and norethindrone compared to levonorgestrel in combined oral contraceptive formulations containing ethinyl estradiol. The cholelithiasis in this case could have possibly been related to the study drug.*

Study CF111-302

Subject (b) (6) (liver adenoma)

This 28-year-old woman started to take DRSP 4.0 mg on (b) (6). The subject completed the study treatment on (b) (6) On (b) (6) the subject informed the investigator of her hepatic adenoma, which was randomly detected during an ultrasound examination performed in (b) (6) by the subject's general practitioner. According to the GP, the subject came on (b) (6) due to pain in the right upper abdomen/gastric area. The laboratory results for liver enzymes were normal. The ultrasound examination showed a single tumor in the left part of the liver (size 1.35 cm). The GP considered that the tumor could not cause the pain and no treatment was administered. Tumor growth was observed via repeated ultrasound examinations (in (b) (6) the size was 1.4 cm and in (b) (6) 1.45 cm). The GP considered the tumor as stable and recommended a CT only if the tumor size got over 2 cm. In the investigator's opinion, liver adenoma is possibly related to hormonal contraception. However, the investigator stated that the subject had been taking hormonal contraception for

several years before the trial (ethinyl estradiol with levonorgestrel from (b) (6) to (b) (6) and it cannot be stated that the event is related to DRSP 4 mg only.

- *Use of COCs in women with a liver adenoma is contraindicated. This adenoma could have been possibly related to her prior COC use or possibly the study drug.*

Study CF111-303

Subject (b) (6) (abdominal pain and vomiting)

This 28-year-old African American subject received LF111 treatment as a switcher from (b) (6) to (b) (6). The subject had a history of a cholecystectomy in 2011 and gastroesophageal reflux disease since 2012. Concomitant therapy included oral metoclopramide. The subject was reported to have upper abdominal pain and vomiting on (b) (6) and admitted to the hospital (day 35 of LF111 treatment). There were no additional diagnostic imaging or laboratory findings. The subject was treated with intravenous fluids, pantoprazole, and metoclopramide. The subject recovered from the SAE and was discharged from hospital on (b) (6). No action was taken regarding the study drug and the subject completed the clinical trial. Abdominal pain and vomiting were not considered to be related to study drug by the investigator.

- *Considering the subject's history of gastroesophageal reflux disease, it is unlikely that the abdominal pain and vomiting were related to the study drug.*

8.2.4.2.3. Adolescent Study (CF111/304)

In the phase 3 study in adolescents, two subjects (2.0%) experienced SAEs (moderate pharyngitis and severe joint dislocation). No instances of hyperkalemia/elevated blood potassium were reported.

- *The two SAEs occurring in the adolescent study were not drug-related.*

Serious Adverse Events: Phase 1 and Phase 2 Studies

No SAEs were reported during the phase 1 studies. The only phase 2 study reporting SAEs was CF11/205. These SAEs were discussed previously, and each event is included in Appendix 2.

8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

8.2.4.3.1. Adult Studies

In the major clinical studies in adults, a minority of subjects had AEs leading to study discontinuation (11.0% of subjects overall; range: 4.8% to 12.3% across studies (Table 28). The most frequent AEs leading to study discontinuation (≥0.5% of all subjects) were acne (1.5%), metrorrhagia (1.3%), menstruation irregular (0.9%), weight increased (0.9%), vaginal hemorrhage (0.8%) and libido decreased (0.5%). Most TEAEs leading to study discontinuation were considered at least possibly related to study drug, and most were of mild or moderate severity.

Table 28. Adverse Events Leading to Study Discontinuation in ≥0.5% of Subjects: Studies CF111/301, CF111/302, CF111/303, and CF111/205 (Safety Set)

	CF111/301 DRSP 4 mg N=713 n (%)	CF111/302 DRSP 4 mg N=858 n (%)	CF111/303 DRSP 4 mg N=1006* n (%)	CF111/205 DRSP 4 mg N=21 n (%)	Total DRSP 4 mg N=2598 n (%)
Subjects with ≥1 AE assoc. with discontinuation	88 (12.3)	82 (9.6)	116 (11.5)	1 (4.8)	287 (11.0)
Acne	21 (2.9)	9 (1.0)	8 (0.8)	0	38 (1.5)
Metrorrhagia	12 (1.7)	3 (0.3)	18 (1.8)	0	33 (1.3)
Menstruation irregular	10 (1.4)	11 (1.3)	3 (0.3)	0	24 (0.9)
Weight increased	2 (0.3)	8 (0.9)	12 (1.2)	1 (4.8)	23 (0.9)
Vaginal hemorrhage	4 (0.6)	12 (1.4)	4 (0.4)	0	20 (0.8)
Libido decreased	2 (0.3)	5 (0.6)	5 (0.5)	0	12 (0.5)
Hyperkalemia	0	0	2 (0.2)	0	2 (0.1)

DRSP = drospirenone; AE = adverse event
*Excluding sites 104 and 120
Source: Summary of Clinical Safety, Page 36, Table 18

8.2.4.3.2. Adolescent Study

In the phase 3 study in adolescents, the incidence and pattern of TEAEs leading to discontinuations were similar to those in the adult studies (Table 29). A small number of subjects (10.8%) had TEAEs leading to premature study discontinuation. The only TEAE leading to study discontinuation in more than one subject was metrorrhagia, which was reported for five subjects (4.9%). Each TEAE leading to premature discontinuation was considered at least possibly related to study drug, and all but one were of mild or moderate severity.

Table 29. Treatment-Emergent Adverse Events Leading to Study Discontinuation: Phase 3 Study in Adolescents (Safety Set)

Preferred Term, n (%)	DRSP 4 mg (N=102)
Subjects with ≥1 TEAE leading to premature discontinuation	11 (10.8)
Metrorrhagia	5 (4.9)
Acne	1 (1.0)
Amenorrhea	1 (1.0)
Depression	1 (1.0)
Mood altered	1 (1.0)
Mood swings	1 (1.0)
Nausea	1 (1.0)

DRSP = drospirenone; TEAE = treatment-emergent adverse event
Source: ISS, Page 73, Table 30

In the phase 2 studies (in addition to Study CF111/205), TEAEs leading to discontinuation were reported during Study CF111/204. In CF111/204, a total of three subjects each experienced one TEAE leading to discontinuation (i.e., mild abdominal pain lower, moderate depression and moderate affective disorder). Each of these TEAEs were possibly related to study drug, and all events resolved within a maximum of 9 days.

In the phase 1 studies, no subjects had TEAEs leading to discontinuation.

8.2.4.4. Treatment Emergent Adverse Events

8.2.4.4.1. Adult Studies

A total of 1302 subjects (50%) experienced at least one treatment-emergent adverse event in the four major clinical studies. The most common (occurring in ≥2% of subjects overall) TEAEs from the phase 3 studies in adults are presented by preferred term below (Table 30). Overall, the most common TEAEs were headache (5.2% of all subjects), nasopharyngitis (4.9% of all subjects) and acne (4.2% of all subjects). All other TEAEs were reported for less than 3% of subjects, overall.

Table 30. Treatment-Emergent Adverse Events Reported in ≥2% of Subjects: Studies CF111/301, CF111/302, CF111/303, and CF111/205 (Safety Set)

Preferred Term n (%)	CF111/301 (N=713)	CF111/302 (N=858)	CF111/303 (N=1006*)	CF111/205 (N=21)	Total (N=2598)
Subjects with ≥1 TEAE	346 (48.5)	329 (38.3)	614 (61.0)	13 (61.9)	1302 (50.1)
Headache	31 (4.3)	38 (4.4)	64 (6.4)	1 (4.8)	134 (5.2)
Nasopharyngitis	22 (3.1)	29 (3.4)	77 (7.7)	0	128 (4.9)
Acne	46 (6.5)	27 (3.1)	35 (3.5)	0	108 (4.2)
Nausea	10 (1.4)	3 (0.3)	35 (3.5)	0	76 (2.9)
Breast pain	8 (1.1)	14 (1.6)	51 (5.1)	0	73 (2.8)
Metrorrhagia	19 (2.7)	10 (1.2)	44 (4.4)	0	73 (2.8)
Weight increased	13 (1.8)	21 (2.4)	34 (3.4)	2 (9.5)	70 (2.7)
Cervical dysplasia	13 (1.8)	26 (3.0)	29 (2.9)	0	68 (2.6)
Dysmenorrhea	1 (0.1)	8 (0.9)	58 (5.8)	0	67 (2.6)

TEAE = treatment-emergent adverse event
* Excluding sites 104 and 120
Source: Adapted from Summary of Clinical Safety, Page 25, Table 10

- *Of note, the most common TEAEs are similar to those reported in other contraceptive trials.*

8.2.4.4.2. Adolescent Study

In the phase 3 study in adolescents, AEs were similar to those observed in the adults (Table 31). Over half of subjects (63.7%) had at least one TEAE. Most of these were mild or moderate in severity. Approximately 22.5% of subjects had TEAEs considered related to study drug. No subjects reported TEAEs which were considered submission specific such as VTEs or hyperkalemia.

Table 31. Treatment-Emergent Adverse Events Reported in ≥2% of Subjects in Adolescent Study

Preferred Term, n (%)	DRSP 4 mg (N=102)
Subjects with ≥1 TEAE	64 (62.7)
Nasopharyngitis	13 (12.7)
Nasopharyngitis	7 (6.9)
Respiratory tract infection viral	7 (6.9)
Abdominal pain	6 (5.9)
Bronchitis	6 (5.9)
Headache	6 (5.9)
Abdominal pain lower	5 (4.9)
Metrorrhagia	5 (4.9)
Viral infection	5 (4.9)
Dysmenorrhea	4 (3.9)
Abdominal distension	3 (2.9)
Diarrhea	3 (2.9)
Influenza	3 (2.9)
Mood altered	3 (2.9)
Nausea	3 (2.9)
Oropharyngeal pain	3 (2.9)
Pyrexia	3 (2.9)
Sinusitis	3 (2.9)
Urinary tract infection	3 (2.9)
Weight increased	3 (2.9)

DRSP = drospirenone; TEAE = treatment-emergent adverse event
Source: Summary of Clinical Safety, Page 26, Table 11

- The TEAEs in the adolescents did not appear to be clinically different from adults using DRSP or demonstrate a new safety signal or trend.

8.2.4.5. Treatment Emergent Adverse Reactions

Adverse reactions are presented in Table 32. The most common ones include acne, metrorrhagia, headache and breast pain. A total of 1,302 subjects (50%) experienced at least one treatment-emergent adverse event during these four studies and 627 of the subjects (24.1%) were thought to experience a treatment-related adverse event (adverse reaction).

Table 32. Adverse Reactions Occurring in ≥1% of Subjects: Studies CF111/301, CF111/302, CF111/303, and CF111/205 (Safety Set)

Preferred Term, n (%)	CF111/301 (N=713)	CF111/302 (N=858)	CF111/303 (N=1006*)	CF111/205 (N=21)	Total (N=2598)
Any adverse reaction	148 (20.8)	135 (15.7)	341 (33.9)	3 (14.3)	627 (24.1)
Acne	42 (5.9)	26 (3.0)	30 (3.0)	0	98 (3.8)
Metrorrhagia	19 (2.7)	9 (1.0)	44 (4.4)	0	72 (2.8)
Headache	11 (1.5)	13 (1.5)	47 (4.7)	0	71 (2.7)
Breast pain	6 (0.8)	8 (0.9)	43 (4.3)	0	57 (2.2)
Weight increased	6 (0.8)	19 (2.2)	23 (2.3)	2 (9.5)	50 (1.9)
Dysmenorrhea	0	5 (0.6)	44 (4.4)	0	49 (1.9)
Nausea	5 (0.7)	2 (0.2)	40 (4.0)	0	47 (1.8)
Vaginal hemorrhage	8 (1.1)	17 (2.0)	20 (2.0)	0	45 (1.7)
Libido decreased	12 (1.7)	10 (1.2)	11 (1.1)	0	33 (1.3)
Breast tenderness	1 (0.1)	0	30 (3.0)	0	31 (1.2)
Menstruation irregular	14 (2.0)	8 (0.9)	8 (0.8)	0	30 (1.2)

Adverse reaction = treatment-related adverse event
* Excluding sites 104 and 120
Source: Adapted from Summary of Clinical Safety, Page 30, Table 14

8.2.4.5.1. Adolescent Study

Approximately 22.5% of subjects had adverse reactions related to study drug (Table 33). No subjects reported adverse reactions such as VTEs or hyperkalemia. A total of 11 subjects (10.8%) had adverse reactions leading to discontinuation.

Table 33. Adverse Reactions in Adolescent Study

Preferred Term, n (%)	DRSP 4 mg (N=102)
Any possible adverse reaction	23 (22.5)
Metrorrhagia	5 (4.9)
Acne	4 (3.9)
Abdominal distension	3 (2.9)
Headache	3 (2.9)
Mood altered	3 (2.9)
Weight increased	3 (2.9)
Breast pain	2 (2.0)
Dysmenorrhea	2 (2.0)
Mood swings	2 (2.0)
Abdominal pain lower	1 (1.0)
Alopecia	1 (1.0)
Amenorrhea	1 (1.0)
Arthralgia	1 (1.0)
Depression	1 (1.0)
Dry eye	1 (1.0)
Hot flush	1 (1.0)
Nausea	1 (1.0)
Uterine hemorrhage	1 (1.0)

DRSP = drospirenone
Adverse reaction = treatment-related adverse event
Source: Summary of Clinical Safety, Page 31, Table 15

8.2.4.6. Laboratory Findings

8.2.4.6.1. Laboratory Findings in Adults

In the phase 3 studies in adults, abnormal laboratory values were reported as AEs in the SOCs of blood and lymphatic system disorders (0.5% of subjects), congenital, familial, and genetic disorders, (0.1% of subjects), investigations (6.8% of subjects) and metabolism and nutrition disorders (1.6% of subjects).

Across all subjects, the incidence of individual TEAE preferred terms relating to laboratory values was low (<1% for each preferred term). Laboratory values reported as AEs in more than 0.5% of all subjects included blood thyroid-stimulating hormone increased (0.9% of subjects) and blood creatine phosphokinase increased (0.7% of subjects).

There were few abnormal laboratory values reported as SAEs. These were blood potassium increased (one subject [0.0%]) and hyperkalemia (six subjects [0.2%]).

Laboratory values reported as TEAEs that led to treatment discontinuation were infrequent (reported for ≤0.1% of subjects overall). The only preferred terms leading to discontinuation of more than one subject across the phase 3 studies in adults were gamma-glutamyltransferase increased (three subjects [0.1%]) and hyperkalemia (two subjects [0.1%]).

- *During long-term studies with LF111, there were no clinically significant changes from baseline in mean values of TSH. The rate of subjects who shifted from normal values at baseline to high values at endpoint in Study CF111/302 were 4.8% in the LF111 group.*
- *The mean increases from baseline (114.0 U/L) to visit 6 (121.3 U/L) in creatinine kinase levels were not deemed to be clinically significant.*
- *Hyperkalemia is discussed elsewhere in this section and 8.2.5.*

8.2.4.6.2. Laboratory Findings in Adolescents

In the phase 3 study in adolescents, abnormal laboratory values were reported as AEs in the SOCs of blood and lymphatic system disorders and investigations. Across all subjects, the incidence of individual TEAE preferred terms relating to laboratory values was low (≤1% for each preferred term). No laboratory values were reported as AEs in more than a single subject. No abnormal laboratory values were reported as SAEs and no laboratory values reported as TEAEs led to treatment discontinuation. No safety signals or trends were identified that would lead to a concern that adolescents would have a different laboratory profile from adults with use.

Phase 1 and Phase 2

In the phase 1 and phase 2 studies, no abnormal laboratory values were reported at SAEs, and no laboratory values reported as TEAEs led to treatment discontinuation.

Safety Data from Excluded Study CF111/303, Sites 104 and 120

As noted in Section 8.1.2, the Applicant closed sites 104 and 120 in Study CF111/303 due to administrative irregularities. From a safety perspective there were no deaths, SAEs or new safety signals identified at these sites. Individual TEAEs from these sites can be found in Appendix 4: TEAEs, Sites 104 and 120.

Vital Signs

No vital signs or physical examination findings were associated with safety concerns during the clinical development program.

Electrocardiograms (ECGs) and QT

Electrocardiogram assessments were done at study entry and the final visit in all phase 1 and selected phase 2 studies. In addition, phase 3 Study CF111/302 evaluated ECGs in a subset of subjects receiving LF111. Overall, no relevant safety concerns regarding ECG findings were observed in the clinical development program for DRSP.

Bleeding – Adult Studies

Scheduled bleeding was defined as any bleeding or spotting that occurred during hormone-free intervals. Up to eight consecutive bleeding/spotting days were considered as scheduled bleeding days. Unscheduled bleeding/spotting days were defined as any bleeding/spotting that occurred while taking active hormones (days 2 to 23), except days which were classified as scheduled bleeding days.

In the phase 3 studies in adults, DRSP was associated with a decrease in the percentage of subjects experiencing bleeding or spotting over time. Overall, the percentage of subjects with scheduled bleeding or spotting decreased from 81.2% in cycle 1 to 26.4% in cycle 13. Similarly, the overall percentage of subjects with unscheduled bleeding or spotting decreased from 61.4% in cycle 1 to 40.3% in cycle 13. The percentages of subjects with scheduled and unscheduled bleeding or spotting generally decreased through cycle 10 and were maintained at a consistent level through cycle 13 (Table 34).

Table 34. Subjects With Scheduled and Unscheduled Bleeding or Spotting: Studies CF111/301, CF111/302, CF111/303, and CF111/205 (Safety Set, N=2598)

	Scheduled		Unscheduled	
Cycle	n/m	Rate and 95% CI (%)	n/m	Rate and 95% CI (%)
Cycle 1	1768/2178	81.2 (79.5, 82.8)	1337/2178	61.4 (59.3, 63.4)
Cycle 2	895/1932	46.3 (44.1, 48.5)	1051/1932	54.4 (52.2, 56.6)
Cycle 3	768/1788	43.0 (40.7, 45.2)	920/1788	51.5 (49.1, 53.8)
Cycle 4	674/1676	40.2 (37.9, 42.6)	836/1676	49.9 (47.5, 52.3)
Cycle 5	545/1554	35.1 (32.7, 37.4)	724/1554	46.6 (44.1, 49.1)
Cycle 6	507/1482	34.2 (31.8, 36.6)	703/1482	47.4 (44.9, 50.0)
Cycle 7	473/1418	33.4 (30.9, 35.8)	641/1418	45.2 (42.6, 47.8)
Cycle 8	427/1339	31.9 (29.4, 34.4)	592/1339	44.2 (41.6, 46.9)
Cycle 9	405/1308	31.0 (28.5, 33.5)	581/1308	44.4 (41.7, 47.1)
Cycle 10	227/859	26.4 (23.5, 29.4)	328/859	38.2 (34.9, 41.4)
Cycle 11	230/759	30.3 (27.0, 33.6)	318/759	41.9 (38.4, 45.4)
Cycle 12	202/726	27.8 (24.6, 31.1)	302/726	41.6 (38.0, 45.2)
Cycle 13	185/700	26.4 (23.2, 29.7)	282/700	40.3 (36.7, 43.9)

n = number of subjects with bleeding or spotting; m = number of subjects with cycle data; CI = confidence interval
Source: Summary of Clinical Safety, Page 41, Table 20

In the phase 3 studies in adults, a total of 91 subjects (0.4%) in the LF111 group withdrew from one of the studies due to bleeding problems or amenorrhea.

Table 35. Adverse Events Related to Bleeding/Amenorrhea Leading to Study Discontinuation in >1 Subject: Studies CF111/301, CF111/302, CF111/303, and CF111/205 (Safety Set)

	DRSP (N=2598)
Preferred Term	n (%)
Metrorrhagia	33 (1.3)
Menstruation irregular	24 (0.9)
Vaginal hemorrhage	20 (0.8)
Menorrhagia	8 (0.3)
Uterine hemorrhage	4 (0.2)
Amenorrhea	2 (0.1)

DRSP = drospirenone
Source: Adapted from Summary of Clinical Safety, Page 36, Table 18

Bleeding – Adolescent Study

The data from the phase 3 study in adolescents were generally consistent with the phase 3 studies in adults. The percentage of subjects with scheduled bleeding or spotting decreased from 98.0% in cycle 1 to 28.4% in cycle 13. The percentage of subjects with scheduled bleeding or spotting generally decreased through cycle 9 and was maintained at a consistent level through cycle 13. In contrast, the percentage of subjects with unscheduled bleeding or spotting was maintained at a relatively consistent level during the study (53.0% in cycle 1 versus 52.2% in cycle 13).

Table 36. Subjects With Scheduled and Unscheduled Bleeding or Spotting: Phase 3 Study in Adolescents (Safety Set)

	Scheduled	Unscheduled
Cycle	n/m (%)	n/m (%)
Cycle 1	98/100 (98.0)	53/100 (53.0)
Cycle 2	56/95 (58.9)	54/95 (56.8)
Cycle 3	44/94 (46.8)	47/94 (50.0)
Cycle 4	41/91 (45.1)	41/91 (45.1)
Cycle 5	41/85 (48.2)	38/85 (44.7)
Cycle 6	33/84 (39.3)	40/84 (47.6)
Cycle 7	29/79 (36.7)	43/79 (54.4)
Cycle 8	24/79 (30.4)	39/79 (49.4)
Cycle 9	20/79 (25.3)	41/79 (51.9)
Cycle 10	24/76 (31.6)	39/76 (51.3)
Cycle 11	24/76 (31.6)	36/76 (47.4)
Cycle 12	20/74 (27.0)	32/74 (43.2)
Cycle 13	19/67 (28.4)	35/67 (52.2)

n = number of subjects with bleeding or spotting; m = number of subjects with cycle data
Source: Summary of Clinical Safety, Page 42, Table 21

- *Inclusion of scheduled and unscheduled bleeding data will be included in the label as safety information.*
- *Information comparing drospirenone to a non-US approved comparator was not evaluated and will not be included in labeling.*

Immunogenicity

Not Applicable as this is not a biologic product.

8.2.5. Analysis of Submission-Specific Safety Issues

Thromboembolic events and hyperkalemia are considered submission specific safety issues for this application for two reasons. First, an increased risk of thrombotic events has been reported in users of combination oral contraceptives COCs containing DRSP. Second, DRSP is a potassium-sparing aldosterone antagonist that has the potential to increase potassium levels. This section will also discuss pregnancy safety issues, endometrial pathology, and bone effects.

Thromboembolic Disorders

Across the clinical development program for LF111, no thromboembolic events were reported in the clinical study safety database.

- *Given the safety profile from the clinical trial database and the fact that this is a progestin only product, it is believed that the thromboembolic absolute risk will be similar to other progestin only products. Based on these findings a postmarketing study to assess cardiovascular adverse events is not necessary to further describe this risk.*

Hyperkalemia

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.

Serum potassium levels were reviewed for all subjects with hyperkalemia in the three phase 3 pivotal studies in adults (see Appendix 3 in this Unireview). A total of 79 subjects taking LF111 had an elevated serum potassium at one point or another during the three studies. The upper limit of normal for potassium was 5.3 mmol/L.

Hyperkalemia findings from Study CF111/301

A total of 12 subjects had an elevated serum potassium during the study. Of these, two were noted at the screening visit. Of the remaining 10 subjects, the highest potassium level was 6.0 in two subjects. Both subjects had normal values on a repeat specimen and both completed the study. All remaining subjects had normal values on repeat except for two subjects who did not have any subsequent lab documented. One of these subjects completed the study and one withdrew from the study.

Hyperkalemia findings from Study CF111/302

A total of 26 subjects taking LF111 had at least one isolated potassium value. Of these, 10 were found at the screening visit. Of the remaining 16 subjects, one had an isolated value of 8.6 which was repeated and found to be 4.1. Of the 15 remaining subjects, one had a documented isolated potassium value (5.5) which persisted. Several subjects did not get follow-up.

A total of nine subjects taking desogestrel had an elevated potassium. Three of these subjects had levels >6.0 mmol/L.

Hyperkalemia findings from Study CF111/303

In this study, a total of 41 subjects had an elevated potassium level. Of these, 19 were detected at the screening visit. Nearly all the serum potassium's returned to normal on subsequent testing. Three subjects (Subjects (b) (6)) were withdrawn from the study due to persistently elevated potassium's. These subjects were reported as SAEs. Table 37 focuses on potassium levels at two cut points (>5.3 and 5.8 mmol/L).

Table 37. Subjects With Elevated Potassium: Studies CF111/301, CF111/302, and CF111/303

	Study CF111/301		Study CF111/302				Study CF111/303	
	LF111 N=713		LF111 N=858		DSG N=332		LF111 N=1006*	
Potassium Level Category	**SCR**	**OT**	**SCR**	**OT**	**SCR**	**OT**	**SCR**	**OT**
Subjects with K>5.3 mmol/L n (%)	2 (0.3)	10 (1.4)	10 (1.2)	16 (1.9)	3 (0.9)	6 (1.8)	19 (1.9)	22 (2.2)
Persistent K>5.3 mmol/L n (%)		1 (0.1)	1 (0.1)	1 (0.1)	0	0	0	0
Subjects with K>5.8 mmol/L n (%)	0	2 (0.3)	4 (0.4)	8 (0.9)	0	3 (0.9)	3 (0.3)	1 (<0.1)
Hemolyzed specimen condition n (%)						1 (0.3)		

K = potassium; SCR = screening; OT = on-treatment; DSG = desogestrel
* excludes sites 104 and 120
Source: Reviewer derived from Applicant's February 18, 2019 submission to the NDA

- *It was surprising to see so many subjects with elevated potassium values at the screening visit and for desogestrel which does not have anti-mineralocorticoid activity.*
- *Many subjects in these studies had mild and isolated elevated serum potassium levels which reverted to normal even though DRSP was continued.*
- *Only a very small number of subjects were withdrawn from the adult studies due to elevated potassium values.*

Bone Loss

DRSP is a progestin that acts by blocking the production of gonadotropin-releasing hormone which in turn causes a reduction in gonadotropins and reduced estrogen production. Of concern is that long term suppression of estrogen can lead to clinically significant bone loss. Bone metabolism parameters (bone alkaline phosphatase and cross-linked c-terminal telopeptides) were assessed during phase two ovarian inhibition studies CF111/202 and CF111/203. These assessments were made at baseline and after two treatment cycles. These markers were also measured in a subgroup of subjects in Study CF111/302 (baseline and after nine treatment cycles). There were no significant safety concerns based on the level of these surrogate metabolism parameters.

- *Bone metabolism markers are not sufficient to predict the long-term effects on bone mineral density. Therefore, the Applicant was required to conduct a one-year phase 4 postmarketing trial to investigate the effect of DRSP on bone mineral density in both adolescent and adult women in comparison with users of non-hormonal contraceptive methods. The primary objective of this trial will be to determine the mean percentage change in BMD at the lumbar spine measured by dual-energy X-ray absorptiometry at 6 and 12 months. Once completed, this information will be incorporated into labeling.*

- *Until the results of the postmarketing study are available, this product will be labeled with a similar warning contained in other progestin products that bone loss may occur.*

Ectopic Pregnancy and Pregnancy Outcomes

One ectopic pregnancy was reported for LF111 (Subject (b) (6) in Study CF111/303). This 35-year-old female with a history of two Cesarean deliveries, two abortions (one spontaneous) started LF111 treatment as a naïve user on (b) (6). Her urine and serum pregnancy (hCG: 1220 IU/L) tests performed on (b) (6) (visit 3) were positive. The ultrasound examination showed right ovarian cyst and no gestational sac. On (b) (6) the subject informed the site that she was diagnosed with ectopic pregnancy. The subject had received intramuscular methotrexate on (b) (6). No complications were reported for that treatment.

The Applicant reported on 14 intrauterine pregnancy outcomes (eight during treatment and six post-treatment) for subjects treated with LF111. The outcomes of the pregnancies were the following: 10 infants (five boys including one set of twins, four girls, and one baby of unknown gender) were born to nine subjects. There were four subjects who underwent elective abortions and one post-study pregnancy resulted in a spontaneous abortion. There was one case of congenital anomaly. This was a case of congenital inguinal and umbilical hernia in a premature baby that was reported in Study CF111/302.

- *For the additional on-treatment pregnancies identified by the Agency two were lost to follow-up and one resulted in an elective abortion.*

Endometrial Safety

Study CF111/205 was a phase 3 endometrial safety study in subjects taking LF111 for 1 year. The study was conducted in Bulgaria.

The primary objective of this trial was to assess the endometrial safety of 4 mg DRSP given in a 24/4 regimen for a total duration of 13 cycles of 28 days each. Endometrial thickness was a secondary objective of the trial. Of 21 subjects who received treatment 17 subjects who completed 13 cycles.

Endometrial thickness by transvaginal sonography and endometrial biopsies were done at screening and at the end of treatment. All second biopsies (of study completers*)* were taken after more than 1 year of treatment. The remaining two biopsies (in drop-out subjects) were taken after 203 and 273 days of treatment.

Visits 1 and 7 endometrial biopsy results are listed below (Table 38).

Table 38. Endometrial Biopsies: Study CF111-205, Safety Set/Completers

	Safety Set (N=21)	Study Completers (N=17)
	N (%)	N (%)
Visit 1		
Inadequate	0	0
Atrophic	0	0
Proliferative	14 (66.7)	12 (70.6)
Secretory	7 (33.3)	5 (29.4)
Hyperplasia	0	0
Visit 7		
Inadequate	4 (20)	4 (23.5)
Atrophic	0	0
Proliferative	12 (60)	11 (64.7)
Secretory	3 (15)	2 (11.8)
Hyperplasia	0	0

Source: Clinical study report CF111/205, Page 82, Tables TT 28 and TT 29

The endometrial thickness was reduced by mean of 2.1 mm (Safety Population) and 2.5 mm (Completers) under treatment.

- *The evaluation of biopsy specimens after one year of treatment with DRSP revealed no cases of suspicious endometrial findings. There were no instances of premalignant or malignant changes in the endometrium.*
- *Since this DRSP-only drug is given in a cyclic fashion the presence of proliferative endometrium is not noteworthy. Continuous progestin generally leads to a progestational secretory pattern consisting of smaller inactive glands and pseudodecidualized stroma.*
- *The number of inadequate endometrial biopsies is also notable. It is unclear whether this was due to a thinned endometrium or procedure issues.*

8.2.6. 'Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Not Applicable

8.2.7. Safety Analyses by Demographic Subgroups

For the phase 3 studies in adults, safety was assessed for subgroups of subjects based on age, BMI, blood pressure, smoking status, and alcohol use.

Age

For the phase 3 studies in adults, safety and bleeding tolerability were analyzed for subgroups of subjects aged ≤35 years (N=2,197) versus >35 years (N=401). No clinically meaningful differences in safety or bleeding tolerability were observed across these age subgroups.

In addition, no clinically meaningful differences in safety or bleeding tolerability between the adult and adolescent subgroups (N=102) were observed.

BMI

For the phase 3 studies in adults, safety and bleeding tolerability were analyzed for subgroups of subjects with a BMI <30 (N=2,172) versus ≥30 kg/m^2 (N=426).

No clinically meaningful differences in safety or bleeding tolerability between these subgroups of subjects were observed. This is clinically relevant and no limitations on BMI will be included in labeling.

Blood Pressure

Estrogen-containing contraceptives in some cases may increase blood pressure readings in some subjects. For the phase 3 studies in adults using DRSP, safety and tolerability were analyzed for subgroups of subjects with systolic blood pressure <130 mmHg and diastolic blood pressure <85 mmHg (N=2,206) versus subjects with systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg (N=392).

No clinically meaningful differences in safety between subgroups of subjects based on blood pressure were observed and no labeling to caution on this issue was necessary.

Smoking Status

For the phase 3 studies in adults, safety and bleeding tolerability were analyzed for subgroups of subjects who were current smokers (N=609), former smokers (N=233) and nonsmokers (1,756). Overall, AEs, TEAEs and treatment-related TEAEs were more common in former smokers than in current smokers or nonsmokers, with increases of incidence of approximately 10% for former smokers for these parameters.

No clinically meaningful differences in bleeding tolerability between subgroups of subjects based on smoking status were observed. As compared to contraceptives that contain estrogen, no limitation of use for smokers over 35 years of age will be necessary.

Alcohol Use

For the phase 3 studies in adults, safety and tolerability were analyzed for subgroups of subjects who drink (N=1,633) versus never use alcohol (N=965). Overall, AEs, TEAEs and treatment-related TEAEs were more common in subjects who drink than in subjects who never use alcohol, with increases of incidence of approximately 9% to 12% for subjects who drink for each parameter. Similarly, the incidence of TEAEs leading to discontinuation was somewhat higher in subjects who drink (12.4%) than in subjects who never use alcohol (8.4%).

No clinically meaningful differences in bleeding tolerability between subgroups of subjects based on alcohol use were observed. Based on these exploratory findings, no further assessment of alcohol interactions was necessary from a clinical perspective.

8.2.8. Specific Safety Studies/Clinical Trials

See Endometrial Safety in Section 8.2.5. No other specific safety studies were conducted for this submission.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

See Endometrial Safety in Section 8.2.5.

Human Reproduction and Pregnancy

Based on currently available data, no risks for specific anomalies have been observed with progesterone-only pills when used for contraception.

Negligible amounts of drospirenone are excreted in the breast milk. For LF111, the average DRSP concentration in breast milk is 5.6 ng/mL over 24 hours. The estimated average infant daily dosage for an exclusively breastfed infant is 840 ng/kg/day, which is considered negligible. (See the Nonclinical Review). Thus, at therapeutic doses of DRSP, no effects on breastfed newborns/infants are anticipated. In general, no adverse effects have been found on milk production or on the health, growth, or development of the infant with use of POPs.

After daily administration of 4 mg LF111 tablets, the average DRSP concentration in breast milk over a 24-hour period is 5.6 ng/mL. Based on this concentration, the estimated average infant daily dosages for an exclusively breastfed infant is 840 ng/kg/day (0.02% of maternal dose). This daily dosage is considered negligible. This information will be included in labeling.

Pediatrics and Assessment of Effects on Growth

Bone mineral density assessment is planned as a Postmarketing Requirement and will include an adolescent cohort. No other safety findings were noted in the adolescent study in Europe and no other concerns were identified during the review that required further pediatric evaluation.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No serious deleterious effects from overdose of DRSP have been reported. Symptoms that may occur in cases of overdose include nausea, vomiting and slight vaginal bleeding. There are no antidotes to DRSP, and treatment in cases of overdose were symptomatic. Serum potassium, serum sodium and evidence of metabolic acidosis need to be monitored in cases of overdose. Labeling will reflect currently available information on overdose.

Drug abuse and dependence on DRSP have not been studied but are not thought to be an issue for drospirenone since it is not a controlled substance.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not Applicable since there is no postmarketing data available on the use of drospirenone only products. There has been an extensive evaluation of the safety issue of hyperkalemia with drospirenone use in combination oral contraceptive products (See section 8.2.5 of this review). No further evaluation of this safety concern is necessary for approval of this DRSP product.

Expectations on Safety in the Postmarket Setting

The Applicant will conduct a postmarketing bone mineral density study in adult and adolescent women as a Postmarketing Requirement.

8.2.11. Integrated Assessment of Safety

See the body of this review.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

There were no statistical issues identified in pivotal Study CF111/303; however, FDA disagreed with the Applicant regarding the number of on-drug pregnancies used in the efficacy evaluation. The Applicant's efficacy evaluation was based on 12 reported pregnancies, but during the review the Clinical and Statistical teams determined that six additional pregnancies occurred on-drug, including two pregnancies that occurred in two excluded sites (i.e., sites 104 and 120) for GCP violations, and one conceived while breastfeeding. The FDA determined that two pregnancies from excluded sites were well-documented on-drug pregnancies and need to be included, while one pregnancy during breastfeeding could be excluded from the Pearl Index (PI) calculation. Therefore, FDA efficacy evaluation was based on 17 pregnancies. The FDA's PI that included the additional on treatment pregnancies was included in labeling for this product.

8.4. Conclusions and Recommendations

From a statistical perspective, Study CF111/303 provided evidence supporting the efficacy of DRSP in the prevention of pregnancy.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was necessary for approval of this DRSP product. This product did not present a new paradigm or safety issue that require input from experts at an Advisory Committee.

10. Pediatrics

The pediatric study requirements for premenarcheal females from birth to 11 years and all males were waived. The study requirements for adolescents age 12-17 are fulfilled by the adolescent study report included in the NDA submission. No new safety signals for the adolescent population were identified in this study. As discussed in section 8.2.9 above, additional bone mineral density data for adolescents will be obtained via a Postmarketing Requirement.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Labeling is complete and acceptable.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
Highlights	The Applicant proposed labeling that included BMI information in the indication	Approved labeling only includes prevention of pregnancy in the indication
Highlights; Contraindications	Pregnancy was included as a contraindication.	Pregnancy has been removed as a contraindication.
Highlights; Contraindications; Warnings & Precautions	Labeling regarding contraindications and warnings /precautions about hyperkalemia are similar to combination products containing DRSP	These are acceptable.
Warnings & Precautions		Instructions regarding thromboembolic event
Warnings & Precautions		Bone Loss (decreased estradiol; unknown if loss of BMD occurs)
Warnings & Precautions		Instructions regarding depression
Clinical Studies (see efficacy section of this review)	Applicant proposed lower number of on-treatment pregnancies and lower Pearl Index	The Agency found additional on-treatment pregnancies and adjusted Pearl Index accordingly for non-breastfeeding subjects

12. Risk Evaluation and Mitigation Strategies

Not applicable for this application.

13. Postmarketing Requirements and Commitment

An analysis of spontaneous postmarketing adverse events will not be sufficient to assess the signal of loss of bone given the anti-estrogenic effects of drospirenone. Therefore, a prospective long-term trial to assess bone mineral density in adults and adolescents is required to determine whether clinically significant bone loss occurs with long-term use. The Applicant in response has proposed the following schedule:

- Final Protocol Submission: 01/2020
- Trial Completion: 02/2023
- Final Report Submission: 04/2023

These milestones were reviewed and found acceptable to the Agency

14. Appendices

14.1. References

Not Applicable

14.2. Financial Disclosure

The Applicant submitted Form FDA 3454 and certified that they have acted with due diligence to obtain the required financial information from all the clinical investigators who participated in the LF111 development program.

The Applicant did not receive financial disclosure information from several phase 1 investigators in Studies 101A, 101B, 102, 103A, 105 and 106. One investigator who participated in three trials (101A, 101B, and 102) died.

All other principal investigators who participated in clinical investigations had no financial information to disclose.

Covered Clinical Study: Study CF111/303

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 41 Principal Investigators		
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)): There were no investigators with disclosable interests. Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: None Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator: None Sponsor of covered study: Exeltis USA, Inc.		
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)

- After review, the clinical reviewer determined that the financial disclosure forms were acceptable.

14.3. Nonclinical Pharmacology/Toxicology

The Applicant did not conduct any new nonclinical carcinogenicity studies with LF111. The Agency referred to the DRSP component in the current Yaz® approved drug product labeling.

14.4. Office of Clinical Pharmacology Appendices

Refer to the clinical pharmacology review in DARRTS.

14.5. Additional Appendices

14.5.1. Appendix 1

APPEARS THIS WAY ON ORIGINAL

Table 39. Schedule of Study Procedures: Study CF111/303

Study Visit	V1a (Screening)	V1b (Medication Dispensation)	V2	V3	V4	V5	V6/EDV	V7 (Follow-Up)
Medication cycle			1	3	6	9	13	10 to 14 Days After V6
			Day 20±2 of Medication Cycle				Day 29 +2	
Informed consent	X							
Medical and gyn. history	X							
Prior medication/ contraceptive devices	X							
Concomitant medication/ contraceptive devices	X		X	X	X	X	X	
Wish of pregnancy[4]	X	X	X	X	X	X	X	
Physical examination	X				X		X	
Vital signs (BP, pulse), weight, height	X	X	X	X	X	X	X	
Gyn. examination	X				X		X	
Transvaginal ultrasound	X						X	
Pap smear if >21 years of age	X						X	
Routine laboratory[1]	X		X[5]	X[6]	X	X[6]	X	
PK analysis			X		X			
Urinalysis	X				X		X	
Serum pregnancy test	X							
Urine pregnancy test[2]		X	X	X	X	X	X	X
Dispensing of LF111		X	X	X	X	X		
Drug accountability			X	X	X	X	X	
Drug acceptability			X				X	
Dispense/collect e-diary		X					X	
Review e-diary			X	X	X	X	X	
Adverse events[3]	X	X	X	X	X	X	X	X

V = visit; EDV = early discontinuation visit; PK = pharmacokinetic; BP = blood pressure
[1] Hematology and biochemistry (sodium, potassium, chloride, creatinine BUN, calcium, glucose, total proteins, a bumin, lipids, gamma glutamyl transferase, total and direct bilirubin, ALP, ALAT, ASAT, CPK, LDH)
[2] Each subject performed a urine dipstick pregnancy test at home at the beginning of each new medication cycle. If positive or equivocal, a quantitative serum test was performed.
[3] On day 10 of each cycle, subjects were called by staff to collect information on adverse events and confirm e-diary compliance.
[4] Subject was asked if she had a wish of pregnancy at each visit. In cases of a positive answer, the subject was discontinued.
[5] Serum potassium was only evaluated for subjects who took medications that may increase serum potassium (angiotensin-converting-enzyme inh bitors, angiotensin–II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, and aldosterone antagonists).
[6] Only electrolytes
Source: Clinical Trial Report CF111/303 page 53 of 1623

14.5.2. Appendix 2

Table 40. Serious Adverse Events (Individual Subjects in Studies 205, 301, 302, and 303)

Study Center/ Subject #	Age (Yrs)/ Race	First Dose–Last Dose	Preferred Term	SAE Start (Day)–Stop (Day)	TEAE?	Severity/ Drug Related (Per MO)	Action Taken
Study CF111-205							
522/(b) (6)	36/Cauc.	(b) (6)	Pyelonephritis, Renal colic. and ureteral stone	(b) (6) 214)–(305)	Yes	Moderate/ Not related	Dose Not Changed
522/	36/Cauc.		Uterine myoma	(b) (6) (375)–Ongoing	Yes	Moderate/ Possibly related	N/A

Study Center/ Subject #	Age (Yrs)/ Race	First Dose– Last Dose	Preferred Term	SAE Start (Day)– Stop (Day)	TEAE?	Severity/ Drug Related (Per MO)	Action Taken
Study CF111-301							
101 (b) (6)	24/Cauc.	(b) (6)	Pyelonephritis	(b) (6) 201)– (215)	Yes	Moderate/ Not related	None
102	32/Cauc.		Replacement of breast implants	196)– (199)	Yes	Severe/ Not related	None
102	25/Cauc.		Pneumothorax, spontaneous	(b) (6) (77)– (87)	Yes	Severe/ Not related	Drug Interrupt.
102	31/Cauc		Joint injury	339)– (341)	Yes	Moderate/ Not related	None
102	33/ Cauc.		Breast implants	(b) (6) (108)– (109)	Yes	Severe/ Not related	None
212	26/ Cauc.		Abd. pain, unexplained	(124)– (125)	Yes	Severe/ Not related	None
212	20/ Cauc.		Lumbar facet syndrome	(313)– (315)	Yes	Severe/ Not related	None
302	33/ Cauc.		Inflammation of tube and ovary	(294)– (313)	Yes	Severe/ Unlikely related	Drug Withdrawn
407	30/ Cauc.		Cholelithiasis	(241)– (246)	Yes	Severe/ Possibly related	None
408	42/ Cauc.		Lower limb fracture	(334)– (363)	Yes	Severe/ Not related	None
Study CF111–302							
252/ (b) (6)	19/ Cauc.		**Hyperkalemia**	256)– (263)	Yes	Moderate/ Likely related	N/A
252/	36/ Cauc.		Concussion	(b) (6) (76)– (78)	Yes	Moderate/ Not related	None
252/	20/ Cauc.		Appendicitis	(62)– (68)	Yes	Moderate/ Not related	None
256/	27/ Cauc.		Abortion spontaneous	339)– (339)	No	Severe/ Not Related	N/A
256/	21/ Cauc.		Elective abortion	316)– (316)	No	Moderate/ Not related	N/A
257/	20/ Cauc.		Appendicitis	(b) (6) (57)– (59)	Yes	Moderate/ Not related	None
351/	28/ Cauc.		Liver adenoma	85)– Ongoing	Yes	Mild/ Possibly related	None
360/	23/ Cauc		Premature delivery	(b) (6) 354)– (354)	No	Severe/ Unlikely related	N/A
360/	29/ Cauc.		Hypersensitivity	(263)– (264)	No	Moderate/ Not related	None
362/	21/ Cauc.		Tension headache	(b) (6) (46)– (47)	Yes	Severe/ Possibly related	None
355/	22/ Cauc.		Elective abortion	(b) (6) 182)– (182)	No	Moderate/ Not related	None
371/	42/ Cauc.		Nephrolithiasis	(b) (6) 246)– 247)	Yes	Severe/ Not related	None
454/	36/ Cauc.		Increased potassium level	164)– (185)	Yes	Mild/ Possibly related	None
565/	35/ Cauc.		Painful appendectomy incision	(b) (6) 48)– (63)	Yes	Mild/ Not related	None

Study Center/ Subject #	Age (Yrs)/ Race	First Dose– Last Dose	Preferred Term	SAE Start (Day)– Stop (Day)	TEAE?	Severity/ Drug Related (Per MO)	Action Taken
751 (b) (6)	26/ Cauc.	(b) (6)	Elective abortion	(b) (6) 105)– (105)	No	Moderate/ Related	None
759	28/ Cauc.		Appendicitis	246)– (247)	Yes	Severe/ Not related	Drug Interrupt.
759	28/ Cauc.		Breast fibroadenoma	(b) (6) 238)– Ongoing	Yes	Moderate/ Not related	N/A
759	40/ Cauc.		Breast fibroadenoma	(b) (6) (243)– Ongoing	Yes	Moderate/ Not related	N/A
852	20/ Cauc.		Wrist fracture	(b) (6) (9)– (60)	Yes	Moderate/ Not related	None
859	23/ Cauc.		Cervical dysplasia (HSIL/CIN1)	(b) (6))– (b) (6) (276)	Yes	Moderate/ Not related	N/A
859	24/ Cauc.		Cervical dysplasia (ASCUS)	(b) (6) (257)– Ongoing	Yes	Severe/ Not related	N/A
CF111–303							
101/ (b) (6)	38/ Cauc.	(b) (6)	Cholecystitis	(b) (6) (373) (378)	Yes	Severe/ Not related	N/A
103/	29/ Cauc.		Illicit drug reaction	135)– (136)	Yes	Severe/ Not related	Dose not changed
103/	26/ Cauc.		Brain aneurysm	20)– 220)	Yes	Moderate/ Unlikely related	Drug withdrawn
108/	31/ Cauc.		Appendicitis	(2)– (4)	Yes	Severe/ Not related	Dose not changed
116/	35/ Cauc.		Ectopic pregnancy	(b) (6) 63)– (109)	Yes	Severe/ Not related	Drug withdrawn
116/	28/ AA		Intractable vomiting	35)– (37)	Yes	Severe/ Possibly related	Dose not changed
116/	28/ AA		Stomach pain	35)– (37)	Yes	Severe/ Not related	Dose not changed
118/	24/ Cauc.		Medication overdose	(96)– (100)	Yes	Moderate/ Not related	Drug withdrawn
119/	27/ Cauc.		Biliary colic Cholelithiasis	346)– (350)	Yes	Severe/ Not related	Drug interrupt.
122/	20/Cauc.		Facial cellulitis	(b) (6) 244)– (260)	Yes	Mild/ Not related	Dose not changed
124/	27/ Cauc.		**Hyperkalemia**	(249)– (283)	Yes	Mild/ Probably related	Drug withdrawn
124/	25/ Other		Multiple trauma due to MVA	(b) (6) 213)– (233)	Yes	Severe/ Not related	Drug withdrawn
125/	29/ Cauc.		**Hyperkalemia**	(188)– (205)	No	Moderate/ Not related	N/A
125/	29/ Cauc.		**Pyelonephritis**	(b) (6) (-5)– (-1)	No	Severe/Not related	N/A
130/	26/ Cauc.		Spontaneous abortion	(b) (6) 108)– (120)	Yes	Moderate/ Unlikely related	N/A
130/	33/ AA		**Hyperkalemia**	(b) (6) 48)– 282)	Yes	Mild/ Related	N/A
130/	29/ Cauc.		**Hyperkalemia**	(81)– (136)	Yes	Mild/ Related	Drug withdrawn

Study Center/ Subject #	Age (Yrs)/ Race	First Dose– Last Dose	Preferred Term	SAE Start (Day)– Stop (Day)	TEAE?	Severity/ Drug Related (Per MO)	Action Taken
130/ (b) (6)	22/ Other (NAm)	(b) (6)	Hyperkalemia	(b) (6) (21)–(28)	Yes	Mild/ Related	N/A
136/	28/ Cauc.		IUGR	342)–(348)	No	Mild/ Not related	N/A

MO = Medical Officer; NAm = Native American; AA = African American; Cauc. = Caucasian; IUGR = intrauterine growth restriction; SAE = serious adverse event; TEAE = treatment-emergent adverse event; MVA = motor vehicle accident; HSIL = high grade squamous intraepithelial lesion; ASCUS = atypical squamous cells of undetermined significance
Relationship to study drug: Related = possible or probable; Not related = unlikely or non-existent
Source: Adapted from ISS, Page 2272 of 2518, Table 14.3.2.2

14.5.3. Appendix 3

Table 41. Summary of Serum Potassium Phase 3 Pivotal Studies in Adults

SID	Study Day/ Visit	Result mmol/L	IE	Specimen Condition Comment	Additional Comment(s) *(Includes concomitant meds, noteworthy symptoms, or ECG)*
Study CF111/301					
(b) (6)	163/V4	5.4	Yes	Normal	Day 249 = 34.4; No symptoms; Completed study
	363/V6	6.0	Yes	Normal	Day 367 = 4.4; No symptoms; Completed study
	250/V5	5.4	Yes	Normal	Day 365 = 5.1; No symptoms; Completed study
	-27/Scr	5.4	Yes	Normal	Subsequently normal range on treatment; Completed study
	171/V4	5.4	Yes	Normal	Day 247 = 4.5; Subsequently normal range on treatment; Completed study
	-42/Scr	5.6	Yes	Normal	Subsequently normal range on treatment; Completed study
	85/V3 163/V4	5.4 5.6	No	Normal	Day 270 = normal range; Day 373 = normal range; Completed study
	169/V4 256/V5	5.8 5.5	No	Normal	Day 368 = 4.4; No symptoms; Completed study
	168/V4 255/V5	6.0 5.6	No	Normal	Day 367 = 4.6; No symptoms; Completed study
	78/V3	5.5	-	Normal	No subsequent lab; WD
	360/V6	5.5	-	Normal	No subsequent lab; Completed study
	80/V3	5.4	Yes	Normal	Day 164 = 5.1; Subsequently normal range on treatment; Completed study
Study CF111/302					
(b) (6)	256/V5	5.7	Yes	Normal	Day 263 = 4.0; ECG = normal; Reported as SAE; Completed study
	257/V5	5.6	Yes	Normal	Day 265/V5 = 4.0; ECG = normal; Completed study
	-30/Scr	5.4	Yes	Normal	Day 48 = 4.5
	83/V3	5.7	Yes	Normal	Day 88 = 3.7
	-12/Scr -8/Scr	7.5 4.2	Yes	Normal	Day 80 = 4.3; ECG = normal; LFU
	163/V4	5.5	Yes	Normal	Day 171 = 4.7; ECG = normal; Completed study
	253/V5	5.4	Yes	Normal	No recorded symptoms; No follow-up; Completed study

SID	Study Day/ Visit	Result mmol/L	IE	Specimen Condition Comment	Additional Comment(s) *(Includes concomitant meds, noteworthy symptoms, or ECG)*
(b) (6)	257/V5	5.5	Yes	Normal	No recorded symptoms; ECG = normal; No follow-up; Completed study
	-29/Scr	5.4	Yes	Normal	Subsequently normal range on treatment Day 78 = 5.3; Day 161 = 4.0; Day 254 = 5.3; Completed study
	-53/Scr	5.9	Yes	Normal	Day -39 = 4.2; Subsequently normal range on treatment; Completed study
	-53/Scr	5.6	Yes	Normal	Day -32 = 5.0; WD
	164/V4 171/V4	5.9 5.8	No	Normal	Day 253 = 5.0; No recorded symptoms; Reported as SAE; Completed study
	-22/Scr	5.7	Yes	Normal	Day -14 = 4.1; Subsequently normal range on treatment; Completed study
(Desogest.)	165/V4	8.1	Yes	Normal	Day 256 = 3.7; No recorded symptoms; Completed study
(b) (6)	-12/Scr -6/Scr	7.3 5.6	No	Normal	Day 79 = 4.0; Subsequently normal range on treatment
	-8/Scr	6.1	Yes	Normal	Day -2 = 4.4; Subsequently normal range on treatment; Completed study
(Desogest.)	253/V5	6.6	Yes	Normal	Day 260 = 4.3; No recorded symptoms; Completed study
(b) (6) (Desogest.)	261/V5	5.4	Yes	Normal	No recorded symptoms; No follow-up; Completed study
(b) (6)	79/V3	8.6	Yes	Normal	Day 129 = 4.1; No recorded symptoms
(Desogest.)	-28/Scr	5.6	Yes	Normal	Day -22 = 3.9; Subsequently normal range on treatment; Completed study
(b) (6)	-36/Scr	5.5	Yes	Normal	Day 96 = 4.7; Subsequently normal range on treatment; Completed study
(Desogest.)	-36	5.9	Yes	Normal	Subsequently normal range on treatment; Completed study
(b) (6) (Desogest.)	165/V4	6.1	Yes	Normal	Subsequently normal range on treatment; Completed study
(b) (6)	177/V4	6.4	Yes	Normal	No follow-up; No recorded symptoms; WD
	253/V5	5.9	Yes	Normal	Day 281 = 3.4; No recorded symptoms; Completed study
(Desogest.)	81/V3	5.5	Yes	Normal	Subsequently normal range on treatment; Completed study
(b) (6)	258/V5	5.4	Yes	Normal	No follow-up; Completed study; No recorded symptoms
	92/V3	6.3	Yes	Normal	Day 98 = 4.0; No recorded symptoms; WD
	93/V3	6.7	Yes	Normal	Day 99 = 4.0; Subsequently normal range on treatment; Completed study
(Desogest.)	92/V3	5.6	Yes	Normal	Day 101 = 4.4; Subsequently normal range on treatment; Completed study
(b) (6)	88/V3	6.1	Yes	Normal	Day 97 = 4.3; Subsequently normal range on treatment; Completed study
(Desogest.)	-8/Scr	5.5	Yes	Normal	Day 96 = 5.0; Migraine headaches; WD
(b) (6)	82/V3	5.9	Yes	Normal	Day 164 = 4.0; Subsequently normal range on treatment; Completed study
	38/EDV	5.4	Yes	Not stated	No follow-up; Took prohibitive med Lamotrigine; Excluded from study

SID	Study Day/ Visit	Result mmol/L	IE	Specimen Condition Comment	Additional Comment(s) *(Includes concomitant meds, noteworthy symptoms, or ECG)*
(b) (6)	-26/Scr	5.5	No	Not stated	Day 81 = 5.5; WD; No follow-up
Study CF111/303					
(b) (6)	78/V3	5.4	Yes	Not stated	Day 162 = 4.5; Subsequently normal values on treatment; Completed study
	-32/Scr	5.4	Yes	Not stated	Day -20 = 4.8; Subsequently normal value on Day 74; LFU
	-19/Scr	5.4	Yes	Not stated	Day -5 = 5.1; Subsequently normal values; LFU
	-16/Scr	5.6	Yes	Not stated	LFU, No further testing
	-30/Scr	5.5	Yes	Not stated	Day 87 = 4.4; Subsequently normal values; Completed study
	21/V2	5.5	Yes	Not stated	No further testing; pregnant
	364/V6	5.4	Yes	Not stated	Day 385 = 4.6; Completed study
	158/V4	5.4	Yes	Not stated	Day 166 = 4.6; Subsequent normal value on Day 246 = 3.8; LFU
	-57/Scr	5.5	Yes	Not stated	Day -26 = 4.8; Subsequently normal values on treatment
	368/V6	5.7	Yes	Not stated	Day 382 = 4.5; Completed study
	354/V6	5.7	Yes	Not stated	Completed study but no follow-up
	-23/Scr	5.5	Yes	Not stated	Day -20 = 5.1; LFU
	171/V4	5.9	Yes	Not stated	Day 178 = 4.8; Subsequently normal values on treatment; Completed study
	22/V2	5.4	Yes	Not stated	Day 29 = 4.7; Subsequently normal values on treatment; LFU
	245/V5	5.5	Yes	Not stated	Day 259 = 4.7; Subsequent normal value on treatment; Completed study
	-19/Scr	5.4	No	Not stated	Day 76 = 5.4; Day 80 = 5.1; Day 169 = 5.1; LFU
	-28/Scr	5.5	Yes	Not stated	Day -22 = 5.1; Subsequent values in normal range; Completed study
	-37/Scr	5.8	Yes	Not stated	Day -26 = 4.7; WD
	246/V5	5.8	Yes	Not stated	Day 249 = 4.8; Subsequent values in normal range; Completed study
	74/V3	5.4	Yes	Not stated	Day 87 = 5.1; Subsequently normal values; Completed study
	-47/Scr	6.2	Yes	Not stated	Day -41 = 4.9; Subsequent values normal; LFU
	277/V6	5.5	Yes	Not stated	Day 284 = 4.5; Non-compliant
	-43/Scr	5.4	Yes	Not stated	Day-32 = 4.5; Subsequent values normal; Completed study
	-19/Scr	5.8	Yes	Not stated	Day 77 = 5.2; LFU
	246/V5	5.4	Yes	Not stated	Day 251 = 5.2; Subsequent values normal; Completed study
	-20/Scr	5.8	Yes	Not stated	Day -15 = 4.0; Subsequent values normal; Completed study
	77/V3	5.6	Yes	Not stated	Day 96 = 3.7; Subsequent values normal; Completed study
	19/V2	5.6	No	Not stated	Day 160 = 5.4; Day 249 = 5.5; Day 265 = 5.5; Early termination; Medication withdrawn; Day 283 = 5.1; Reported as SAE

SID	Study Day/ Visit	Result mmol/L	IE	Specimen Condition Comment	Additional Comment(s) *(Includes concomitant meds, noteworthy symptoms, or ECG)*
(b) (6)	19/V2	5.4	Yes	Not stated	Day 27 = 4.3; Subsequent values normal; WD
	-39/Scr	5.9	Yes	Not stated	Day -32 = 4.7; Subsequent values normal; Completed study
	22/V2	5.7	No	Not stated	Day 75 = 5.5; Day 159 = 5.0; Subsequent values normal; Completed study
	188/V6	5.4	No	Not stated	Day 202 = 5.6; Day 205 = 4.6; Non-compliance; Reported as an SAE
	-42/Scr	5.4	No	Not stated	Day 77 = 5.5; Day 169 = 5.0; WD
	247/V5	5.5	No	Not stated	Day 290 = 5.4; Day 303 = 5.4; Reported as an SAE; WD
	81/V3	5.6	No	Not stated	Day 88 = 5.8; Day 115 = 5.9; Day 122 = 5.8; Drug withdrawn; Day 136 = 4.9; Reported as an SAE
	21/V6	5.7	Yes	Not stated	Day 28 = 4.8; WD due to non-compliance; Reported as an SAE
	76/V3	5.5	Yes	Not stated	Day 81 = 4.9; Subsequent values normal; Completed study
	-40/Scr	5.4	Yes	Not stated	Day -33 = 3.9; LFU
	-92/Scr	6.0	Yes	Not stated	Day -69 = 5.2; LFU
	-41/Scr	5.6	No	Not stated	Day -34 = 4.6; Day 76 = 5.4; Day 84 = 4.3; Day 160 = 4.9; Day 245 = 5.7; Day 247 = 5.0; Day 365 = 4.3; Completed study
	-149/Scr	5.7	Yes	Not stated	Day -59 = 4.4; Day 60 = 4.5; WD due to noncompliance

SID = subject identification number; V = visit; EDV = early discontinuation visit; IE = isolated serum potassium elevation; Scr = screening visit; desogest. = desogestrel 0.075 mg; LFU = lost to follow-up; WD = withdrew from study; SAE = serious adverse event; ECG = electrocardiogram; IE = isolated elevation of potassium
Normal potassium values =3.5 to 5.3 mmol/L
Source: Medical Reviewer

14.5.4. Appendix 4: TEAEs, Sites 104 and 120

TEAEs leading to withdrawal

- Subject Number (b) (6) Subject withdrew due to acne
- Subject Number Menorrhagia and vulvovaginal pruritis. The subject withdrew from the study due to menorrhagia.
- Subject Number (b) (6): Dysmenorrhea, breast tenderness, dizziness. The subject withdrew from the study due to worsening dysmenorrhea.

Other TEAEs, Sites 104 and 120

- Subject Number (b) (6): Weight gain, amenorrhea and acne
- Subject Number : Oral infection
- Subject Number : Pyrexia, infection, metrorrhagia
- Subject Number : Menorrhagia
- Subject Number : Vaginitis, vaginosis

- Subject Number (b) (6): Vaginosis, urinary infection, folliculitis
- Subject Number : Breast enlargement
- Subject Number : Thermal burn, increased blood cholesterol and triglycerides
- Subject Number : Anemia
- Subject Number : Hyperhidrosis, urticaria, ecchymosis, bacterial vaginosis
- Subject Number : Chest pain, cough, dyspareunia
- Subject Number : Acne
- Subject Number : Rash, folliculitis, breast atrophy
- Subject Number : Cervical dysplasia
- Subject Number : Bacterial vaginosis
- Subject Number : Loss of consciousness, hematuria
- Subject Number : Depression
- Subject Number : Ligament sprain, melanocytic nevus, bacterial vaginosis, urinary tract infection
- Subject Number (b) (6): Wisdom teeth removal, vaginal yeast infection

Other Non-TEAEs, Sites 104 and 120

<u>All of the following non-TEAEs were non-serious</u>

- Subject Number (b) (6) Cervical dysplasia at screening
- Subject Number Cervical dysplasia at screening
- Subject Number Cervical dysplasia 3 weeks post early discontinuation
- Subject Number Amenorrhea prior to initiating treatment
- Subject Number Bacterial vaginosis after the screening visit prior to treatment
- Subject Number Eczema post treatment

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/

RONALD J ORLEANS
05/23/2019 03:02:41 PM

GERALD D WILLETT
05/23/2019 03:07:57 PM

AUDREY L GASSMAN
05/23/2019 03:08:36 PM