CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216285Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 216285	Submission Date(s): 08/30/2021
Proposed Brand Name	
Generic Name	Drospirenone (DRSP) 3.5 mg
Clinical Pharmacology Reviewer	Mohammad (Ahsan) Akbar, PhD
Clinical Pharmacology Secondary Reviewer	Yanhui Lu, PhD
OCP Division	Division of Cardiometabolic and Endocrine Pharmacology (DCEP)
OND Division	Division of Urology, Obstetrics and Gynecology (DUOG)
Sponsor	Exeltis USA, Inc.
Submission Type	Original-1
Formulation; Strength(s)	Chewable tablet, 3.5 mg
Indication	Prevention of pregnancy

1. EXECUTIVE SUMMARY

Drospirenone (DRSP) is a fourth-generation progestin derived from spironolactone. In May 2019, Slynd® (NDA 211367), containing 4 mg DRSP, was approved in the United States for the use by females of reproductive potential to prevent pregnancy via the 505(b)(2) regulatory pathway using YAZ (DRSP 3 mg/ethinyl estradiol 0.02 mg) (NDA 021676) as a listed drug. The Applicant owns Slynd®. The Applicant has developed DRSP 3.5 mg chewable tablets . This new dosage form of DRSP offers an alternative form to oral contraceptive users who may have difficulty or a dislike of swallowing whole tablets. DRSP chewable tablets have the same dosing regimen as Slynd® except that the dose of DRSP differs (3.5 mg for DRSP chewable tablets versus 4 mg for Slynd®). In addition, the administration method of DRSP 3.5 mg chewable tablets differs from that of Slynd®. DRSP 3.5 mg chewable tablets must be chewed completely before swallowing, while Slynd® 4 mg tablets are swallowed whole.

The NDA contains a comparative bioavailability (BA)/bioequivalence (BE) (study 2020-FLE1-SLINC-PK-04 (BLCL-DRS-FDA-04)) comparing the proposed drug and Slynd®, a food effect study (study 2020-FLE1-SLINC-PK-06 (BLCL-DRS-FDA-06)), and an oral irritation study for the proposed product. In the development program, the Applicant also evaluated (b) (4) (b) (4) and assessed the effect of water intake on the systemic exposure of DRSP for the DRSP 4 mg chewable tablets (b) (4) (b) (4). The Applicant conducted these studies to establish a scientific bridge through the demonstration of BE between Slynd® (DRSP) 4 mg tablets and DRSP 3.5 mg chewable tablets to support this NDA. The Applicant submitted this NDA via the 505(b)(2) regulatory pathway. They intended to cross-reference the NDA of Slynd® and rely on FDA's previous findings of safety and efficacy of the DRSP component of YAZ (DRSP 3 mg/ethinyl estradiol 0.02 mg) (NDA 021676).

1.1. RECOMMENDATIONS

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

1.2. SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

The key clinical pharmacology review assessments are summarized in Table 1.

Table 1: The key clinical pharmacology review issue and assessments

Review issue	Key assessments
Pharmacokinetics (PK) bioavailability (BA)/bioequivalence (BE)	The Applicant conducted a comparative BA/BE study (study 2020-FLE1-SLINC-PK-04 (BLCL-DRS-FDA-04)) in healthy adult female subjects to assess BE between the proposed product (DRSP 3.5 mg chewable tablets) and reference product (Slynd® 4

	mg tablets) under fasting condition. The proposed product was chewed and swallowed without water while the reference product was chewed and swallowed with water. The Applicant demonstrated that the proposed product (Test-2) was bioequivalent (BE) to the reference product. The Test-2-to-reference geometric mean ratios (GMRs) and corresponding 90% confidence interval (CI) for C_{max} (113.81% (90% CI: 107.07% – 120.97%)) and AUC_{0-72} (92.18% (90% CI: 89.27 – 95.18)) of DRSP were all within the acceptance BE range of 80 to 125%.
Food effect assessment	The Applicant conducted a single-dose, open-label, randomized, two-sequence, two-treatment, two-period crossover study (Study 2020-FLE1-SLINC-PK-06 (BLCL-DRS-FDA-06)) to assess the effect of food on the BA of DRSP 3.5 mg chewable tablets in healthy adult female subjects. Ingestion of a high-fat high-caloric meal 30 minutes before the administration of DRSP 3.5 mg chewable tablets reduced the absorption (C_{max}) rate of DRSP (GMR (90% CI): 90.54% (77.64% – 105.59%)) but showed no significant effect on the extent of absorption (AUC_{0-72}) (GMR(90% CI): 107.0% (103.46% – 110.67%)). DRSP T_{max} was significantly delayed (median delay = 2.25 h; 90% CI: 1.50 – 3.25 h) in Test (fed) treatment, as compared with Reference (fasting) treatment. The effect of food on the PK of DRSP is not considered clinically meaningful.

2. QUESTION BASED REVIEW

2.1. GENERAL ATTRIBUTES

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of DRSP 3.5 mg chewable tablets formulation?

The Applicant, Exeltis USA, Inc., submitted this 505(b)(2) application for DRSP 3.5 mg chewable tablets. The main objective of this 505(b)(2) NDA is to provide results from study 2020-FLE1-SLINC-PK-04 (BLCL-DRS-FDA-04), study 2020-FLE1-SLINC-PK-06 (BLCL-DRS-FDA-06), (b) (4) (b) (4) to assess the (b) (4) food and water intake effects on DRSP 3.5 mg chewable tablets. Study 2020-FLE1-SLINC-PK-04 (BLCL-DRS-FDA-04) was a single-dose, open-label, randomized, six-sequence, three-treatment, three-period crossover study in healthy (n = 48 with age ≥18 and ≤ 40 years) female subjects under

fasting condition. The food effect study was a single-dose, open-label, randomized, two-sequence, two-treatment, two-period crossover study (Study 2020-FLE1-SLINC-PK-06 (BLCL-DRS-FDA-06)) to assess the effect of high-fat-high-calorie food on the BA of DRSP 3.5 mg chewable tablets in healthy female subjects (n = 22 with age range: 18-39 years). In all studies, the to-be-marketed formulation of DRSP 3.5 mg chewable tablets were used as the test product. The Applicant also [redacted] assessed the effect of water intake on the systemic exposure of DRSP for the DRSP 4 mg chewable tablets [redacted].

2.2. GENERAL CLINICAL PHARMACOLOGY

2.2.1 Is the drospirenone 3.5 mg chewable tablets formulation appropriately bridged to the Slynd® 4 mg tablets according to the pivotal clinical pharmacology study 2020-FLE1-SLINC-PK-04 (BLCL-DRS-FDA-04) data?

Results from study 2020-FLE1-SLINC-PK-04 support an adequate bridge between the DRSP 3.5 mg chewable tablets and Slynd® 4 mg tablets. Results demonstrated that a single dose of the test product has similar exposure to the reference product in healthy adult female subjects under fasting condition.

In the study, subjects were randomized to the following treatments:

- **Test product 1 (Test-1):** DRSP 4 mg chewable tablets chewed and swallowed without water (a product that the Applicant is not seeking for approval)
- **Test product 2 (Test-2):** DRSP 3.5 mg chewable tablets chewed and swallowed without water (the proposed product of this NDA)
- **Reference:** Slynd® (DRSP 4 mg) tablets swallowed whole with water

DRSP plasma concentration versus time profiles following administration of Test-1, Test-2, and Reference products are displayed in Figure 1 and pharmacokinetic (PK) parameters are shown in Table 1.

Figure 1: Mean (arithmetic) DRSP plasma concentration versus time profile following administration of Test-1, Test-2, and Reference products in linear scale

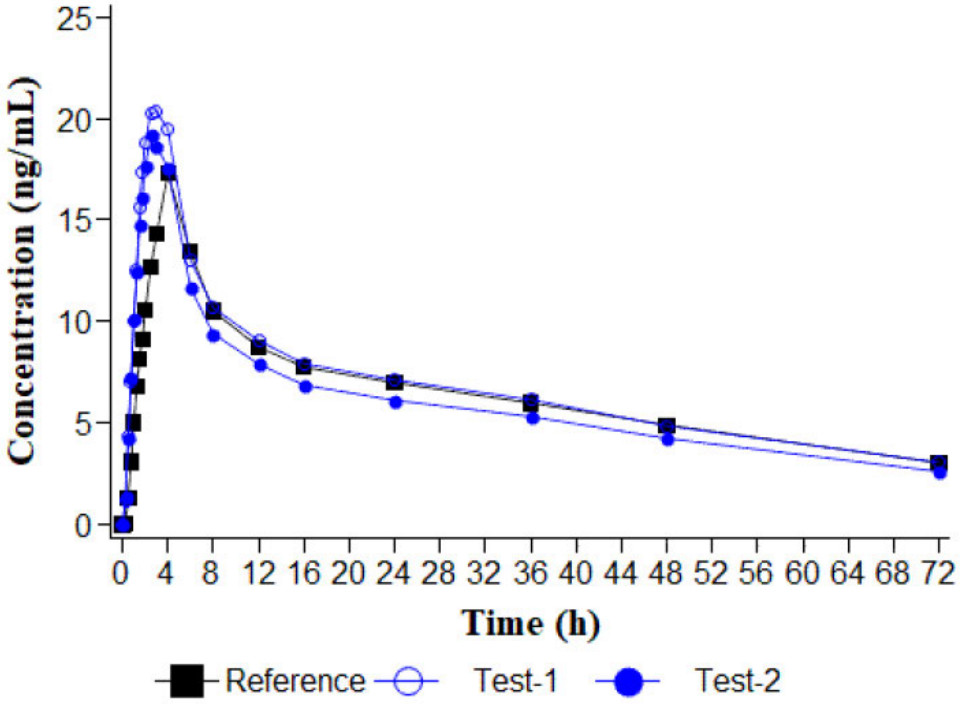

Table 1: Means (arithmetic) and coefficients of variation (CV%) of DRSP PK parameters following administration of Test-1, Test-2, and Reference products

Parameter (unit)	Test-1 (n = 39)	Test-2 (n = 37)	Reference (n = 39)
C_{max} (ng/mL)	22.94 (28.7%)	21.07 (24.7%)	18.53 (26.6%)
T_{max} (h)	2.50 (1.25 - 6.02)	2.50 (1.00 - 4.00)	4.00 (2.00 - 8.00)
AUC_{0-72} (ng.h/mL)	487.03 (21.1%)	424.86 (22.0%)	458.83 (18.5%)
λ_z (1/h)	0.020 (31.7%)	0.020 (32.4%)	0.020 (32.3%)
$t_{1/2}$ (h)	38.80 (35.5%)	37.93 (31.9%)	39.13 (34.1%)

n - Number of Subjects
T_{max} values are median with range between parenthesis

The Applicant reported that Test-2 (i.e., DRSP 3.5 mg chewable tablets) was BE to Reference. The PK results showed that the Test-2-to-Reference GMRs and corresponding 90% CIs for C_{max} and AUC_{0-72} of DRSP were all within the acceptable BE range of 80 to 125% (Table 2). These findings were reanalyzed and confirmed by the clinical pharmacology reviewer.

Table 2: Total intrasubject coefficient of variation (ISCV), Least Square Means (LSM), Test-2/Reference geometric means ratio (GMR) and 90% confidence intervals for C_{max} and AUC_{0-72}

Geometric LSmeans					
Parameter	**Total ISCV%**	**Test-2**	**Reference**	**Test-2-to-Reference GMR (%)**	**90% CI**
C_{max}	15.6	20.58	18.08	113.81	107.07 - 120.97
AUC_{0-72}	8.2	418.31	453.80	92.18	89.27 - 95.18
$AUC_{0-\infty}$	10.0	557.32	623.26	89.42	85.97 - 93.01

LSmeans values are given in ng/mL for C_{max} and ng.h/mL for AUC
Total ISCV% - Total Intrasubject Coefficient of Variation
Reference – Slynd 4 mg tablet
Test 2 – drospirenone 3.5 mg chewable tablet

However, Test-1 (i.e., DRSP 4 mg chewable tablets) was not BE to Reference. The PK results showed that C_{max} of DRSP from Test 1 was approximately 24% higher and the upper limit of the corresponding 90% CI is above the upper limit of the no effect range of 125.00%. For AUC_{0-72}, the corresponding 90% CI is within the acceptance interval of 80.00 to 125.00% (Table 3).

Table 3: Total intrasubject coefficient of variation (ISCV), Least Square Means (LSM), Test-1/Reference geometric means ratio (GMR) and 90% confidence intervals for C_{max} and AUC_{0-72}

Geometric LSmeans					
Parameter	**Total ISCV%**	**Test-1**	**Reference**	**Test-1-to-Reference GMR (%)**	**90% CI**
C_{max}	20.8	22.35	18.03	123.94	114.49 - 134.17
AUC_{0-72}	10.0	481.81	453.72	106.19	102.18 - 110.35
$AUC_{0-\infty}$	12.3	650.46	622.12	104.55	99.71 - 109.63

LSmeans values are given in ng/mL for C_{max} and ng.h/mL for AUC
Total ISCV% - Total Intrasubject Coefficient of Variation
Reference – Slynd 4 mg tablet
Test 1 – drospirenone 4 mg chewable tablet

A total of 48 subjects were enrolled into the study. Out of 48 subjects, a total of 10 subjects (subject ID (b) (6) were excluded from the BE assessment between Test-2 and Reference, as these patients did not complete either Test-2 period or reference period. The Applicant reported the protocol violation in the attachment 1 of the statistical analysis report, and all protocol deviations were classified as "Not Important", i.e., it was considered that they did not have a relevant impact on the PK analysis. Therefore, no subject was excluded from the PK analysis population because of a protocol violation.

The Applicant reported that the Test-2 product was well-tolerated. For safety evaluations, refer to clinical review.

In the study, all the samples were analyzed with a validated bioanalytical method (see section 2.3. analytical section) with acceptable accuracy and precision.

Considering the above findings, the proposed drug DRSP 3.5 mg chewable tablets and the reference listed drug, Slynd® 4 mg tablets, are considered bioequivalent and thus the

Applicant has established an adequate scientific bridge for reliance on the Agency's previous findings of safety and efficacy for Slynd®.

2.2.2 Does food affect the pharmacokinetics of drospirenone 3.5 mg chewable tablets formulation?

The Applicant conducted a single-dose, open-label, randomized, two-sequence, two-treatment, two-period crossover study (Study 2020-FLE1-SLINC-PK-06 (BLCL-DRS-FDA-06)) to assess the effect of food on the BA of DRSP 3.5 mg chewable tablets in healthy female subjects (n = 22 with age range: 18-39 years). The subjects were randomized to the following treatments with a washout period of 14 days:

- **Test:** Drospirenone 3.5 mg chewable tablets were chewed and swallowed without water, in the morning, 30 minutes after the start of a high-fat-high-calorie meal.

- **Reference:** Drospirenone 3.5 mg chewable tablets were chewed and swallowed without water, in the morning, after an overnight fasting of at least 10 hours.

The Applicant reported the mean (arithmetic) DRSP plasma concentration time profiles in linear scale following administration of Test (fed) and Reference (fasting) treatments in Figure 2 and the PK parameters in Table 4 as shown below.

Figure 2: The mean (arithmetic) DRSP plasma concentration time profiles following administration of Test (fed) and Reference (fasting) treatments

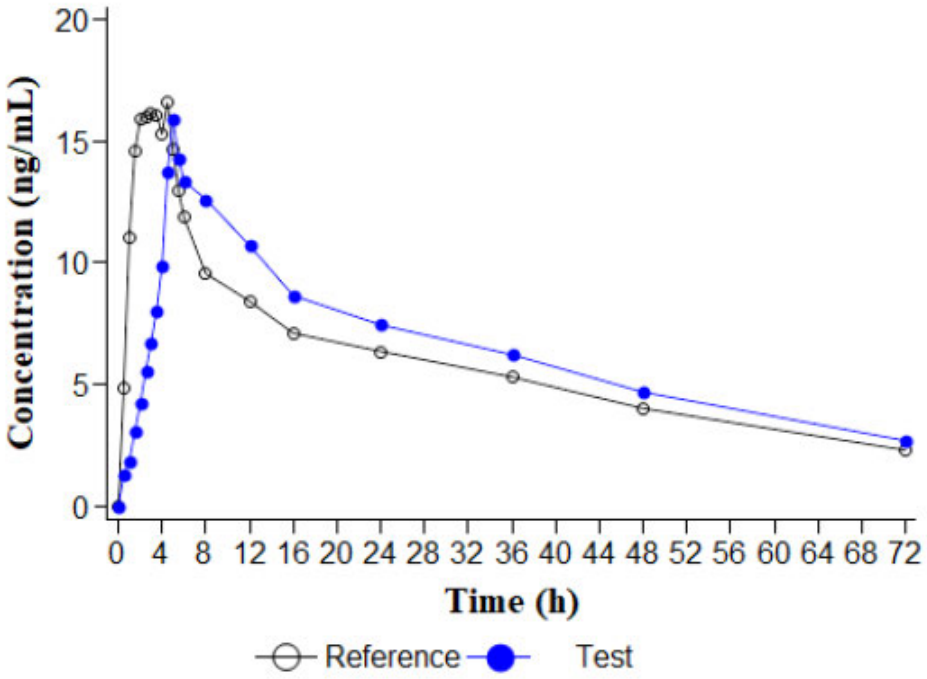

Table 4: The mean (arithmetic) and coefficients of variation (CV%) of DRSP PK parameters following administration of Test and Reference treatments

Parameter (unit)	Test (Fed) (n = 19)	Reference (Fasting) (n = 19)
C_{max} (ng/mL)	17.88 (27.3%)	19.51 (24.0%)
T_{max} (h)	5.00 (3.00 - 16.00)	2.50 (1.00 - 5.52)
t_{lag} (h)	0.00 (0.00 - 1.00)	0.00 (0.00 - 0.00)
AUC_{0-72} (ng.h/mL)	454.48 (20.0%)	422.05 (20.7%)
$AUC_{0-\infty}$ (ng.h/mL)	593.10 (24.2%)	532.19 (23.8%)
λ_z (1/h)	0.023 (31.3%)	0.023 (23.4%)
$t_{1/2}$ (h)	32.89 (36.1%)	31.39 (27.0%)
Cl/F (L/h)	6.24 (24.3%)	6.95 (24.2%)
Vd/F (L)	282.90 (28.0%)	305.44 (24.5%)

n - Number of Subjects
T_{max} and t_{lag} values are median with range between parenthesis

The results showed that the ingestion of a high-fat high-caloric meal 30 minutes before the administration of DRSP 3.5 mg chewable tablets delayed the absorption rate (C_{max}) of DRSP but showed no significant effect on the extent of absorption ($AUC_{0-\infty}$ and AUC_{0-72}). DRSP T_{max} was significantly delayed (median delay = 2.25 h; 90% CI: 1.50 – 3.25 h) in Test (fed) treatment, as compared with Reference (fasting) treatment.

Food reduced the C_{max} of DRSP by approximately 10% and the lower limit of the 90% CI for the Test-to-Reference GMR of the ln-transformed C_{max} is outside the no effect boundary of 80.00% to 125.00%. Food had minimal effect on AUC and both limits of the 90% CI were included in the no effect boundary of 80.00% to 125.00% (Table 5).

Table 5: Total intrasubject coefficient of variation (ISCV), Geometric Least Square Means (LSmeans), Test/Reference geometric means ratio (GMR) and 90% confidence intervals (CI) for C_{max}, $AUC_{0-\infty}$, and AUC_{0-72}

		Geometric LSmeans			
Parameter	Total ISCV%	Test	Reference	Test-to-Reference GMR (%)	90% CI
C_{max}	27.4	17.16	18.96	90.54	77.64 - 105.59
AUC_{0-72}	5.9	442.45	413.49	107.00	103.46 - 110.67
$AUC_{0-\infty}$	5.3	573.93	518.29	110.74	107.46 - 114.11

LSmeans values are given in ng/mL for C_{max} and ng.h/mL for AUC
Total ISCV% - Total Intrasubject Coefficient of Variation
Reference – Fasting conditions for drospirenone 3.5 mg chewable tablet
Test – Fed conditions for drospirenone 3.5 mg chewable tablet

The Applicant concluded that the ingestion of a high-fat-high-caloric meal 30 minutes before the administration of drospirenone 3.5 mg chewable tablets delayed the absorption

rate but showed no significant effect on the extent of absorption. Because food decreased DRSP C_{max} by approximately 10% and the lower limit of the 90% CI is outside of acceptable limit, the Applicant proposed to administer the drug on an empty stomach in the label. However, considering that C_{max} of the proposed product was 13% higher compared to the reference product under fasting condition in the BE study 2020-FLE1-SLINC-PK-04 (see Table 2), it is expected that the C_{max} of DRSP from the proposed formulation would be similar to that of the reference product under fed conditions. Therefore, clinical pharmacology review team recommends that the proposed drug can be administered with or without food.

A total of twenty-two (22) subjects were randomized and received at least one dose of investigational product. Out of 22 subjects, nineteen (19) subjects completed the study. The Applicant reported that no subject was excluded from the study analysis because of the protocol deviation.

The proposed product was well tolerated in both treatment conditions. For safety evaluations, refer to clinical review.

2.2.3 Does water intake affect the pharmacokinetics of drospirenone 3.5 mg chewable tablets formulation?

No dedicated studies were conducted to evaluate the effect of water intake on the PK of the proposed product. However, the Applicant evaluated the effect of water intake on DRSP 4 mg chewable tablets (b) (4) (b) (4) (b) (4) chewed and swallowed with or without water versus Reference product. (b) (4) (b) (4)

(b) (4)

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The results are not discussed here as they are not relevant to this NDA proposal.

(b) (4)

The [redacted] PK parameters (C_{max} and AUC_{0-72}) were not impacted when DRSP 4 mg chewable tablets were chewed and swallowed with or without water. [redacted] The CMC review team confirmed that though there are differences in the quantitative composition of these two products (i.e., 4 mg DRSP versus 3.5 mg DRSP, [redacted] and addition of peppermint flavor), none of these changes are significant from the drug product quality perspective to have any impacts on water effects. Therefore, clinical pharmacology review team recommends that DRSP 3.5 mg chewable tablets can be taken with or without water.

2.3. ANALYTICAL SECTION

The concentrations of DRSP in human EDTA K_2 plasma samples from clinical studies 2020-FLE1-SLINC-PK-04, 2020-FLE1-SLINC-PK-06, [redacted] were determined by a validated HPLC method using MS/MS detection (14ANE=2449V (version 01)). The Applicant conducted a validation study for the bioanalytical method as shown in Table 7. The validation study results met the analytical method acceptance criteria.

Table 7: Summary of bioanalytical method validation to measure the concentration of DRSP in human plasma

Analyte	Drospirenone
Internal standard (IS)	Drospirenone- d_4
Method description	The method involved a solid-phase extraction procedure with reversed phase 60 mg cartridges and sub-sequent derivatization with Girard-P solution. Drospirenone and internal standard were measured by reversed phase high performance liquid chromatography coupled to a tandem mass spectrometry detector (LC/MS/MS)
Limit of quantitation	0.25 ng/mL
Average recovery of drug (%)	73.90 % (QC1), 76.79 % (QC2) and 73.31 % (QC3)
Average recovery of IS (%)	72.18%
Standard curve concentrations (units/mL)	CS1: 0.25, CS2: 0.50, CS3: 2.50, CS4: 10.00, CS5: 20.00, CS6: 40.00, CS7: 80.00 and CS8: 100.00 ng/mL

Information Requested	Data
QC concentrations (ng/mL)	LLQC: 0.25, QC1: 0.75, QC2: 35.18; QC3: 75.38, ULQC: 100.50, LDQC: 150.75, HDQC: 1005.00 ng/mL
QC Intraday precision range (%)	6.71% for LLQC, 2.24% for QC1, 2.29% for QC2, 1.06% for QC3 and 1.31% for ULQC
QC Intraday accuracy range (%)	97.26% for LLQC, 102.66% for QC1, 93.63% for QC2, 99.00% for QC3 and 94.28% for ULQC
QC Interday precision range (%)	8.63% for LLQC, 8.09% for QC1, 3.37% for QC2 and 6.98% for QC3
QC Interday accuracy range (%)	92.81% for LLQC, 96.26% for QC1, 94.28% for QC2 and 96.81% for QC3
Bench-top stability (hrs)	Confirmed up to 24 hours at room temperature. Observed change: -8.08% for QC1 and -9.70% for QC3
Stock stability (days)	Confirmed up to 466 days at -20 °C for drospirenone stock solution prepared in methanol. Observed change: -0.29% Confirmed up to 469 days at -20 °C for drospirenone –d_4 stock solution prepared in methanol. Observed change: -0.67%
Processed stability (hrs)	Confirmed up to 148 hours at room temperature Observed change: 4.85% for QC1 and -3.50% for QC3
Freeze-thaw stability (cycles)	4 cycles in human EDTA K_2 at -20 °C (Observed change: 0.38% for QC1 and 8.31% for QC3 4 cycles in human EDTA K_2 at -80 °C. Observed change: 2.53% for QC1 and 8.41% for QC3
Long-term storage stability (days)	Confirmed up to 1121 days in human EDTA K_2 at -20 °C. Observed change: 0.00% for QC1 and 5.62% for QC3 Confirmed up to 435 days in human EDTA K_2 at -80 °C. Observed change: -5.44% for QC1 and 3.18% for QC3
Dilution integrity	Concentration diluted 2-fold (LDQC): Accuracy: 96.88%, Precision: 1.07% Concentration diluted 20-fold (HDQC): Accuracy: 93.80%, Precision: 1.05%
Selectivity	No interfering peaks noted in blank plasma samples

Source: Applicant's method validation report (14ANE-2449V, Version 01)

The performance results of the bioanalytical method for DRSP for studies 2020-FLE1-SLINC-PK-04, 2020-FLE1-SLINC-PK-06, (b) (4) are summarized in Table 8, 19, and 10 respectively.

Table 8: Summary of bioanalytical method performance for the 2020-FLE1-SLINC-PK-04 to measure the concentration of DRSP in human plasma

Reference standard	DRSP (Purity: 100%)	
Internal Standard	DRSP-d_4 (Purity: 98%)	
Method used	The method was based on solid phase extraction technique followed by LC/MS/MS analysis using API-4000.	
Calibration curve standard and quality control (QC) samples	Sets of 8 non-zero calibration curve standards (ranged from 0.25 ng/mL to 100 ng/mL) and quality control samples (QC1 = 0.75 ng/mL, QC2 = 50 ng/mL, QC3 = 75 ng/mL, QC4 = 5 ng/mL and LDQC = 150 ng/mL) were prepared at room temperature.	
Calibration standard performance	Accuracy (% nominal): 99.10% to 100.78%	Acceptable
Quality control samples performance	Between-run precision (CV%): 1.95% to 3.86% Between-run accuracy (% nominal): 99.34% to 101.52%	Acceptable
Study samples stability	The maximum study sample storage period was 65 days at -20ºC (from August 15, 2020 to October 19, 2020) which is covered by the established long-term stability period of 1121 days at -20ºC in human EDTA K_2 plasma.	
Incurred sample reanalysis	A total of 178 samples out of a total 2550 analyzed samples (approximately 7%) was selected, reassayed, and evaluated for Incurred Samples Reanalysis (ISR). The ISR assay complied with the acceptance criteria (at least 67% of incurred samples should be within 20% of the mean). The percentage of tested incurred samples within 20% of the mean was 97.75%.	Acceptable

Source: Applicant's bioanalytical report for BLCL-DRS-FDA-04

Table 9: Summary of bioanalytical method performance for the 2020-FLE1-SLINC-PK-06 to measure the concentration of DRSP in human plasma

Reference standard	DRSP (Purity: 100%)
Internal Standard	DRSP-d_4 (Purity: 98%)
Method used	The method was based on solid phase extraction technique followed by LC/MS/MS analysis using API-4000.
Calibration curve standard and quality control (QC) samples	Sets of 8 non-zero calibration curve standards (ranged from 0.25 ng/mL to 100 ng/mL) and quality control samples (QC1 = 0.75 ng/mL, QC2 = 50 ng/mL, QC3 = 75 ng/mL, QC4 = 5

	ng/mL and LDQC = 150 ng/mL) were prepared at room temperature.	
Calibration standard performance	Accuracy (% nominal): 99.14% to 100.85%	Acceptable
Quality control samples performance	Between-run precision (CV%): 1.27% to 4.99 % Between-run accuracy (% nominal): 99.41% to 101.28%	Acceptable
Study samples stability	The maximum study sample storage period was 33 days (from September 10, 2020 to October 13, 2020) at -20ºC which is covered by the long-term stability period of 1121 days at -20ºC in human EDTA K_2 plasma.	
Incurred sample reanalysis	A total of 82 samples out of a total 820 analyzed samples (approximately 10%) was selected, reassayed, and evaluated for Incurred Samples Reanalysis (ISR) assay. The ISR assay complied with the acceptance criteria (at least 67% of incurred samples should be within 20% of the mean). The percentage of tested incurred samples within 20% of mean was 100.00%.	Acceptable

Source: Applicant's bioanalytical report for BLCL-DRS-FDA-06

Table 10: Summary of bioanalytical method performance for the 2019-FLE1-SLINC-PK-01 to measure the concentration of DRSP in human plasma

Reference standard	DRSP (Purity: 100%)	
Internal Standard	DRSP-d_4 (Purity: 98%)	
Method used	The method was based on solid phase extraction technique followed by LC/MS/MS analysis using API-4000.	
Calibration curve standard and quality control (QC) samples	Sets of 8 non-zero calibration curve standards (ranged from 0.25 ng/mL to 100 ng/mL) and quality control samples (QC1 = 0.75 ng/mL, QC2 = 50 ng/mL, QC3 = 75 ng/mL, QC4 = 5 ng/mL and LDQC = 150 ng/mL) were prepared at room temperature.	
Calibration standard performance	Accuracy (% nominal): 98.10% to 103%	Acceptable
Quality control samples performance	Between-run precision (CV%): 3.12 % to 9.67 % Between-run accuracy (% nominal): 103.85% to 105.99%	Acceptable

Study samples stability	The maximum study sample storage period was 66 days at -20ºC (from January 07, 2020 to March 13, 2020) which is covered by the long-term stability period of 1121 days at -20ºC in human EDTA K_2 plasma.	
Incurred sample reanalysis	A total of 186 samples out of a total 2720 analyzed samples (approximately 7%) was selected, reassayed, and evaluated for Incurred Samples Reanalysis (ISR) assay. The ISR assay complied with the acceptance criteria (at least 67% of incurred samples should be within 20% of the mean). The percentage of tested incurred samples within 20% of mean was 98.39%.	Acceptable

Source: Applicant's bioanalytical report for BLCL-DRS-FDA-01

The method validation and performance of analytical runs for DRSP for studies 2020-FLE1-SLINC-PK-04, 2020-FLE1-SLINC-PK-06, (b) (4) are acceptable.

The clinical pharmacology review team requested inspections of the analytical and clinical sites for Study 2020-FLE1-SLINC-PK-04 in a consult request to Division of New Drug Study Integrity (DNDSI), Office of Study Integrity and Surveillance (OSIS). DNDSI declined to conduct an on-site inspection and determined that an inspection was not warranted. OSIS inspected the analytical site in June 2019 and clinical site in August 2019 and recommended that no further action was needed.

3. LABELING RECOMMENDATIONS

Recommendations (Preliminary):
The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology has the following labeling recommendations for revisions to the Applicant's proposed language.

[Note: The blue text is the recommended revision and strikethrough text in red color is the deletion]

Section/Proposed Language	Recommendation / Comment
(b) (4)	

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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