CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214154Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)

Date:	3/29/2021
Reviewer(s):	Huei-Ting Tsai, PhD, Epidemiologist Division of Epidemiology II
Team Leader (acting):	Wei Liu, PhD, Senior Staff Fellow Division of Epidemiology II
Division Director:	David Moeny, R.Ph, MPH, USPHS, Epidemiologist Division of Epidemiology II
OPE Director:	Judith Zander, MD
FDA Sentinel Team Lead:	Michael D. Nguyen, MD
OSE Deputy Director:	Robert Ball, MD, MPH, ScM
Subject:	ARIA Sufficiency Memo
Drug Name(s):	Nextstellis
Application Type/Number:	NDA 214154
Applicant/sponsor:	Mayne Pharma LLC
OSE RCM #:	RCM 2021-143

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*	
Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	X

1. BACKGROUND INFORMATION

1.1. Medical Product

Nextstellis® is a combination oral contraceptive (COC) product, containing 3mg drospirenone (DRSP), a progestin, and 14.2 estetrol (E4), an estrogen, in each tablet. The E4 is a novel estrogen so this product is considered a New Molecular Entity (NME). The indicated use of Nextstellis in its labeling is for females of reproductive potential to prevent pregnancy. Other DRSP-containing COC products are also approved for treating symptoms of premenstrual dysphoric disorder, moderate acne, and to raise folate levels.

Two multi-center, open-label, one-arm studies of Nextstellis have been conducted, one in Europe/Russia (NCT02817828; C301, N=1,553) and the other in North America (NCT02817841; C302, N=1,864). The pre-approval trials excluded women with history of venous thromboembolism (VTE, including deep vein thrombosis and pulmonary embolism), presence or history of arterial thromboembolism (ATE, including angina pectoris, ischemic heart disease, cerebral stroke and transient ischemic attack) or any arterial hypertension (controlled or uncontrolled) defined by blood pressure value of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. These two pre-approval studies showed Nextstellis meets the efficacy criteria in preventing pregnancy in women 16-50 years of age.

1.2. Describe the Safety Concern

Use of COCs is known to increase the risk of venous thromboembolism (VTE) and arterial thromboembolism (ATE)[1], due to the thrombogenic potential of estrogen and, to a lesser extent, the progestin component. The incidence of VTE among users of COCs is higher (3 to 9 / per 10,000-woman years), compared with women who are non-users of combined hormonal contraceptives and non-pregnant (1 to 5/ per 10, 000)[2]. As E4 is an NME, the safety profile has not been fully characterized in the approval trials.

Further, while approximately 40% of US women have a BMI>30[3], the pre-approval studies only included a small portion of obese women (BMI≥30), 432 (23%) and 89 (6%) of study subjects in the US and Europe/Russia study, respectively, and no women with BMI>35 were enrolled. Though only one VTE case was reported in the Europe/Russia study with BMI of 21.4, the review team is concerned that the VTE and ATE risk has not been adequately assessed in the pre-approval studies. The tentative labeling of Nextstellis under section 8.9 Body Mass Index (BMI)/ Body Weight states "The safety and efficacy of Nextstellis in (b) (4) with BMI (b) (4) 35 (b) (4) evaluated". Because use of COCs is known

[1] Roach RE, Helmerhorst FM, Lijfering WM, Stijnen T, Algra A, Dekkers OM, Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. Cochrane Database of Systemic Reviews 2015, Issue 8. Art. No.: CD011054. DOI. 10.1002/14651858. CD011054. pub2. Accessed 04 February 2021.

[2] Food and Drug Administration. FDA drug safety communication: updated information about the risk of blood clots in women taking birth control pills containing drospirenone. Silver Spring (MD): FDA; 2012

[3] Prevalence of obesity and severe obesity among adults: United States, 2017-2018, Source: US CDC National Health and Nutrition Examination Survey, 2017–2018. https://www.cdc.gov/nchs/data/databriefs/db360-h.pdf

to increase the risk of VTE and ATE, and obesity is another strong risk factor, it is important to quantify the VTE and ATE risk among obese users. This additional safety information will enable informed decision-making for physicians and patients based on patients' benefit-risk profile. Therefore, the Division of Urology, Obstetrics and Gynecology (DUOG) requested a postmarketing requirement (PMR) to quantify VTE and ATE risk with E4/DRSP use in the US population and the study should have adequate statistical power to assess VTE and ATE risk among obese users.

Previously, FDA has issued PMR for VTE and ATE safety concern in COC products listed in the table below when the ARIA modular program is unavailable or insufficient. The regulatory scenario with Annovera is different than Nextstellis in the following ways: a) in the Annovera clinical development program, there was an imbalance in the clinical trials with 4 investigator confirmed VTEs, all of whom had BMI >29, and b) the Annovera (b) (4) recommended stopping enrollment of new subjects with BMI >29. In contrast, the strength of the evidence in the Nextellis clinical development program is lower with only 1 VTE case in a woman with a BMI of 21. Thus, the purpose of the Nextstellis PMR is to expand the total safety database and follow up a single case identified in two pre-approval studies.

Because of the stronger signal in the Annovera clinical program, the FDA also undertook a sequential analysis in Sentinel, in addition to the sponsor's PMR to provide early detection of a grossly increased risk of VTE and ATE. However, with the current capabilities and data available in the Sentinel system, this analysis is proving to be less feasible than anticipated.

Product (approval date)	Health Outcome of Interest [FDAAA Study Purpose]	ARIA Sufficiency and PMR Description
NATAZIA (dienogest & estradiol valerate) (5/6/2010)	To assess VTE and ATE risks in a study population representative of the actual users of the study medication [To assess a known serious risk]	Insufficient. The ARIA system had not been activated at the time of approval. Thus, FDA required a prospective, controlled, long-term cohort PMR study with at least 50,000 women from the US and Europe with at least 3 years of follow-up to be conducted by expanding the ongoing European postmarketing comparative safety surveillance study (INAS-EV).
ANNOVERA (segesterone acetate &	To assess fatal and non-fatal VTE and ATE in a study population representative of actual	Insufficient. The ARIA system was determined to be insufficient due to lack of credible methods for measuring BMI and smoking, which are well-established

ethinyl estradiol) vaginal system (8/10/2018)	users of the product in the US. [To assess signals of serious risk]	risk factors for VTE/ATE. FDA required a controlled long-term cohort study comparing Annovera to other vaginal, intrauterine and oral contraceptives with sufficient power to rule out a 1.5 to 2.0-fold increased risk for VTE. FDA decided to supplement the PMR with sequential surveillance "for early detection of a large increase in the risk of non-fatal venous thromboembolism/arterial thromboembolism in the United States population."
TWIRLA (levonorgestrel & ethinyl estradiol) transdermal system (2/14/2020)	To assess fatal and non-fatal VTE and ATE in US women of reproductive age using Twirla and other CHCs primarily for contraceptive reasons. [To assess signals of serious risk]	Insufficient. ARIA was determined to be insufficient for a prospective study design that is required to adequately collect and control for important study covariates, especially BMI and smoking. FDA required a PMR study consisting of a prospective, controlled, observational cohort study comparing the risk of VTE and ATE among Twirla users to Xulane in US women. The study was powered to detect a 1.5 to 2.0-fold increased risk, adjusting for BMI, smoking and other factors.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

The purpose of this PMR study is to quantify VTE and ATE risk in women of

reproductive age who are new users of Nextstellis, compared to women who use other DRSP-containing COC products (first comparator) or other COCs not containing DRSP (second comparator), for the purpose of birth control.

1.5. Effect Size of Interest or Estimated Sample Size Desired

The study should be powered to obtain at least 90% statistical power to detect a 1.5 – 2-fold increased risk for VTE in new users of Nextstellis along with adequate control for possible confounders, especially age, BMI, and smoking status, among other covariates.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

Women of reproductive age who newly initiate Nextstellis or a comparator COC for the purpose of birth control.

2.2 Is ARIA sufficient to assess the intended population?

Yes. The specific indication for COC use is usually inadequately captured within administrative claims data. However, a 'rule-out' approach can be used to exclude users who had diagnosis or medication codes relevant to other indications of COC that is not for the purpose of birth control.

3 EXPOSURES

3.1 Treatment Exposure(s)

The exposure of interest is new use of Nextstellis. The exposed group consists of women who are new users of Nextstellis and without previous exposure to hormonal contraception of any form.

3.2 Comparator Exposure(s)

The comparator is women who are new users of other COCs. The first control group is new users of other DRSP-containing COCs. The second control group is new users of other oral COCs not containing DRSP.

3.3 Is ARIA sufficient to identify the exposure of interest?

Yes.

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcomes of interest include incident fatal and non-fatal VTE and ATE (stroke and AMI), diagnosed and/or treated in hospital, emergency room, or outpatient settings.

4.2 Is ARIA sufficient to assess the outcome of interest?

ARIA is sufficient to ascertain non-fatal VTE in all settings and fatal VTE in hospital or emergency room setting in administrative claims data. The mini-sentinel project conducted a systemic review of the performance of inpatient and outpatient VTE ICD-9 algorithms in administrative claims data.[4] The review reported a range of positive predictive value (PPV) of 65%–95% where the highest PPV was with combined use of ICD-9-CM codes 415.x (pulmonary embolism), 451.x, and 453.x (deep vein thrombosis) as a VTE event.

ARIA also permits adequate identification of hospitalized ATE (AMI and stroke) events. The Sentinel Working Group identified hospitalized AMI patients using ICD-9-CM codes 410.x1 and 410.x0 in the principal or primary position and reported an overall PPV of 86% (95% CI: 79.2% to 91.2%) with PPVs ranging from 76% to 94% across the 4 data partners involved in this assessment.[5] Acute stroke (ischemic or hemorrhagic) was an outcome evaluated as part of Sentinel's Health Outcome of Interest Validation and Literature Reviews. The review found that the PPV for algorithms to identify stroke was > 80% using inpatient claims (in principal position) with ICD-9-CM diagnosis codes 430, 431, 433.x, 434.x, or 436. ARIA is currently unable to ascertain immediate fatal out-of-hospital ATE, or VTE as noted in most administrative claims data.

Validation studies for VTE and ATE defined using the ICD-10 diagnosis and procedural codes have not been conducted in Sentinel data; however, outcome definitions based on the ICD-9 codes are validated[6] and trend analyses[7] show that the incidence of ATE and VTE are consistent when mapping the codes from ICD-9 to ICD-10, which supports the sufficiency of ARIA to identify these outcomes.

5 COVARIATES

5.1 Covariates of Interest

[4] Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying venous thromboembolism using administrative and claims data. *Pharmacoepidemiology and drug safety.* 2012;21 Suppl 1:154-162.
[5] Cutrona SL, Toh S, Iyer A, et al. Validation of acute myocardial infarction in the Food and Drug Administration's Mini-Sentinel program. *Pharmacoepidemiology and drug safety.* 2013;22(1):40-54.
[6] Sentinel Evaluation of the risk of thrombotic event after immunoglobulin administration report https://www.sentinelinitiative.org/assessments/vaccines-blood-biologics/thromboembolic-events-after-immunoglobulin-administration
[7] Deliverables of Sentinel coding trend analysis for venous vein thrombosis. https://www.sentinelinitiative.org/sites/default/files/surveillance-tools/validations-literature/Deep_Vein_Thrombosis_Trend_Report.pdf

Covariates of interest for the proposed study include:

- Demographic variables (age, calendar year)
- Risk factors to VTE and ATE (hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, chronic kidney disease, obesity or overweight, smoking, gynecological conditions including polycystic ovarian syndrome, pregnancy and post-partum, cancer, surgery, recent hospitalization, immobility, prior VTE and ATE, family history of thrombotic disease)
- Concomitant or recent treatment (beta blocker, ace inhibitors, non-steroidal anti-inflammatory drugs, statins, and hormonal contraceptives]

5.2 Is ARIA sufficient to assess the covariates of interest?

No. ARIA is not sufficient to assess the covariates of interest, including BMI, smoking and personal and family's history of thrombotic disease. These covariates have been well-established risk factors for VTE and ATE and are not adequately captured within administrative claims database or electronic health records.[8] Obesity and smoking are well-established risk factors for ATE/VTE[9], failure to adjust for differences in BMI and smoking between comparison groups may result in confounding, hence invalidating the risk estimates. Because obese women were underrepresented in Nextstellis phase-3 studies, and approximately 40% of US females are obese, it's critical for this PMR to obtain information on BMI at baseline and during the follow-up so that we can assess VTE and ATE risk in this important subgroup population. Incomplete capture or missingness of these important confounders in administrative claims data makes a prospective primary collection (e.g., gathering data through repeated surveys or interviews or self-reports) of these covariables needed.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

A prospective cohort study with sufficient confounding control for known confounders such as age, BMI, smoking, and family history of VTE/ATE, among other covariates.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

ARIA is not sufficient for a prospective cohort study design that is required to adequately collect and control for important study covariates, especially BMI and smoking.

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[8] Liu W, Cosgrove A, Dutcher S et al., Confounding Variable Capture in Large Healthcare Administrative Claims Database: A Trend Analysis in the Sentinel System, Poster of the 35th International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Philadelphia, PA, USA, Aug 24-28, 2019

[9] Gregson J, Kaptoge S, Bolton T et al. Cardiovascular Risk Factors Associated With Venous Thromboembolism. JAMA Cardiol. 2019 Feb 1;4(2):163-173. doi: 10.1001/jamacardio.2018.4537. PMID: 30649175; PMCID: PMC6386140.

7 NEXT STEPS

We determined the ARIA is insufficient to conduct this PMR because of lack of the capacity for a prospective cohort study design with adequately collection and control of important study covariates, such as BMI and smoking. Therefore, DUOG plans to issue a PMR with tentative PMR language drafted as follows:

" A prospective, observational cohort study comparing the risks for fatal and non-fatal venous thromboembolism (VTE) and arterial thromboembolism (ATE) in new users of Nextstellis, estetrol monohydrate (E4) and drospirenone (DRSP), to new users of combined oral contraceptives (COCs) containing drospirenone (first comparator) and new users of COCs containing other progestogens (second comparator) in U.S. women of reproductive age using COCs primarily for contraceptive reasons. This study should have sufficient confounding control for known risk factors of VTE including age, body mass index (BMI), and smoking status, among others. The study should be sufficiently powered to detect a 1.5 to 2.0-fold increase in risk of VTE in new users of Nextstellis. Further, the study should be sufficiently powered for a stratified analysis by BMI to detect a 1.5 to 2.0-fold increase in VTE risk of Nextstellis in obese women for both comparators."

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/s/

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03/30/2021 08:14:52 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 26, 2021
To:	Samantha Bell, B.S., B.A., R.A.C. Regulatory Project Manager **Division of Urology, Obstetrics, and Gynecology (DUOG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Jina Kwak, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	NEXTSTELLIS (drospirenone and estetrol tablets)
Dosage Form and Route:	tablets for oral use
Application Type/Number:	NDA 214154
Applicant:	Mayne Pharma LLC

1 INTRODUCTION

On April 15, 2020, Mayne Pharma LLC submitted for the Agency's review a New Drug Application (NDA) 214154 for NEXTSTELLIS (drospirenone and estetrol tablets), for oral use. This NDA proposes an indication for the prevention of pregnancy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Urology, Obstetrics, and Gynecology (DUOG) on April 24, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for NEXTSTELLIS (drospirenone and estetrol tablets), for oral use.

2 MATERIAL REVIEWED

- Draft NEXTSTELLIS (drospirenone and estetrol tablets), for oral use PPI and IFU received on April 15, 2020, and received by DMPP and OPDP on March 18, 2021.
- Draft NEXTSTELLIS (drospirenone and estetrol tablets), for oral use Prescribing Information (PI) received on April 15, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 18, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

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03/26/2021 12:40:59 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 24, 2021

To: Samantha Bell
Regulatory Project Manager
Division of Urology, Obstetrics and Gynecology (DUOG)

From: Jina Kwak
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter
Team Leader, OPDP

Subject: OPDP Labeling Comments for NEXTSTELLIS (drospirenone and estetrol) tablets, for oral use

NDA: 214154

In response to DUOG consult request dated April 24, 2020, OPDP has reviewed the proposed product labeling (PI), Patient Package Insert (PPI), Instructions for Use (IFU) and carton and container labeling for NEXTSTELLIS (drospirenone and estetrol) tablets, for oral use (Nextstellis).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DUOG (Samantha Bell) on March 18, 2021 and we have no additional comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DUOG (Samantha Bell) on March 22, 2021 and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Jina Kwak: 301-796-4809 or Jina.kwak@fda.hhs.gov

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/s/

JINA KWAK
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Clinical Inspection Summary

Date	March 11, 2021
From	Ling Yang, M.D., Ph.D., FAAFP Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Anandi Kotak, M.D., Clinical Reviewer Mark Hirsch, M.D., Clinical Team Leader Samantha Bell, Regulatory Project Manager Division of Urology, Obstetrics and Gynecology (DUOG)
NDA #	214154
Applicant	Mayne Pharma LLC
Drug	Estetrol Monohydrate (E4)/Drospirenone (DRSP)
NME (Yes/No)	No
Review Priority	Standard
Proposed Indication	Use by females of reproductive potential to prevent pregnancy
Consultation Request Date	June 12, 2020
Summary Goal Date	March 15, 2021
PDUFA Date	April 15, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Studies MIT-Es0001-C301 and MIT-Es0001-C302 were submitted to the Agency in support of this New Drug Application (NDA) for Estetrol Monohydrate (E4)/Drospirenone (DRSP) oral tablets for the proposed indication of "use by females of reproductive potential to prevent pregnancy".

A consult to conduct Good Clinical Practice (GCP) inspections for NDA 214154 was received from the Division of Urology, Obstetrics and Gynecology (DUOG) on 06/12/2020 that identified the sponsor Estetra SPRL (original owner of the studies submitted) and the following clinical investigators (CIs):

- Dr. Klaus Peters/Germany; Site #034; Study MIT-Es0001-C301
- Dr. Janusz Tomaszewski/Poland; Site #067; Study MIT-Es0001-C301
- Dr. Mark Jacobs/USA; Site #208; Study MIT-Es0001-C302
- Dr. Celine Bouchard/Canada; Site #290; Study MIT-Es0001-C302

The ongoing COVID-19 global pandemic has significantly limited the Office of Regulatory Affairs (ORA)'s ability to conduct onsite GCP inspections. As a result, onsite inspections or remote data assessment of source records for the CIs were not conducted due to travel and local restrictions. A remote regulatory assessment (RRA) of the sponsor Estetra SPRL was conducted by FDA.

In addition, Health Canada (HC) shared with the Office of Scientific Investigations (OSI) the remote inspections findings/results of Dr. Bouchard (Site #290; Study MIT-Es0001-C302) and the Contract Research Organization (CRO) (b) (4)
Similarly, the European Medicines Agency (EMA) conducted remote inspections of the sponsor and the CRO (b) (4) and shared with the OSI their inspectional findings.

The OSI reviewed of inspection reports provided both by HC and the EMA and included the findings into this Clinical Inspection Summary (CIS).

Based on FDA's RRA of the sponsor, the sponsor's study oversight appears adequate and the data generated by the sponsor appear acceptable in support of the NDA.

Although a few GCP findings were reported by HC and the EMA, based on the nature of the findings, they are unlikely to affect the reliability of the efficacy and safety data in support of this application.

II. BACKGROUND

Mayne Pharma LLC submitted NDA 214154 for E4/DRSP oral tablets on 04/15/2020. E4/DRSP is an estrogen/progestin combination oral contraceptive indicated for use by females of reproductive potential to prevent pregnancy. The sponsor submitted data from two single-arm, open label, multicenter Phase 3 Studies, MIT-Es0001-C301 and MIT-Es0001-C302, to support the approval of the NDA. The two studies are identical, except that Study MIT-Es0001-C301 was conducted in Europe and Russia, and enrolled subjects 18-50 years old; Study MIT-Es0001-C302 was conducted in the US and Canada, and enrolled subjects 16-50 years old. The studies were conducted under IND 110682 and was originally owned by Estetra SPRL, who transferred the ownership to Mayne Pharma on 04/08/2020.

Study MIT-Es0001-C301

Study MIT-Es0001-C301 was a single-arm, Phase 3, open-label, multicenter study to evaluate the contraceptive efficacy and safety of E4/DRSP.

The primary study objective was to evaluate the contraceptive efficacy of E4/DRSP using the Pearl Index in subjects 18-35 years old. The secondary study objectives were to evaluate the contraceptive efficacy of the product using the method failure Pearl Index and life-table analysis in subjects 18-35 years old; and to evaluate the contraceptive efficacy of the product using the Pearl Index, the method failure Pearl Index (which reflects the pregnancy rate due to method failure only) and life-table analysis in the overall study population.

The primary efficacy endpoint was the number of on-treatment pregnancies assessed by the Pearl Index in the intent-to-treat (ITT) population of women 18-35 years old with at-risk cycles (i.e., the subject confirmed in the diary that sexual intercourse occurred during the cycle and no other methods of birth control, including condoms, were used).

Eligible subjects were treated with 15 mg E4/3 mg DRSP for a maximum of 13 consecutive cycles. The product was taken once daily at approximately the same time of the day in a 24/4-day regimen,

i.e., 24 active tablets followed by 4 placebo tablets (4-day hormone-free interval). Subjects were required to record their daily pill intake, use of other contraceptive methods, the occurrence of sexual intercourse and daily bleeding/spotting episodes in a subject diary. Contraceptive efficacy was calculated using the Pearl Index, the method failure Pearl Index and life-table analysis.

The study screened a total of 1774 subjects, enrolled 1577 subjects in 69 study sites in Europe (Belgium-8, Czech Republic-12, Finland-8, Germany-7, Hungary-11, Norway-4, Poland-6, and Sweden-3) and Russia (10). The first subject was enrolled on 06/28/2016 and the last subject completed the study on 04/26/2018.

Study MIT-Es0001-C302

Study MIT-Es0001-C302 was a single-arm, Phase 3, open-label, multicenter study to evaluate the contraceptive efficacy and safety of E4/DRSP in the US and Canada.

The primary study objective was to evaluate the contraceptive efficacy of E4/DRSP using the Pearl Index in subjects 16-35 years old. The secondary study objectives were to evaluate the contraceptive efficacy of the product using the method failure Pearl Index and life-table analysis in subjects 16-35 years old; and to evaluate the contraceptive efficacy of the product using the Pearl Index, the method failure Pearl Index and life-table analysis in the overall study population.

The primary efficacy endpoint was the number of on-treatment pregnancies assessed by the Pearl Index in the ITT population of women 16-35 years old with at-risk cycles (i.e., as the subject confirmed in the diary that sexual intercourse occurred during the cycle and no other methods of birth control, including condoms, were used).

Eligible subjects were treated with 15 mg E4/3 mg DRSP for a maximum of 13 consecutive cycles. The product was taken once daily at approximately the same time of the day in a 24/4-day regimen, i.e., 24 active tablets followed by 4 placebo tablets (4-day hormone-free interval). Subjects were required to record their daily pill intake, use of other contraceptive methods, the occurrence of sexual intercourse and daily bleeding/spotting episodes in a subject diary. Contraceptive efficacy was calculated using the Pearl Index, the method failure Pearl Index and life-table analysis.

The study screened a total of 2918 subjects, enrolled 2148 subjects in 77 study sites in North America (US-70 and Canada-7). The first subject was enrolled on 08/30/2016 and the last subject completed the study on 11/16/2018.

Rationale for Site Selection

Four CIs: Drs. Klaus Peters (Site #034), Janusz Tomaszewski (Site #067), Mark Jacobs (Site #208) and Celine Bouchard (Site #290) were requested for GCP inspections in support of the application approval. These sites were selected based on enrolling a high number of subjects to the study treatment arms that may have an impact in the review division's clinical decision-making process.

The review division also requested an inspection of the sponsor to assess clinical study oversight adequacy, site procedures, record keeping and reporting procedures regarding patient eligibility, adverse events (AEs) reporting, and assessment of protocol deviations. Previously, FDA received an anonymous complaint (b) (4) alleging that the sponsor did not adequately assess and report safety

information for its E4 containing products in clinical studies. Specifically, the complainant alleged that the sponsor did not have a global safety database for this product that includes cumulative AEs from clinical studies conducted in the US, Europe, and Japan. Safety data were disbursed among several different CROs, and the complainant raised questions about the sponsor's ability to conduct ongoing evaluation of the product's risk/benefit profile, signal detection, and follow-up of serious AEs (SAEs). The complainant noted that the sponsor's pharmacovigilance (PV) system had recently been outsourced to a vendor.

III. RESULTS

FDA Inspection

Estetra SPRL/Sponsor
Rue Saint Georges 5-7
4000 Liège
Belgium

Due to the COVID-19 pandemic, travel to the sponsor site was not possible. An RRA was conducted on 01/21-02/12/2021 for Studies MIT-Es0001-C301 and MIT-Es0001-C302. During the RRA, video conferences via WebEx and Microsoft Teams and document sharing via online platforms were used to exchange information.

The RRA reviewed the sponsor's organizational structure and responsibilities; contractual agreements and oversight of transferred regulatory obligations to the CRO; standard operating procedures (SOPs/guidelines) to assure the integrity of data collection; registration of the studies; financial disclosure and investigator agreements; protocol deviations related to key safety and efficacy endpoints; safety evaluation with AEs and SAEs reporting; electronic trial master file (eTMF) review; record retention; electronic records and electronic signatures; and quality assurance system and audits. The RRA also investigated the complaint (complaint (b) (4) regarding the sponsor's deficiencies with the PV system during the RRA.

Study data were managed using the following data management systems: Clinical Data Management System (to collect study data); Clinical Study Management System (to manage the study process and communications); ARGUS [to track SAEs and serious adverse reactions (SARs)]; Intralinks (to submit safety report to the CIs); J-Review [sponsor's real time access to the electronic case report forms (eCRF)]; (b) (4) Secure Web Portal (to post reports and study documents) and IxRS Website [subject allocation and investigational product (IP) management].

This assessment did not find evidence that the sponsor failed to review AEs from the studies submitted or other clinical studies involving the E4 containing products reported by the compliant. The sponsor has contracted (b) (4), an outside vendor, to handle post-marketing AEs monitoring and reporting.

At the end of the inspection, the listed items below were discussed with the sponsor:

- An investigation was not conducted in accordance with the investigational plan. Specifically, the sponsor did not report protocol deviations for two subjects. Subject #s (b) (6) had post screening/enrollment menstrual cycles of 37 days and no prior history of combined oral contraceptive use that met the exclusion criteria #1 (for subjects who are not using hormonal contraception at screening, a menstrual cycle length shorter than 21 days or longer than 35 days) in Study MIT-Es0001-C301. The medical monitors noted the sponsor approved the subjects' continuation in the study. However, these protocol deviations were not reported in the clinical study report.
- The sponsor failed to provide the required monthly aggregate study safety report per the medical monitoring plan for 3 months (02/2018, 03/2018 and 05/2018).

Outside the above findings, the RRA revealed adequate adherence to the regulations and the investigational plan.

Reviewer's Comments: The two protocol deviations should have been included in the submission. Although the above findings were noted, they appear unlikely to have significant impact on the primary efficacy and safety analyses.

Additional Information: Review of HC and the EMA Inspection Findings

Health Canada (HC) shared with the OSI the remote inspections findings/results of Dr. Bouchard (Site #290; Study MIT-Es0001-C302) and the CRO (b) (4) Similarly, the EMA conducted remote inspections of the sponsor and (b) (4) and shared with OSI their inspectional findings. OSI reviewed of inspection reports provided both by HC and the EMA and included the findings into this CIS. We summarize the findings below:

Note: The information below must be redacted should this CIS be made public as it was received from the EMA and HC under the terms of the confidentiality agreement between the two agencies.

1. **Dr. Celine Bouchard, Site 290**
   1000 Chemin Sainte-Foy, Suite 302
   Quebec, QC G1S 2L6
   Canada

(b) (4)

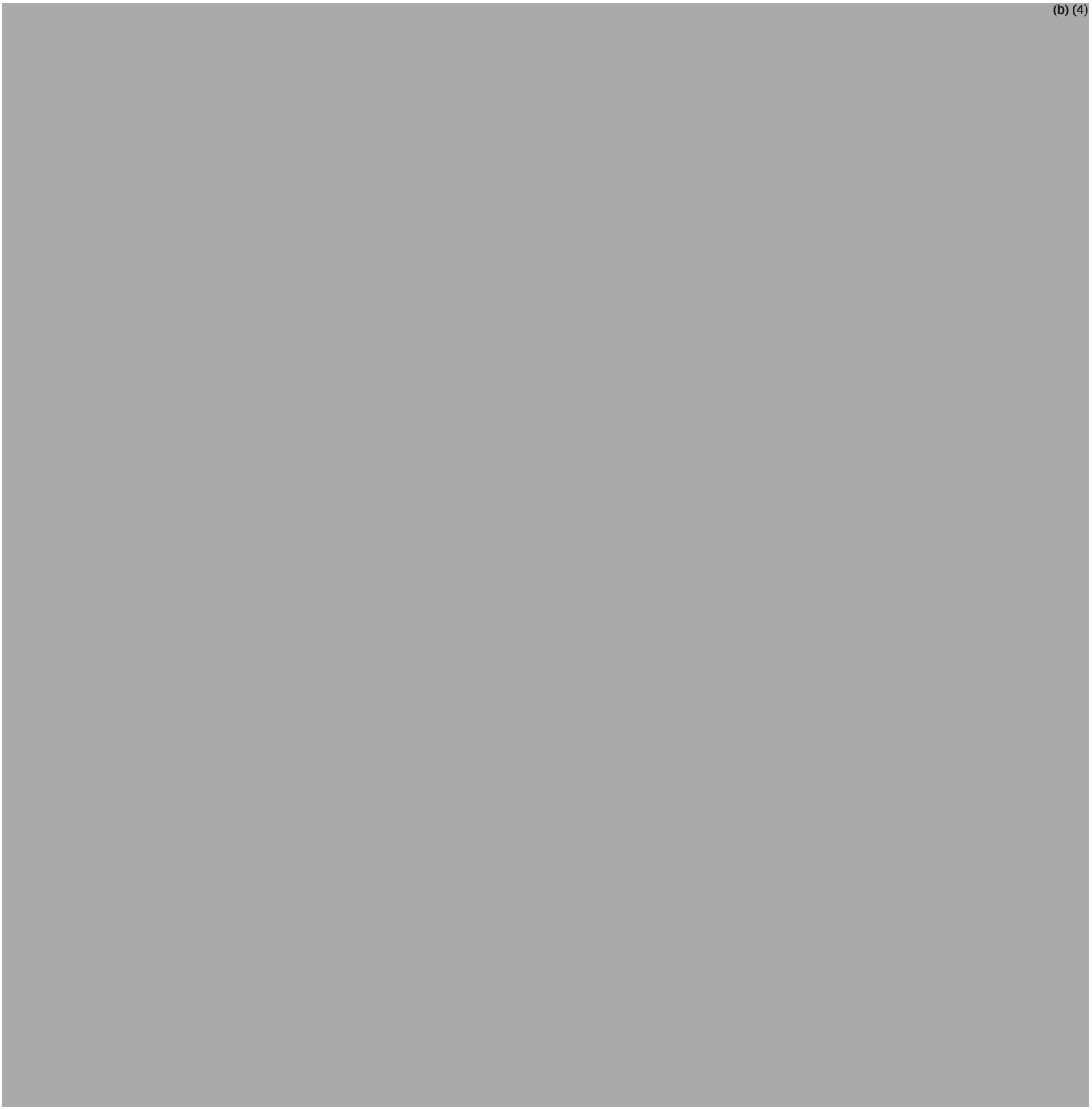
(b) (4)

Reviewer's Comments: The above identified issues do appear to be mainly procedure-related. These findings appear unlikely to significantly affect the primary safety or efficacy analyses.

2. (b) (4)

The EMA Inspection of the CRO, (b) (4)

(b) (4)



Reviewer's Comment: The above findings would not have been considered a regulatory violation by FDA. The findings appear mainly procedure-related.

3. **Estetra SPRL/Sponsor**
   Rue Saint Georges 5-7
   4000 Liège
   Belgium

The EMA conducted a remote inspection (b) (4)

Data quality is acceptable to support the approval.

{See appended electronic signature page}

Ling Yang, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
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CC:
Central Doc. Rm.\NDA 214154
DUOG\Deputy Division Director\Audrey Gassman
DUOG\CDTL\Gerald Willett
DUOG\Reviewer\Anandi Kotak
DUOG\Project Manager\Samantha Bell
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Min Lu

OSI\DCCE\GCPAB\Reviewer\Ling Yang
OSI\DCCE\Program Analysts\Yolanda Patague

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 8, 2020
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 214154
Product Name and Strength:	Nextstellis (drospirenone and estetrol) tablets, 3 mg/14.2 mg
Applicant/Sponsor Name:	Mayne Pharma LLC (Mayne)
OSE RCM #:	2020-805-3
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on November 25, 2020 and December 4, 2020 for Nextstellis. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised carton labeling for Nextstellis (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[a] and in response to recommendations made by the Office of Pharmaceutical Quality (OPQ).[b]

2 CONCLUSION

In response to our previous recommendation, the Applicant states that Mayne did not intend to include (b) (4) on the carton labeling. It was inadvertently included in the template used to create the label. As such, the Applicant implemented all of our previous recommendations and we find the carton labeling acceptable from a medication safety perspective. However, we defer to the Office of Pharmaceutical Quality (OPQ) regarding the acceptability of the revisions

[a] Baugh D. Label and Labeling Review for Nextstellis (NDA 214154). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 17. RCM No.: 2020-805-2.
[b] Bell, S. Information Request for Nextstellis (NDA 214154). 2020 NOV 30. Available in DARRTS via: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af805b4bde&_afrRedirect=254228851160471

made to the carton labeling based on their recommendations. We have no additional recommendations at this time.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 17, 2020
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 214154
Product Name and Strength:	Nextstellis (drospirenone and estetrol) tablets, 3 mg/14.2 mg
Applicant/Sponsor Name:	Mayne Pharma LLC (Mayne)
OSE RCM #:	2020-805-2
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 9, 2020 for Nextstellis. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container label and carton labeling for Nextstellis (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations. However, the Applicant now proposes to include (b) (4) on the carton labeling which has prompted additional recommendations.

3 RECOMMENDATIONS FOR MAYNE PHARMA LLC

We recommend the following be implemented prior to approval of this NDA:

A. It appears you intend to include (b) (4) on the carton labeling. However, it is unclear what information you intend to include in (b) (4). To assist in our evaluation of the proposed labeling, provide the following information:

[a] Baugh D. Label and Labeling Review for Nextstellis (NDA 214154). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 23. RCM No.: 2020-805-1.

i. Rationale for including (b) (4) on the carton labeling.
ii. A (b) (4) to verify the information represented in (b) (4) on the labeling.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 23, 2020
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 214154
Product Name and Strength:	Nextstellis (drospirenone and estetrol) tablets, 3 mg/14.2 mg
Applicant/Sponsor Name:	Mayne Pharma LLC (Mayne)
OSE RCM #:	2020-805-1
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on October 8, 2020 for Nextstellis. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container label and carton labeling for Nextstellis (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. Although most of our previous recommendations were implemented, we reiterate our recommendations regarding the expiration date format and temperature statement and provide an additional recommendation for the linear barcode, in Section 3 below.

3 RECOMMENDATIONS FOR MAYNE PHARMA LLC

We recommend the following be implemented prior to approval of this NDA:

[a] Baugh D. Label and Labeling Review for Nextstellis (NDA 214154). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 SEP 14. RCM No.: 2020-805.

a. The expiration date format is not defined on the container label and carton labeling. We are unable to assess the expiration date format from a medication safety perspective (e.g., risk for degraded drug medication errors). To minimize confusion and reduce the risk for deteriorated product medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the product package label include a year, month, and non-zero day. Additionally, FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the product package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. A hyphen or a space may be used to separate the portions of the expiration date.
b. The storage statement on the carton labeling lacks sufficient details (lower limit of numerical temperature range), which may increase the risk of wrong storage errors. Revise the storage statement to read 'Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].' Ensure the temperature statements contain the temperature scale designation (i.e., "°C" or "°F") after each numerical value.
c. It is unclear whether the linear barcode on the blister container label contains, at a minimum, the appropriate National Drug Code (NDC) number. The NDC number must be contained within the linear barcode per 21 CFR 201.25. Ensure the linear barcode on the blister label contains, at a minimum, the NDC number, in accordance with 21 CFR 201.25.

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BRIANA B RIDER
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LABEL, LABELING, AND PACKAGING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 14, 2020
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 214154
Product Name, Dosage Form, and Strength:	Nextstellis (drospirenone and estetrol) tablets, 3 mg/14.2 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Mayne Pharma LLC (Mayne)
FDA Received Date:	April 15, 2020, May 18, 2020, July 17, 2020, and August 14, 2020
OSE RCM #:	2020-805
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 REASON FOR REVIEW

As part of the approval process for Nextstellis (drospirenone and estetrol) tablets, the Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the proposed labels and labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other – Information Request	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Nextstellis labels and labeling for areas of vulnerability that could lead to medication errors.

We note, in Section 16 (How Supplied/Storage and Handling) of the Prescribing Information (PI) submitted July 17, 2020 the following (b) (4) the Applicant stated that they intend to distribute this product as 1 blister card per carton (b) (4) and they submitted a revised PI on August 14, 2020 (b) (4)

We note the established name is denoted as 'estetrol/drospirenone tablets' on the labels and labeling. We defer to the Office of Pharmaceutical Quality (OPQ) to determine how the established name should be presented on the labels and labeling.

We identified the following areas of vulnerability:

GENERAL COMMENTS (container [pouch/pocket] and carton):

- The established name lacks prominence with the proprietary name and is difficult to read.
- The layout of the proprietary name, active ingredients, dosage form, and strength is not consistent with the presentation of the proprietary name, active ingredient, dosage form, and strength for drug products.[a]
- The format of the expiration date is not defined. Therefore, we are unable to assess the expiration date format from a medication safety perspective.

CARTON LABELING

- As currently presented, there is no placeholder for a product identifier on the carton labeling.
- The storage statement lacks sufficient details (numerical temperature range), which may increase risk of wrong storage errors.
- The dosage statement (b) (4) does not align with the language proposed in the PI, is incomplete (e.g., lacks route of administration and instruction to take consecutively for 28 days) and may contribute to confusion.
- The principal display panel lacks the following important warning: 'This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases'.

CONTAINER LABEL

- The blister label does not contain a linear barcode. A linear barcode is required on the immediate container label per 21 CFR 201.25(c)(2).

CALENDAR STICKER

- The calendar stickers and associated instructions can be improved for clarity.

PRESCRIBING INFORMATION

- Storage information is not included in Section 16 (How Supplied/Storage and Handling) of the Prescribing Information (PI) as required by 21 CFR 201.27(c)(17)(iv).
- The (b) (4) is used throughout the PI. However, the proposed proprietary name, Nextstellis, was found to be conditionally acceptable.
- The route of administration is misspelled in the dosage and administration section of the Highlights of the PI (HPI).

[a] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

- Section 2.1 [redacted] of the PI instructs that [redacted] using a Day 1 start". However, Table 1 provides instruction for 'Day 1 Start' [redacted] Start'. We are concerned that the inconsistency may lead to confusion.
- The instructions on [redacted] As such, we are concerned that important dosing information presented in Section 2.2 may be overlooked.
- The strength, 3 mg, lacks a space between the number and unit of measure (i.e., 3mg) in Section 3 'Dosage Forms and Strengths' of the HPI, which may negatively impact the readability.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the label and labeling where important information should be added or further clarified to help ensure the safe use of this product. See our recommendations in Sections 4.1 and 4.2 and we advise they be implemented prior to the approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF UROLOGY, OBSTETRICS, AND GYNECOLOGY (DUOG)

A. Prescribing Information (PI)

1. General

   a. The [redacted] is used throughout the PI. The proposed proprietary name, Nextstellis, was found to be conditionally acceptable on July 13, 2020.[b] We recommend replacing the [redacted] with the proprietary name, Nextstellis, throughout the PI.

2. Dosage and Administration Section (Highlights of PI)

   a. The route of administration (i.e., mouth) is spelled incorrectly (i.e., mount) in the Dosage and Administration Section of the highlights of the PI. We recommend revising to reflect the correct spelling of 'mouth'.

3. Dosage and Administration Section (Full PI)

   a. The instruction provided under the heading [redacted] Nextstellis using a 'Day 1 start'. However, the instructions which are associated with the heading 'Starting Nextstellis in [redacted] with no current use of hormonal contraception' in Table 1, include 'day 1 start' [redacted] We are concerned that the inconsistency may lead to confusion. We recommend revision to ensure the 'start day' information is expressed consistently across the labeling.

[b] Baugh, D. Proprietary Name Review for NEXTSTELLIS (NDA 214154). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 13. RCM No.: 2020-40006921.

b. Currently, instructions on [redacted] (b) (4) . We are concerned that important dosing information presented in Section 2.2 may be overlooked. Conside [redacted] (b) (4) to improve readability and minimize the risk of important information being overlooked.

2. Dosage Forms and Strengths (Highlights of PI)

   a. The strength of 3 mg lacks a space between the number and unit of measure (i.e., 3mg). Lack of space between the numerical strength and unit of measure may negatively impact the readability (e.g., the 'm' can sometimes be mistaken as a zero or two zeros). To improve readability, place adequate space between the strength and unit of measure (i.e., 3 mg instead of 3mg).

3. How Supplied/Storage and Handling Section

   a. Section 16 (How Supplied/Storage and Handling) does not include storage and handling information as required by 21 CFR 201.27(c)(17)(iv). As such, Section 16 of the PI should be revised to include special handling and storage conditions.

4.2 RECOMMENDATIONS FOR MAYNE

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels and Carton Labeling)

1. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2. The layout of the proprietary name, active ingredients, dosage form, and strength is not consistent with the presentation of the proprietary name, active ingredient, dosage form, and strength for drug products.[c] In addition, the established name is not in parentheses. The presentation should be reformatted to list the active ingredients in parentheses below the proprietary name followed by the dosage form and strength as follows:

Nextstellis (drospirenone and estetrol) tablets 3 mg/14.2 mg	OR	Nextstellis (drospirenone and estetrol tablets) 3 mg/14.2 mg

[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

3. The expiration date format is not defined on the container label and carton labeling. We are unable to assess the expiration date format from a medication safety perspective (e.g., risk for degraded drug medication errors). To minimize confusion and reduce the risk for deteriorated product medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the product package label include a year, month, and non-zero day. Additionally, FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the product package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. A hyphen or a space may be used to separate the portions of the expiration date.

B. Carton Labeling

1. As currently presented, there is no placeholder for a product identifier on the carton labeling. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act (DSCSA).[d] The Act requires manufacturers and re-packagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance. If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder for the human-readable and machine-readable (2-D data matrix barcode) product identifier to the carton labeling. The DSCSA guidance on product identifiers recommends the format of the human-readable portion be located near the 2D data matrix barcode as follows:

   NDC: [insert NDC]
   Serial: [insert serial number]
   LOT: [insert lot number]
   EXP: [insert expiration date]

2. The storage statement (b) (4) lacks sufficient details (numerical temperature range), which may increase risk of wrong storage errors. We recommend revising the storage statement to include all information needed to store the product properly.
3. (b) (4) does not align with the language proposed in the Prescribing Information, is incomplete (b) (4) and may contribute to confusion. We recommend you

[d] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

(b) (4) Alternatively, consider revising the dosage statement to read: 'Recommended dosage: See Prescribing Information.'

4. The principal display panel (PDP) lacks the following important warning: (b) (4) does not protect against HIV-infection (AIDS) and other sexually transmitted diseases' which is present in Section 17 (Patient Counseling Information) of the Prescribing Information. We recommend you add this warning to the PDP. For example, consider adding: "This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases." or a similar statement.

C. Container Label (Blister)

1. The blister label does not contain a linear barcode. A linear barcode is required on the immediate container label per 21 CFR 201.25(c)(2). Add a linear barcode that contains, at a minimum, the appropriate National Drug Code (NDC) number to the blister label.

D. Calendar Stickers

1. The calendar stickers and associated instructions can be improved for clarity. The instructions read: (b) (4) Consider revising the instructions to read: 'Peel the sticker off for the day you plan to start your tablets'. Additionally, consider utilizing a 3-letter abbreviation for days of the week (b) (4) to minimize the risk of confusion.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nextstellis received on July 17, 2020 from Mayne Pharma LLC.

Table 2. Relevant Product Information for Nextstellis	
Initial Approval Date	N/A
Active Ingredient	drospirenone and estetrol
Indication	Pregnancy prevention
Route of Administration	oral
Dosage Form	tablet
Strength	3 mg/14.2 mg
Dose and Frequency	One tablet daily
How Supplied	Carton contains 1 blister card that contain 28 tablets (24 active tablets and 4 placebo tablets)
Storage	(b) (4) Keep out of the reach and sight of children.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 10, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, '214154' and 'estetrol'. Our search identified no previous reviews.

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APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following drospirenone and estetrol labels and labeling submitted by Mayne Pharma LLC (Mayne).

- Container label received on April 15, 2020
- Carton labeling (containing one blister card) received on April 15, 2020
- Blister card label received on April 15, 2020
- Instructions for Use received on May 18, 2020, available from \\CDSESUB1\evsprod\nda214154\0004\m1\us\114-labeling\draft\labeling\1-14-1-3-draft-pi-ifu-text.pdf.
- Prescribing Information (Image not shown) received on August 14, 2020, available from\\CDSESUB1\evsprod\nda214154\0014\m1\us\114-labeling\draft\labeling\1-14-1-3-draft-uspi-text-redlined.docx
- Patient Package Insert (image not shown) received on May 18, 2020, available from \\CDSESUB1\evsprod\nda214154\0004\m1\us\114-labeling\draft\labeling\1-14-1-3-draft-pi-ifu-text.pdf.

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DENISE V BAUGH
09/14/2020 12:46:44 PM

BRIANA B RIDER
09/15/2020 01:18:04 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 214154
Submission Number	001
Submission Date	4/15/2020
Date Consult Received	5/8/2020
Drug Name	Estetrol monohydrate / Drospirenone
Indication	Oral Contraception (Section 3.1)
Therapeutic dose	14.2 mg estetrol anhydrous and 3 mg of drospirenone once daily (Section 3.1)
Clinical Division	DUOG

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 5/8/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review for IND-110682 dated 08/15/2017 in DARRTS (link);
- Previous IRT review for IND-110682 dated 01/31/2018 in DARRTS (link);
- Sponsor's clinical study protocol # MIT-Es0001-C106 (SN0001; link);
- Sponsor's clinical study report # MIT-Es0001-C106 (SN0001; link);
- Sponsor's QT assessment report # MIT-Es0001-C106 (SN0001; link);
- Sponsor's statistical analysis plan # MIT-Es0001-C106 (SN0001; link);
- Investigator's brochure Ver 6.0 (SN0035; link);
- Sponsor's proposed product label (SN0001; link);
- Highlights of clinical pharmacology and cardiac safety (Previous; SN0001; link)

1 SUMMARY

No significant QTc prolongation effect of estetrol and drospirenone was detected in this QT assessment.

The effect of estetrol and drospirenone were evaluated in MIT-Es0001-C106. This was a phase 1, randomized, double-blind, multiple-dose, parallel group with a nested crossover study to evaluating the QT effects of estetrol combination with drospirenone at therapeutic and supratherapeutic concentrations in healthy women. The highest dose evaluated was 75 mg estetrol and 15 mg drospirenone administered once daily for 10 days, which covers the worst case exposure scenario (UGT2B7 inhibition, section 3.1). The data were analyzed using exposure response analysis as the primary analysis, which did not suggest that estetrol and drospirenone are associated with significant QTc prolonging effect (refer to section 4.5) – see Table 1 for overall results. The findings of this analysis are further supported by the available nonclinical data (sections 3.1.2) and categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	Treatment	Concentration* (ng/mL)	ΔΔQTcF (msec)	90% CI (msec)
QTc	E4 75 mg / DRSP 15 mg QD	214.3	0.4	(-2.8 to 3.6)

**Concentration of DRSP; For further details on the FDA analysis please see section 4.*

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

No QT labeling language was proposed by the sponsor in the label submitted to SDN001 (link). Our proposal is provided below (addition). Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology At a dose 5 times the maximum approved recommended dose, <TRADENAME> does not prolong the QT interval to any clinically relevant extent.
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Estetra SPRL (Mithra Pharmaceuticals) is developing a new Combined Oral Contraceptive (COC) containing the synthetic form of a natural estrogen, Estetrol (E4) with a progestin, Drospirenone (DRSP) for prevention of pregnancy in females of reproductive potential. Progestins inhibit ovulation primarily by a central feedback mechanism resulting in decreased luteinizing hormone secretion by the pituitary. Estrogen contributes to contraceptive efficacy because of its inhibitory effect on follicle stimulating hormone secretion. E4 is a synthetic analogue of a native human estrogen produced by the fetal liver during human pregnancy. Its concentration increases throughout the pregnancy in the fetal and maternal plasma and reaches its maximum at the end of the pregnancy (about 1 ng/mL

in the maternal plasma). DRSP is a synthetic steroid hormone with progestagenic activity. DRSP is also the progestogenic component used in the other commercial COC products at 3 mg daily dose.

The product is formulated as immediate-release film-coated tablet formulation containing 14.2 mg of estetrol anhydrous and 3 mg of drospirenone for oral administration. The proposed therapeutic dose is one tablet consisting of 14.2 mg estetrol anhydrous and 3 mg of drospirenone once daily (one tablet is administered daily for 24 days followed by inert tablet for 4 days). The peak concentrations of 14.3 ng/mL (Tmax: ~1 h) for E4 and 40.7 ng/mL (Tmax: ~2 h) for DRSP are expected at steady-state with the proposed therapeutic dose (Day 10; Study # MIT-Es0001-C106).

The studies indicate that E4 is mainly metabolized UGT2B7. Thus, concomitant administration of E4 with an inhibitor of UGT2B7 is expected to result in increased exposures of E4 (Cmax: ~36% & AUC: ~25%; Study # MIT-Es0001-C110). However, the impact on the pharmacokinetics of DRSP was not significant. The sponsor proposes to contraindicate use of the product in patients with hepatic impairment and hepatic impairment. In general, the products containing DRSP are contraindicated in patient with renal impairment or hepatic impairment.

The sponsor characterized the QT effects of E4 and DRSP in their thorough QT study (Study # MIT-Es0001-C106). This was a phase 1, randomized, double-blind, multiple-dose, parallel group with a nested crossover study to evaluating the QT effects of estetrol combination with drospirenone at therapeutic and supratherapeutic concentrations in healthy women. Subjects in Group 1 (n=28) received a therapeutic dose of E4/DRSP once daily for 10 days followed by a supratherapeutic dose once daily for another 10 days. Subjects in Group 2 (n=28) received E4/DRSP placebo, 400 mg oral moxifloxacin, and oral moxifloxacin placebo in a nested crossover fashion. Continuous ECGs were planned for 24 hours on Day -1 (baseline), Day 1, 10, 20 and 21 and extracted at pre-defined PK matching timepoints (-0.5, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h). Blood samples for the determination of E4 and DRSP concentrations were planned at pre-dose and for 24 hours following dosing on the same days (Day 1, 10, 20, and 21). The primary analysis was based on concentration-QTc modeling of the relationship between E4 and DRSP plasma concentrations and ΔQTcF (see Appendix for details).

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's non-clinical overview (m2.4), the previous highlights of clinical pharmacology and clinical safety (link), and the previous IRT reviews (Dt: 08/15/2017 and 01/31/2018).

In HEK-293 cells expressing the human ether-a-go-go related gene (hERG), E4 at a concentration of 28.17 μM decreased hERG tail current amplitude by only 7.1%, while the positive control E-4031 decreased hERG tail current amplitude by 83.6% (ES-T30; TS Table 2.6.3.4).

E4 had no effect on heart rate, blood pressure or electrocardiogram parameters and did not induce arrhythmia in conscious telemetered female cynomolgus monkeys, at single oral dose levels up to and including the highest tested dose of 100 mg/kg (ES-T23; TS Table 2.6.3.4).

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for E4 in combination with DRSP was based on exposure-response analysis, please see section 3.2.3 for additional details.

Sponsor's report included by-time analysis results for all intervals. Sponsor used the following model: ΔQTcF = Time + Treatment + Time * Treatment.

An unstructured covariance structure was used to specify the repeated measures (time within subject).

Reviewer's comment: *FDA reviewer used different linear mixed effect model for by-time analysis. FDA reviewer also adjusted for baseline values as a fixed effect covariate. Time trend is similar with consistent differences. FDA reviewer's analysis shows that reduction in change from baseline in PR was observed at both combinations of E4 and DRSP. Please see section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

Exposure-response analysis was used for assay sensitivity analysis. By-time analysis for assay sensitivity also shows that assay sensitivity was established by the moxifloxacin arm.

Reviewer's comment: *FDA reviewer's analysis also shows that assay sensitivity was established by moxifloxacin arm. Please see 4.3 and 4.5 for additional details.*

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline, HR (<45 or >100 bpm), PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *FDA reviewer's analysis results are similar to the sponsor's analysis. Please see section 4.4 for additional details.*

3.2.3 Exposure-Response Analysis

The sponsor performed PK-PD analyses to explore the relationship between the change from baseline in QTc intervals (ΔQTcF) and plasma concentrations of E4 and DRSP using a linear mixed-effects modeling approach. The sponsor's model used change-from-baseline QTcF (ΔQTcF) as the dependent variable and time (categorical), treatment (therapeutic and supratherapeutic doses of E4/DRSP and corresponding placebo), and time-by-treatment interaction as fixed effects.

The sponsor's model predicted placebo-corrected change from baseline QTcF (90% upper confidence interval) values of -0.43 (2.72) for E4 and 0.06 (3.26) ms for DRSP at the mean peak plasma levels for the highest studied dose of 75 mg E4 and 15 mg DRSP, respectively, administered orally once daily for 10 days. The conclusions from the concentration-QTc analysis for the full model with interaction, the full model without interaction, the model

with E4 alone the model with DRSP alone were similar. The model with DRSP alone was selected as the primary model.

Reviewer's comment: The results of the reviewer's analysis agreed with the sponsor's conclusion. Refer to section 4.5 for our exposure-response analysis.

3.2.4 Safety Analysis

A total of 183 TEAEs were reported by 47 (73.4%) subjects. Thirty-eight (59.4%) subjects reported TEAEs that were mild in severity, and 8 (12.5%) subjects reported TEAEs that were moderate in severity.

Two serious adverse events (SAEs) were reported: complicated migraine and deep vein thrombosis. No deaths were reported.

Two subjects had study drug withdrawn early due to a TEAE: 1 due to complicated migraine and 1 due to elevated liver enzymes.

Reviewer's comment: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 bpm) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY TIME ANALYSIS

The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The default model also includes a compound symmetry (cs) covariance matrix to explain the associated between repeated measures (time within subject * treatment).

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of ΔΔQTcF Timecourse (unadjusted CIs).

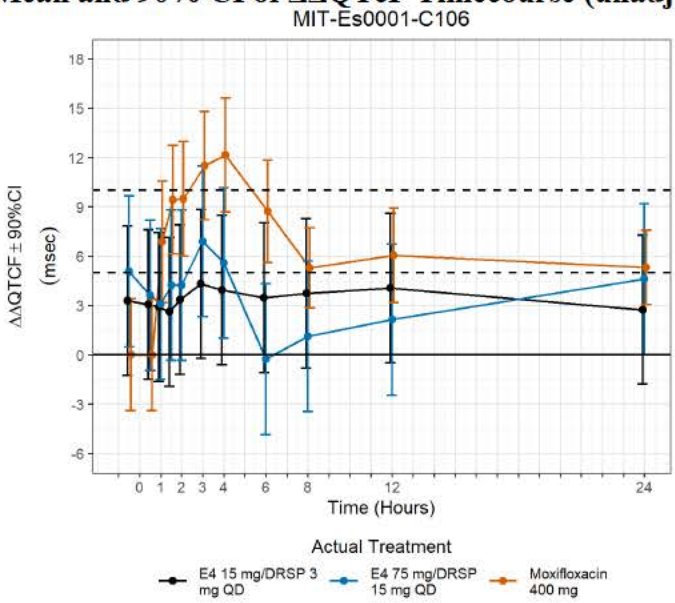


Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTc

Actual Treatment	N	Time (Hours)	ΔΔQTCF (msec)	90.0% CI (msec)
E4 15 mg/DRSP 3 mg QD	32	3.0	4.3	(-0.2 to 8.8)
E4 75 mg/DRSP 15 mg QD	31	3.0	6.9	(2.3 to 11.5)

Reviewer's comment: *At the supratherapeutic dose level, the upper confidence interval for the largest mean increase in ΔΔQTcF exceeded 10 msec. However, the by-time analysis was not the primary analysis and the study was not designed to exclude a 10-msec increase using this analysis.*

4.3.1.1 Assay sensitivity

The primary method for establishing assay sensitivity for this study was based on exposure response analysis - see section 4.5.1.1 for details.

Statistical reviewer also performed by-time analysis for moxifloxacin arm using linear mixed model. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associated between repeated measures within period. The time-course of changes in ΔΔQTcF is shown in Figure 1 and shows the expected time-profile with a mean effect of > 5 msec after Bonferroni adjustment for 4 time points (Table 3).

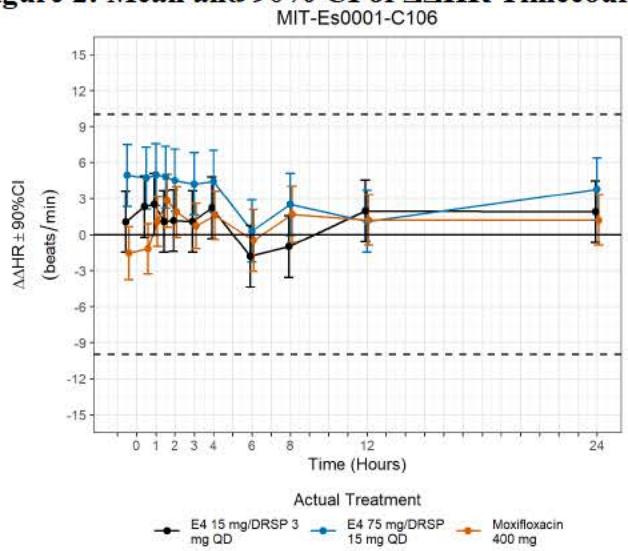
Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTc

Actual Treatment	N	Time (Hours)	ΔΔQTCF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	31	4.0	12.2	(8.7 to 15.6)	(7.3 to 17.0)

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

Figure 2: Mean and 90% CI of ΔΔHR Timecourse



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups. The maximum ΔΔPR values by treatment are shown in Table 4.

Figure 3: Mean and 90% CI of ΔΔPR Timecourse

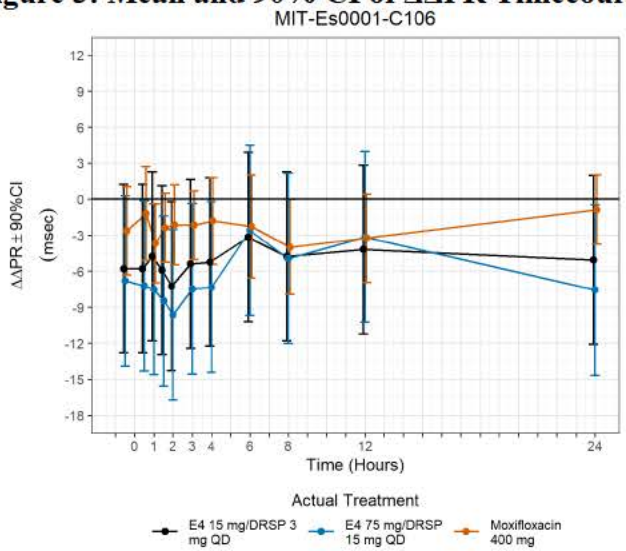


Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔPR

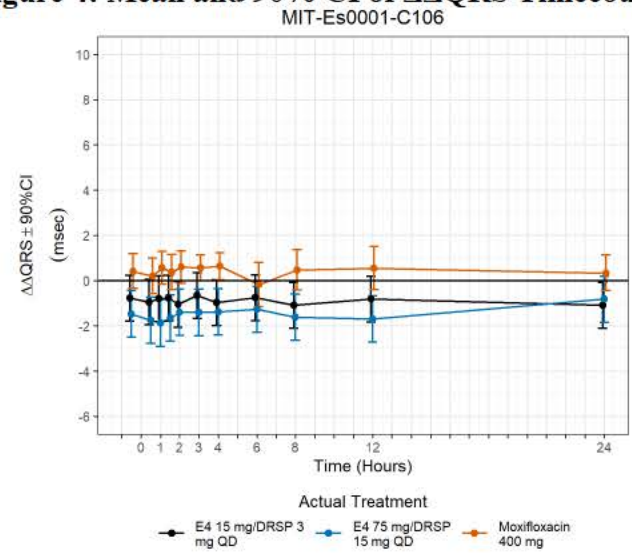
Actual Treatment	N	Time (Hours)	ΔΔPR (msec)	90.0% CI (msec)
E4 15 mg/DRSP 3 mg QD	32	6.0	-3.2	(-10.2 to 3.9)
E4 75 mg/DRSP 15 mg QD	31	6.0	-2.6	(-9.7 to 4.5)

Reviewer's comment: *By-time analysis shows reduction of PR in both combinations of E4 and DRSP.*

4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Timecourse



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

None of the subjects experienced QTcF greater than 500 msec or ΔQTcF greater than 60 msec in both dose levels of E4 and DRSP.

4.4.2 HR

None of the subjects experienced HR greater than 100 beats/min in both dose levels of E4 and DRSP.

4.4.3 PR

None of the subjects experienced PR greater than 220 msec in both dose levels of E4 and DRSP.

4.4.4 QRS

None of the subjects experienced QRS greater than 120 msec in both dose levels of E4 and DRSP.

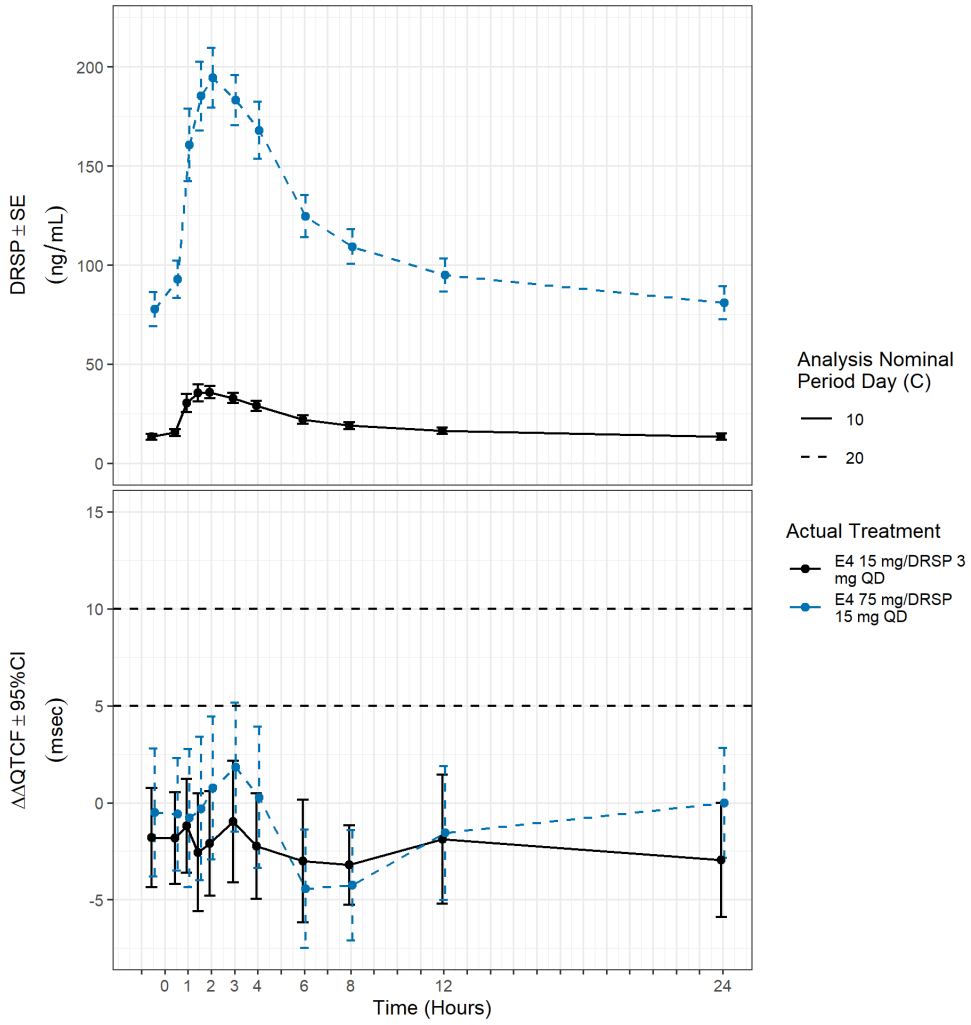
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between ΔQTcF and concentration of E4 and DRSP in healthy subjects. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

Prior to evaluating the relationship between concentration of E4 or DRSP and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between concentration of E4 or DRSP and ΔΔQTc and 3) presence of non-linear relationship.

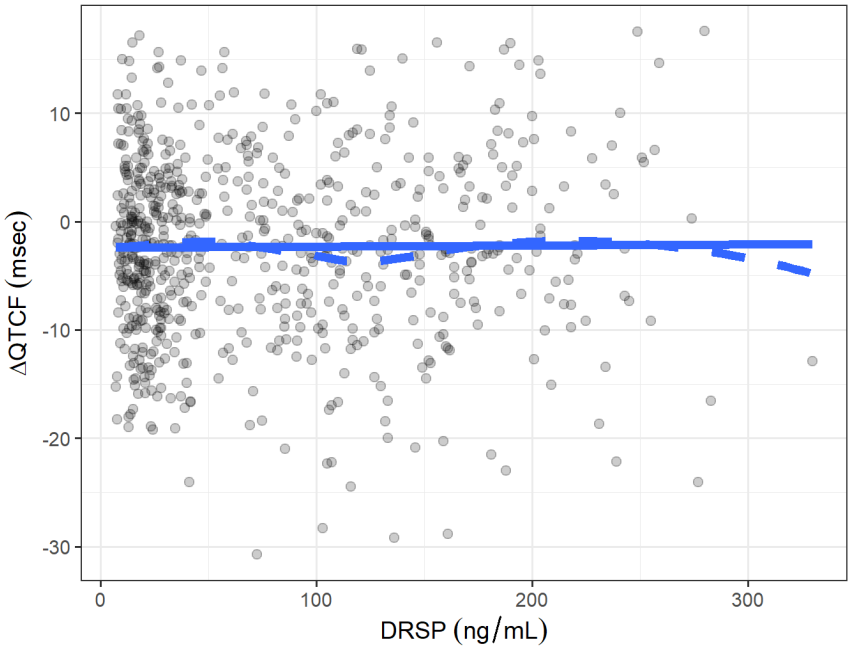
An evaluation of the time-course of DRSP concentration and changes in ΔΔQTcF is shown in Figure 5. There was no apparent correlation between the time at maximum effect on ΔΔQTcF and peak concentrations of DRSP indicating no significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and the maximum change in heart rate is below 10 bpm (Sections 4.3.2 and 4.4.2).

Figure 5: Time course of drug concentration (top) and QTc (bottom)



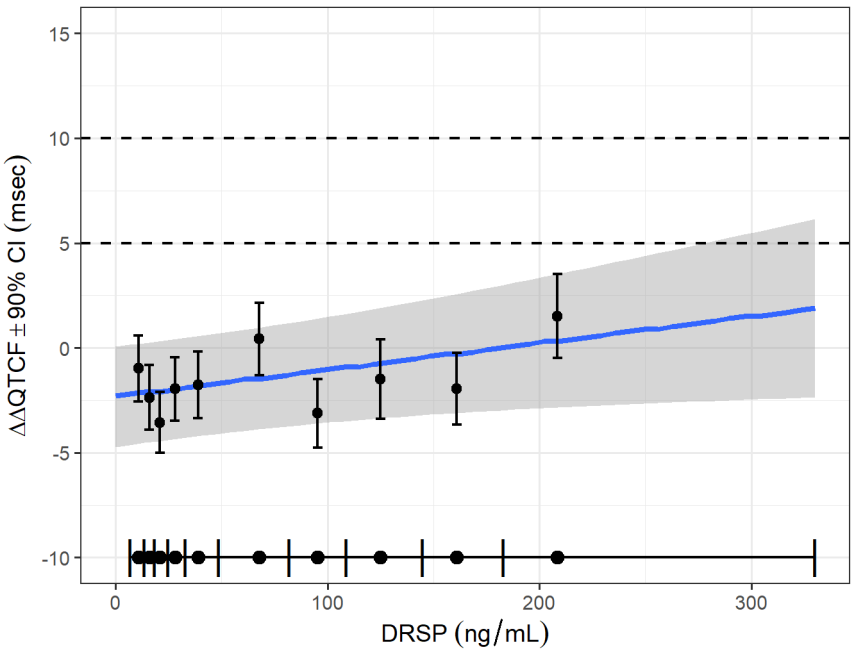
After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between DRSP concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between DRSP concentration and ΔQTc and supports the use of a linear model.

Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provide in Table 1.

Figure 7: Goodness-of-fit plot for QTc

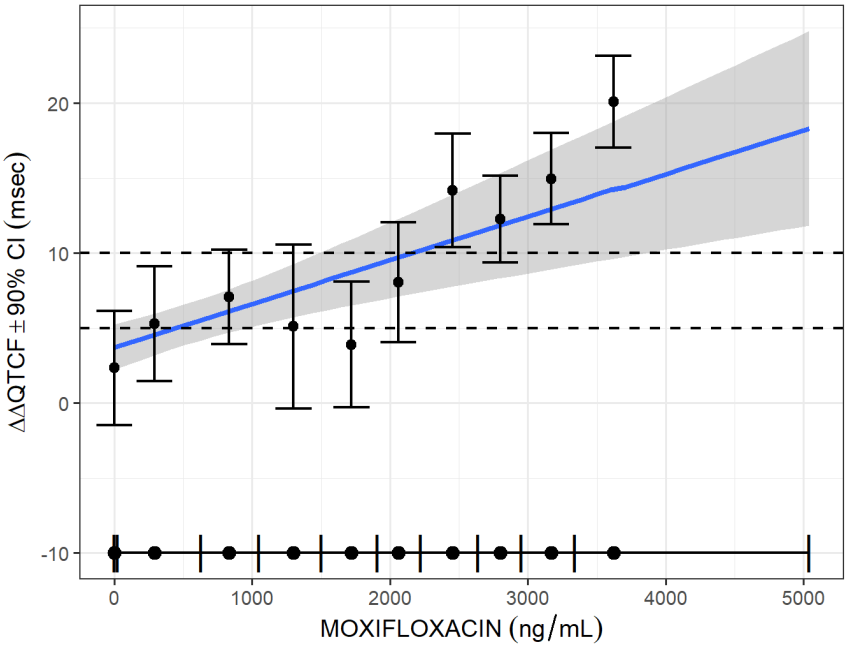


4.5.1.1 Assay sensitivity

To demonstrate assay sensitivity, the sponsor included oral moxifloxacin 400 mg as a positive control to detect small increases from baseline for QTcF in this study. The PK profile in the moxifloxacin group are generally consistent with the ascending, peak, and

descending phases of historical data (data not shown). Concentration-response analysis of moxifloxacin data indicated a positive slope in the relationship between ΔQTcF and the plasma concentration of moxifloxacin. The lower limit of the two-sided 90% confidence interval at the observed mean peak concentrations of moxifloxacin is above 5 ms. Therefore, assay sensitivity is established. The goodness-of-fit plot for moxifloxacin is shown in Figure 8.

Figure 8: Goodness-of-fit plot for ΔΔQTc for moxifloxacin



Assay sensitivity was also established using by time analysis. Please see section 4.3.1.1 for additional details.

5 APPENDIX

5.1 EVALUATION OF CLINICAL QT ASSESSMENT PLAN

1. Product Information			
Generic Name	Estetrol monohydrate / Drospirenone	Brand Name	Not available
Drug class	Combined Oral Contraceptive		
Combination product	Yes		
Indication	Oral Contraception (Section 3.1)		
Therapeutic Dose	14.2 mg estetrol anhydrous and 3 mg of drospirenone once daily (Section 3.1)		
Maximum Tolerated Dose	Not identified		
Dosage Form	Tablet	Route of Administration	Oral

2. Clinical Cardiac Safety
Refer to the Sponsor's summary of clinical safety (m2.7.3; Section 4.3)

3. QT Studies								
3.1 Primary Studies								
Protocol number / Population	**ECG Quality**		**Arms**		**Sample size**		**ECG & PK assessments**	
	Assessment	**Ok?**	**Arms**	**High dose covers?**	**No subjects**	**Ok?**	**Timing**	**Ok?**
Protocol number: MIT-	Central read? Yes Blinded? Yes	Yes	Highest dose: 75 mg E4 / 15 mg DRSP for 10 days	High clinical	64	Yes	Baseline: Time-matched	Yes

Es0001-C106 Population: Healthy volunteers Design: Parallel with nested crossover	Replicates? Yes		Placebo: Yes Positive control: Yes				Timing: 0.5 1.0 1.5 2, 3, 4, 6, 8, 12, 24 on day 10 and day 20.	

3.1 Secondary Studies
Not applicable.

3.3 Data pooling	
Data pooling?	No
Did sponsor propose an assessment for heterogeneity?	N/A
Is the data pooling appropriate?	N/A

4. Analysis plan

4.1 Study Objective related to QT	
What QTc effect size is the analysis trying to exclude?	10 ms (E14)

4.2 Dose Justification

The peak concentration observed with the actual highest dose (i.e., 75 mg E4 / 15 mg DRSP for 10 days) used in the study is expected to offer ~5-fold margin over the therapeutic exposures (i.e., 15 mg E4 / 3 mg DRSP) associated with the maximum proposed dose at the steady-state. Based on the safety profile of single and multiple oral E4/DRSP doses observed in Study MIT-Es0001-C103, a therapeutic dose of 15 mg E4 / 3 mg DRSP is considered safe. The supratherapeutic dose level is aimed to result in Cmax levels 2-fold above those observed in patients with organ impairment or on concomitant drugs that result in high plasma levels, based on drug-drug- interactions. Depending on the results of drug-drug interaction study MIT-Es0001-C110 the supratherapeutic dose level may be changed up- or downwards, up to a maximum of 120 mg E4 / 24mg DRSP.	
4.3 QT correction method	
Is an HR increase or decrease greater than 10 bpm?	No
Primary method for QT correction	QTcF
4.4 Assay Sensitivity	
Assay sensitivity methods proposed by sponsor	☒ Moxifloxacin ☐ Exposure-margin ☐ QT bias assessment ☐ Not applicable (objective is large mean effects) ☐ Other
4.5 By Time Analysis	
4.5.1 Investigational drug	
Primary analysis	No

Did the sponsor use IUT or descriptive statistics?	IUT
For IUT: Does the sponsor use MMRM to analyze longitudinal values that considers the correlation across time-points or use ANCOVA by time-point without considering correlation?	MMRM
For IUT: Is the MMRM model specified correctly with regards to covariance structure, covariates, etc?	Yes
The analysis for QTcF was based on a linear mixed-effects model with change-from-baseline QTcF (ΔQTcF) as the dependent variable and time (categorical), treatment (therapeutic and supratherapeutic doses of E4/DRSP and corresponding placebo), and time-by-treatment interaction as fixed effects. An unstructured covariance matrix was specified for the repeated measures at post-baseline timepoints within subjects. If the model with unstructured covariance matrix failed to converge, other covariance matrices such as compound symmetry and autoregressive were to be considered. From this analysis, the LS mean and 2-sided 90% CIs were calculated for the contrast "E4/DRSP versus placebo" at each dose of E4/DRSP and each postbaseline timepoint, respectively.	
4.5.2 Positive control	
Primary analysis	No
Did the sponsor adjust for multiplicity?	Unknown

By-timepoint analysis was performed for the contrast “moxifloxacin versus placebo” at post-baseline timepoints on Day 1 and Day 21. That is, the linear mixed-effects model was used with ΔQTcF as the dependent variable, time (i.e., post-baseline timepoint: categorical), treatment (moxifloxacin and moxifloxacin-placebo), and time-by-treatment interaction as fixed effects. Sequence (placebo-moxifloxacin or moxifloxacin-placebo) was also included in the model as an additional covariate for this nested crossover design. An unstructured covariance matrix was specified for the repeated measures at post-baseline timepoints for subject within visit. If the model with an unstructured covariance matrix failed to converge, another covariance matrix such as compound symmetry and autoregressive was to be considered.	
4.6 Concentration-QTc analysis	
4.6.1 Investigational drug	
5.Primary analysis	Yes
What is the dependent variable in the sponsor’s model?	Single delta
White paper model?	Yes
Which concentration covariate(s) are included in the model?	Multiple
Did the sponsor propose an assessment of delayed effects?	Yes
Did the sponsor propose an assessment of linearity?	Yes
Did the sponsor propose model selection criteria?	Yes

What methods did the sponsor use for predicting the QT effect?	☒ Model-based confidence intervals ☐ Bootstrap-derived confidence intervals
The relationship between E4 and DRSP plasma concentrations and ΔQTcF was quantified using a linear mixed-effects modeling approach. A full model was considered with ΔQTcF as the dependent variable, time-matched concentrations of E4 and DRSP and their interaction as the exploratory variates (0 for placebo), treatment (active = 1 or placebo = 0) and time (i.e., nominal post-baseline timepoint) as categorical factors, and random intercept and slopes per subject.	
4.6.2 Positive control	
Primary analysis	Yes
Same model as investigational drug	No
4.7 Categorical analysis	
QTc?	Yes
ΔQTc?	Yes
PR?	Yes
QRS?	Yes
HR?	Yes
T-wave morphology?	Unknown

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