1 TITLE PAGE

Clinical Trial Protocol: MIT-Es0001-C302

Study Title:	A Multicenter, Open-label, Single-Arm Study to Evaluate the Contraceptive Efficacy and Safety of a Combined Oral Contraceptive Containing 15 mg Estetrol and 3 mg Drospirenone
Study Short Title:	E4 FREEDOM (**F**emale **R**esponse concerning **E**fficacy and safety of **E**stetrol/**D**rospirenone as **O**ral contraceptive in a **M**ulticenter study)
Study Number:	MIT-Es0001-C302
ClinicatTrials.gov registration No.	NCT02817841
IND Number:	110,682
Investigational Product:	15 mg Estetrol/3 mg Drospirenone
Indication:	Prevention of pregnancy
Sponsor:	Estetra SPRL Rue Saint Georges 5-7 4000 Liège Belgium Telephone: +32 4 349 28 22 Fax: +32 4 349 28 21
Safety Monitor:	PRA Health Sciences PRA Pharmacovigilance Department Telephone: +1 (800) 772-2215 Fax: +1 (888) 772-6919 Email: CHOSafety@prahs.com
Original Protocol Date:	07 June 2016 Final Version 1.1
Amendment 1.0	
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Date	10 July 2017

Confidentiality Statement

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2 SYNOPSIS

Sponsor: Estetra SPRL
Investigational Product: 15 mg Estetrol (E4)/3 mg Drospirenone (DRSP)
Study Title: A Multicenter, Open-label, Single-Arm Study to Evaluate the Contraceptive Efficacy and Safety of a Combined Oral Contraceptive (COC) Containing 15 mg E4 and 3 mg DRSP.
Study Number: MIT-Es0001-C302
Study Phase: Phase 3
Primary Objective – Efficacy: To evaluate the contraceptive efficacy of 15 mg E4/3 mg DRSP using the Pearl Index in subjects aged 16 to 35 years, inclusive, at the time of screening. **Primary efficacy endpoint:** The number of on-treatment pregnancies as assessed by the Pearl Index in subjects aged 16 to 35 years, inclusive, at the time of screening.
Secondary Efficacy Objectives: 1. To evaluate the contraceptive efficacy of 15 mg E4/3 mg DRSP using the method failure Pearl Index and life-table analysis in subjects aged 16 to 35 years, inclusive, at the time of screening. 2. To evaluate the contraceptive efficacy of 15 mg E4/3 mg DRSP using the Pearl Index, the method failure Pearl Index and life-table analysis in the overall study population. **Secondary efficacy endpoints:** 1. The number of on-treatment pregnancies as assessed by the method failure Pearl Index and the cumulative pregnancy rate in subjects aged 16 to 35 years, inclusive, at the time of screening. 2. The number of on-treatment pregnancies as assessed by the Pearl Index, the method failure Pearl Index and the cumulative pregnancy rate in the overall study population.
Other Secondary Objectives: 1. To evaluate cycle control and bleeding pattern associated with 15 mg E4/3 mg DRSP. 2. To evaluate general safety of 15 mg E4/3 mg DRSP.

3. To evaluate the impact of 15 mg E4/3 mg DRSP on physical, psychological, and social functioning and well-being.
4. To assess the effect of various individual characteristics/ covariates (body weight, race, smoking, and fed/fasted condition) on the pharmacokinetics (PKs) of 15 mg E4/3 mg DRSP (Population PK Substudy).

Other secondary endpoints:

1. Cycle control and bleeding patterns based on vaginal bleeding information recorded daily by the subjects in the diaries.
2. Safety data in the overall study population obtained from routine laboratory parameters, vital signs, and physical, gynecological and breast examinations, evaluated as the number, frequency, type and intensity of adverse events (AEs) and serious adverse events (SAEs).
3. Change from baseline to end of treatment in the different items of well-established questionnaires.
4. Plasma E4 and DRSP concentration data from a subset of approximately 500 subjects for the development of a population PK model (Population PK Substudy).

Study Design:

Multicenter, open-label, single-arm study.

Study Population:

Approximately 2000 healthy female subjects at risk for pregnancy, between 16 and 50 years old, inclusive (at the time of screening), and requesting contraception will be enrolled in the study and initiate the investigational product. In total 1800 subjects will be 16 to 35 years old, inclusive (at the time of screening). Recruitment may be stopped when 2000 subjects have initiated the investigational product if the required number of subjects for the primary analysis (1800 subjects in the age group up to and including 35 years) has been reached. Recruitment in the age group > 35 years will be stopped when 200 subjects have initiated the investigational product. Approximately 500 of these subjects will be included in the Population PK Substudy.

Study Locations:

This clinical study will be conducted in up to approximately 80 centers in North America (United States of America and Canada).

Eligibility criteria:

❖ **Inclusion criteria:**

A subject will be considered for inclusion in the study if she meets all of the following criteria:

1. Heterosexually active female at risk for pregnancy and requesting contraception.
2. Negative serum pregnancy test at subject screening.
3. Aged 16 to 50 years (inclusive) at the time of signing the informed consent (IC).

4. Willing to use the investigational product as the primary method of contraception for 13 consecutive cycles.
5. Good physical and mental health on the basis of medical, surgical and gynecological history, physical examination, gynecological examination, clinical laboratory, and vital signs.
6. Body mass index (BMI) below or equal to (≤) 35.0 kg/m^2.
7. Able to fulfill the requirements of the protocol and have indicated a willingness to participate in the study by providing written IC.
8. Willing and able to complete the diaries and questionnaires.

❖ **Exclusion Criteria**

A subject will be excluded from participation if she meets any of the following 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.
2. Clinically relevant abnormal laboratory result at screening in the opinion of the investigator with an understanding of the central laboratory normal range.
3. Known hypersensitivity to any of the investigational product ingredients.
4. Currently pregnant or with the intention to become pregnant during the course of the study.
5. Currently breastfeeding or before two spontaneous menstruations have occurred after cessation of breastfeeding prior to start of trial medication.
6. Less than 6 weeks since last delivery/2nd trimester abortion and before spontaneous menstruation has occurred following a delivery or 2nd trimester abortion.
7. Smoking nicotine-containing products if ≥ 35 years old.
8. Dyslipoproteinemia requiring active treatment with antilipidemic agent.
9. Diabetes mellitus with vascular involvement (nephropathy, retinopathy, neuropathy, other) or diabetes mellitus of more than 20 year duration.
10. Any arterial hypertension (controlled and uncontrolled) defined by blood pressure values of:
    a. systolic blood pressure ≥ 140 mmHg and/or,
    b. diastolic blood pressure ≥ 90 mmHg.
11. Personal history of deep vein thrombosis or pulmonary embolism.
12. Current prolonged immobilization or major surgery with prolonged immobilization planned in the next 12 months.
13. Known inherited or acquired hypercoagulopathies (e.g. antiphospholipid syndrome) or thrombogenic mutations (e.g. factor V Leiden, prothrombin mutation, protein S, protein C and antithrombin deficiencies).
14. Current treatment with anticoagulants.
15. Presence or history of arterial thromboembolism (e.g. angina pectoris, ischemic heart disease, cerebral stroke or transient ischemic attack).
16. Complicated valvular heart disease (pulmonary hypertension, atrial fibrillation, subacute bacterial endocarditis).

17. History of pregnancy-related cardiomyopathy or moderately or severely impaired cardiac function.
18. Systemic lupus erythematosus.
19. Presence or history of migraine with aura at any age or migraine without aura if ≥35 years old.
20. Within the past 6 months, has had undiagnosed (unexplained) abnormal vaginal bleeding, or any abnormal bleeding that is expected to recur during the trial (e.g., bleeding from cervical polyp, recurrent bleeding after sex).
21. In case of Chlamydial or gonococcal infection at screening, when no treatment initiated at subject enrollment.
22. Abnormal Pap test (written documentation of prior test or test at screening exam) based on the following criteria:
    - Pap test in the past 18 months with ASC-US unless:
      - less than 21 years of age; or
      - a repeat Pap test at least 6 months later was normal; or
      - reflex HPV testing was performed and was negative for high-risk oncogene human-papilloma-virus (HPV).
    - Pap test in the past 18 months with LSIL unless less than 21 years of age.
    - Pap test in the past 18 months with ASC-H, atypical glandular cells, HSIL or malignant cells.
23. Presence of an undiagnosed breast mass.
24. Current symptomatic gallbladder disease.
25. History of COC-related cholestasis.
26. Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
27. Presence or history of pancreatitis if associated with hypertriglyceridemia.
28. Porphyria.
29. Presence or history of hepatocellular adenoma or malignant liver tumor.
30. Renal impairment (GFR < 60 mL/min/1.73m²).
31. Hyperkaliemia or presence of conditions that predispose to hyperkaliemia such as renal impairment, hepatic impairment, adrenal insufficiency and women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium concentration (e.g. ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonist and non-steroidal anti-inflammatory drugs).
32. History of organ transplantation within 5 years before screening or chronic disease potentially necessitating organ transplantation during the anticipated course of the study.
33. Presence or history of hormone-related malignancy.
34. History of non-hormone-related malignancy within 5 years before screening. Subjects with a non-melanoma skin cancer are allowed in the study.
35. Current regular use or regular use within 1 month prior to subject enrollment of drugs potentially triggering interactions with COCs including but not limited to:

a. Cytochrome P450 3A4 (CYP 3A4) inducers: barbiturates, primidone, bosentan, felbamate, griseofulvin, oxcarbazepine, topiramate, carbamazepine, phenytoin, rifampicin, St John's wort.
b. CYP 3A4 inhibitors: azole antifungals, phenylbutazone, modafinil, cimetidine, verapamil, macrolides, diltiazem and grapefruit juice.
c. Human immunodeficiency virus (HIV)/Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

36. Use of an injectable hormonal method of contraception within 10 months (300 days) prior to screening of an injection with a 3-month duration, within 6 months (180 days) prior to screening of an injection with a 2-month duration, within 3 months (90 days) prior to screening of an injection with a 1-month duration.
37. History of alcohol or drug abuse (including laxatives) within 12 months prior to screening.
38. Any prior procedure, disease or condition that could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the investigational product.
39. Uncontrolled thyroid disorders.
40. Participation in another investigational drug clinical study within 1 month (30 days) or have received an investigational drug within the last 3 months (90 days) prior to study entry. Subjects who participated in an oral contraceptive clinical study, using FDA/EU approved active ingredients, may be enrolled 2 months (60 days) after completing the preceding study.
41. Sponsor, the Contract Research Organization (CRO) or Investigator's site personnel directly affiliated with this study.
42. Is judged by the Investigator to be unsuitable for any reason.

Investigational Product; Dose; and Mode of Administration:

The investigational product is a 15 mg E4/3 mg DRSP tablet administered orally once daily in a 24/4-day regimen (i.e. 24 days of active tablets followed by 4 days of placebo tablets).

Duration of the study:

Overall treatment duration is up to thirteen 28-day cycles, i.e., 12 months.

Those subjects who discontinue due to a pregnancy wish will be followed-up for a maximum of one year after study discontinuation for return of spontaneous menstruation and until pregnancy or initiation of a contraceptive method (whichever occurs first).

Statistical Methods:

For the efficacy analyses, the pregnancy rates will be expressed as:

- Pearl Index (number of pregnancies per 100 woman years due to method and user failure) with a two-sided 95% confidence interval (CI);
- Method failure Pearl Index (number of pregnancies per 100 woman years due to method failure only) with a two-sided 95% CI;
- Life-table analysis (cumulative pregnancy rate).

For Pearl index calculations, thirteen 28-day cycles constitute one woman-year.

Primary Efficacy Analysis:

Pearl Index for subjects aged 16 to 35 years, inclusive, at the time of screening.

Secondary Efficacy Analyses:

- Method failure Pearl Index and life-table analysis for subjects aged 16 to 35 years, inclusive, at the time of screening.
- Pearl Index, method failure Pearl Index and life-table analysis for the overall study population (16 to 50 years).

Additional Summaries:

- Occurrence of scheduled and unscheduled vaginal bleeding/spotting in the overall study population.
- Compliance analysis based on tablet intake in the overall study population.
- Number, frequency, type and intensity of AEs and SAEs in the overall study population.
- Descriptive summaries for other safety parameters including clinical labs, physical exams, gynecological exams, and vital signs.
- Descriptive summaries of scores of well-being questionnaires.
- Population PK model (using plasma E4 and DRSP concentration data from a subset of approximately 500 subjects). PK parameters will include, but not be limited to:
  - Apparent clearance (CL/F).
  - Central volume of distribution (V/F).
  - Lag time of Absorption (tlag), if necessary.
  - Relative bioavailability for fed vs fasted state
  - Maximum concentration (C_{max}).
  - Time to C_{max} (T_{max}).
  - Extent of exposure for the dosing interval (AUC_{tau}).
  - Terminal half-life ($t_{1/2}$).

Continuous variables will be summarized using descriptive statistics (mean, median, 25th percentile, 75th percentile, standard deviation (SD), standard error of the mean (SEM), minimum, maximum, and number of subjects) and all categorical variables will be summarized using frequency distributions (number and percentage of subjects), as appropriate.

Initial estimates of PK parameters (e.g., CL/F, V/F, tlag) will be determined using exploratory compartmental analyses. These estimates will be employed to build an appropriate population PK model. The primary parameters will include (but not be limited to) CL/F, V/F, tlag and relative bioavailability for fed vs fasted. The impact of individual characteristics (body weight, race, smoking, and fed/fasted condition) on the PK parameters will be explored and included in the population model if significant. Individual estimates of

the parameters and additional PK variables will be generated based on the population model. Covariate analyses will be performed separately for the PK of E4 and DRSP.

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4 LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APC	Active protein C
ASC-H	Atypical squamous cells with possible high-grade squamous intraepithelial lesion
ASC-US	Atypical squamous cells of undetermined significance
AST	Aspartate aminotransferase
BMI	Body mass index
CBG	Corticosteroid binding globulin
CFR	Code of federal regulations
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CIS	Carcinoma in situ
COC	Combined oral contraceptive
CRO	Contract research organization
CYP 3A4	Cytochrome P450 3A4
DRSP	Drospirenone
E2	Estradiol
E2V	Estradiol valerate
E4	Estetrol
eCRF	Electronic case report form
EE	Ethinylestradiol
EMA	European medicines agency
FDA	Food and drug administration
EMR	Electronic medical records
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GMP	Good manufacturing practice

HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
IB	Investigator's brochure
IC	Informed consent
ICH	International conference on harmonization of technical requirements for registration of pharmaceuticals for human use
IRB	Institutional review board
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LGSIL	Low-grade squamous intraepithelial lesion
LH	Luteinizing hormone
LNG	Levonorgestrel
MedDRA	Medical dictionary for regulatory activities
PP	Per-protocol
Q-LES-Q-SF	Quality of life enjoyment and satisfaction questionnaire short form
RP	Reference period
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	standard deviation
SEM	standard error of mean
SHBG	Sex hormone binding globulin
STI	Sexually transmitted infection
TEAE	Treatment emergent adverse event
t-PA	Tissue-type plasminogen activator
VTE	Venous thromboembolism
WHO	World health organization

5 DEFINITION OF THE TERMS

Barrier Contraception	Birth control methods which physically block or otherwise prevent sperm from entering the uterus and reaching the egg for fertilization, including spermicides, sponges, condoms, diaphragms, and cervical caps.
Pre-treatment pregnancy	Pre-treatment pregnancies are pregnancies with an estimated date of conception before the first intake of trial medication.
On-treatment pregnancy	On-treatment pregnancies are pregnancies with an estimated date of conception within the in-treatment period i.e. Day 1 to 7 days after the last intake of investigational product (whether active or inactive tablet).
Post-treatment pregnancy	Post-treatment pregnancies are pregnancies with an estimated date of conception after the in-treatment period i.e. more than 7 days after the intake of investigational product (whether active or inactive tablet).
Pearl Index	The Pearl index is defined as the number of pregnancies per 100 woman-years of exposure: $Pearl\ Index = \frac{1300 \times \text{number of "on − treatment" pregnancies}}{\text{number of women − 28 − day equivalent cycles of treatment}}$ The Pearl Index calculation only takes into account at risk cycles defined as cycles during which: - no other contraceptive methods were used and, - the subject confirms that she has had intercourse.
Method failure Pearl Index	The method failure Pearl Index is calculated using the same method used for the Pearl Index, but includes only those pregnancies that were classified as method failure and not the pregnancies due to user failure, i.e. incorrect intake of the contraceptive method.
Starters/Switchers	- Starters: all subjects who have not used hormonal contraceptive(s) for 3 months before first investigational treatment intake. - Switchers: all subjects who have used a hormonal contraceptive during the 3 months before first investigational treatment intake. - True new users: all subjects who have never been using hormonal contraception.
Vaginal bleeding	Evidence of vaginal blood loss that requires the use of sanitary protection with a tampon, pad or pantyliner.
Vaginal spotting	Evidence of minimal vaginal blood loss that does not require new use of sanitary protection, including pantyliners.

6 STUDY ADMINISTRATIVE STRUCTURE

The study will be performed in approximately 80 centers in North America with approximately 90% of subjects in United States of America and 10% of subjects in Canada.

Estetra SPRL is the Sponsor of this study.

The Contract Research Organization (CRO) PRA Health Sciences will perform the following activities on behalf of the Sponsor for this study: regulatory submissions, project management (including site contracts, third party vendor management, etc.), clinical operations, clinical monitoring, medical and safety monitoring, data management, analysis and reporting.

Central facilities will be used for the analysis and storage of laboratory assessments. Details of the central facilities and handling of samples will be provided in separate manuals.

On the approval date of this protocol, the administrative structure and the external organizations supporting the study were as follows:

Sponsor	Estetra SPRL Rue Saint Georges 5-7 4000 Liège Belgium Telephone: +32 4 349 28 22 Fax: +32 4 349 28 21
CRO	PRA Health Sciences 4130 ParkLake Avenue, Suite 400 Raleigh, NC 27612 USA Telephone: +1 (919) 786-8200 Fax: +1 (919)786-8201
Central Laboratory (for both laboratory and Population pharmacokinetic (PK) Substudy sample analysis)	Eurofins Central Laboratory Lancaster 2430 New Holland Pike Lancaster, PA 17601 USA PRA Health Sciences - Early Development Services Bioanalytical Laboratory 11070 Strang Line Road

Lenexa, KS 66215
USA

7 INTRODUCTION

7.1 Background

Combined oral contraceptives (COCs) are medications taken orally combining a progestin and an estrogen. The function of the progestin is to inhibit ovulation by a central feedback mechanism resulting in decreased luteinizing hormone (LH) secretion by the pituitary gland. The estrogen component also contributes to contraceptive activity by inhibiting the secretion of follicle-stimulating hormone (FSH) but its major function is to provide stability to the endometrium and consequently to provide acceptable cycle control and bleeding pattern. COCs are widely used in the industrialized world. They have been shown to be highly effective in terms of contraception.

The potent synthetic estrogen, ethinylestradiol (EE), is the most frequently used estrogen in COCs. EE is easily absorbed when administered orally. Products containing EE generally have a good bleeding profile; however EE is also responsible for most of the side effects experienced by COC users. Among those, a rare but potentially very serious event is venous thromboembolism (VTE). The increased risk of thromboembolism among COC users is principally due to the strong impact of EE on hepatic synthesis functions, which leads to an increased production of several proteins involved in the coagulation and inflammatory pathways. As a consequence, an imbalance appears between pro- and anticoagulant circulating factors in favor to pro-coagulation. Beside the thromboembolism risk, EE is also associated with water retention (responsible of breast tension, edema, weight increase, nausea, headache and liability of humor) as well as with an increased risk of cholangiopathy.

To improve the safety profile of COCs, research and development has focused on two main approaches. First, the dose of EE has been progressively lowered from > 75 µg to as low as 10 µg. As EE doses decrease, the incidence of irregular and potentially unacceptable bleeding profiles increases. The second approach has been to replace EE with a naturally occurring estrogen: new COCs containing estradiol (E2) or estradiol valerate (E2V) have recently been developed, with the prospect of decreasing the metabolic impact from the estrogen component of COCs.

Estetra SPRL is developing a new COC containing a synthetic form of natural estrogen, estetrol (E4), in association with drospirenone (DRSP), a well-characterized and widely used contraceptive progestin. E4 is only produced by the human fetal liver during pregnancy and reaches the maternal circulation through the placenta. E4 has been isolated in maternal urine as early as week 9 of gestation. At term, the hormone is found at relatively high concentrations (about 1 ng/mL) in maternal plasma and over ten times higher in fetal plasma.

7.2 Prior Clinical Experience

Estetrol

In two Phase 1 clinical studies (PR3050 and PR3054) performed in healthy postmenopausal women, E4 was associated with a good safety and tolerability profile when it was taken orally as a single dose up to 100 mg and as daily multiple doses up to 40 mg during 28 consecutive days. Oral intake of multiple rising doses of E4 demonstrated an anti-gonadotropic activity characterized by a dose-dependent decrease in both FSH and LH levels. This study also documented a significant increase in endometrial thickness in accordance with E4's estrogenic actions.

Estetrol/Drospirenone

The safety and efficacy of E4 in combination with DRSP were studied in healthy premenopausal women enrolled in two Phase 2 clinical studies called ES-C01 and ES-C02.

Data from ES-C01 showed that 5 or 10 mg E4 combined with 3 mg DRSP administered in a 24/4-day regimen for three treatment cycles exert a complete inhibition of ovulation.[1] Ovarian activity decreases with increasing dose of E4. In addition, very limited to no impact on hepatic metabolism was observed with the E4/DRSP combinations as demonstrated by measurement before and after three treatment cycles of triglycerides[2] and surrogate markers of hemostasis such as D-dimer, Prothrombin fragment 1+2, inhibitors of coagulation (Active Protein C [APC] sensitivity, antithrombin III, APC resistance, protein S activity), liver factors (fibrinogen and prothrombin), endothelial factors (E-selectin and tissue-type plasminogen activator [tPA]) and carrier proteins (corticosteroid binding globulin [CBG], sex hormone binding globulin [SHBG] and ceruloplasmin).[2] Decrease from baseline in the carrier proteins was noted after one cycle of treatment. These findings suggest limited impact of the E4/DRSP combination on the coagulation pathway.

The combination of 3 mg DRSP with either 15 mg E4 or 20 mg E4 administered in a 24/4-day regimen was evaluated in the ES-C02 study, a six-cycle treatment study focusing on vaginal bleeding pattern and cycle control. A high rate of expected withdrawal bleeding (96.5%) and a low incidence of unscheduled bleeding/spotting episodes (16.9%) were observed with the 15 mg E4/3 mg DRSP combination. In addition, the E4/DRSP combinations demonstrated a good safety and tolerability profile. A low frequency of adverse events (AEs) with the 15 mg E4/3 mg DRSP combination was recorded and all AEs were similar to those classically observed with COCs. Finally, no ovulations were observed during this study demonstrating the potential for high contraceptive reliability of the E4/DRSP combinations studied.

From the different studies performed thus far with E4, it can be concluded that an E4-containing COC is well tolerated. No safety concern was observed with any E4 combination. However, until further evaluation in larger populations, the classical COC contraindications will apply to the 15 mg E4/3 mg DRSP combination.

Based on the results obtained from the Phase 2 studies, the regimen of 15 mg E4 combined with 3 mg DRSP was selected as the optimal combination (minimum effective dose) for the Phase 3 program.

8 STUDY OBJECTIVES

8.1 Primary Objective(s)

The primary objective of this study is to evaluate the contraceptive efficacy of 15 mg E4/3 mg DRSP using the Pearl Index in subjects aged 16 to 35 years, inclusive, at the time of screening.

8.2 Secondary Efficacy Objective(s)

The secondary objectives of this study are:

1. To evaluate the contraceptive efficacy of 15 mg E4/3 mg DRSP using the method failure Pearl Index and life-table analysis in subjects aged 16 to 35 years, inclusive, at the time of screening.

2. To evaluate the contraceptive efficacy of 15 mg E4/3 mg DRSP using the Pearl Index, the method failure Pearl Index and life-table analysis in the overall study population.

8.3 Other Secondary Objective(s)

1. To evaluate cycle control and bleeding pattern associated with 15 mg E4/3 mg DRSP.

2. To evaluate general safety of 15 mg E4/3 mg DRSP.

3. To evaluate the impact of 15 mg E4/3 mg DRSP on physical, psychological, and social functioning and well-being.

4. To assess the effect of various individual characteristics/ covariates (body weight, race, smoking, and fed/fasted condition) on the PKs of 15 mg E4/3 mg DRSP (Population PK Substudy).

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a multicenter, open-label, single-arm study.

The total duration of the study, including the screening, will range from 387 to 467 days for the participating subjects, which is approximately a year and one month. Those subjects who discontinue due to a pregnancy wish will be followed-up for a maximum of one year after study discontinuation for return of spontaneous menstruation and until pregnancy or initiation of a contraceptive method (whichever occurs first).

Approximately 2000 healthy female subjects at risk for pregnancy, between 16 and 50 years old (inclusive, at the time of screening), and requesting contraception will be enrolled in the study and initiate the investigational product. In total, 1800 subjects will be 16 to 35 years old (inclusive). Recruitment may be stopped when 2000 subjects have initiated the investigational product if the required number of subjects for the primary analysis (1800 subjects in the age group up to 35 years) has been reached. Recruitment in the age group > 35 years will be stopped when 200 subjects have initiated the investigational product.

Eligible subjects will be treated with 15 mg E4/3 mg DRSP for up to 13 consecutive cycles. The treatment must be 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).

The primary objective of the study is to evaluate the contraceptive efficacy of the new COC, using the Pearl Index calculation (which reflects the pregnancy rate associated with a contraceptive method) among the subjects aged 16 to 35 years inclusive.

The contraceptive efficacy will also be evaluated using the method failure Pearl Index (which reflects the pregnancy rate due to method failure only) and life-table analysis in the subjects aged 16 to 35 years inclusive and in the overall study population.

The general safety will be evaluated by the determination of routine laboratory parameters, vital signs, by performing physical, gynecological and breast examinations and by recording number, frequency, type and intensity of AEs and serious adverse events (SAEs).

Participating subjects will be asked to record daily in a subject diary their bleeding/spotting episodes. This will allow evaluating the bleeding pattern and the cycle control associated with the investigational product.

Treatment compliance will be assessed using data from the subject diary across the entire study and by cycle. The subject diary will also be used to determine whether or not a cycle is at risk for the Pearl Index calculation.

Physical, psychological and social functioning and well-being associated with the investigational product will be assessed with well-established questionnaires. A study schedule of events is provided in Appendix 1. Details and descriptions of study procedures are contained in the following sections.

Population PK will be assessed using plasma E4 and DRSP concentration data from a subset of approximately 500 subjects to address the relationship between E4 and DRSP PK parameters and various individual characteristics (e.g., body weight, race, smoking, and fed/fasted condition). Blood samples for PK analysis will be obtained at Visits 3 and 4 between Days 10 and 14 of Cycles 2 and 4 (see Section 9.6.4.2).

9.2 Rationale for Study Design

The design of this study is in line with the final minutes of the Advisory Committee for Reproductive Health Drugs meeting (FDA)[3] held on January 23 and 24, 2007, the recommendations made by Kapp et al.[4] and the requirements of the European Medicines Agency (EMA) and the EMEA/CPMP/EWP/519/98 Rev 1 Guideline on Clinical Investigation of Steroid Contraceptives in Women[5] which states that:

- Studies including an active comparator are not generally requested for efficacy purposes;
- The duration of efficacy studies should be six months to one year or more;
- For any new contraceptive, at least 400 women should have completed one year of treatment.

This study is a multicenter, open-label, single-arm study which will allow quantification of the efficacy of the investigational product by calculating the pregnancy rate. The size of the study is also adequate to allow an assessment of the general safety and bleeding profile associated with the investigational product.

The study design was discussed with FDA during end of phase 2 meeting as well as EMA during scientific advice (EMA/CHMP/SAWP/629721/2012).

9.3 Selection of Study Population

This study will include healthy female subjects at risk for pregnancy, between 16 and 50 years old (inclusive) at the time of screening, and expressing the need for and desire to use contraception for at least 13 consecutive cycles.

The following eligibility criteria will be checked at Visit 1 and Visit 2 (see Sections 9.5.1 and 9.5.2).

9.3.1 Inclusion Criteria

A subject will be considered for inclusion in the study if she meets all of the following criteria:

1. Heterosexually active female at risk for pregnancy and requesting contraception.
2. Negative serum pregnancy test at subject screening.
3. Aged 16 to 50 years (inclusive) at the time of signing the informed consent (IC).
4. Willing to use the investigational product as the primary method of contraception for 13 consecutive cycles.
5. Good physical and mental health on the basis of medical, surgical and gynecological history, physical examination, gynecological examination, clinical laboratory, and vital signs.
6. Body mass index (BMI) below or equal to (≤) 35.0 kg/m^2.
7. Able to fulfill the requirements of the protocol and have indicated a willingness to participate in the study by providing written IC.
8. Willing and able to complete the diaries and questionnaires.

9.3.2 Exclusion Criteria

A subject will be excluded from participation if she meets any of the following 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.
2. Clinically relevant abnormal laboratory result at screening in the opinion of the investigator with an understanding of the central laboratory normal range.
3. Known hypersensitivity to any of the investigational product ingredients.
4. Currently pregnant or with the intention to become pregnant during the course of the study.
5. Currently breastfeeding or before two spontaneous menstruations have occurred after cessation of breastfeeding prior to start of trial medication.
6. Less than 6 weeks since last delivery/2nd trimester of abortion and before spontaneous menstruation has occurred following a delivery or 2nd trimester of abortion.
7. Smoking nicotine-containing products if ≥ 35 years old.
8. Dyslipoproteinemia requiring active treatment with antilipidemic agent.
9. Diabetes mellitus with vascular involvement (nephropathy, retinopathy, neuropathy, other) or diabetes mellitus of more than 20-year duration.
10. Any arterial hypertension (controlled and uncontrolled) defined by blood pressure values of:
    a. systolic blood pressure ≥ 140 mmHg and/or,
    b. diastolic blood pressure ≥ 90 mmHg .
11. Personal history of deep vein thrombosis or pulmonary embolism.
12. Current prolonged immobilization or major surgery with prolonged immobilization planned in the next 12 months.

13. Known inherited or acquired hypercoagulopathies (e.g. antiphospholipid syndrome) or thrombogenic mutations (e.g. factor V Leiden, prothrombin mutation, protein S, protein C, and antithrombin deficiencies).
14. Current treatment with anticoagulants.
15. Presence or history of arterial thromboembolism (e.g. angina pectoris, ischemic heart disease, cerebral stroke or transient ischemic attack).
16. Complicated valvular heart disease (pulmonary hypertension, atrial fibrillation, subacute bacterial endocarditis).
17. History of pregnancy-related cardiomyopathy or moderately or severely impaired cardiac function.
18. Systemic lupus erythematosus.
19. Presence or history of migraine with aura at any age or migraine without aura if ≥ 35 years old.
20. Within the past 6 months, has had undiagnosed (unexplained) abnormal vaginal bleeding, or any abnormal bleeding that is expected to recur during the trial (e.g., bleeding from cervical polyp, recurrent bleeding after sex).
21. In case of Chlamydial or gonococcal infection at screening, when no treatment initiated at subject enrollment.
22. Abnormal Pap test (written documentation of prior test or test at screening exam) based on the following criteria:
    - Pap test in the past 18 months with ASC-US unless:
        - less than 21 years of age; or
        - a repeat Pap test at least 6 months later was normal; or
        - reflex HPV testing was performed and was negative for high-risk oncogene human-papilloma-virus (HPV).
    - Pap test in the past 18 months with LSIL unless less than 21 years of age.
    - Pap test in the past 18 months with ASC-H, atypical glandular cells, HSIL or malignant cells.
23. Presence of an undiagnosed breast mass.
24. Current symptomatic gallbladder disease.
25. History of COC-related cholestasis.
26. Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
27. Presence or history of pancreatitis if associated with hypertriglyceridemia.
28. Porphyria.
29. Presence or history of hepatocellular adenoma or malignant liver tumors.
30. Renal impairment (GFR < 60 mL/min/1.73m²).
31. Hyperkaliemia or presence of conditions that predispose to hyperkaliemia such as renal impairment, hepatic impairment, adrenal insufficiency and women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium concentration (e.g. ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonist and non-steroidal anti-inflammatory drugs).

32. History of organ transplantation within 5 years before screening or chronic disease potentially necessitating organ transplantation during the anticipated course of the study.
33. Presence or history of hormone-related malignancy.
34. History of non-hormone-related malignancy within 5 years before screening. Subjects with a non-melanoma skin cancer are allowed in the study.
35. Current regular use or regular use within 1 month prior to subject enrollment of drugs potentially triggering interactions with COCs including but not limited to:
    - Cytochrome P450 3A4 (CYP 3A4) inducers: barbiturates, primidone, bosentan, felbamate, griseofulvin, oxcarbazepine, topiramate, carbamazepine, phenytoin, rifampicin, St John's wort.
    - CYP 3A4 inhibitors: azole antifungals, phenylbutazone, modafinil, cimetidine, verapamil, macrolides, diltiazem and grapefruit juice.
    - Human immunodeficiency virus (HIV)/Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors.
36. Use of an injectable hormonal method of contraception within 10 months (300 days) prior to screening of an injection with a 3-month duration, within 6 months (180 days) prior to screening of an injection with a 2-month duration, within 3 months (90 days) prior to screening of an injection with a 1-month duration.
37. History of alcohol or drug abuse (including laxatives) within 12 months prior to screening.
38. Any prior procedure, disease or condition that could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the investigational product.
39. Uncontrolled thyroid disorders.
40. Participation in another investigational drug clinical study within 1 month (30 days) or have received an investigational drug within the last 3 months (90 days) prior to study entry. Subjects who participated in an oral contraceptive clinical study, using FDA/EU approved active ingredients, may be enrolled 2 months (60 days) after completing the preceding study.
41. Sponsor, CRO or Investigator's site personnel directly affiliated with this study.
42. Is judged by the Investigator to be unsuitable for any reason.

9.3.3 Subject Identification

Subject study identification numbers will be assigned at the Screening Visit. Subject numbers will be consecutive at each study site beginning with 001. Site numbering will begin at the number 201. Subject identification will consist of the site number (3 digits) followed by the subject number (3 digits), e.g., the first subject at Site 201 would be 201001 and the fifth subject at Site 235 would be 235005. Subject numbers will be consecutive at each study site beginning with 001. Subject identification numbers will be used throughout the trial.

9.4 Study Treatment

9.4.1 Identity of Investigational Products

The investigational products are manufactured by Haupt Pharma, Munster, Germany, in accordance with applicable current Good Manufacturing Practice (GMP).

The following investigational products will be administered:

Dosage form description	24 pink tablets containing 15 mg E4/3 mg DRSP 4 white placebo tablets
Package description	Blister pack (PVC/Aluminum) containing 28 tablets (24 pink and 4 white tablets)
Dose per time unit	1 tablet daily
Dispensing	Dispense the blister as follows per subject: - 4 blisters on Visit 2 and then 3 blisters on Visits 4 (Cycle 4), 5 (Cycle 7) and 6 (Cycle 10). - 1 spare blister on Visit 2 and, if necessary, on Visit 4, 5 and/or 6.

9.4.1.1 Labeling

The investigational product will be labeled according to regulations and local requirements and will contain at minimum the following information:

- Drug name or number/code
- Protocol number
- Blister content (24 pink tablets containing 15 mg E4/3 mg DRSP and 4 white placebo tablets)
- Lot number
- Expiry date
- For oral administration
- Storage conditions
- Caution: New Drug – Limited by Federal (or United States) law to investigational use.
- Treatment number
- Manufacturer's name and address
- Keep out of reach of children

9.4.1.2 Storage and Drug Accountability

The Investigator will be responsible for the suitable storage of the investigational product in compliance with the storage instructions and must restrict access to the study personnel only. Under no circumstances will the Investigator allow the investigational products to be used other than as directed by this protocol. The investigational product must be protected from unauthorized access (e.g. in a locked storage facility). Appropriate storage conditions at the site must be ensured either by controlled room temperature or by completion of a temperature log in accordance with local requirements and storage instructions on a regular basis, showing minimum and maximum temperatures reached over the time interval. The Principal Investigator will have overall responsibility for the use of the investigational product at the site. The Principal Investigator or Designee will confirm receipt of the investigational product and will verify the contents of the shipment, using an interactive web response system (IWRS) upon receipt of the product. The Investigator or Designee shall maintain accurate investigational product inventory records, including the quantities and date of receipt of supplies from the Sponsor, and the quantities and dates of dispensing to each study subject. Shipping and handling of all investigational products will be conform to ICH-GCP guidelines, GMP and Local regulatory guidelines.

At Visits 3, 4, 5, and 6, the Investigator should collect the investigational product (unused and empty) including spare blister if used (even if partially used) of the completed treatment cycles for drug accountability. Unused spare blister will be left for the subject. Used spare blisters will be replaced by a new spare blister. At Visit 7, the Investigator should collect all unused investigational product including spare blister (used or not), empty blisters for final drug accountability.

At completion of the study, to satisfy regulatory requirements regarding drug accountability, all investigational products will be stored, inventoried, reconciled, and destroyed or returned to the Sponsor according to applicable regulations. A written explanation must be provided for any discrepancies. The study monitor must review all records of drug accountability prior to the return or destruction of any supplies.

This drug accountability log must be available for inspection during an audit (e.g., by Sponsor or a regulatory agency). At the conclusion of the study, the Investigator must provide a copy of this record to the Sponsor.

9.4.2 Method of Assigning Subjects to Treatment

This is a 1-treatment arm open-label study. The subject will undergo screening where pretreatment clinical evaluations and specific procedures will be completed at the Screening Visit. Authorized site personnel will acknowledge that the subject met all of the specified inclusion criteria and none of the exclusion criteria before subject enrolment.

At enrollment visit, after IWRS contact, investigational product packs labeled with study information will be assigned to the subject.

9.4.3 Treatment Compliance

Treatment compliance for the investigational product will be assessed based on the response values entered by the subject in the diary on a daily basis (see Section 9.6.1). A comparison will be made between the number of tablets expected to be used, based on the total number of treatment days, and the number of tablets taken according to the subject's diary.

In addition, the data will be used to identify when a pill has been missed.

At each visit, the diary entries will be compared to the returned tablets to ensure consistency but the diary data will be used for compliance assessment. In case of discrepancy between the diary data and the returned tablets, the investigator will discuss with the subject and document this in the source data.

9.4.4 Selection of Doses and Timing of Administration in the Study

The daily dose used in this study, i.e. 15 mg E4 and 3 mg DRSP, has been selected on the basis of the data generated during the Phase 2 program. It was associated with a high inhibition of ovarian function, no ovulation, a good safety profile, and the most favorable bleeding pattern/cycle control observed among the different E4 combinations that were evaluated (see Section 7.2).

The investigational product is administered once daily following a 24/4-day regimen, i.e. one 15 mg E4/3 mg DRSP active tablet per day for 24 consecutive days followed by one placebo tablet per day for 4 consecutive days.

This 28-day cyclic regimen must be taken for up to 13 consecutive cycles. The treatment must be taken once daily at approximately the same time of the day.

9.4.4.1 Instructions for starting the first pack of tablets

- Women who did not use any contraceptive method or who used a barrier contraceptive method will be instructed to begin the investigational product on the first day of the next menstrual bleeding. Starting on Days 2-5 is also allowed, but a condom must be used until the subject has completed 7 days of uninterrupted active tablet intake. If the menstrual cycle prior to start of first pack of tablets is shorter than 21 days or longer than 35 days, the subject should not start the investigational product and will be withdrawn from the study (section 13.4). The subject should contact the study staff as soon as possible to schedule an Early Termination Visit (section 9.5.4) and to discuss an alternative contraception to use (section 9.6.4.9).
- Women switching from another COC or progestin-only pill will start the investigational product at the time when the next pill pack of the previous pill would have been due.
- Women switching from a hormonal vaginal ring or transdermal patch will start the investigational product when the next application would have been due.

- Women switching from an injectable hormonal method of contraception will start the investigational product on the first day of spontaneous menstrual bleeding following an interval after the last injection, which can vary depending of the form:
  – 10 months after the injection of a product with a 3-month duration;
  – 6 months after the injection of a product with a 2-month duration;
  – 3 months after the injection of a product with a 1-month duration.
  Starting on Days 2-5 is also allowed, but a condom must be used until the subject has completed 7 days of uninterrupted active tablet intake.
- Women switching from an intrauterine or dermally implantable contraceptive will start the investigational product on the day of removal. A condom must be used until the subject has completed 7 days of uninterrupted active tablet intake.

The first day of the first pink tablet intake after enrollment is Day 1. The subject places one of the 7 self-adhesive day label strips that corresponds to her Day 1 starting day onto the card of the blister to indicate the day she started. The study staff will show the subject how to fix the first label.

She then starts taking one tablet daily, at approximately the same time of the day, beginning with the first pink tablet in the top row. The subject completes her 28-tablet regimen when she has taken the last tablet in the blister pack.

9.4.4.2 Dosing Instructions

Each time investigational product is dispensed to the subject, site personnel will instruct the subject as follows:

- Take one pink tablet every day for 24 consecutive days (Day 1 through Day 24), followed by one white placebo tablet every day for 4 consecutive days (Day 25 through Day 28).
- When the pack of tablets is empty, start the next pack on the next day after the last white tablet of the previous pack has been taken. When starting a new pack of tablets, take the first pink tablet of the pack. There should be no interruption between two blister packs.
- Take the investigational product at approximately the same time each day throughout the study. The time of day should be determined by the subject.
- Return all blister packs to site personnel at the following visit.

9.4.4.3 Instructions in case of missed tablet(s) or in conditions potentially reducing the contraceptive efficacy

If the subject has vomiting or diarrhea within 4 hours of tablet intake, she should take another tablet from the extra pack (spare blister) as a replacement.

If the subject inadvertently misses one or more of the tablets, the following instructions must be followed[6]:

- If one active pink tablet is late (< 24 hours since a tablet should have been taken) or if one active pink tablet has been missed (24 to < 48 hours since a tablet should have been taken):
  - Take the late or missed active pink tablet as soon as possible.
  - Continue taking the remaining active pink tablets at the usual time (even if it means taking two active pink tablets on the same day).
  - Use of condom is not required.
- If two or more consecutive active pink tablets have been missed (≥ 48 hours since a tablet should have been taken):
  - If between Day 1 & Day 17:
    - Take the most recent missed active pink tablet as soon as possible (any other missed tablets should be discarded).
    - Continue taking the remaining active pink tablets at the usual time (even if it means taking two tablets on the same day).
    - Use condom or avoid sexual intercourse until 7 days of uninterrupted active pink tablet intake.
    - Consider emergency contraception as per current practice if the woman had unprotected intercourse during the missed pill interval.
  - If between Day 18 & Day 24:
    - Omit the hormone-free interval by finishing the active pink tablets in the current pack and starting a new pack the next day.
    - If unable to start a new pack immediately, use condoms or avoid sexual intercourse until 7 days of uninterrupted active pink tablet intake from the new pack.
    - If this occurs during the last cycle, the subject should contact the study staff to know what she has to do with the next contraception.

If the subject inadvertently misses any of the white placebo tablets:

- Skip the missed white placebo tablet(s) and the remaining tablets are taken at the regular time.
- Use of condoms is not required during this time.

Anytime a subsequent cycle of the product/pack is started later than the day following administration of the last white tablet, the subject should use condoms until she has taken pink tablets daily for 7 consecutive days.

9.4.4.4 In case of short-term intake of drugs that may decrease the efficacy of the COC

Subject is allowed to take drugs potentially decreasing the efficacy of the COC for a maximal period of 10 consecutive days (for example, CYP 3A4 inducers). Subjects must be instructed to use condoms when these drugs are used and during 7 days of uninterrupted pink tablet intake after finishing the medication.

9.4.4.5 Use of the investigational product in case of bleeding/spotting episode

Scheduled bleeding is expected to begin within a few days of taking the last active tablet (i.e. pink tablet), but may begin sooner or later. If spotting occurs while on the usual regimen of one tablet daily, the subject should continue medication without interruption. She should be instructed that this type of bleeding is often transient and without significance. However, if the bleeding is persistent or prolonged, nonfunctional causes may be considered and the subject should be advised to call the Investigator who will decide the best management for the subject. The bleeding profile will be recorded by the subject on a subject diary.

9.4.4.6 Use of the investigational product in the event of a missed menstrual period

A missed menstrual period may occur even if the subject adhered to the prescribed dosage regimen. However, as the contraceptive method used in this study is still under investigation, a rapid detection of any pregnancy is necessary. For this reason, if the subject presents a missed period, she will be instructed to use the home urine pregnancy test provided by the study staff to rule out pregnancy before continuing the contraceptive regimen (see Section 9.6.2).

9.4.5 Blinding

This is an open-label study.

9.4.6 Restrictions

9.4.6.1 Prior and Concomitant Therapy

Medications with an end date occurring before the first investigational product dose date in the treatment period will be identified as prior medications. Medications with a start date occurring on or after the first investigational product dose date in the treatment period or medications

with a start date prior to the first investigational product dose date and an end date on or after the first investigational product dose date will be identified as concomitant medications.

Unauthorized Prior Therapies:

- Use of an injectable hormonal method of contraception within 10 months (300 days) prior to screening for an injection with a 3-month duration, within 6 months (180 days) prior to screening for an injection with a 2-month duration, within 3 months (90 days) prior to screening for an injection with a 1-month duration.
- Use of drugs potentially triggering interactions with COC within one month prior to subjects' enrollment. This includes, but is not limited to:
  - CYP 3A4 inducers: barbiturates, primidone, bosentan, felbamate, griseofulvin, oxcarbazepine, topiramate, carbamazepine, phenytoin, rifampicin, St John's wort.
  - CYP 3A4 inhibitors: azole antifungals, phenylbutazone, modafinil, cimetidine, verapamil, macrolides, diltiazem and grapefruit juice.
  - HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

Unauthorized Concomitant Therapies:

- Use of any contraceptive method other than the investigational product.
  Note: use of condoms is only allowed during the course of the study to avoid transmission of sexually transmitted infections (STIs), or in case of missed tablets, or when unauthorized concomitant therapies are used. Condom use must be recorded in the subject diary.
- Daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium concentration (e.g. ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonist and non-steroidal anti-inflammatory drugs).
- Use of drugs potentially triggering interactions with COC. This includes, but is not limited to:
  - CYP 3A4 inducers: barbiturates, primidone, bosentan, felbamate, griseofulvin, oxcarbazepine, topiramate, carbamazepine, phenytoin, rifampicin, St John's wort.
  - CYP 3A4 inhibitors: azole antifungals, phenylbutazone, modafinil, cimetidine, verapamil, macrolides, diltiazem and grapefruit juice.
  - HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors.
    These drugs or herbal products may decrease the effectiveness of hormonal contraceptives or increase breakthrough bleeding. Subjects must be instructed to use a back-up contraceptive method when these drugs are used, up to and

including the next 7 days after finishing the concomitant therapy and to record this back-up contraception in the subject diary (see Section 9.6.1). It is the responsibility of the Investigator to ensure that any change in concomitant medications during the study is recorded in the source documentation and entered in the electronic case report form (eCRF).

Warning: oral contraceptives may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may be affected (e.g. cyclosporine). Consult the prescribing information of concomitant drugs for possible interactions with oral contraceptives.

9.4.6.2 Condoms and other contraceptive methods

Use of condoms is allowed during the course of the study only to avoid transmission of STIs or in case of missed tablet(s) or unauthorized concomitant therapies. Condom use must be recorded in the subject diary. Use of any other contraceptive methods must also be recorded in the subject diary (see Section 9.6.1). The cycles during which condom(s) or other contraceptive method(s) than the investigational product were used will be excluded from the Pearl Index calculation.

9.4.7 Treatment beyond the clinical trial

Post-treatment contraceptive counseling should be given to each subject at Visit 6 and at the Early Termination Visit in case of premature study termination. Post-treatment contraceptive treatment should be started no later than on the day following the last tablet intake of the trial medication.

9.5 Study Activities

The following sections provide details of the study activities which are summarized in the Schedule of Events (Appendix 1). The study will include 1 Screening Visit (Visit 1), 1 enrollment Visit (Visit 2), 4 in-treatment Visits (Visits 3 to 6) and 1 exit Visit (Visit 7).

At any time during the study, an Unscheduled Visit may occur in case of suspicion of pregnancy.

9.5.1 Visit 1: Screening Visit

The subject must be fasting for at least 8 hours (overnight fast) before the Screening Visit. Prior to conducting any screening procedures, subjects will be given a full description of the nature of the study. The purpose, timing, procedures, and risks of the study will be explained to the subject, including requirements for enrollment and participation in the study, medication restrictions during the study, and requirements for washout of certain medications that the subject may already be taking. The eligible subject who is willing to participate in the study will then be required to provide written consent. The Investigator or a designated medically

qualified member of the study staff will interview potential participants to establish their eligibility for inclusion in the study.

Potential subjects will be screened according to the inclusion and exclusion criteria within 45 days prior to the subject enrollment visit (Visit 2). Subjects who were eligible for the study but did not enroll within 45 days of screening (Visit 1) can be re-screened. Re-screening requires all Visit 1 assessments to be repeated. The Investigator will maintain a log of all subjects screened for participation and record the reason(s) for excluding potential subjects.

The following will be performed to determine eligibility:

1. Obtain signed IC from subjects. Subjects will receive a copy of the IC (see Section 10.3);
2. Review and document inclusion and exclusion criteria (see Sections 9.3.1 and 9.3.2);
3. Record demographic information (see Section 9.6.4.4);
4. Obtain medical and surgical history (see Section 9.6.4.6);
5. Obtain gynecological history including identification of the previous contraceptive method used, if any (see Section 9.6.4.7);
6. Obtain prior medication use information (see Section 9.6.4.5);
7. Perform a physical examination (see Section 9.6.3.4);
8. Perform a gynecological examination including breast examination (see Section 9.6.3.6);
9. Obtain cervical cytology (see Section 9.6.3.6);
10. Perform a Chlamydia test (see Section 9.6.3.6);
11. Perform a gonorrhea test (see Section 9.6.3.6);
12. Collect fasting (8-hour) blood samples for hematology, biochemistry and pregnancy test (see Sections 9.6.2.1 and 9.6.3.3);
13. Measure vital signs (see Section 9.6.3.7);
14. Measure height and weight, and calculate BMI (see Section 9.6.3.5);
15. Schedule the next study visit.

9.5.2 Visit 2: Subject Enrollment

The Visit 2 will occur within 45 days after the Screening Visit (Visit 1), when the entire laboratory results of the subject have been received.

On the basis of the laboratory results, the Investigator must assess the eligibility of the subject.

In case of positive Chlamydia or gonorrhea test result (see Section 9.6.3.6), the subject will be treated before enrollment. Choice of treatment is left at the Investigator's discretion.

During Visit 2, the following procedures will be performed:

1. Review, confirm and document inclusion and exclusion criteria (see Sections 9.3.1 and 9.3.2);
2. Obtain prior medication use information (see Section 9.6.4.5 and Section 9.4.6 for restrictions);
3. If all screening assessments are acceptable and all inclusion criteria and no exclusion criteria have been met, the subject will be enrolled in the study;
4. Perform a Chlamydia and gonorrhea test, if indicated (see Section 9.6.3.6);
5. Measure vital signs (see Section 9.6.3.7);
6. Dispense investigational products for Cycle 1-4 and one spare blister pack and give the subject the instructions for use (see Section 9.4.4.2);
7. Dispense subject diary and give the subject the instructions for use (see Section 9.6.1);
8. Dispense home urine pregnancy test kits with the instructions for use. Subject should perform a urinary pregnancy test just before the intake of the first pink tablet, preferably with first urine in the morning. The result has to be recorded in the diary. The subject should only start with the trial medication when the pregnancy test is negative (not pregnant). If the pregnancy test is positive, the subject should not take any trial medication and contact the Investigator. The Investigator should arrange for an Unscheduled Visit (see Section 9.5.5) to confirm the pregnancy, complete the Pregnancy Report Form if the pregnancy is confirmed (see Section 9.6.2.1) and the subject should be withdrawn;
9. Query the subject as to the occurrence of any AE(s) and record any AE(s) observed or spontaneously volunteered by the subject (see Section 9.6.3.1);
10. Dispense the questionnaires and give the subject the instructions for completion (see Section 9.6.4.11);

11. Schedule or confirm the next study visit and the follow-up phone call;

12. Instruct the subject to come to the next visit with her subject diary and the unused investigational product, including empty blisters, spare and boxes;

13. Instruct any subject not on a hormonal contraceptive and who does not start the investigational product at the enrollment visit to contact the site immediately if her next menses occurs at earlier than 21 days or is delayed such that her cycle length exceeds 35 days, and that she should not start the investigational product if either of these happens;

14. Instruct the subject to contact the site immediately if she decides to discontinue the investigational product and, if possible, to not discontinue the investigational product before contacting the site;

15. Complete a follow-up call within 7 days following the expected start date of the treatment to remind the subject to complete the diary entries.

9.5.3 Treatment Period (from Cycle 1 Day 1 until Cycle 13 Day 28)

9.5.3.1 Visit 3 (Cycle 2, between Day 1 and Day 14)

The following procedures will be performed:

1. Perform a Chlamydia and gonorrhea test, if indicated (see Section 9.6.3.6);

2. Measure vital signs (see Section 9.6.3.7);

3. Query the stop date of the previous contraceptive method;

4. Investigational product return and drug accountability (see Section 9.4.1.2);

5. Collect and review completed subject diary pages and return the diary to the subject (see Section 9.6.1);

6. Ensure appropriate completion of the questionnaires;

7. Collect blood samples from the subjects participating in the Population PK Substudy according to the sampling scheme outlined in Section 9.6.4.2. *Note that Visit 3 for the subjects in the Population PK Substudy should be performed between Days 10 and 14*;
8. Query the subject as to the occurrence of any TEAE(s) and record any TEAE(s) observed or spontaneously volunteered by the subject (see Section 9.6.3.1);

9. Obtain concomitant medication use (see Section 9.6.4.5 and Section 9.4.6 for restrictions);

10. Schedule or confirm the next study visit;

11. Instruct the subject to come to the next visit with her subject diary and the unused investigational product, including empty blisters, spare and boxes;

12. Instruct the subject to contact the site immediately if she decides to discontinue the investigational product and, if possible, to not discontinue the investigational product before contacting the site.

9.5.3.2 Visit 4 (Cycle 4, between Day 1 and 14)

The following procedures will be performed:

1. Perform a Chlamydia and gonorrhea test, if indicated (see Section 9.6.3.6);

2. Measure vital signs (see Section 9.6.3.7);

3. Measure weight and calculate BMI (see Section 9.6.3.5);

4. Collect blood samples from the subjects participating in the Population PK Substudy according to the sampling scheme outlined in Section 9.6.4.2. *Note that Visit 4 for the subjects in the Population PK Substudy should be performed between Days 10 and 14*;
5. Investigational product return and drug accountability (see Section 9.4.1.2);

6. Dispense investigational products for the next 3 cycles and remind the subject the instructions for use (see Section 9.4.4.2);

7. Collect and review completed subject diary pages and return the diary to the subject (see Section 9.6.1);

8. Query the subject as to the occurrence of any TEAE(s) and record any TEAE(s) observed or spontaneously volunteered by the subject (see Section 9.6.3.1);

9. Obtain concomitant medication use (see Section 9.6.4.5 and Section 9.4.6 for restrictions);

10. Schedule or confirm the next study visit;

11. Instruct the subject to come to the next visit in a **fasted state**, with her subject diary and the unused investigational products, including empty blisters, spare and boxes;

12. Instruct the subject to contact the site immediately if she decides to discontinue the investigational product and, if possible, to not discontinue the investigational product before contacting the site.

9.5.3.3 Visit 5 (Cycle 7, between Day 1 and 14)

The following procedures will be performed:

1. Perform a Chlamydia and gonorrhea test, if indicated (see Section 9.6.3.6);
2. Measure vital signs (see Section 9.6.3.7);
3. Measure weight and calculate BMI (see Section 9.6.3.5);
4. Investigational product return and drug accountability (see Section 9.4.1.2);
5. Dispense investigational products for the next 3 cycles and remind the subject the instructions for use (see Section 9.4.4.2);
6. Collect and review completed subject diary pages and return the diary to the subject (see Section 9.6.1);
7. Query the subject as to the occurrence of any TEAE(s) and record any TEAE(s) observed or spontaneously volunteered by the subject (see Section 9.6.3.1);
8. Obtain concomitant medication use (see Section 9.6.4.5 and Section 9.4.6 for restrictions);
9. Collect fasting (8-hour) blood samples for biochemistry (see Sections 9.6.3.3);
10. Schedule or confirm the next study visit;
11. Instruct the subject to come to the next visit with her subject diary and the unused investigational products, including empty blisters, spare and boxes;
12. Instruct the subject to contact the site immediately if she decides to discontinue the investigational product and, if possible, to not discontinue the investigational product before contacting the site.

9.5.3.4 Visit 6 (Cycle 10, between Day 1 and 14)

The following procedures will be performed:

1. Perform a Chlamydia and gonorrhea test, if indicated (see Section 9.6.3.6);
2. Measure vital signs (see Section 9.6.3.7);
3. Investigational product return and drug accountability (see Section 9.4.1.2);
4. Dispense investigational products for the next 3 cycles and remind the subject the instructions for use (see Section 9.4.4.2);

5. Collect and review completed subject diary pages and return the diary to the subject (see Section 9.6.1);

6. Dispense the questionnaires and give the subject the instructions for completion (see Section 9.6.4.11);

7. Query the subject as to the occurrence of any TEAE(s) and record any TEAE(s) observed or spontaneously volunteered by the subject (see Section 9.6.3.1);

8. Obtain concomitant medication use (see Section 9.6.4.5 and Section 9.4.6 for restrictions);

9. Give the subject counseling about the next contraceptive method to use at the end of the study (see Section 9.6.4.9);

10. On the day the subject is expected to start the next contraceptive method (±1 day), perform a follow-up call to ensure subject's compliance with this method (see Section 9.6.4.9).

11. Schedule or confirm the next study visit;

12. Instruct the subject to come to the next visit in a **fasted state** with her subject diary and the unused investigational products, including empty blisters, spare and boxes;

13. Instruct the subject to contact the site immediately if she decides to discontinue the investigational product and, if possible, to not discontinue the investigational product before contacting the site.

9.5.3.5 Visit 7 (Cycle 14, between Day 16 and 23), End of Treatment Visit

The following procedures will be performed:

1. Perform a physical examination (see Section 9.6.3.4);

2. Measure weight and calculate BMI (see Section 9.6.3.5);

3. Perform a gynecological examination including breast examination (see Section 9.6.3.6);

4. Collect fasting (8-hour) blood samples for hematology, biochemistry and pregnancy test (see Sections 9.6.2.1 and 9.6.3.3);

5. Measure vital signs (see Section 9.6.3.7);

6. Investigational product return and drug accountability (see Section 9.4.1.2);

7. Collect and review completed subject diary pages (see Section 9.6.1);
8. Ensure appropriate completion of the questionnaires;
9. Query the subject as to the occurrence of any TEAE(s) and record any TEAE(s) observed or spontaneously volunteered by the subject (see Section 9.6.3.1);
10. Obtain concomitant medication use (see Section 9.6.4.5 and Section 9.4.6 for restrictions);
11. Complete the End of Study Form.

9.5.4 Early Termination Visit

A subject who desires early termination or is withdrawn from the study after the enrollment visit (Visit 2) (section 13.4) will require an Early Termination Visit.

- Any subject who contacts the study site with a desire to discontinue study participation should be instructed at each visit to contact the study staff before discontinuing the study drug to be counseled about alternative contraception to use prior to the Early Termination Visit (see Section 9.6.4.9). Study sites may provide any prescription or non-prescription contraceptive to the subject as is medically appropriate per local standard of care other than an IUD or implant. If necessary, an unscheduled visit can occur to provide contraception (see Section 9.5.5).
- A subject who presents to the study site for a scheduled visit and desires to discontinue study participation or is withdrawn from the study at that visit should be counseled about alternative contraception to use prior to the Early Termination Visit (see Section 9.6.4.9). Study sites may provide any prescription or non-prescription contraceptive to the subject as is medically appropriate per local standard of care other than an IUD or implant.
- A subject who presents to the study site for a scheduled visit who has not taken the study product for 16 days or more should have the scheduled visit procedures and the Early Termination Visit procedures completed at that time. The subject should be counseled about alternative contraception (see Section 9.6.4.9). Study sites may provide any prescription or non-prescription contraceptive to the subject as is medically appropriate per local standard of care.

The Early Termination Visit should occur between 16 and 23 days after the last investigational product intake or immediately if the investigational product was never started. The procedures listed in Visit 7 (see Section 9.5.3.5) will be performed and the End of Study Form will be completed.

Study site personnel will attempt to follow the progress of every subject admitted to the study through to study completion. If a subject fails to return for a scheduled visit, a reasonable effort should be made to contact the subject and ascertain the reason(s) for not returning. As a minimum, the site staff will contact the subject twice by phone and, if no response, will send a letter by registered mail.

If a subject does not complete the study for any reason (including Investigator discretion), the reason and circumstances for the subject's early termination must be fully documented.

The Sponsor or Designee must be informed in a timely manner if any subject withdraws from the study, regardless of the cause. Withdrawn subjects may not be re-enrolled in the study and will not be replaced.

9.5.5 Unscheduled Visit

At any time of the study, an Unscheduled Visit could occur in case of suspicion of pregnancy based on a positive pregnancy test performed at home by the subject, in case the Investigator judges it necessary to examine a subject who would present a potential significant adverse event in the Investigator's opinion, or if alternative contraception is needed for a subject planning early termination. Additional assessments can be performed at the Investigator's discretion.

9.6 Study Variables and Procedure Descriptions

9.6.1 Subject Diary

Subject diaries will be given to the participating subjects at Visit 2. Subjects will be instructed on how to complete it by the Investigator or Designee.

The following information is to be recorded in the subject diary:

- Date of the intake of the first tablet at each cycle;
- Tablet intake on a daily basis;
- Absence or occurrence of vaginal bleeding/spotting event(s) on a daily basis:
    - 0 = Absence of vaginal bleeding or spotting;
    - 1 = Spotting: evidence of minimal vaginal blood loss that does not require new use of sanitary protection, including pantyliners;
    - 2 = Bleeding: evidence of vaginal blood loss that requires the use of sanitary protection with a tampon, pad or pantyliner;
- Use of contraceptive method other than the investigational product (e.g. condom) during the cycle;
- Occurrence of heterosexual intercourse during the cycle;
- Result of the urine pregnancy test(s) performed at home (at cycle 1 before the first pill intake and at subsequent cycles in case of absence of menstruation).

At Visits 3, 4, 5, 6 and 7, the completed pages of the subject diary will be collected and reviewed by the Investigator. At Visits 3, 4, 5, and 6 the subject diary will be returned to the subject for further completion. At Visit 7, the fully completed last pages of the subject diary will be returned by the subject.

9.6.2 Efficacy Assessments

Contraceptive efficacy will be based on the Pearl Index, the method failure Pearl Index and the cumulative pregnancy rate.

On-treatment pregnancies are defined as pregnancies with an estimated date of conception within the in-treatment period (Day 1 to 7 days after the intake of investigational product, whether active or inactive tablet).

Pre-treatment pregnancies are pregnancies with an estimated date of conception before the first intake of trial medication.

Post-treatment pregnancies are pregnancies with an estimated date of conception after the in-treatment period (> 7 days after the intake of investigational product, whether active or inactive tablet).

9.6.2.1 Pregnancy Testing and Estimating Date of Conception

The occurrence of pregnancies will be evaluated during the study by performing:

- At Screening Visit (Visit 1) and Visit 7: a serum pregnancy test;
- Just before intake of the first study medication and in case of missing menstrual period, the subject will perform a urine pregnancy test at home. For that purpose, home pregnancy kits will be provided to all subjects at Visit 2 and the subjects will be instructed on how to use it. In case of positive urine pregnancy test result, the subject will be instructed to contact the study staff immediately and the subject will be instructed not to take the investigational product. An appointment will be scheduled with the study staff for the pregnancy follow-up as soon as possible. The subject will be asked to record in the subject diary (see Section 9.6.1) the result of the urine pregnancy test performed at home;

At any time: the subject is asked to contact immediately the study staff in the event of a suspected pregnancy. An appointment will be scheduled with the study staff for the pregnancy confirmation as soon as possible. The Investigator and or Designee will make every effort to see the subject as soon as possible to perform a serum pregnancy test.

All subjects for whom a pregnancy is suspected due to a positive serum pregnancy test will be carefully evaluated and assessed to determine the estimated date of conception. The preferred method is to perform an ultrasound to define the estimated age of the pregnancy; the estimated date of conception will then be calculated from this result. In addition, information about all

pregnancy tests, about bleeding and study drug intake (which must be reconciled with subject diary data), information about concomitant medications (which must be reconciled with information in the eCRF) will be obtained. The Sponsor and Site Monitor must be notified and available information captured. All information must be documented using the Pregnancy Report Form.

Information pertaining to the reporting of pregnancy should be captured on the Pregnancy Report Form. This form will be used for initial and follow-up reporting. The form should be completed and returned to the PRA Safety team. The subject will be followed until the outcome of pregnancy is known.

9.6.2.2 Pregnancy Reporting

Pregnancy will not be considered an AE but, because of its importance, information about each pregnancy should be treated in an urgent manner. The Sponsor or Designee must be notified within 24 hours of the suspected diagnosis and all follow-up information should be obtained promptly.

If during the course of the study, a subject is found to be pregnant, the investigational product will be discontinued and study participation terminated.

The site will submit a Pregnancy Report Form to the Safety Monitor.

The following contact will be used for all communications with the Safety Monitor/Drug Safety of this study:

PRA Safety & Risk Management

Fax: +1 (888) 772-6919

Email: CHOSafety@prahs.com

All pregnancies identified during the course of the study in a subject who was using the investigational product will be monitored to completion, i.e., approximately 9 month follow-up in the case of live birth or until outcome information is obtained. Information will also be collected on any maternal or fetal complications. Miscarriage and any congenital abnormalities or birth defects will be classified as SAEs. Pregnancy outcome information will be recorded on specific forms and the data will be analyzed within the drug safety assessment. Every attempt should be made to obtain outcome data including hospital or medical records.
If a subject becomes pregnant and states she never started the investigational product, the pregnancy does not have to be monitored if the subject returns all of the investigational product (proving she never started the investigational product).

9.6.3 Safety Variables

Safety evaluations will include the following:

- General safety will be assessed in terms of occurrence of AEs/SAEs;
- Extent of exposure
- Clinical laboratory evaluations
- Physical examination
- Gynecological examination
- Vital signs

9.6.3.1 Adverse Events

AEs will be assessed from the time of signing the IC until exit from the study. At every study visit from Visit 2, subjects will be asked an indirect standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed any current medication regimens (both prescription and over-the-counter medications).

Definition of Terms

Adverse Event (AE): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. In addition to novel events, an AE may be an exacerbation of a pre-existing medical condition that was present before the subject was assigned to a treatment group. Each AE is described using all three of the following classifications: expected or unexpected; related or unrelated; and serious or non-serious. Additionally, intensity of the event is also described.

Treatment-emergent adverse event (TEAE): A TEAE is any AE not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatment. Since the starting point for AEs collection is the signing of the IC, not the start of the study treatment, the AEs recorded prior to first investigational product administration are designated as AEs while those that occur or worsen after the initiation of the investigational product are designated as TEAEs.

Exacerbation of Pre-Existing Medical Condition: An increase in the frequency or severity of a medical condition that is present before first investigational product administration. Any medical condition that is present before first investigational product administration and that does not deteriorate should not be reported as an AE.

Expected: The determination of whether an AE is expected is based on previous experience with the investigational product, as follows:

Expected AEs are AEs that have already been identified during the investigational product's use, or are a known complication of standard medical procedures that may be conducted as part of the clinical study.

Expected AEs are defined as those described in the Investigator's Brochure (IB). If an event increases in intensity or severity from that described in the IB, it will be considered unexpected. Unexpected AEs are all other AEs which are not deemed anticipated. Note that anticipated AEs which are more severe must also be considered unanticipated AEs.

Severity: The severity of each AE should be recorded as mild, moderate, or severe according to the following definition:

Mild – transient and well-tolerated by the study subject,

Moderate – causes discomfort and a temporary interference with daily living,

Severe – substantially interferes with daily living to the point of being incapacitating and/or life threatening.

Adverse Event Causality:

The Investigator will evaluate the relationship of each AE to study drug and/or study procedures according to the following definitions:

Category	**Criteria**	**Final Reporting of Relationship to Study Drug**
Highly probable	-Event or laboratory test abnormality, with plausible time relationship to drug intake. -Cannot be explained by disease or other drugs. -Response to withdrawal plausible (pharmacologically, pathologically).	Related

Category	Criteria	Final Reporting of Relationship to Study Drug
	-Event pharmacologically and/or phenomenologically related. -Rechallenge satisfactory, if necessary.	
Probable	-Event or laboratory test abnormality, with reasonable time relationship to investigational drug intake. -Unlikely to be attributed to disease or other drugs. -Response to withdrawal clinically reasonable. -Rechallenge not required.	
Possible	-Event or laboratory test abnormality, with reasonable time relationship to investigational drug intake. -Could also be explained by disease or other drugs. -Information on drug withdrawal may be lacking or unclear.	
Unlikely	-Event or laboratory test abnormality, with a time to investigational product intake that makes a relationship improbable (but not impossible). -Disease or other drugs provide plausible explanations.	Not Related

Category	Criteria	Final Reporting of Relationship to Study Drug
Not Related	Event due to underlying or concurrent illness, complications, concurrent treatments or effect of another concurrent drug/therapy and is not associated to the investigational drug.	

Serious: An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death: the AE causes or contributes to the death. Death is usually considered to be the outcome of an event; the event that leads to death is defined as the SAE.
- A life-threatening adverse event: if, in the view of the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization: the AE requires at least a 24-hour inpatient hospitalization or prolongs a hospitalization beyond the expected length of stay. Hospital admissions for surgery planned before study entry, for social reasons or for normal disease management procedures are not to be considered SAE according to this criterion. Where the protocol or the standard management of the disease under study requires planned hospitalizations for disease or treatment management, this should not be considered a serious criterion leading to expedited reporting.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect: an adverse outcome in a child or fetus of a patient exposed to the investigational product before conception or during pregnancy.
- Important medical event: such an event may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment; it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purpose of this study, all events that meet the regulatory definition of an SAE that occur at any time during the study will be reported to the Sponsor as SAEs. Any SAE requires

expedited reporting to Sponsor regardless of its relationship to the investigational product. Non-SAEs are all other AEs not deemed serious.

Investigator Obligations

Assessing and Following: The Investigator is responsible for assessing all AEs that occur at any time during the study. The Investigator must make a determination of relatedness, seriousness, and intensity on the Adverse Events page of the eCRF for each AE. All AEs must be followed to adequate resolution or stabilization. If the AE has not resolved or stabilized by the time the subject completes the final study visit, the Investigator will follow the status of the subject's AE for at least 30 days beyond the subject's final study visit, unless directed otherwise by the Sponsor.

Documenting: All AEs during the study will be documented in the subject's medical record. This information will then be transcribed on the AEs page of the eCRF by designated study personnel. Required information includes a description of the event, date of onset, date of resolution, if death occurred, the action taken to manage the AE, as well as relatedness, seriousness, and intensity.

AE information must be recorded regardless of its relatedness to the use of the investigational product. AEs resulting from concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported.

Reporting: 1) The Investigator is responsible for reporting AEs to the Institutional Review Board (IRB) according to agreements and instructions from that committee that oversees this research, as well as according to applicable regulations. 2) Additionally, all **AE**s will be reported to the Sponsor or Designee on the eCRF, and **all SAEs**, whether expected or unexpected, related or unrelated, must be reported to PRA Drug Safety , by 24/7 e-mail or facsimile using the "Serious Adverse Event Report" form provided by the Sponsor or Designee, **within 24 hours** after the Investigator first learns of the event In addition to the form, the following completed eCRF pages containing relevant information must also be faxed/mailed to the PRA Drug Safety: Medical History and Current Medications. The Investigator is responsible for reporting any new or relevant follow-up information on the SAEs within 24 hours after the investigator learns of the new information. The Investigator should cooperate and furnish additional information, including copies of pertinent records if necessary, to assist the safety team in their evaluation of the event.

Medical Emergencies and Emergency Protocol Deviations

In medical emergencies, the Investigator will use medical judgment and remove the subject from immediate harm. The Investigator will then immediately notify the Safety Monitor and the IRB regarding the type of emergency and the course of action taken.

An investigator shall notify the Safety Monitor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency.

Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the Safety Monitor is required for any changes in or deviations from the protocol. All deviations must be documented on the eCRF.

The following contact will be used for all communications with the Safety Monitor/Drug Safety of this study:

PRA Safety & Risk Management

Fax: +1 (888) 772-6919
Email: CHOSafety@prahs.com

Sponsor Reporting Obligations

Sponsor or Designee will forward all reportable AEs to the appropriate regulatory authorities, ECs, and participating Investigators according to 21 Code of Federal Regulations (CFR) 312, and any other applicable regulations.

9.6.3.2 Extent of Exposure

The extent of exposure to the investigational product will be determined from the first and last dosing dates during the treatment period and is derived as the last dose date – the first dose date + 1.

9.6.3.3 Clinical Laboratory Evaluations

Methods for blood sample collection, processing, and shipment are described in instructional materials provided to investigational sites.

Any remaining retainable biological samples will be stored at the central laboratory or designee at the latest until the marketing authorization. These samples may be used for future additional analysis in the context of the E4/DRSP development program.

At Visit 1 and 7, blood hematology, biochemistry and lipids will be assessed (see Appendix 2). At Visit 5, the following biochemistry parameters will be assessed: glycaemia, glycated hemoglobin, total cholesterol, HDL- and LDL-cholesterol, triglycerides, Lactate dehydrogenase (LDH) 1 and LDH 2, renal function (urea, creatinine, and glomerular filtration rate [GFR]) and ionogram (Na, K, Cl, Ca^{2+}, P, HCO^{3-}). Subject should be fasting for 8 hours before blood collection.

All out-of-range laboratory values that are considered by the Investigator to be clinically significant will be recorded as AEs (see Section 9.6.3.1)

9.6.3.4 Physical Examination

A physical examination will be performed at Screening Visit and Visit 7. The physical examination will include an evaluation of the following: body as a whole, skin, head, eyes, ears, nose, and throat (HEENT), neck, cardiovascular, respiratory, musculoskeletal, neurologic, lymphatic/thyroid, abdomen.

When reporting the results of the physical examination, the use of the "Abnormal" category will be reserved for findings that are considered clinically significant, in the opinion of the Investigator; the "Normal" category will include "Abnormal" results that are not clinically significant, as well as no findings.

All abnormal findings will be recorded as AEs (see Section 9.6.3.1).

9.6.3.5 Height, Weight and Body Mass Index

Height will be recorded at Screening Visit only. Weight will be recorded at Screening Visit, Visit 4, Visit 5 and Visit 7. At each center the same balance will be used for all measurements. Subjects will wear only indoor clothing without shoes. BMI will be calculated at the Screening Visit, Visit 4, Visit 5 and Visit 7 using the following formula:

$$\frac{Weight}{Height^2}\ (\mathrm{kg/m^2}).$$

9.6.3.6 Gynecological Examination, Chlamydia test, Gonorrhea test and Cervical Cytology

A gynecological examination will be performed at Screening Visit and Visit 7. The gynecological examination will include an evaluation of the following: breast examination (performed by palpation) and assessment of the adnexa, cervix, uterus, vagina, and external genitalia.

When reporting the results of the gynecological examination, the use of the "Abnormal" category will be reserved for findings that are considered clinically significant, in the opinion of the Investigator; the "Normal" category will include "Abnormal" results that are not clinically significant, as well as no findings.

All abnormal findings will be recorded as AEs (see Section 9.6.3.1).

A Chlamydia testing will be performed using a vaginal swab:

- At Screening (Visit 1) for all subjects.
- At Visits 2, 3, 4, 5 and 6 for subjects who reported a change in sexual partner since the last study visit.

In case of positive Chlamydia test result, the subject will be treated, at the Investigator's discretion as this infection can influence the vaginal bleeding pattern. In case of positive Chlamydia test result at screening, the subject will start treatment before she is enrolled.

A gonorrhea testing will be performed using a vaginal swab:

- At Screening (Visit 1) for all subjects.
- At Visits 2, 3, 4, 5, and 6 for subjects who reported a change in sexual partner since the last study visit.

In case of positive gonorrhea test result, the subject will be treated, at the Investigator's discretion as this infection can influence the vaginal bleeding pattern. In case of positive gonorrhea test result at screening, the subject will start treatment before she is enrolled.

For cervical cytology, Pap testing will be performed at Screening in all women 20 years 0 months of age or older if no documented Pap test has been performed in the last 18 months. The enrollment visit cannot be performed until this Pap test result is available and the subject meets entry criteria. A copy of any Pap test or follow-up testing used for determination of study eligibility or during study follow-up must be obtained and included in the study record. If not available at the time of the visit for which the documentation is required then the Pap test should be performed per protocol. The results of the Pap test will be reported using the Bethesda Pap Smear Classification[7] as detailed in Appendix 3. If the Pap test at the Screening Visit presents abnormal result (i.e. dysplasia, cervical intraepithelial neoplasia, squamous intraepithelial lesion, carcinoma in situ, invasive carcinoma), the subject cannot be enrolled in the study. Enrollment of a subject with an ASCUS interpretation is permitted if the subject is less than 21 years of age or HPV reflex test is negative for high-risk oncogene virus. If the ASCUS interpretation was done on the Pap test performed in the past 18 months, enrollment of the subject is allowed if a repeat Pap test 6 months later was normal.

All abnormal findings in cervical cytology after subject enrolment that are considered by the Investigator to be clinically significant will be recorded as AEs (see Section 9.6.3.1).

9.6.3.7 Vital Signs

Vital signs will be measured at Screening Visit, Visits 2, 3, 4, 5, 6, and 7.

Vital signs will include sitting systolic and diastolic blood pressures and heart rate. Blood pressure measurements will be made using a sphygmomanometer with an appropriate cuff size for the individual subject. Measurements will be taken while the subject is seated after at least 5 minutes at rest.

All abnormal findings in vital signs that are considered by the Investigator to be clinically significant will be recorded as AEs (see Section 9.6.3.1).

9.6.4 Other Evaluations

Other assessments include the following:

- Vaginal bleeding pattern will be assessed based on the incidence of vaginal bleeding/spotting episodes;
- Compliance will be assessed based on tablet intake;
- Demographics;
- Prior/Concomitant medication use;
- Medical/surgical history;
- Gynecological history;
- Pregnancy risk and back-up contraception use;
- Acceptability of trial medication;
- Subjects' well-being;
- Contraceptive counseling;
- Return of spontaneous menstruation and return to fertility.

9.6.4.1 Incidence of vaginal bleeding/spotting

Subjects will be asked to record in the subject diary (see Section 9.6.1) the absence or the occurrence of vaginal bleeding or spotting on a daily basis using the following definitions:

0 = Absence of vaginal bleeding or spotting;

1 = Spotting: evidence of minimal vaginal blood loss that does not require new use of sanitary protection, including pantyliners;

2 = Bleeding: evidence of vaginal blood loss that requires the use of sanitary protection with a tampon, pad or pantyliner.

9.6.4.2 Population Pharmacokinetic Substudy

Population PK will be assessed using plasma E4 and DRSP concentration data from a subset of approximately 500 subjects to address the relationship between PK parameters and various individual characteristics (e.g., body weight, race, smoking, and fed/fasted condition). Blood samples for PK analysis will be obtained at Visits 3 and 4 between Days 10 and 14 of Cycles 2 and 4.

All subjects enrolled in the Population PK Substudy will be required to check-in to the site for Visits 3 and 4 between Days 10 and 14 of Cycles 2 and 4, respectively.

Two PK samples will be taken from the subjects in the Population PK Substudy at Visits 3 and 4. All subjects included in the Substudy will provide a sample for PK analysis at the time they check into the site (PK sampling 1). An additional blood sample (PK sampling 2) will be collected approximately two hours after the first sample.

Depending on the time scheduled for the study site visit (Visit 3 & 4), subjects will be instructed on when they need to take their medication – either as usually done at home or on site.

- If the appointement is scheduled in the morning and the subject usually takes her study medication in the morning, she should take it at the study site. One blood sample will be taken before dosing and the second blood sample will be taken within 2-hour postdose.
- If the appointement is scheduled in the morning and the subject usually takes her study medication in the evening, she should take it in the evening before the visit at their regular time. The subject should record the time of the dosing in the Diary.
- A subject who usually takes her study medication during the day should take it at usual time and come to the site when possible to have the 2 blood samples taken. The subject should record the time of dosing in the Diary.

The following timings will be recorded by the site personnel in the eCRF:

- The exact times of the last study medication dosing and the PK samplings 1 and 2.
- The time of the last meal intake before the last study medication dosing before study visit.

Plasma concentration data will be used to build an appropriate population PK model.

Only a selection of the sites will participate in the Population PK Substudy.

9.6.4.3 Compliance

Compliance (see also Section 9.4.3) to the investigational product will be evaluated using data recorded in the subject diary. Subjects will be asked to record tablet intake in the subject diary (see Section 9.6.1) on a daily basis.

9.6.4.4 Demographics

Demographic data include age, education, ethnicity and race.

9.6.4.5 Prior and Concomitant Medication Use

Medications with an end date occurring before the first investigational product dose date in the treatment period will be identified as prior medications. Medications with a start date occurring on or after the first investigational product dose date in the treatment period or medications

with a start date prior to the first investigational product dose date and an end date on or after the first treatment start date will be identified as concomitant medications.

MEDICATION HISTORY – PRIOR MEDICATION USE

Any medications taken in the last month prior to the Screening Visit will be recorded at Screening Visit and Visit 2 with the start and stop dates (see Section 9.4.6 for restrictions).

All hormonal contraceptives used via the following routes and within the timeframe specified prior to the Screening Visit will be recorded and the start and stop dates will also be recorded as specified below:

- Progestational implants; progestin, estrogen, or progestational injectable drug therapy within 12 months;
- Intrauterine hormonal contraceptives within 6 months;
- Oral, intravaginal or transdermal combined or progestin-only contraceptives within 3 months.

CONCOMITANT MEDICATION USE

Subjects will be queried at Visits 3, 4, 5, 6, and 7 concerning the use of medications (see Section 9.4.6 for restrictions). Concurrent medications used by the subjects will be documented including the name of the drug, the dose, the frequency, and route of administration, the date of initiation and discontinuation, and the reason for administration.

The reason for use or change of dose of a concomitant therapy may need to be reported as an AE (see Section 9.6.3.1).

9.6.4.6 Medical/Surgical History

The medical and surgical history of the subject will be recorded at the Screening Visit.

This includes a review of:

- All body systems,
- Cardiovascular risk factors: diabetes mellitus, dyslipoproteinemia, arterial hypertension, alcohol and illicit drug consumption, and tobacco use,
- Previous surgical intervention(s), including indication, date and outcome.

9.6.4.7 Gynecological History

The gynecological history of the subject will be recorded at the Screening Visit.

This includes:

- Gravidity and parity status;
- Menstrual cycle length for starters;
- Dysmenorrhea;
- Previous contraceptive method used. This includes, but is not limited to COC, progestin-only oral contraceptive, barrier methods, intrauterine devices, etc;
- History of pregnancy during accurate hormonal contraceptive use.

9.6.4.8 Pregnancy Risk and Back-up Contraception Use

Subject will be asked to record in the subject diary (see Section 9.6.1) for each cycle the occurrence of intercourse and the use of back-up contraception (e.g. use of condoms) if any.

9.6.4.9 Contraceptive Counseling

At Visit 6, the subject will be counseled about her future contraception. The choice of the contraceptive method is left to the Investigator's discretion.

A subject who desires early termination or is withdrawn from the study (see Section 13.4) after the enrollment visit (Visit 2) will be counseled about future contraception.

- Any subject who contacts the study site with a desire to discontinue study participation should be instructed at each visit to contact the study staff before discontinuing the study drug to be counseled about alternative contraception to use prior to the Early Termination Visit. Study sites may provide any prescription or non-prescription contraceptive to the subject as is medically appropriate per local standard of care other than an IUD or implant. If necessary, an unscheduled visit can occur to provide contraception (see section 9.5.5).
- A subject who presents to the study site for a scheduled visit and desires to discontinue study participation or is withdrawn from the study at that visit should be counseled about alternative contraception to use prior to the Early Termination Visit. Study sites may provide any prescription or non-prescription contraceptive to the subject as is medically appropriate per local standard of care other than an IUD or implant.
- A subject who presents to the study site for a scheduled visit who has not taken the study product for 16 days or more should have the scheduled visit procedures and the Early Termination Visit procedures completed at that time. The subject should be counseled about alternative contraception. Study sites may provide any prescription or non-prescription contraceptive to the subject as is medically appropriate per local standard of care.

On the day the subject is expected to start this contraception (± 1 day), the Investigator/Designee will contact the subject by phone to ensure her compliance with the counseled contraceptive method.

9.6.4.10 Acceptability of Trial Medication

The acceptability of the trial medication will be assessed by analysis of discontinuation rates and reasons for discontinuations. Subject's premature discontinuation must be documented on the Treatment Discontinuation Form, including the most important reason for discontinuation. The most important reason for discontinuation will be categorized as AE, lost to follow-up, subject request, protocol deviation, pregnancy, pregnancy wish or other. Subjects that complete the study must be documented on the End of Study Form.

9.6.4.11 Subjects' well-being

Subjects' well-being will be evaluated using two well-established questionnaires: the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form and the Menstrual Distress Questionnaire.

The baseline questionnaires will be given to the subject at Visit 2. The subject will be instructed to fill them in at home on or before the first day of study medication intake (Day 1). At the next visit, the study site personnel will ensure for the questionnaire completion.

The end-of-treatment questionnaires will be given to the subject at Visit 6. The subject will be instructed to fill them in at home between Day 7 and Day 14 of the 13th treatment cycle. At the next visit, the study site personnel will ensure for the questionnaire completion.

In case of premature study discontinuation, the subjects will be asked to fill in the questionnaires during the Early Termination Visit.

9.6.4.12 Return of spontaneous menstruation and return to fertility

Each woman who discontinues the study early due to a pregnancy wish will be followed after study treatment discontinuation to evaluate return of spontaneous menstruation and return of fertility.

They will be contacted every 6-8 weeks for a maximum of one year after study discontinuation. The date of the first spontaneous menstruation after study discontinuation will be recorded in the eCRF and follow-up will be continued. Once a pregnancy is reported or once a new contraceptive method has been started, the expected date of pregnancy term or of contraceptive treatment initiation will be recorded in the eCRF and no further follow-up contact will be done.

In case of pregnancy, the estimated date of conception will be derived from the expected date of pregnancy term.

10 ETHICS

10.1 Ethics Committee

The protocol and supporting documents for this study will be reviewed and approved by an appropriately constituted IRB prior to study initiation.

All reviews and approvals will be in accordance with Good Clinical Practice (GCP) as contained in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines (E6) and United States (US) CFR governing Institutional Review Boards (IRBs) (Title 21, Part 56).

A letter from the IRB documenting approval of the Investigator (who must be identified by name), the protocol (must be identified by title) and the subject consent form must be received by Estetra SPRL (referred hereafter as Sponsor) or its Designee prior to study initiation. A progress report will be submitted by the Investigator to the IRB at intervals specified by the IRB, but not less than annually. A copy of this progress report will be sent to Sponsor. After completion of the study, the Investigator will submit a signed clinical safety summary of the study to the IRB.

10.2 Ethical Conduct of Study

The study will be conducted in accordance with GCP as contained in ICH Guidelines and US CFR governing the protection of human subjects (Title 21, Part 50) and the obligations of clinical Investigators (Title 21, Parts 312.60 through 312.69). The study will also be conducted in accordance with the World Medical Association Declaration of Helsinki and all amendments.

Sponsor or Designee is responsible for the ongoing safety evaluation of the investigational product and will expedite the notification of all participating Investigators and regulatory authorities of findings that are both serious and unexpected and/or that could adversely affect the safety of subjects, the conduct of the study or alter the IRB's approval to continue the study.

10.3 Subject Information and Consent

The Investigator will ensure that written IC is obtained from each subject in accordance with applicable regulations.

Subjects will be interviewed at the Screening Visit by qualified staff at the site and will be provided with a full description of the nature and purpose of the study. The subject will be given adequate time to consider the requirements and risks associated with participation in the study. Each subject will provide written and signed IC prior to participating in any study procedures. The original signed consent forms will be retained on file at the clinical site and a copy will be given to the subject. Source documentation will also document that IC was obtained prior to the subject's participation in the study.

10.4 Subject Confidentiality

The Sponsor ensures that the following have permission to review all study-related documents: monitor, auditor, IRB and regulatory authorities. The subject's identity and study-related records will remain confidential throughout the duration of the study data collection and reporting process.

A unique subject identification code will be assigned to each potential study subject. The identification code protects the subject's identity and is used in lieu of the subject's name when reporting subject data. The data will always maintain the confidentiality of the subject.

The Investigator or Designee will review the subject data, which will be referenced using the subject identifier. At the conclusion of the study, the data obtained may be presented to regional regulatory authorities but the subject's identity will not be revealed. In addition, if any clinical data obtained from the study are published in scientific journals or presented at scientific meetings, the subject's identity will not be revealed.

11 QUALITY CONTROL AND ASSURANCE

The Sponsor and Designee will implement and maintain quality control procedures to ensure that this study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP and applicable regulatory requirements.

The Sponsor or Designee will routinely conduct monitoring and/or auditing visits to the study centers to verify the adherence to the study protocol, the protection of the rights and well-being of the subjects; and the accuracy and completeness of reported study data recorded on the source documentation.

12 PLANNED STATISTICAL METHODS

Detailed plans for the statistical methods will be provided in a Statistical Analysis Plan which will be finalized prior to database lock.

12.1 Determination of Sample Size

Sample size is based on needing a sufficient number of cycles such that the difference between the Pearl Index and the upper limit of the two-sided 95% confidence interval (CI) for the Pearl Index does not exceed 1. Assuming that the true Pearl Index is 1.0 and that a Poisson model is used to derive the CIs, then at least 12,337 at risk cycles are required for a power of 90% in the 16 to 35 year old population.[8.] If a not at risk cycle rate of 20% and a dropout rate of approximately 45% (assuming that we have an average of 4 cycles for subjects that discontinue) are assumed, approximately 1800 16 to 35 year old subjects need to be enrolled and initiate the investigational product. Additionally, it is planned for a maximum of 200 subjects > 35 years to be enrolled and initiate the investigational product. Therefore, in total, approximately 2000 subjects will be enrolled in the study and initiate the investigational product. Additionally, a subset of approximately 500 subjects will be enrolled in the PK Substudy.

12.2 Analysis Populations and Datasets

Statistical analysis and data tabulation will be performed using the following analysis populations unless specified otherwise:

- Screened population includes all subjects who signed an IC form.
- Enrolled population includes all enrolled subjects.
- Safety population includes all enrolled subjects who receive at least one dose of test article.
- Intention-to-Treat (ITT) population includes all enrolled subjects who receive at least one dose of test article. The ITT population is the same as the Safety population for this study.
- Per-protocol (PP) population includes all subjects in the ITT population who complete the study and do not have any important protocol deviations that impact the statistical analysis. The PP population may differ for the different endpoints.
- PK population includes all subjects enrolled in the PK Substudy who provide concentration data for at least one sample.

12.3 General Statistical Procedures

All the analyses will be conducted with SAS using procedures appropriate for the particular analysis.

The descriptive statistics for all the continuous variables presented will be mean, median, 25th percentile, 75th percentile, standard deviation (SD), standard error of mean (SEM), minimum, maximum, and number of subjects.

Categorical variables will be summarized using counts and percentages.

Baseline will be defined as the most recent assessment prior to first dose of study medication.

12.4 Efficacy Analyses

The efficacy analysis will be based on the Pearl Index. The Pearl Index, defined as the number of pregnancies per 100 women-years of treatment, will be calculated as

$$Pearl\ Index = \frac{1300 \times \text{number of on} - \text{treatment pregnancies}}{\text{number of women} - \text{28 day equivalent cycles of treatment}}$$

Only at risk cycles, i.e. cycles in which no other methods of birth control (including condoms) are used and during which the subjects confirmed that sexual intercourse has occurred, will be included in the denominator of the Pearl Index calculation. The subject diary data will be used to determine whether additional birth control methods were used and whether the subject has had intercourse.

Note that if conception occurs in a cycle, then that cycle will be included in the denominator even if other methods of birth control were used during that cycle or the subject did not confirm that they had had sexual intercourse. Cycles after the cycle of conception will be excluded from the denominator. All on-treatment pregnancies will be included in the numerator for the Pearl Index.

On-treatment pregnancy is defined as pregnancy with an estimated date of conception within the on-treatment period, i.e. Day 1 to 7 days after the intake of investigational product (whether active or inactive tablet). In cases where the date of conception cannot be established unequivocally (e.g. subjects is lost to follow-up), this pregnancy will be considered an on-treatment pregnancy. For calculation purposes a cycle will be defined as 28 days.

The method failure Pearl Index is calculated using the same method as the Pearl Index, but includes only those pregnancies that were classified as method failure and not pregnancies due to user failure, i.e. incorrect intake of the contraceptive product. Compliance data will be used to determine if the pregnancy was due to user failure.

Each on-treatment pregnancy will be reviewed and classified as either a method failure or a user failure pregnancy prior to database lock. Pregnancies will only be designated as user

failures if there is documentation that the subject did not use the test article correctly during the treatment cycle the conception occurred, including the instructions to be followed in case of missed pill(s).

12.4.1 Efficacy Endpoints

The efficacy endpoints are:

- Pearl Index for subjects aged of 16 to 35 years, inclusive, at screening;
- Pearl Index for all ages;
- Method failure Pearl Index for subjects aged 16 to 35 years old, inclusive, at screening;
- Method failure Pearl Index for all ages.

The primary efficacy endpoint will be the Pearl Index in the ITT population aged 16 to 35 years, inclusive, at Screening with at risk cycles (cycles in which no other methods of birth control (including condoms) are used and during which the subjects confirmed that sexual intercourse has occurred). Subjects in this age group will not be censored on their 36th birthday for the pregnancy assessment.

12.4.2 Statistical Analysis

12.4.2.1 Confidence Intervals for the Pearl Indices

The 95% CI for the Pearl Indices will be presented for the 16 to 35 year age group and overall and for method failure for the ITT population including only at risk cycles in the denominator. For historical comparison the Pearl Index will also be calculated using the same method as described above including all at risk cycles and cycles where the subject did not have intercourse and did not use back-up contraception in the denominator.

The 95% CI for Pearl Indices will be calculated based on using a Poisson distribution.

12.4.2.2 Life-Table Rates

In addition, the cumulative pregnancy rate, as determined by life-table methods, together with the corresponding 95% CIs will be presented for all pregnancies and for all method failure pregnancies in the ITT population. This will be repeated for all ages and for subject's age 16 to 35 years inclusive at Screening.

Life-table analyses will provide one-year life-table pregnancy rates for each efficacy endpoint (i.e. for all pregnancies as used in the Pearl Index and for all method failure pregnancies as used in the method failure Pearl Index). The life-table analysis will evaluate the cumulative probability of pregnancy by cycle using PROC LIFETEST in SAS where the time variable is the cycle

where the estimated conception occurred for subjects who had an on-treatment event of pregnancy. Subjects who did not have an on-treatment event of pregnancy will be censored on the cycle at which they discontinued from the study. Cumulative probabilities of pregnancy and 95% CIs will be calculated based on Kaplan-Meier estimates through Cycle 13. Additionally, the estimated survivor function against time (cycle) will be provided.

12.4.3 Statistical Subgroup Analyses

If the sample size is adequate, subgroup analyses will be performed for the following categories:

- BMI categories (< 30, ≥ 30);
- Race category (White, Black, Asian, Other);
- Starters/Switchers;
- Smokers/Non-smokers;
- Age (16-25; 25-35 and > 35 years old).

12.5 Safety Analyses

Safety variables will be summarized for the Safety population using descriptive statistics and frequency distributions as defined in the following sections.

12.5.1 Adverse Events

TEAEs will be classified into a standardized terminology using the Medical Dictionary for Regulatory Activities (MedDRA) system organ classifications and preferred terms. The latest available version of MedDRA will be used as coding dictionary. Prior to database lock, the coding will be updated using the current version of MedDRA. The incidence of TEAEs will be summarized for the Safety population. Although a preferred term or system organ class may be reported more than once for a subject, each subject will only be counted once in the incidence count for that preferred term or system organ class. Summaries of the following types will be provided:

- Overall summary of TEAEs.
- Summary of TEAEs by MedDRA system organ class, MedDRA preferred term, investigational product relationship, and intensity.
- Summary of TEAEs by MedDRA preferred term and investigational product relationship in descending order of frequency.
- Summary of treatment-emergent SAEs by MedDRA system organ class, MedDRA preferred term, and investigational product relationship.

- Summary of TEAEs by MedDRA system organ class, MedDRA preferred term, and investigational product relationship for the primary events leading to premature discontinuation from the study.

These summaries will present the number and percentage of subjects reporting an AE for each classification level as well as the number of events reported. The denominator for calculating the percentages for summaries will be based on the number of subjects in the overall Safety population.

All AEs, SAEs and deaths, SAEs considered to be related to treatment, and AEs leading to premature discontinuation from the study will also be provided in data listings including non-treatment emergent events.

12.5.2 Extent of Exposure

The duration of exposure in days will be summarized using descriptive statistics for the Safety/ITT population. Duration of exposure will be calculated as the difference between last tablet intake date and the first tablet intake date plus 1.

Additionally, these summaries will present the number and percentage of subjects exposed for at least 26 weeks and at least 52 weeks. The denominators for calculating the percentages will be based on the number of subjects in the Safety population.

12.5.3 Clinical Laboratory Evaluations

For continuous clinical laboratory analytes, the absolute value and change from baseline will be summarized by analyte and visit using descriptive statistics for the Safety population. Categorical laboratory analytes, classified as normal or abnormal, will be summarized by analyte and visit using the number and percentage of subjects in each category for the Safety population. The denominators for calculating the percentages will be based on the number of subjects with non-missing assessments at a particular visit for the Safety population.

Shifts to values outside of the normal range will be presented by analyte and visit and will be summarized by the number and percentage of subjects with evaluable shifts. An evaluable shift is one where both the Screening Visit value and the on-treatment or early termination value are recorded for subjects in the Safety population. The denominators for calculating the percentages will be the number of subjects with an evaluable shift.

All clinical laboratory values, abnormal clinical laboratory values, and clinical significant laboratory values will also be provided in data listings.

12.5.4 Physical examination

Physical examination assessments will be summarized for the Safety population by visit. For each body system and assessment category, the number and percentage of subjects will be

presented. The denominators for calculating the percentages will be based on the number of subjects evaluated for a particular body system.

12.5.5 Gynecological examination

Gynecologic examination assessments will be summarized for the Safety population by visit. For each assessment category, the number and percentage of subjects will be presented.

12.5.6 Vital Signs

Vital sign measurements for the Safety population will be summarized using descriptive statistics by visit. The change from baseline will also be summarized in the same manner.

12.5.7 Height, Weight and BMI

Weight measurements and BMI calculation for the Safety population will be summarized using descriptive statistics by visit. The change from baseline will also be summarized in the same manner.

Height at baseline (Visit 1) will be summarized using descriptive statistics.

12.6 Other Assessments or Analyses

12.6.1 Bleeding and spotting

Bleeding/spotting data will be summarized according to the methods suggested by Mishell et al. [9].

Table 1: Bleeding and spotting definitions

Term	Definition
Bleeding	Evidence of vaginal blood loss that requires the use of sanitary protection with a tampon, pad or pantyliner.
Spotting	Evidence of minimal vaginal blood loss that does not require new use of sanitary protection, including pantyliners.
Episode of Bleeding/Spotting	Bleeding/spotting days bounded on either end by 2 days of no bleeding or spotting.
Scheduled Bleeding/Spotting	Any bleeding/spotting that occurs during the hormone-free interval (i.e. Days 25 – 28) and continues through Days 1-3 of the subsequent active cycle, and Any bleeding/spotting that occurs while taking active hormones during Days 1-7 of the first cycle.
Unscheduled Bleeding	Any bleeding that occurs while taking active hormones that does not meet the criteria for scheduled bleeding.
Unscheduled Spotting	Any spotting that occurs while taking active hormones that does not meet the criteria for scheduled spotting.

Bleeding patterns will be analyzed in the ITT and PP populations using data from the subject diary. Criteria for exclusion of cycles from the PP analysis of bleeding patterns will be defined in the statistical analysis plan (SAP) based on specific protocol deviations thought to have a potential to impact the subjects bleeding patterns that occurred during that cycle. Vaginal bleeding will be classified as spotting or bleeding and scheduled and unscheduled based on the definitions in Table 1.

There will be two types of reference periods (RP) evaluated for this study:

- Reference period based on 28-days (or cycle) – 13 cycles
- Reference period based on 91 days

The analysis will include all subjects in the respective analysis population with at least 1 evaluable reference period. One or two consecutive days with missing bleeding information will be interpolated with the bleeding information from the previous day. For three or more consecutive days with missing bleeding information, missing data will be interpolated using the worst bleeding observation of the bordering days.

Summaries of bleeding/spotting data include but are not limited to the following:

- Number and percentage of subjects with unscheduled bleeding and/or spotting episodes for each reference period.

- Percentage of subjects with bleeding and/or spotting including both scheduled and unscheduled for each day presented in a graphical display.
- Number and percentage of subjects with absence of any bleeding or spotting for each reference period.
- Descriptive statistics (e.g., mean, SD, median, minimum, and maximum) for the number of days of bleeding and/or spotting, bleeding only, and spotting only within a reference period for:
    - Total Days (Unscheduled + Scheduled)
    - Unscheduled Days
    - Scheduled Days

Additionally, bleeding data may be summarized for some subgroups specified in Section 12.4.3.

12.6.2 Disposition

The disposition of subjects will be summarized including the number of subjects screened, enrolled, treated, discontinued (including reason for discontinuation) and completed. In addition, the number of subjects included in each of the analysis populations will be summarized. The cumulative discontinuation rate, as determined by life-table methods, together with the corresponding 95% CIs will be presented.

12.6.3 Demographic and Other Pre-treatment Characteristics

Subject demographic as well as medical history will be summarized for each analysis population using descriptive statistics for continuous variables and frequency distributions (number and percentage of subjects) for categorical variables. Summaries will be provided overall and by race and BMI categories in the Safety/ITT and PP populations.

12.6.4 Prior and Concomitant Medications

Medication usage will be coded using the World Health Organization (WHO) Drug Dictionary. Medications will be presented by WHO Drug Anatomical/Therapeutic/Chemical category and WHO Drug preferred name. Summaries will be presented for prior (prior to treatment period) medication use and concomitant (during treatment period) medication use.

Medications with an end date occurring before the first investigational product dose date in the treatment period will be identified as prior medications. Medications with a start date occurring on or after the first investigational product dose date in the treatment period or medications with a start date prior to the first investigational product dose date and an end date

on or after the first investigational product dose date will be identified as concomitant medications. All summaries will present the number and percentage of subjects for each medication. The denominators for calculating the percentages will be based on the number of subjects in the Safety population.

12.6.5 Treatment Compliance

Treatment compliance by cycle will be presented using the subject diaries based on number of tablets taken divided by the number of tablets that should have been taken. The number and percentage of subjects missing no tablets, 1 tablet, 2 tablets and more than 2 tablets will be summarized for each cycle. Summaries will be presented using descriptive statistics in the Safety population.

12.6.6 Protocol Deviations

The number and percentage of subjects who had an important protocol deviation will be summarized for the enrolled population.

12.6.7 Quality of Life

The total score of the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) (Appendix 4) will be derived by summing the first 14 items to obtain the raw total score, which is then transformed into a percentage maximum using the following formula: (raw score – 14)/56. The absolute values and change from baseline of the percentage maximum, how satisfied the subject has been with the medication and how would the subject rate the overall life satisfaction and contentment during the past week will be summarized descriptively by visit.

The Menstrual Distress Questionnaire will be scored according to the manual (Appendix 5) [10]. The absolute values and change from baseline for the scores for pain, water retention, autonomic reactions, negative affect, impaired concentration, behavior change, arousal and control will be summarized descriptively by visit. Summaries will be provided overall and by switchers and starters separately.

12.6.8 Follow-Up Evaluations

The number and percentage of subjects who had pregnancy confirmation, returned to menses and received a new contraceptive method after the treatment termination will be summarized. The denominator used for the percentages will be the number of subjects in the Safety population who discontinued study medication due to a pregnancy wish.

The time from last dose of study medication to return of menses will be summarized using descriptive statistics in the Safety population.

The following will be summarized using descriptive statistics for subjects in the Safety population who discontinued study medication due to a pregnancy wish who selected the corresponding fertility information:

- Time from last dose of study medication to estimated date of conception;
- Time from last dose of study medication to new contraceptive method.

12.6.9 Population Pharmacokinetic Substudy

Plasma concentration data for E4 and DRSP will be summarized using descriptive statistics by cycle and sampling time range (ranges will be defined in the Statistical Analysis Plan) for the PK population. Descriptive summaries will be provided overall and by race, BMI categories (< 30, ≥ 30), smoking status (smokers, non-smokers), and fed/fasted condition. Additionally, concentration data will be displayed graphically with regression lines overall, and by race, BMI categories, and smoking status for each cycle.

Individual plasma concentration-time data will be pooled for the PK analyses. Initially, the data will be subjected to exploratory compartmental analysis to determine the primary parameters such as:

- Apparent clearance (CL/F).
- Central volume of distribution (V/F).
- Lag time of Absorption (tlag), if necessary.
- Relative bioavailability for fed vs fasted state.

The initial estimates obtained from the exploratory analyses will be employed using Bayesian analysis to build an appropriate population PK model. The analyzed parameters will include, but not be limited to:

- Maximum concentration (C_{max}).
- Time to maximum concentration (T_{max}).
- Extent of exposure for dosing interval (AUC_{tau}).
- Terminal half-life ($t_{1/2}$).

The estimated population mean values will be utilized in conjunction with the individual subject concentrations to determine inter-individual variability. If inter-individual variability is unable to be assessed on any individual parameter, the population mean values alone may be used. The impact of individual characteristics on the parameters will be explored and included in the population model if significant. Individual estimates of the above parameters and additional PK variables will be generated based on the population model. The basic model will be evaluated for random scatteredness by residual variability analysis. The model will further be validated using various diagnostic techniques, as necessary. Covariate analyses will be performed separately for the PK of E4 and DRSP.

13 STUDY MANAGEMENT

13.1 Monitoring

The Investigator will be responsible for preparing and maintaining adequate and accurate source documents (medical records, raw data collection forms, etc.) designed to record all observations and other pertinent data for each subject treated with the study drug. The Investigator will allow representatives of the Sponsor, contract Designees, authorized regulatory authority inspectors, and the ECs to have direct access to all documents pertaining to the study. The Investigator is to immediately notify the Sponsor (or its representative) of any regulatory authority inspections. The Investigator will be informed about the outcome of any Sponsor audit.

This study will be monitored regularly, by or under supervision of a monitor from the Sponsor' representative. The frequency of monitoring visits will be agreed upon by the Sponsor's representative and the study staff.

Monitoring visits will take place on a regular basis according to the enrollment rate and number of subjects enrolled at each investigational site. During these visits, the monitor will check the completion of the eCRF entries, compliance with the study protocol and with GCP - ICH, and their agreement with the source data. The monitor will also verify the correct use of the study drug. At a final visit, the monitor will check all remaining material including the remaining quantities of the study drug and will organize their return to the Sponsor or Designee. At each visit, the Investigator and staff will be expected to cooperate with the Sponsor's representative(s) for the purposes of review and verification of protocol compliance, AE reporting, eCRFs, source documents, clinical supplies and inventory records, and any additional records as may have been previously arranged between the Investigator and the Sponsor's representative(s).

The Investigator and/or other designated study personnel are expected to contact the Sponsor's representative with any study concerns and/or questions. Contact details are provided in the Site Operations Manual for the site.

13.2 Protocol amendments

The Sponsor may propose to amend this protocol at any time.

No change to the protocol will be implemented until the Sponsor, the competent authorities and the IRB have reviewed and approved the amendment.

In the event of an emergency, the Investigator shall implement any medical procedures deemed appropriate for subject safety. All such procedures must have written documentation and be promptly reported to the Sponsor.

13.3 Protocol deviations

A protocol deviation is any change, divergence or departure from the IRB approved protocol (intentional or unintentional). All deviations are to be documented at the site and reported to the IRB according to the IRB's guidelines.

In the event of an emergency, the Investigator shall implement any medical procedures deemed appropriate for subject safety. All such procedures must have written documentation and be promptly reported to the Sponsor.

13.4 Withdrawal of Subjects

Withdrawn subjects are those who do not complete all evaluations and procedures outlined in the protocol. Subjects who discontinue taking study drug for any reason must also be withdrawn from the study. Subjects may be withdrawn from the study because of one of the following:

- Adverse Event: An AE that, in the opinion of the Investigator or Sponsor, suggests that continued participation in the study is not in the subject's best interest for safety reasons. The occurrence of a VTE or an arterial thromboembolic event will automatically lead to the immediate cessation of the study drug and is an absolute reason for discontinuing the subject participation in the trial. Only 1 AE can be noted to be the reason for withdrawal. All AEs that are present when the subject withdraws from the study will be followed as described in Section 9.6.3.1.
- Lost to Follow-up: Confirmed at minimum by two phone calls and a traceable letter without answer.
- Subject Request: Subject requests for any reason to be withdrawn or withdraws her consent.
- Protocol Deviation: A subject may be withdrawn from the study at the discretion of the Investigator or Sponsor due to poor compliance with protocol requirements that may compromise the study results or subject safety.
- Pregnancy: If a subject becomes pregnant during the study, the subject will be withdrawn from the study and followed through conclusion of the pregnancy.
- Pregnancy wish.
- Other: Other reasons include but are not limited to: Investigator decision that it is in the subject's best interest to be withdrawn, administrative reasons, relocation of subject, etc.

If a subject is withdrawn from the study after enrolment visit (Visit 2), all Visit 7 assessments should be completed (see Section 9.5.3.5) and the subject should be counseled about alternative contraception to use (see Section 9.6.4.9). Subjects withdrawn from the study will not be replaced.

13.5 Termination of the Study

If the study is terminated prematurely or suspended, the appropriate IRB and regulatory authority(ies) will be promptly informed of the termination or suspension and will be provided the reason(s) for the termination or suspension. All obligations and responsibilities of the Sponsor and the Investigator under GCP, the US CFR and the Declaration of Helsinki will remain in force if the study is terminated prematurely.

14 DOCUMENTATION REQUIREMENTS AND RECORDKEEPING

14.1 Source Documentation, Data access and Monitoring

The eCRFs represent a record of the subject's experience in the study, therefore, the eCRF data must be supported by original (or source) medical records, as appropriate. EMR (Electronic Medical Records) recorded directly into the eCRF is also considered source data when there are no other written or electronic records preceding the eCRF entry.

Prior to enrolling a subject in the study, the Investigator must document his/her review of subject eligibility criteria in the source records for the subject, including the Investigator's signature and date on any medical and laboratory reports indicating a review of the source data occurred. The Investigator will continue to follow this practice for any subsequent medical and laboratory reports generated as a result of the clinical study.

The Investigator agrees that the Sponsor or its designated agents, the IRB, the EMA, FDA or foreign regulatory agencies will have reasonable access to study source documentation for purposes of audit or inspection and monitoring visit review both during and after completion of the study. Monitoring visits provide the Sponsor and Designee with the opportunity to evaluate the progress of the study; to verify the accuracy and completeness of eCRFs; to ensure that all protocol requirements, applicable regulations and Investigator's obligations are being fulfilled; and to resolve any inconsistencies in the study records.

14.2 Data Capture in electronic CRFs and Discrepancy Management

Site personnel will be responsible for the completion and correction of eCRFs according to the protocol and other instructions provided by the Sponsor or their Designee. The Investigator is responsible for ensuring the completeness and accuracy of the data as evidenced by the Investigator's signature and date once the subject has completed the study and all required study data has been entered into the eCRF. Information recorded by the subject into a Diary Card will be entered into the eCRFs by the site personnel.

Since site personnel will enter data directly into a validated eCRF, programmatic data validation procedures will be employed to identify data discrepancies to site personnel at the time of entry and/or upon saving the data. Designated site personnel will resolve any discrepancies via the eCRF. Any additional findings upon clinical review by the Sponsor or their Designee will be entered into the system for review and resolution by site personnel. A full audit trail of data changes following entry will be captured during the study in the electronic data management system. The Investigator will be provided with a copy of all eCRF data for retention.

14.3 RECORD KEEPING

In compliance with ICH guidelines, the Investigator shall maintain adequate records for the study including copies of eCRFs for individual subjects, medical records, laboratory reports,

consent forms, test article disposition records, safety reports, information regarding participants who discontinued and other pertinent data. The Investigator shall maintain these records for a period of at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the test article. These records should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Sponsor will inform the Investigator/institution as to when these records no longer need to be retained.

15 OTHER INFORMATION

15.1 Financing and Insurance

Financing and insurance is addressed in a separate agreement.

15.2 Publication and Disclosure Policy

The data that will be obtained in this study will be the property of the Sponsor, who will make reasonable efforts to assure that the results are published in a peer-reviewed journal. As some of the information concerning the investigational product and development activities at the Sponsor may be of strictly confidential nature, any manuscript or other presentation of data must first be reviewed by the Sponsor before its submission.

16 REFERENCE LIST

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2 Mawet, M. *et al.* Unique effects on hepatic function, lipid metabolism, bone and growth endocrine parameters of estetrol in combined oral contraceptives. *The European journal of contraception & reproductive health care : the official journal of the European Society of Contraception*, 1-13, doi:10.3109/13625187.2015.1068934 (2015).

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17 APPENDICES

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Appendix 1. Study Schedule of Events

Table 2: Schedule of Events

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Early Termination Visit[12]
Treatment Cycle	**Screening Visit**	**Subject Enrollment[1]**	**During Cycle 2**	**During Cycle 4**	**During Cycle 7**	**During Cycle 10**	**During Cycle 14**	
Treatment Cycle Day			**Cycle Day 1 – 14[11]**	**Cycle Day 1 - 14[11]**	**Cycle Day 1 - 14**	**Cycle Day 1 – 14**	**Cycle Day 16-23**	
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Demographics	X							
Medical and surgical History	X							
Gynecological History	X							
Physical Examination	X						X	X
Weight, Height and BMI[2]	X			X	X		X	X
Gynecological Examination (including breast)	X						X	X
Cervical Cytology (Pap)[3]	X							
Chlamydia Testing	X[4]	X[5]	X[5]	X[5]	X[5]	X[5]		
Gonorrhea Testing	X[4]	X[5]	X[5]	X[5]	X[5]	X[5]		
Blood sample for Population PK Substudy[6]			X	X				

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Early Termination Visit[12]
Treatment Cycle	**Screening Visit**	**Subject Enrollment[1]**	**During Cycle 2**	**During Cycle 4**	**During Cycle 7**	**During Cycle 10**	**During Cycle 14**	
Treatment Cycle Day			**Cycle Day 1 – 14[11]**	**Cycle Day 1 - 14[11]**	**Cycle Day 1 - 14**	**Cycle Day 1 – 14**	**Cycle Day 16-23**	
Serum Pregnancy Test[7]	X						X	X
Dispense Home Urine Pregnancy Test Kits		X[8]						
Fasted clinical Laboratory tests (hematology and biochemistry)	X[9]				X[10]		X[9]	X[9]
Vital Signs	X	X	X	X	X	X	X	X
Enrollment		X						
Investigational Product Dispensing		X		X	X	X		
Investigational Product Return and Drug Accountability			X	X	X	X	X	X
Subject Diary Dispensing		X						
Subject Diary Review and Return			X	X	X	X	X	X
AE Assessment		X						
TEAE Assessment			X	X	X	X	X	X
Prior Medication	X	X						
Concomitant Medication			X	X	X	X	X	X

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Early Termination Visit[12]
Treatment Cycle	**Screening Visit**	**Subject Enrollment[1]**	**During Cycle 2**	**During Cycle 4**	**During Cycle 7**	**During Cycle 10**	**During Cycle 14**	
Treatment Cycle Day			**Cycle Day 1 – 14[11]**	**Cycle Day 1 - 14[11]**	**Cycle Day 1 - 14**	**Cycle Day 1 – 14**	**Cycle Day 16-23**	
Stop Date of the Previous Contraceptive Method (if any)			X					
Questionnaires dispensing		X				X		
Questionnaires completion check			X				X	X
Contraceptive Counseling						X	X	X[13]
Follow-up Call		X[14]				X[15]		
End of Study Form							X	X
Return of spontaneous menstruation and return to fertility[16]								

[1] Subject enrollment will occur within 45 days after the Screening Visit.

[2] Height will be recorded at Screening Visit only.

[3] A written documentation of prior Pap test performed within 18 month before screening is allowed. No Pap test will be performed in subjects less than 20 years of age.

[4] Chlamydia and gonorrhea testing at screening should be performed for all subjects.

[5] Chlamydia and gonorrhea testing during Visits will be performed for subjects who reported a change in sexual partner since last test.

[6] Applies only to the approximately 500 subjects who participate in the Population PK Substudy.

[7] Pregnancy test (serum) also indicated in case of suspicion of pregnancy.

[8] Subject should perform urinary pregnancy test at home just before the first pill intake. Result should be recorded in the diary.

[9] Complete hematology and biochemistry (including glycaemia, glycated hemoglobin, total cholesterol, HDL- and LDL-cholesterol, and triglycerides) (see Appendix 2).

[10] At Visit 5, the following biochemistry parameters will be assessed: glycaemia, glycated hemoglobin, LDH 1 and LDH 2, total cholesterol, HDL- and LDL-cholesterol, triglycerides, renal function (urea and creatinine), GFR, and ionogram (Na, K, Cl, Ca^{2+}, P, HCO^{3-}).

[11] Visit 3 and 4 for the subjects in the Population PK Substudy should be performed between Days 10 and 14 of Cycles 2 and 4.

[12] The Early Termination Visit should occur between 16 and 23 days after the last investigational product intake or immediately if the study product was never started.

[13] In case of early termination or withdrawal of subject who did not undergo a Visit 6: contraceptive counseling should be provided as soon as the site is aware of the subject's desire for termination.

[14] Within 7 days following the expected start of treatment to remind the subject to complete the diary entries.

[15] On the day the subject is expected to start the next contraceptive method (± 1 day) to ensure subject's compliance.

[16]Women who discontinue the study due to a pregnancy wish will be followed up for a maximum of one year after study discontinuation for return of spontaneous menstruation and until pregnancy or initiation of a contraceptive method (whichever occurs first).

AE=adverse event; BMI=body mass index; GFR=glomerular filtration rate; HDL=high-density lipoprotein; LDL=low-density lipoprotein; TEAE=treatment-emergent adverse event; LDH=lactate dehydrogenase

Appendix 2. Clinical Laboratory Evaluations

Hematology

Hemoglobin	Mean cell volume
Hematocrit	White blood cell & Differential
Red blood cell count	Platelet count

Serum Chemistries

Albumin	Total protein
Alanine aminotransferase (ALAT)	Serum creatinine
Aspartate aminotransferase (ASAT)	GFR
Blood urea nitrogen	Sodium
Gamma glutamyl transferase (GGT)	Potassium
Glucose	Calcium
Glycated hemoglobin	Chloride
Lactate dehydrogenase (LDH) 1 and LDH 2	Bicarbonate
Total bilirubin	Phosphorus

Lipid Profile

Total cholesterol	Triglycerides
High density lipoprotein cholesterol	Low density lipoprotein cholesterol

Appendix 3. Bethesda Pap Smear Classification[7]

SPECIMEN TYPE:

Indicate conventional smear (Pap smear) vs. liquid-based preparation vs. other

STATEMENT ON SPECIMEN ADEQUACY

- Satisfactory for evaluation *(describe presence or absence of endocervical/transformation zone component and any other quality indicators, e.g., partially obscuring blood, inflammation, etc.)*
- Unsatisfactory for evaluation *(specify reason)*
    - Specimen rejected/not processed *(specify reason)*
    - Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of *(specify reason)*

GENERAL CATEGORIZATION *(optional)*

- Negative for Intraepithelial Lesion or Malignancy
- Other: See Interpretation/Result *(e.g., endometrial cells in a woman ≥45 years of age)*
- Epithelial Cell Abnormality: See Interpretation/Result (*specify* 'squamous' or 'glandular' *as appropriate*)

INTERPRETATION/RESULT

NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY

(When there is no cellular evidence of neoplasia, state this in the General Categorization above and/or in the Interpretation/Result section of the report—whether or not there are organisms or other non-neoplastic findings)

Non-neoplastic Findings (optional to report)

- Non-neoplastic cellular variations
    - Squamous metaplasia
    - Keratotic changes
    - Tubal metaplasia
    - Atrophy

- Pregnancy-associated changes

- Reactive cellular changes associated with:
  - Inflammation (includes typical repair)
    - Lymphocytic (follicular) cervicitis
  - Radiation
  - Intrauterine contraceptive device (IUD)

- Glandular cells status post hysterectomy

Organisms

- *Trichomonas vaginalis*
- Fungal organisms morphologically consistent with *Candida* spp.
- Shift in flora suggestive of bacterial vaginosis
- Bacteria morphologically consistent with *Actinomyces* spp.
- Cellular changes consistent with herpes simplex virus
- Cellular changes consistent with cytomegalovirus

OTHER

- Endometrial cells *(in a woman ≥45 years of age)*

(Specify if "negative for squamous intraepithelial lesion")

EPITHELIAL CELL ABNORMALITIES:

- SQUAMOUS CELL
  - Atypical squamous cells
    - of undetermined significance (ASC-US)
    - cannot exclude HSIL (ASC-H)
  - Low-grade squamous intraepithelial lesion (LSIL) *(encompassing: HPV/ mild dysplasia/CIN 1)*

- High-grade squamous intraepithelial lesion (HSIL) (*encompassing: moderate and severe dysplasia, CIS; CIN 2 and CIN 3*)
  - with features suspicious for invasion *(if invasion is suspected)*
- Squamous cell carcinoma

- GLANDULAR CELL
  - Atypical
    - endocervical cells (NOS or *specify in comments*)
    - endometrial cells (NOS or *specify in comments*)
    - glandular cells (NOS or *specify in comments*)
  - Atypical
    - endocervical cells, favor neoplastic
    - glandular cells, favor neoplastic
  - Endocervical adenocarcinoma in situ
  - Adenocarcinoma
    - endocervical
    - endometrial
    - extrauterine
    - not otherwise specified (NOS)

OTHER MALIGNANT NEOPLASMS: *(specify)*

ADJUNCTIVE TESTING

Provide a brief description of the test method(s) and report the result so that it is easily understood by the clinician.

COMPUTER-ASSISTED INTERPRETATION OF CERVICAL CYTOLOGY

If case examined by an automated device, specify device and result.

Appendix 4. Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)

Taking everything into consideration, during the past week how satisfied have you been with your……

	Very Poor	Poor	Fair	Good	Very Good
…..physical health?	1	2	3	4	5
…..mood?	1	2	3	4	5
…..work?	1	2	3	4	5
…..household activities?	1	2	3	4	5
…..social relationships?	1	2	3	4	5
…..family relationships?	1	2	3	4	5
…..leisure time activities?	1	2	3	4	5
…..ability to function in daily life?	1	2	3	4	5
…..sexual drive, interest and/or performance?*	1	2	3	4	5
…..economic status?	1	2	3	4	5
…..living/housing situation?*	1	2	3	4	5
…..ability to get around physically without feeling dizzy or unsteady or falling?*	1	2	3	4	5
…..your vision in terms of ability to do work or hobbies?*	1	2	3	4	5
…..overall sense of well being?	1	2	3	4	5
…..medication? (If not taking any, check here _____ and leave item blank.)	1	2	3	4	5
…..How would you rate your overall life satisfaction and contentment during the past week?	1	2	3	4	5

*If satisfaction is very poor, poor or fair on these items, please UNDERLINE the factor(s) associated with a lack of satisfaction.

Appendix 5. Menstrual Distress Questionnaire (Form C – Cycle)[1]

Directions:

The list below shows common symptoms and feelings associated with menstruation. For each item, choose the descriptive category below that best describes your experience during each of the three time periods indicated. That is, for each item, decide whether you have "no experience of symptom", or whether your experience is "present, mild", "present, moderate", "present, strong" or "present, severe. Then write the number of the category in the space provided. If none of the categories exactly describes your experience, choose the one that most closely matches what you feel.

Be sure to rate every item. When you are finished return the completed form to the person who gave it to you.

Descriptive Categories

0 No experience of symptom
1 Present, mild
2 Present, moderate
3 Present, strong
4 Present, severe

	Most recent flow	**Four days before**	**Remainder of cycle**
1. Muscle stiffness			
2. Headache			
3. Cramps			
4. Backache			
5. Fatigue			
6. General aches and pains			
7. Weight gain			
8. Skin blemish or disorder			
9. Painful or tender breasts			
10. Swelling (breasts, abdomen, ..)			
11. Dizziness, faintness			
12. Cold sweats			
13. Nausea, vomiting			

[1]

	Most recent flow	Four days before	Remainder of cycle
14. Hot flashes			
15. Loneliness			
16. Anxiety			
17. Mood swings			
18. Crying			
19. Irritability			
20. Tension			
21. Feeling sad or blue			
22. Restlessness			
23. Insomnia			
24. Forgetfulness			
25. Confusion			
26. Poor judgment			
27. Difficulty concentrating			
28. Distractible			
29. Minor Accidents			
30. Poor motor coordination			
31. Poor school/work performance			
32. Take naps, stay in bed			
33. Stay at home			
34. Avoid social activities			
35. Decreased efficiency			
36. Affectionate			
37. Orderliness			
38. Excitement			
39. Feelings of well-being			
40. Bursts of energy, activity			
41. Feelings of suffocation			
42. Chest pains			
43. Ringing in the ears			
44. Heart pounding			
45. Numbness, tingling			
46. Blind Spots, fuzzy vision			

Appendix 6. Sponsor Signatures

Study Title:	A Multicenter, Open-label, Single-Arm Study to Evaluate the Contraceptive Efficacy and Safety of a Combined Oral Contraceptive Containing 15 mg Estetrol and 3 mg Drospirenone
Study Number:	MIT-Es0001-C302
Original protocol date:	07 June 2016 – Version 1.1
Amendment 1.0 date:	14 December 2016
Amendment 1.1 date	10 July 2017

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signature:_____ Date:_____

[redacted]
Medical Advisor

Signature:_____ Date:_____

[redacted]
Senior Medical Advisor

Signature:_____ Date:_____

[redacted]
Clinical Project Leader

Signature:_____ Date:_____

[redacted]

Qualified Person for Pharmacovigilance

Signature:_____ Date:_____

[redacted]

Clinical Manager

Signature:_____ Date:_____

[redacted]

Chief Scientific Officer

Appendix 7. Contract Research Organization Signatures

Study Title:	A Multicenter, Open-label, Single-Arm Study to Evaluate the Contraceptive Efficacy and Safety of a Combined Oral Contraceptive Containing 15 mg Estetrol and 3 mg Drospirenone
Study Number:	MIT-Es0001-C302
Original protocol date:	07 June 2016 – Version 1.1
Amendment 1.0 date:	14 December 2016
Amendment 1.1 date	10 July 2017

This clinical study protocol was subject to critical review and has been approved by PRA Health Sciences.

Signature:_____ Date:_____

[redacted]
Principal Biostatistician
PRA Health Sciences

Signature:_____ Date:_____

[redacted]
Drug Safety Associate
PRA Health Sciences

Signature:_____ Date:_____

Lead Data Manager
PRA Health Sciences

Appendix 8. Investigator Signature

Study Title:	A Multicenter, Open-label, Single-Arm Study to Evaluate the Contraceptive Efficacy and Safety of a Combined Oral Contraceptive Containing 15 mg Estetrol and 3 mg Drospirenone
Study Number:	MIT-Es0001-C302
Original protocol date:	07 June 2016 – Version 1.1
Amendment 1.0 date:	14 December 2016
Amendment 1.1 date	10 July 2017

This clinical study protocol was reviewed and has been approved by the Investigator.

Name:_____

Function: _____

Institution:_____

Signature:_____ Date:_____

Appendix 9. Protocol Amendment - Summary of changes

Modified sections in Protocol: MIT-Es0001-C302 Amendment Version 1.0

This section summarizes changes that have been performed between original protocol (Final Version 1.1 (07 June 2016) and Amendment Version 1.0 (14 December 2016).

***Note*: wherever applicable, deleted text has been crossed out and added text has been printed in bold and italic characters.**

2 SYNOPSIS

Other Secondary Objectives:

[…]

4. To assess the effect of various individual characteristics/ covariates (body weight, race, ~~and~~ smoking, ***and fed/fasted condition***) on the pharmacokinetics (PKs) of 15 mg E4/3 mg DRSP (Population PK Substudy).

[…]

- **Eligibility criteria:**

Exclusion Criteria

A subject will be excluded from participation if she meets any of the following criteria:

[…]

7. Smoking ***nicotine-containing products*** if ≥ 35 years old~~, at screening~~.

16. Complicated valvular heart disease (pulmonary hypertension, ~~arterial~~ ***atrial*** fibrillation, subacute bacterial endocarditis).

25. History of COC-related cholestasis.

[…]

Statistical Methods:

[…]

Additional Summaries:

[…]

- Population PK model (using plasma E4 and DRSP concentration data from a subset of approximately 500 subjects). PK parameters will include, but not be limited to:
  - […]
  - ***Relative bioavailability for fed vs fasted state***
  - […]

Initial estimates of PK parameters (e.g., CL/F, V/F, tlag) will be determined using exploratory compartmental analyses. These estimates will be employed to build an appropriate population PK model. The primary parameters will include (but not be limited to) ~~C_{max}, T_{max}, AUC_{tau}, and $t_{1/2}$~~ ***CL/F, V/F, tlag and relative bioavailability for fed vs fasted***. The impact of individual characteristics (body weight, race, ~~and~~ smoking, ***and fed/fasted condition***) on the PK parameters will be explored and included in the population model if significant.

[…]

7 INTRODUCTION

7.1 Background

[…]

The potent synthetic estrogen, ethinylestradiol (EE), is the most frequently used estrogen in COCs. EE is easily ~~observed~~ ***absorbed*** when administered orally.

[…]

8 STUDY OBJECTIVES

8.3 Other Secondary Objective(s)

4. To assess the effect of various individual characteristics/ covariates (body weight, race, ~~and~~ smoking, ***and fed/fasted condition***) on the PKs of 15 mg E4/3 mg DRSP (Population PK Substudy).

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

[…]

The total duration of the study, including the screening, will range from ~~382~~ ***387*** to ~~447~~ ***467*** days for the participating subjects, which is approximately a year and one month.

[…]

Population PK will be assessed using plasma E4 and DRSP concentration data from a subset of approximately 500 subjects to address the relationship between E4 and DRSP PK parameters and various individual characteristics (e.g., body weight, race, ~~and~~ smoking***, and fed/fasted condition***). Blood samples for PK analysis will be obtained at Visits 3 and 4 between Days 10 and 14 of Cycles 2 and 4 (section 9.6.4.2).

9.3 Selection of Study Population

[…]

9.3.2 Exclusion Criteria

A subject will be excluded from participation if she meets any of the following criteria:

2. […]

7. Smoking ***nicotine-containing products*** if ≥ 35 years old~~, at screening~~.

16. Complicated valvular heart disease (pulmonary hypertension, ~~arterial~~ ***atrial*** fibrillation, subacute bacterial endocarditis).

19. Presence or history of migraine with aura at any age or migraine without aura if ~~≥~~ ≥ 35 years old.

25. History of COC-related cholestasis.

26-42. […]

9.4 Study Treatment

9.4.4 Selection of Doses and Timing of Administration in the Study

9.4.4.1 Instructions for starting the first pack of tablets

- Women who did not use any contraceptive method or who used a barrier contraceptive method will be instructed to begin the investigational product on the first day of the next menstrual bleeding. Starting on Days 2-5 is also allowed, but a condom must be used until the subject has completed 7 days of uninterrupted active tablet intake. ***If the menstrual cycle prior to start of first pack of tablets is longer than 35 days or shorter than 21 days, the subject should not start the investigational product and will be withdrawn from the study (section 13.4). The subject should contact the study staff as soon as possible to schedule an Early Termination Visit (section 9.5.4) and to discuss an alternative contraception to use (section 9.6.4.9).***

- […]

- Women switching from an injectable hormonal method of contraception will start the investigational product on the first day of ~~the~~ ***spontaneous*** menstrual bleeding ***following an interval after the last injection***, which can vary depending of the form:
  - 10 months after the injection of a product with a 3-month duration~~,~~ ;
  - 6 months after the injection of a product with a 2-month duration ~~and~~;
  - 3 months after the injection of a product with a 1-month duration.

  Starting on Days 2-5 is also allowed, but a condom must be used until the subject has completed 7 days of uninterrupted active tablet intake.

- Women switching from an intrauterine or dermally implantable contraceptive will start the investigational product on the day of removal. ***A condom must be used until the subject has completed 7 days of uninterrupted active tablet intake.***

[…]

9.4.4.2 Dosing Instructions

[…]

- […]

- ***Return all blister packs to site personnel at the following visit.***

9.4.4.3 Instructions in case of missed tablet(s) or in conditions potentially reducing the contraceptive efficacy

If the subject has vomiting or diarrhea within 4 hours of tablet intake, she should take another tablet from the extra pack as a replacement.

If the subject inadvertently misses one or more of the tablets ~~or~~

- ~~In case of vomiting within 4 hours after the tablet intake or,~~
- ~~In case of diarrhea within 4 hours after the tablet intake,~~

the following instructions must be followed:[6]

- […]
- If two or more consecutive active pink tablets have been missed (≥ 48 hours since a tablet should have been taken):
  - If between Day 1 & Day 17:

- **[…]**
- ***Consider emergency contraception as per current practice if the woman had unprotected intercourse during the missed pill interval.***

- […]

- ~~A new pack of tablets should be started immediately after the day the last white tablet was taken. There should be no interruption between two blister packs.~~ Anytime a subsequent cycle of the product/pack is started later than the day following administration of the last white tablet, the subject should use condoms until she has taken pink tablets daily for 7 consecutive days.
- ~~Return all blister packs to site personnel at the following visit.~~

9.5 Study Activities

[…]

9.5.1 Visit 1: Screening Visit

[…]

Potential subjects will be screened according to the inclusion and exclusion criteria within ~~30~~ ***45*** days prior to the subject enrollment visit (Visit 2). ***Subjects who were eligible for the study but did not enroll within 45 days of screening (Visit 1) can be re-screened. Re-screening requires all Visit 1 assessments to be repeated.*** The Investigator will maintain a log of all subjects screened for participation and record the reason(s) for excluding potential subjects.

[…]

9.5.2 Visit 2: Subject Enrollment

The Visit 2 will occur within ~~30~~ ***45*** days after the Screening Visit (Visit 1), when the entire laboratory results of the subject have been received.

[…]

During Visit 2, the following procedures will be performed:

1-10. […]

11. Schedule or confirm the next study visit ***and the follow-up phone call***;

12. […]

13. Instruct the subject to contact the site immediately if she decides to discontinue the investigational product and, if possible, to not discontinue the investigational product before contacting the site;

14. […]

9.5.3 Treatment Period (from Cycle 1 Day 1 until Cycle 13 Day 28)

9.5.3.1 Visit 3 (Cycle 2, between Day 1 and Day 14)

[…]

12. Instruct the subject to contact the site immediately if she decides to discontinue the investigational product and, if possible, to not discontinue the investigational product before contacting the site.

9.5.3.2 Visit 4 (Cycle 4, between Day 1 and 14)

[…]

12. Instruct the subject to contact the site immediately if she decides to discontinue the investigational product and, if possible, to not discontinue the investigational product before contacting the site.

9.5.3.3 Visit 5 (Cycle 7, between Day 1 and 14)

[…]

12. Instruct the subject to contact the site immediately if she decides to discontinue the investigational product and, if possible, to not discontinue the investigational product before contacting the site.

9.5.3.4 Visit 6 (Cycle 10, between Day 1 and 14)

[…]

13. Instruct the subject to contact the site immediately if she decides to discontinue the investigational product and, if possible, to not discontinue the investigational product before contacting the site.

9.5.3.5 Visit 7 (Cycle 14, between Day 16 and 23), End of Treatment Visit

1-10. […]

11. Complete the ***End of*** Study ~~Termination~~ Form.

9.5.4 Early Termination Visit

~~In case of early termination or withdrawal of subject (see Section 13.5), the procedures listed in Visit 7 (see Section 9.5.3.5) will be performed and Treatment Discontinuation Form will be~~

~~completed. In addition, the subject will be counseled about the next contraceptive method to use (see Section 9.6.4.9).~~

A subject who desires early termination or is withdrawn from the study after the enrollment visit (Visit 2) (see Section 13.4) will require an Early Termination Visit.

- ***Any subject who contacts the study site with a desire to discontinue study participation should be instructed at each visit to contact the study staff before discontinuing the study drug to be counseled about alternative contraception to use prior to the Early Termination Visit (see Section 9.6.4.9). Study sites may provide any prescription or non-prescription contraceptive to the subject as is medically appropriate per local standard of care other than an IUD or implant. If necessary, an unscheduled visit can occur to provide contraception (see Section 9.5.5).***
- ***A subject who presents to the study site for a scheduled visit and desires to discontinue study participation or is withdrawn from the study at that visit should be counseled about alternative contraception to use prior to the Early Termination Visit (see Section 9.6.4.9). Study sites may provide any prescription or non-prescription contraceptive to the subject as is medically appropriate per local standard of care other than an IUD or implant.***
- ***A subject who presents to the study site for a scheduled visit who has not taken the study product for 16 days or more should have the scheduled visit procedures and the Early Termination Visit procedures completed at that time. The subject should be counseled about alternative contraception (see Section 9.6.4.9). Study sites may provide any prescription or non-prescription contraceptive to the subject as is medically appropriate per local standard of care.***

An Early Termination Visit should occur between 16 and 23 days after the last investigational product intake or immediately if the investigational product was never started. The procedures listed in Visit 7 (see Section 9.5.3.5) will be performed and the End of Study Form will be completed.

[…]

9.5.5 Unscheduled Visit

At any time of the study, an Unscheduled Visit could occur in case of suspicion of pregnancy based on a positive pregnancy test performed at home by the subject ~~or~~, in case the Investigator judges it necessary to examine a subject who would present a potential significant adverse event in the Investigator's opinion, ***or if alternative contraception is needed for a subject planning early termination.*** Additional assessments can be performed at the Investigator's discretion.

9.6 Study Variables and Procedure Descriptions

9.6.2 Efficacy assessments

9.6.2.2 Pregnancy Reporting

[…]

All ~~on-treatment~~ pregnancies identified during the course of the study ***in a subject who was using the investigational product*** will be monitored to completion, i.e., approximately 9 month follow-up in the case of live birth or until outcome information is obtained. […].

If a subject becomes pregnant and states she never started the investigational product, the pregnancy does not have to be monitored if the subject returns all of the investigational product (proving she never started the investigational product).

9.6.3 Safety variables

9.6.3.6 Gynecological Examination, Chlamydia test, Gonorrhea test and Cervical Cytology

[…]

Enrollment of a subject with an ~~ASC-US~~ ***ASCUS*** interpretation is permitted if the subject is less than 21 years of age or HPV reflex test is negative for high-risk oncogene virus.

[…]

9.6.4.2 Population Pharmacokinetic Substudy

Population PK will be assessed using plasma E4 and DRSP concentration data from a subset of approximately 500 subjects to address the relationship between PK parameters and various individual characteristics (e.g., body weight, race, ~~and~~ smoking, ***and fed/fasted condition***). Blood samples for PK analysis will be obtained at Visits 3 and 4 between Days 10 and 14 of Cycles 2 and 4.

[…]

Two PK samples will be taken from the subjects in the Population PK Substudy at Visits 3 and 4. All subjects included in the Substudy will provide a sample for PK analysis at the time they check into the site ***(PK sampling 1)***. An additional blood sample ***(PK sampling 2)*** will be collected approximately two hours after the first sample.

Depending on the time scheduled for the study site visit (Visit 3 & 4), subjects will be instructed on when they need to take their medication – either as usually done at home or on site.

- ***If the appointement is scheduled in the morning and the subject usually takes her study medication in the morning, she should take it at the study site. One blood sample will be taken before dosing and the second blood sample will be taken within 2-hour postdose.***
- ***If the appointement is scheduled in the morning and the subject usually takes her study medication in the evening, she should take it in the evening before the visit at their regular time. The subject should record the time of the dosing in the Diary.***

- ***A Subject who usually takes her study medication during the day should take it at usual time and come to the site when possible to have the 2 blood samples taken. The subject should record the time of dosing in the Diary.***

The ~~exact times of~~ ***following timings*** ~~the last study medication dosing and the PK sampling~~ will be recorded by the site personnel in the eCRF:

- ***The exact times of the last study medication dosing and the PK samplings 1 and 2.***
- ***The time of the last meal intake before the last study medication dosing before study visit.***

[…]

9.6.4.9 Contraceptive counseling

At Visit 6 ~~and at the Early Termination Visit in case of premature study termination~~, the subject will be counseled about her future contraception. The choice of the contraceptive method is left ~~at~~ ***to*** the Investigator's discretion.

A subject who desires early termination or is withdrawn from the study (see Section 13.4) after the enrollment visit (Visit 2) will be counseled about future contraception.

- ***Any subject who contacts the study site with a desire to discontinue study participation should be instructed at each visit to contact the study staff before discontinuing the study drug to be counseled about alternative contraception to use prior to the Early Termination Visit. Study sites may provide any prescription or non-prescription contraceptive to the subject as is medically appropriate per local standard of care other than an IUD or implant. If necessary, an unscheduled visit can occur to provide contraception (see Section 9.5.5).***
- ***A subject who presents to the study site for a scheduled visit and desires to discontinue study participation or is withdrawn from the study at that visit should be counseled about alternative contraception to use prior to the Early Termination Visit. Study sites may provide any prescription or non-prescription contraceptive to the subject as is medically appropriate per local standard of care other than an IUD or implant.***
- ***A subject who presents to the study site for a scheduled visit who has not taken the study product for 16 days or more should have the scheduled visit procedures and the Early Termination Visit procedures completed at that time. The subject should be counseled about alternative contraception. Study sites may provide any prescription or non-prescription contraceptive to the subject as is medically appropriate per local standard of care.***

[…]

9.6.4.11 Subjects' well-being

[…]

The baseline questionnaires will be given to the subject at Visit 2. The subject will be instructed to fill them in at home on ***or before*** the first day of study medication intake (Day 1). At the next visit, the study site personnel will ensure for the questionnaire completion.

9.6.4.12 Return of spontaneous menstruation and return to fertility

Each woman who discontinues the study ***early*** due to a pregnancy wish will be followed after study treatment discontinuation to evaluate return of spontaneous menstruation and return of fertility.

They will be contacted ~~by phone~~ every 6-8 weeks for a maximum of one year after study discontinuation.

[…]

12 PLANNED STATISTICAL METHODS

12.6 Other Assessments or Analyses

12.6.7 Quality of Life

[…]

The absolute values and change from baseline for the scores for pain, water retention, autonomic reactions, negative affect, impaired concentration, behavio~~u~~r change, arousal and control will be summarized descriptively by visit.

[…]

12.6.9 Population Pharmacokinetic Substudy

Plasma concentration data for E4 and DRSP will be summarized using descriptive statistics by cycle and sampling time range (ranges will be defined in the Statistical Analysis Plan) for the PK population. Descriptive summaries will be provided overall and by race, BMI categories (< 30, ≥ 30), ~~and~~ smoking status (smokers, non-smokers)***, and fed/fasted condition***. Additionally, concentration data will be displayed graphically with regression lines overall, and by race, BMI categories, and smoking status for each cycle.

Individual plasma concentration-time data will be pooled for the PK analyses. Initially, the data will be subjected to exploratory compartmental analysis to determine the ~~basic~~ ***primary*** parameters such as:

- [...]
- ***Relative bioavailability for fed vs fasted state.***

The initial estimates obtained from the exploratory analyses will be employed using ~~non-linear mixed-effect modeling~~ ***Bayesian analysis*** to build an appropriate population PK model. The analyzed parameters will include, but not be limited to:

[…]

13 STUDY MANAGEMENT

13.4 Withdrawal of Subjects

[…]

If a subject is withdrawn from the study ~~following the start of study drug~~ ***after enrolment visit (Visit 2)***, all Visit 7 assessments should be completed ***(see Section 9.5.3.5)*** ***and the subject should be counseled about alternative contraception to use (see Section 9.6.4.9)***. Subjects withdrawn from the study will not be replaced.

17 Appendices

Appendix 1 Study Schedule of Events

Table 2: Schedule of Events

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	***Early Termination Visit***[12]
Treatment Cycle	**Screening Visit**	**Subject Enrollment**[1]	**During Cycle 2**	**During Cycle 4**	**During Cycle 7**	**During Cycle 10**	**During Cycle 14 / ~~Early termination Visit~~**	
Treatment Cycle Day			**Cycle Day 1 – 14**[11]	**Cycle Day 1 - 14**[11]	**Cycle Day 1 - 14**	**Cycle Day 1 – 14**	**Cycle Day 16-23**	
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Demographics	X							
Medical and surgical History	X							
Gynecological History	X							
Physical Examination	X						X	***X***
Weight, Height and BMI[2]	X			X	X		X	***X***
Gynecological Examination (including breast)	X						X	***X***
Cervical Cytology (Pap)[3]	X							

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	***Early Termination Visit***[12]
Treatment Cycle	**Screening Visit**	**Subject Enrollment**[1]	**During Cycle 2**	**During Cycle 4**	**During Cycle 7**	**During Cycle 10**	**During Cycle 14 / ~~Early termination Visit~~**	
Treatment Cycle Day			**Cycle Day 1 – 14**[11]	**Cycle Day 1 - 14**[11]	**Cycle Day 1 - 14**	**Cycle Day 1 – 14**	**Cycle Day 16-23**	
Chlamydia Testing	X[4]	X[5]	X[5]	X[5]	X[5]	X[5]		
Gonorrhea Testing	X[4]	X[5]	X[5]	X[5]	X[5]	X[5]		
Blood sample for Population PK Substudy[6]			X	X				
Serum Pregnancy Test[7]	X						X	***X***
Dispense Home Urine Pregnancy Test Kits		X[8]						
Fasted clinical Laboratory tests (hematology and biochemistry)	X[9]				X[10]		X[9]	***X***[9]
Vital Signs	X	X	X	X	X	X	X	***X***
Enrollment		X						
Investigational Product Dispensing		X		X	X	X		
Investigational Product Return and Drug Accountability			X	X	X	X	X	***X***

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	***Early Termination Visit***[12]
Treatment Cycle	**Screening Visit**	**Subject Enrollment**[1]	**During Cycle 2**	**During Cycle 4**	**During Cycle 7**	**During Cycle 10**	**During Cycle 14 / ~~Early termination Visit~~**	
Treatment Cycle Day			**Cycle Day 1 – 14**[11]	**Cycle Day 1 - 14**[11]	**Cycle Day 1 - 14**	**Cycle Day 1 – 14**	**Cycle Day 16-23**	
Subject Diary Dispensing		X						
Subject Diary Review and Return			X	X	X	X	X/	***X***
AE Assessment		X						
TEAE Assessment			X	X	X	X	X	***X***
Prior Medication	X	X						
Concomitant Medication			X	X	X	X	X	***X***
Stop Date of the Previous Contraceptive Method (if any)			X					
Questionnaires dispensing		X				X		
Questionnaires completion check			X				X	***X***
Contraceptive Counseling						X	X	***X***[13]
Follow-up Call		X~~13~~*14*				X~~14~~*15*		
End of Study Form							X	***X***

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	***Early Termination Visit***[12]
Treatment Cycle	**Screening Visit**	**Subject Enrollment**[1]	**During Cycle 2**	**During Cycle 4**	**During Cycle 7**	**During Cycle 10**	**During Cycle 14 / ~~Early termination Visit~~**	
Treatment Cycle Day			**Cycle Day 1 – 14**[11]	**Cycle Day 1 - 14**[11]	**Cycle Day 1 - 14**	**Cycle Day 1 – 14**	**Cycle Day 16-23**	
Return of spontaneous menstruation and return to fertility[~~15~~*16*]								

[1] Subject enrollment will occur within ~~30~~ ***45*** days after the Screening Visit.

[…]

[12] The Early Termination Visit should occur between 16 and 23 days after the last investigational product intake or immediately if the study product was never started.

[~~12~~*13*] In case of early termination or withdrawal of subject who did not undergo a Visit 6***: contraceptive counseling should be provided as soon as the site is aware of the subject's desire for termination.***

[~~13~~*14*] ~~Approximately~~ ***Within*** 7 days following the expected start of treatment to remind the subject to complete the diary entries.

[~~14~~*15*] […]

[~~15~~*16*] […]

Appendix 6 Sponsor Signatures

[…]

Signature: ***Date:***

Karina Putineanu

Head of Clinical Development

~~Signature: Date:~~

~~Linda Lebon~~

~~Regulatory Affairs & Drug Development Expert~~

[…]

Modified sections in Protocol: MIT-Es0001-C302 Amendment Version 1.1

This section summarizes changes that have been performed between Amendment Version 1.0 (14 December 2016) and Amendment Version 1.1 (10 July 2017)

***Note*: wherever applicable, deleted text has been crossed out (double strikethrough) and added text has been printed in bold, underlined and italic characters.**

2 SYNOPSIS

Study Population: Approximately 2000 healthy female subjects at risk for pregnancy, between 16 and 50 years old, inclusive (at the time of screening), and requesting contraception will be enrolled in the study ***and initiate the investigational product***. In total 1800 subjects will be 16 to 35 years old, inclusive (at the time of screening). Recruitment may be stopped when 2000 subjects have ~~been enrolled~~ ***initiated the investigational product*** if the required number of subjects for the primary analysis (1800 subjects in the age group up to and including 35 years) has been reached. Recruitment in the age group > 35 years will be stopped when 200 subjects have ~~been enrolled~~ ***initiated the investigational product***. Approximately 500 of these subjects will be included in the Population PK Substudy.
Study Locations: This clinical study will be conducted in up to approximately ~~70~~ ***80*** centers in North America (United States of America and Canada).
[…]
Duration of the study:

Overall treatment duration is ***up to*** thirteen 28-day cycles, i.e., 12 months. […]
Statistical Methods: […] For Pearl index calculations, thirteen 28-day cycles constitute one woman-year. […]

6 STUDY ADMINISTRATIVE STRUCTURE

The study will be performed in approximately ~~70~~ ***80*** centers in North America with approximately 90% of subjects in United States of America and 10% of subjects in Canada.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

[…]

Approximately 2000 healthy female subjects at risk for pregnancy, between 16 and 50 years old (inclusive, at the time of screening), and requesting contraception will be enrolled in the study ***and initiate the investigational product***. In total, 1800 subjects will be 16 to 35 years old (inclusive). Recruitment may be stopped when 2000 subjects have ~~been enrolled~~ ***initiated the investigational product*** if the required number of subjects for the primary analysis (1800 subjects in the age group up to 35 years) has been reached. Recruitment in the age group > 35 years will be stopped when 200 subjects have ~~been enrolled~~ ***initiated the investigational product***.

Eligible subjects will be treated with 15 mg E4/3 mg DRSP for ***up to*** 13 consecutive cycles.
[…]

9.4 Study Treatment

9.4.4 Selection of Doses and Timing of Administration in the Study

[…]

This 28-day cyclic regimen must be taken for ***up to*** 13 consecutive cycles. The treatment must be taken once daily at approximately the same time of the day.

[…]

9.5 Study Activities

9.5.2 Visit 2: Subject Enrollment

[…]

13. Instruct any subject not on a hormonal contraceptive and who does not start the investigational product at the enrollment visit to contact the site immediately if her next menses occurs at earlier than 21 days or is delayed such that her cycle length exceeds 35 days, and that she should not start the investigational product if either of these happens;

[…]

12 PLANNED STATISTICAL METHODS

12.1 Determination of Sample Size

[…]. If a not at risk cycle rate of 20% and a dropout rate of approximately 45% (assuming that we have an average of 4 cycles for subjects that discontinue) are assumed, approximately 1800 16 to 35 year old subjects need to be enrolled ***and initiate the investigational product***. Additionally, it is planned ~~to enroll~~ ***for a*** maximum of 200 subjects > 35 years ***to be enrolled and initiate the investigational product***. Therefore, in total, approximately 2000 subjects will be enrolled in the study ***and initiate the investigational product***. Additionally, a subset of approximately 500 subjects will be enrolled in the PK Substudy.

12.4 Efficacy Analyses

[…]

12.4.2 Statistical Analysis

12.4.2.2 Life-Table Rates

[…]

Cumulative probabilities of pregnancy and 95% CIs will be calculated based on Kaplan-Meier estimates ~~for~~ ***through*** Cycle 13. Additionally, the estimated survivor function against time (cycle) will be provided.

Appendix 6. Sponsor Signatures

Signature:_____ Date:_____

~~Karina Putinceanu~~

~~Head of Clinical Development~~

Françoise Bruyère
Clinical Manager

Appendix 7. Contract Research Organization Signatures

Signature:_____ Date:_____

~~Lyn Taylor~~

Jess Read
Principal Biostatistician
PRA Health Sciences

Signature:_____ Date:_____

~~Ramdas Kanase~~

Vijaya Vundurti
Drug Safety Associate
PRA Health Sciences

Signature:_____ Date:_____

~~LaTonya Bufford~~

Douglas Stewart
Lead Data Manager
PRA Health Sciences