CLINICAL STUDY PROTOCOL

A prospective, multi-center, randomized, cross-over study to assess the effect of norgestrel 75 mcg on cervical mucus and ovarian activity during perfect use, after one delayed intake and after a missed pill

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PROTOCOL SYNOPSIS

Title

A prospective, multi-center, randomized, cross-over study to assess the effect of norgestrel 75 mcg on cervical mucus and ovarian activity during perfect use, after one delayed intake and after a missed pill.

Investigator(s), Study site(s)

2 clinical sites in the United States (US): Oregon Health & Science University, Portland, Oregon and University of California Davis Health, Sacramento, California

Phase: IIa

Indication

Oral contraception

Objectives:

Primary objective

- To determine the effect on cervical mucus score of a delayed intake of 6 hours or of a missed pill of norgestrel 75 mcg compared to the effect observed during reported perfect daily use

Subordinate primary objective

- To estimate the duration of the protective effect of cervical mucus after last pill intake of norgestrel 75 mcg during reported perfect use

Secondary objectives

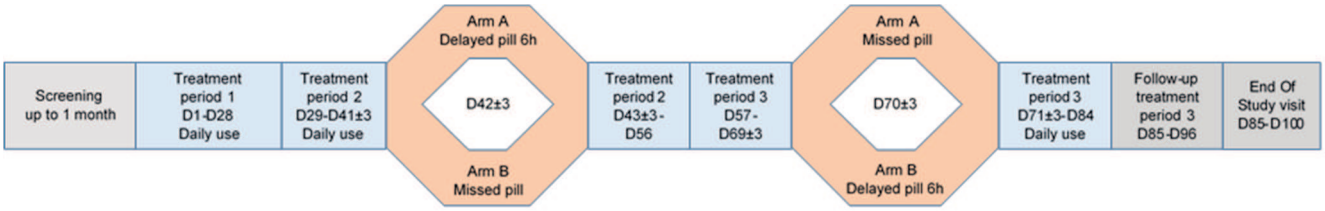
- To evaluate and compare the percentage of subjects with a protective cervical mucus score during reported perfect daily use, during a treatment period with a delayed intake of 6 hours and during a treatment period with a missed pill of norgestrel 75 mcg.
- To evaluate and compare the ovarian activity during reported perfect daily use, during a treatment period with a delayed intake of 6 hours and during a treatment period with a missed pill of norgestrel 75 mcg.
- To assess if a combination of cervical mucus score and ovarian status can be considered as a measure of protection from conception during reported perfect daily use, during a treatment period with a delayed intake of 6 hours and during a treatment period with a missed pill of norgestrel 75 mcg.
- To determine levonorgestrel pharmacokinetics after a single dose of norgestrel 75 mcg, at steady state, after a delayed intake of 6 hours and after a missed pill.
- To assess the safety of norgestrel 75 mcg taken daily for 12 weeks.

Study design

This is an exploratory, prospective, multi-center, randomized, cross-over study to assess the effect of norgestrel 75 mcg on cervical mucus and ovarian activity during reported perfect daily use, after a delayed intake of 6 hours and after a missed pill.

Study subject participation will be approximately 4.5 months long (up to one month for screening, three 28-day treatment periods, up to 12 days of follow-up and up to 5 days for the end of study visit (EOS) after the last pill intake or follow-up visit) (see Figure 1 below).

Figure 1 Design of the study



Screening period

Screening period will start with the screening visit performed during the luteal phase of the menstrual cycle and end with the start of next menses. The following visit (enrollment visit) is intended to start within 5 days after onset of menses, but subjects will be allowed to delay this visit for up to one cycle if necessary.

Treatment period 1:

- Treatment: norgestrel 75 mcg
  - Treatment initiation within 5 days of start of menses (enrollment visit)
  - Continue at the same time daily throughout the study (except for specific days in treatment periods 2 and 3, see below)
- Regular visits:
  - Scheduled twice a week (every 3-4 days)
  - Procedures
    - Cervical mucus sampling,
    - Transvaginal ultrasound (TVUS)*,
    - Blood sampling for hormone levels (progesterone (P4), estradiol (E2), FSH, LH)
- Extra visits:
  - To be initiated two days after a regular visit TVUS shows an ovarian follicle ≥15 mm in one dimension
  - To occur every other day for a maximum of 3 visits before a postovulatory image is obtained
  - Procedures
    - Cervical mucus sampling, TVUS, and blood sampling for hormone levels (P4, E2, FSH, LH)
    - Extra visits to be stopped when a post ovulatory image is obtained or if a postovulatory image is not obtained at the third extra visit
- PK sampling (levonorgestrel):
  - Day 1 from before treatment to 24 h post treatment (4 samples per subject)
  - Study week 3, 1st visit (Steady State): from before treatment to 5-9 h post treatment (1-2 samples per subject)

Treatment period 2:

- Starts on day 29
- Randomization at first visit of treatment period 2, either in:
  - Arm A: delayed pill intake of 6 hours on day 42±3 of treatment period 2 followed by missed pill on day 70±3 of treatment period 3
    OR
  - Arm B: missed pill on day 42±3 of treatment period 2 followed by delayed pill intake of 6 hours on day 70±3 of treatment period 3
- Regular visits: same as in treatment period 1 except for delayed/missed pill period (DMP period, see below)
- Extra visits:
  - Same as in treatment period 1

* TVUS always to be performed after cervical mucus sampling

- Extra visits will be suspended during the DMP period and can start again afterwards if applicable

- DMP period (Days 41 to 43 ±3)
  - 3 consecutive days
  - $V2_{R-1}$ (Day 41±3):
    - Study pill intake. The time of intake will be defined as $T2_{R-1}$
    - Cervical mucus sampling at $T2_{R-1}$ + 8h
    - PK sampling: at $T2_{R-1}$ + 8h (1 sample per subject)
    - TVUS
    - Blood sampling for hormone levels (P4, E2, FSH, LH)
  - $V2_R$ (Day 42±3):
    - Delayed pill intake of 6 hours (Arm A, intake at $T2_{R-1}$ + 6h) or missed pill (Arm B)
    - Cervical mucus sampling: at $T2_{R-1}$ +3h (Arm A) or $T2_{R-1}$ + 6h (Arm B)
    - PK sampling: at $T2_{R-1}$ +3h, $T2_{R-1}$ + 5.5h, $T2_{R-1}$ + 7.5h in Arm A (3 samples per subject) or $T2_{R-1}$ + 6h in Arm B (1 sample per subject)
  - $V2_{R+1}$ (Day 43±3):
    - PK sampling: at $T2_{R-1}$ - 30 min (1 sample per subject)
    - Cervical mucus sampling: at $T2_{R-1}$ - 30 min
    - Study pill intake at $T2_{R-1}$
    - TVUS
    - Blood sampling for hormone levels (P4, E2, FSH, LH)
- Study week 5
  - 1st visit: PK sampling within 30 minutes of mucus sampling (1 sample per subject)

<u>Treatment period 3:</u>

- Starts on day 57
- Regular visits: same as in treatment period 1 except for DMP period (see below)
- Extra visits before Day 84:
  - Same as in period 1
  - Extra visits will be suspended during DMP period and can start again afterwards if applicable
- Extra visits after Day 84 (follow-up visits)
  - Extra visits could continue after the last day of treatment intake (Day 84) until the criteria for stopping them are fulfilled
  - To occur every other day for a maximum of 6 visits (3 before and 3 after a postovulatory image is obtained)
  - Procedures – visits before a post-ovulatory image is obtained
    - Cervical mucus sampling, TVUS, and blood sampling for hormone levels (P4, E2, FSH, LH)
    - Extra visits to be stopped if a postovulatory image is not obtained at the third extra visit
  - Procedures – visits after a post-ovulatory image is obtained
    - Cervical mucus sampling and blood sampling for hormone levels (P4)
    - Extra visits to be stopped if P4 > 30 nmol/L at one visit or > 10 nmol/L at two consecutive visits or after 3 visits after a postovulatory image is obtained
- DMP period
  - 3 consecutive days
  - $V3_{R-1}$ (Day 69±3):
    - Study pill intake. The time of intake will be defined as $T3_{R-1}$
    - Cervical mucus sampling: at $T3_{R-1}$ + 8h
    - PK sampling: at $T3_{R-1}$ + 8h (1 sample per subject)
    - TVUS
    - Blood sampling for hormone levels (P4, E2, FSH, LH)
  - $V3_R$ (Day 70±3):
    - Missed pill (Arm A) or delayed pill intake of 6 hours (Arm B, intake at $T3_{R-1}$ + 6h)
    - Cervical mucus sampling: at $T2_{R-1}$ +3h (Arm B) or $T2_{R-1}$ + 6h (Arm A)

- PK sampling: at $T3_{R-1}$ + 6h in Arm A (1 sample per subject) or $T3_{R-1}$ +3h, $T3_{R-1}$ + 5.5h, $T3_{R-1}$ + 7.5h in Arm B (3 samples per subject)
- $V3_{R+1}$ (Day 71±3):
  - PK sampling: at $T3_{R-1}$ - 30 min (1 sample per subject)
  - Cervical mucus sampling: at $T3_{R-1}$ - 30 min
  - Study pill intake at $T3_{R-1}$
  - TVUS
  - Blood sampling for hormone levels (P4, E2, FSH, LH)

- Study week 9
  - 1st visit: PK sampling within 30 minutes of mucus sampling (1 sample per subject)

End of study visit:
The subjects will be scheduled for their EOS visit within 5 days of taking their last pill or their last extra visit (follow-up visit).

See also Schedule of assessments for details.

Population

Inclusion criteria

- Women in good overall health with no chronic medical conditions that result in periodic exacerbations that require significant medical care
- Women between 18 and 35 years inclusive at the screening visit
- BMI< 32 kg/m²
- Regular menstrual cycles between 21 and 35 days when not using hormonal contraception.
  - Subjects postpartum or post-abortal must have one normal menstrual cycle (2 menses) prior to enrollment.
  - Subjects previously using IUD or taking hormonal contraception (or any other hormonal treatment, except an injectable treatment) need to have at least one menstrual cycle (2 menses) without the treatment before screening.
  - Subject previously using an injectable (DMPA), must have had their last injection at least 9 months before screening.
- Women not at risk of pregnancy: not sexually active, or willing to protect all acts of intercourse with condoms, or have a sterile partner or have undergone previous tubal ligation (including validated Essure), or be in a same sex relationship.
- Women able to give informed consent form to participate in the study and in the opinion of the investigator able to follow all study requirements, use the study medication and record the requested information appropriately
- Intact uterus and both ovaries
- At least one progesterone concentration > 3 ng/mL (>10 nmol/L) during the luteal phase of the screening period

Exclusion criteria

- Pregnant as confirmed by positive high-sensitivity urine pregnancy test at $V1_1$ (enrollment visit)
- Trying to conceive or desire to conceive in the next 3 months
- Currently breastfeeding, or within the last 2 months
- Known Polycystic Ovarian Syndrome (PCOS)
- Cancer (or past history of any carcinoma or sarcoma)
- Known abnormal thyroid status, if in clinical judgment of the investigator it cannot be controlled during the study
- Known hypersensitivity to the ingredients of the test active substances or its excipients
- Current acute liver disease and/or benign liver tumors
- Have vaginal or cervical infection including clinical evidence of bacterial vaginosis
- Evidence of abnormal cervical lesion
- History of excisional or ablative treatment procedure on cervix (ie. Loop Electrosurgical Excision Procedure (LEEP), Cryotherapy, Cold Knife Cone)

- Undiagnosed abnormal uterine bleeding
- Prior malabsorptive-type bariatric surgery
- Known or suspected alcoholism or illicit drug abuse
- Use of any hormonal contraception or IUD other than the study medication during the study (including ulipristal acetate for emergency contraception in the past 5 days)
- Use of any medications that can interfere with the metabolism of progestin-based contraceptives (e.g CYP3A4 enzymes inducers or inhibitors, etc)
- Unstable diabetes mellitus
- Current participation in any other trial of an investigational medicine or participation in the past two months (or within 5 elimination half-lives for chemical entities or 2 elimination half-lives for antibodies, whichever is the longer) before screening
- Abnormalities in laboratory results or TVUS performed at screening visit recognized as clinically significant by the investigator
- Conditions not suitable for frequent TVUS examinations, (e.g. virgo intacta)
- In custody or submitted to an institution due to a judicial order
- Relative or household member of the investigator's or sponsor's staff

Sample size: This study will screen approximately 70 subjects to achieve at least 45 completed subjects.

Study treatment and randomization
The investigational product is norgestrel 75 mcg, supplied in blister package of 28 tablets. It will be taken orally at the same time everyday in a continuous regimen.

The study medication will be provided only to subjects included in this study following the procedures set out in the protocol. In this study, all subjects will receive the study medication at the same dosing regimen. The randomization in this study will allocate subjects evenly to either:

- Arm A (delayed pill in treatment period 2 and missed pill in treatment period 3) or,
- Arm B (missed pill in treatment period 2 and delayed pill in treatment period 3).

Randomization will occur during the 1st visit of treatment period 2.

Pharmacodynamic parameters

- Cervical mucus score between 0 and 12
- Ovarian activity score between 0 and 7 and associated ovarian status*

Pharmacokinetic parameters

- Levonorgestrel PK populations parameters (CL and V) as well as derived parameters (C_{24h}, C_{max} and AUC)

Safety parameters

- Adverse events
- Bleeding patterns
- Laboratory parameters

Statistical analysis

- Significance of the mean change from baseline ($V2_{R-1}$ or $V3_{R-1}$) to post infringement assessments ($V2_R$ or $V2_{R+1}$ and $V3_R$ or $V3_{R+1}$) of cervical mucus score
- Significance of the mean change from baseline to post delayed pill assessments of cervical mucus score.

* The ovarian status are:
OSq = quiescence defined as a OAS ≤ 3
OSa = ovarian activity defined as a OAS = 4 or 5
OSalp = ovulation with abnormal luteal phase defined as a OAS = 6 at only one visit
OSnlp = ovulation with normal luteal phase defined as a OAS = 6 at two consecutive visits or OAS = 7

- Significance of the mean change from baseline to post missed pill assessments of cervical mucus score.
- Significance of the difference between infringement type in the mean change from baseline.
- Percentage of subjects with mucus score ≤ 4, 27h, 30h and 48h after the last treatment intake
- Percentage of subjects with an absence of risk increase further to delayed intake.
- Percentage of subjects with an absence of risk increase further to missed pill.
- Percentage of subjects with a transient of risk increase further to delayed intake.
- Percentage of subjects with a transient of risk increase further to missed pill.
- Percentage of subjects with a prolonged risk increase further to delayed intake.
- Percentage of subjects with a prolonged risk increase further to missed pill.
- Percentage of subjects with no signals of loss of protection in treatment period 1 (no infringement (i.e. no delayed or missed pill) to intake schedule), in treatment period with a delay of 6 hours in pill intake and in treatment period with a missed pill.
- Percentage of subjects with a cervical mucus score ≤ 4; between 5 and 8, and ≥ 9 during reported perfect daily use, during a treatment period with a delayed pill intake of 6 hours and during a treatment period with a missed pill of norgestrel 75 mcg.
- Percentage of subjects with each ovarian status during reported perfect daily use, during a treatment period with a delayed pill intake of 6 hours and during a treatment period with a missed pill of norgestrel 75 mcg.
- Percentage of subjects with each binary and ternary conception protection status (protected/not protected and minimum/medium/maximum).

Adverse events (AEs)

AEs will be coded using the MedDRA dictionary.

Frequencies of subjects (occurrence rate) with treatment-emergent AEs, regardless of relationship to study treatment and sorted by system organ class and preferred term will be summarized.

Frequencies of subjects with possible treatment-related AEs will also be displayed. Serious and non-serious possibly-related AEs will be described on a case by case basis and the relationship with the treatment intake will be discussed.

Frequency tables of AEs, displayed by intensity will also be provided.

Study Duration and dates

Subjects will be evaluated for a period of approximately 4.5 months (screening up to 1 month, treatment phase 3 months, extra follow-up and end of study visit up to 16 days).

Besides the screening visit, a total of approximately 28 visits will be required for this study but 4-7 additional visits per menstrual cycle may be required if an ovarian follicle of ≥ 15mm in one dimension is visualized on TVUS.

Subject recruitment is expected to begin in Q2 2018 and is planned to continue through the beginning of Q1 2019.

Table 1 Schedule of assessments

Study periods	**Screening visit**	**Treatment phase**											**Follow up(a)**	**End of study visit**
		Treatment period 1	**Treatment period 2**					**Treatment period 3**						
Days	**-**	**D1 to D28**	**D29 to D56**					**D57 to D84**					**D85 to D96**	**Between D85 and D100**
		D1 to D28	**D29 to D40 ±3 And D44±3 to D56**	**D41±3 to D43±3**				**D57 to D68 ±3 And D72±3 to D84**	**D69±3 to D71±3**					
Visits	**V0**	**$V1_1$ to $V1_x$**	**$V2_1$ to $V2_x$**					**$V3_1$ to $V3_x$**					**$V4_1$ to $V4_x$**	**$V4_y$**
		Visits twice a week if follicle < 15 mm Visits every other day for a maximum of 6 days if a growing follicle ≥ 15 mm identified upon TVUS(b)	Visits twice a week if follicle < 15 mm Visits every other day for a maximum of 6 days if a growing follicle ≥ 15 mm identified upon TVUS(b)	Delayed/missed pill period Three consecutive days				Visits twice a week if follicle < 15 mm Visits every other day for a maximum of 6 days if a growing follicle ≥ 15 mm identified upon TVUS(b)	Delayed/missed pill period Three consecutive days				Visits every other day for a maximum of 12 days if a growing follicle ≥ 15 mm identified upon TVUS(c)	
				$V2_{R-1}$	**$V2_RA$**	**$V2_RB$**	**$V2_{R+1}$**		**$V3_{R-1}$**	**$V3_RA$**	**$V3_RB$**	**$V3_{R+1}$**		
Informed consent	X													
Inclusion/ exclusion criteria	X	X												
Randomisation			X(d)											
Demographics	X													
Medical, surgical and gynecological history	X													
Physical & gynecological examination	X													
Vital signs(e)	X													X
Laboratory tests	X													X
Pap smear(f)	X													
STI screening	X													
High-sensitivity urine pregnancy test (β-HCG)		X(g)												X
Dispensation of study medication (h)		X	X											

Study periods	**Screening visit**	**Treatment phase**											**Follow up(a)**	**End of study visit**
		Treatment period 1	**Treatment period 2**					**Treatment period 3**						
Days	**-**	**D1 to D28**	**D29 to D56**					**D57 to D84**					**D85 to D96**	**Between D85 and D100**
		D1 to D28	**D29 to D40 ±3 And D44±3 to D56**	**D41±3 to D43±3**				**D57 to D68 ±3 And D72±3 to D84**	**D69±3 to D71±3**					
Visits	**V0**	**$V1_1$ to $V1_x$**	**$V2_1$ to $V2_x$**					**$V3_1$ to $V3_x$**					**$V4_1$ to $V4_x$**	**$V4_y$**
		Visits twice a week if follicle < 15 mm Visits every other day for a maximum of 6 days if a growing follicle ≥ 15 mm identified upon TVUS(b)	Visits twice a week if follicle < 15 mm Visits every other day for a maximum of 6 days if a growing follicle ≥ 15 mm identified upon TVUS(b)	Delayed/missed pill period Three consecutive days				Visits twice a week if follicle < 15 mm Visits every other day for a maximum of 6 days if a growing follicle ≥ 15 mm identified upon TVUS(b)	Delayed/missed pill period Three consecutive days				Visits every other day for a maximum of 12 days if a growing follicle ≥ 15 mm identified upon TVUS(c)	
				$V2_{R-1}$	**$V2_RA$**	**$V2_RB$**	**$V2_{R+1}$**		**$V3_{R-1}$**	**$V3_RA$**	**$V3_RB$**	**$V3_{R+1}$**		
Study medication intake		X	X	X(i)	X(j)		X(k)	X	X(i)		X(j)	X(k)		
Diary completion		X	X	X	X	X	X	X	X	X	X	X		X
TVUS	X	X	X	X			X	X	X			X	X(l)	
Mucus analysis		X(m)	X	X(n)	X(o)	X(p)	X(q)	X	X(n)	X(p)	X(o)	X(q)	X	
PK samples		X(r)(s)	X(t)	X(u)	X(v)	X(w)	X(x)	X(t)	X(u)	X(w)	X(v)	X(x)		
P4	X	X	X	X			X	X	X			X	X	
E2, FSH, LH		X	X	X			X	X	X			X	X(y)	
Prior and concomitant treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events and bleeding patterns	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes:

(a) Only if follicle ≥ 15 mm is observed after Day 73 AND the criteria for stopping the extra-visits were not fulffilled by Day 84
(b) Extra visits will be stopped before 6 days if there is no postovulatory image after 6 days
(c) Extra visits will be stopped before 12 days if there is no postovulatory image after 6 days or if the P4 levels are > 30 nmol/L at 1 visit or > 10 nmol/L at 2 consecutive visits.
(d) Randomisation at 1st visit of treatment period 2
(e) Vital signs include heart rate, systolic and diastolic blood pressure after at least 2-minute rest and height and weight (at screening only).
(f) Pap smear to be performed according to current US guideline if an abnormal cervical lesion is detected during the gynecological examination
(g) At $V1_1$ only, before first pill intake
(h) At $V1_1$, last visit of treatment period 1 and last visit of treatment period 2
(i) Study pill intake will be at 9 am ± 1 hour and will be noted as $T2/3_{R-1}$ (actual treatment time at Day 41 or Day 69)
(j) Study pill intake at $T2/3_{R-1}$+ 6h ± 15 min
(k) Study pill intake at $T2/3_{R-1}$ ± 30 min

(l) TVUS up to observation of postovulatory image
(m) At $V1_1$, the mucus analysis will be performed before the 1st study medication intake
(n) Mucus analysis to be performed at $T2/3_{R-1}$ +8 h ± 30 min.
(o) Mucus analysis to be performed at $T2/3T_{R-1}$ +3h ± 15 min.
(p) Mucus analysis to be performed at $T2/3_{R-1}$ +6 h ± 15 min.
(q) Mucus analysis to be performed within 30 min before study medication intake
(r) Blood sampling for PK analysis at D1: subjects with even study number at predose, 2 h ± 15 min, 6 h ± 15 min and 12 h ± 30 min post-treatment and subjects with odd study number at 1 h ± 15 min, 4 h ± 15 min , 8 h ± 30 min and 24 h ± 30 min post-treatment
(s) Blood sampling for steady state during first visit in week 3: subjects with odd numbers at predose, and between 0.5 h and 2h (morning visit), and subject with even numbers between 5 h and 9 h post-treatment (afternoon visit)
(t) Blood sampling for compliance during 1st visit of weeks 5 and 9 within 30 min of cervical mucus sampling
(u) Blood sampling for PK analysis at $T2/3_{R-1}$ +8h ± 30 min
(v) Blood sampling for PK analysis at $T2/3_{R-1}$ +3h ± 15 min, $T2/3_{R-1}$ + 5.5h ± 15min, $T2/3_{R-1}$ + 7.5h ± 30min
(w) Blood sampling for PK analysis at $T2/3_{R-1}$ + 6h ±15min
(x) Blood sampling for PK analysis at $T2/3_{R-1}$ within 30 min before study medication intake
(y) No E2, FSH and LH measurements during extra-visits after postovulatory image is observed

ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
BMI	Body Mass Index
BP	Blood Pressure
BSL	Baseline
CBC	Complete Blood Count
CDC	Centers for Disease Control and prevention
CO2	Carbon Dioxide
COC	Combined Oral Contraception
CRO	Contract Research Organization
DMP	Delayed/Missed Pill
E2	Estradiol
e-CRF	electronic Case Report Form
EOS	End-Of-Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FLS	Follicle Like Structure
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent-To-Treat
IUD	Intra-Uterine Device
K2-EDTA	Di Potassium-Ethylene Diamine Tetraacetic Acid
LC-MS/MS	Liquid Chromatography with double Mass Spectrometry
LH	Luteinizing Hormone
LNG	Levonorgestrel
LUF	Luteinized Unruptured Follicle
NG	Norgestrel
OAS	Ovarian Activity Score

OC	Oral contraceptives
OS (q, a, alp, nlp)	Ovarian Status (quiescence, ovarian activity, ovulation with abnormal luteal phase, ovulation with normal luteal phase)
P4	Progesterone
PCOS	Polycystic Ovary Syndrome
PD	Pharmacodynamics
PI	Principal Investigator
PHI	Protected Health Information
PK	Pharmacokinetic(s)
POP	Progestin Only Pill
PP	Per-Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SPC	Summary of Product Characteristics
STI	Sexually Transmitted Infection
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T2_{R-1}/T3_{R-1}$	Time of treatment intake on the day before delayed intake/missed pill per Randomization arm, in treatment period 2/3
TVUS	TransVaginal Ultrasound
USP	United States Pharmacopeia
WHO	World Health Organization
WoA	Waiver of Authorization
WHRU	Women's Health Research Unit

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1. INTRODUCTION AND BACKGROUND

Oral contraceptives (OCs) are the most widely used hormonal method of contraception in the United States (US). Combined estrogen-progestin OCs (COCs) are the most frequently-prescribed OCs in the US, while progestin-only pills (POPs) are less frequently prescribed. POPs are mainly prescribed to breastfeeding women or when the use of a COC is contra-indicated.

POPs prevent conception by suppressing ovulation in approximately half of the cycles in users, thickening the cervical mucus to inhibit sperm penetration, lowering the midcycle LH and FSH peaks, slowing the movement of the ovum through the fallopian tubes, and altering the endometrium (McCann 1994).

Because of the lower dose of progestin in POPs compared to the dose in COCs, the reliance on mechanisms of action other than ovulation inhibition, and the potential importance of consistent daily pill taking, POPs are perceived to be not as effective as COCs. However, when used as directed, POPs seem to be as highly effective as a COC, with a perfect-use failure rate estimated at 0.3% and a typical use failure rate estimated at 9% (Trussell, 2011; Curtis, 2016). A recent Cochrane review concluded that no firm conclusion is possible concerning the comparative efficacy of POPs or whether such pills are as effective as COCs (Grimes A, 2013).

Opill® (norgestrel (NG) 75 mcg) is a 2nd generation synthetic progestin-only oral contraceptive approved in the US in 1973, (under the proprietary name Ovrette®) at a daily dose of 75 mcg and first marketed in 1974 in the US. NG is a mixture of two enantiomers, only one of which levonorgestrel (LNG) being the active form. LNG have been marketed in the US and in Europe for more than 30 years in a wide variety of contraceptive products (including combined and progestin-only oral contraceptives, implant, vaginal ring, intrauterine system, and emergency contraceptives)..

Approval for marketing in the US by the Food and Drug Administration (FDA) was based upon the results of eight clinical trials of continuous daily oral NG 75 mcg. The study sites represented all major US geographic regions and participants were 53% Caucasian and 47% African-American. There was a combined 2 575 women, of whom 2 173 completed at least one cycle of medication (28 days), and 21 856 28-day cycles of exposure in women aged 15 to 49 years. Thirty-seven pregnancies were confirmed during the eight clinical investigations, resulting in an overall use effectiveness (Pearl Index) of 2.0 pregnancies per 100 women-years of use. Eighteen pregnancies were confirmed to be a result of method failure and 19 pregnancies occurred among women who omitted 1 or more pills during the cycle in which the conception took place. The theoretical use effectiveness rate among women experiencing a method failure therefore has a Pearl Index of 0.98 per 100 women-years (N = 2 173; 21 854 cycles; 1 821 women-years).

As with other POPs, Opill® has only few contra-indications, the most relevant is having history of breast cancer. The World Health Organization (WHO) and the US Medical Eligibility Criteria for Contraceptive Use, 2016, list “current breast cancer” as the single condition that represents an unacceptable health risk (category 4) for a woman if she uses POPs. Only a few other conditions are listed for which the use of POPs is not usually recommended unless other, more appropriate, methods are not available. The main adverse reactions consist in the disturbance of the menstrual cycles, and other few and moderate hormonal reactions such as delayed follicular atresia or ovarian cysts.

2. RATIONALE, BENEFITS AND RISKS

NG, as with other POPs, is currently prescribed with the advice that it should be taken without interruption every day at the same time to achieve maximum contraceptive effectiveness. Any pill taken more than 3 hours late is considered a missed pill due to diminishing effects on cervical mucus (Han L 2017).

It has also been emphasized that the effect of progestins on cervical mucus is the most immediate level of protection provided by POPs, but offering a full protection for less than 24 hours (McCann 1994).

In fact, there are only very few studies assessing the PK of oral NG/LNG for use as POP and no data linking the PK to the pharmacodynamic (PD) action of POPs. In one study where five subjects were given a single dose of 30 mcg LNG (Weiner 1976), the mean plasma half-life was 13.7 hours with large variability between subjects (7.95 to 23.23 hours). Twenty four hours after drug intake, the plasma concentrations were 0.05 to 0.14 ng/mL. The plasma levels observed in 3 subjects taking 30 mcg LNG daily for 3 weeks were between 0.10 and 0.40 ng/mL when measured 12 hours after the oral administration each day during the 3-week treatment period. Brenner et al. (1977) found that serum levels of LNG were 0.2 to 0.5 ng/mL 24 hours after oral administration of 75 mcg NG.

In addition, there are very few clinical data assessing the temporality of the effect of POPs on cervical mucus. In healthy women given 350 mcg of norgestrienone for 13 days, cervical mucus displayed changes in its macromolecular structure, i.e. an extreme degree of compactness, an appearance typical of the late luteal phase (Chretien et al. 1980). The cervical mucus remained extremely dense 24 hours after the last dose of norgestrienone but, 12 hours later, few samples exhibited meshes large enough to permit the easy passage of sperm cells and, 48 hours after the last dose mucus was considered as not protective. Lebech et al. (1970) found that sperm penetration of the cervical mucus was totally inhibited in 3 out of 4 subjects treated with 0.5 mg/day megestrol acetate but returned to normal 38 hours after the ingestion of the last dose. However, interpretation of the results of these continuous low-dose progestogen contraceptive studies is hampered by the small sample sizes, the incomplete description of the methodology, and the absence of statistical analysis and it is not known whether such results can be extrapolated to NG 75 mcg.

Regarding ovarian activity, it was shown that 75 mcg NG daily for 30 days inhibited or suppressed LH and FSH peaks and the rise of serum progesterone (P4) and urinary pregnanediol during the luteal phase, suggesting that even if there was follicular rupture, this was associated with luteal insufficiency (Moghissi and Marks, 1971). In another study where 29 subjects received 30 mcg LNG daily, an ovulation defined as follicular rupture associated with P4 level above 30 nmol/L was observed in 28% of all studied 57 cycles (Rice CF, 1999). However, there is no study analysing both ovarian activity and cervical mucus in women treated with NG and no data are available regarding the effect of delayed or missed pill on these parameters.

In the light of limited PK and PD data on NG and POPs in general that supports the clinical guidance of taking it everyday at the same time within a three hour window, this exploratory study aims to determine the PD mechanisms underlying the contraceptive protection of NG 75 mcg. Primarily, the study will evaluate whether these PD mechanisms are impacted by a delayed intake or a missed pill.

The main PD endpoints will be the cervical mucus assessed according to the WHO guidelines excluding the volume component as already described (Dunson et al, 1998; Petta et al, 1998) and the ovarian activity measured with a Ovarian Activity Score (OAS) (see Appendix 3).

3. OBJECTIVES

The primary objective of the study is to determine the effect of a delayed intake of 6 hours or of a missed pill on cervical mucus score compared to cervical mucus score during reported perfect daily use of norgestrel 75 mcg.

The subordinate primary objective is to estimate the duration of the protective effect of cervical mucus after last pill intake of norgestrel 75 mcg during reported perfect use.
The protective effect of cervical mucus is considered as present when the score is below or equal 4.

The secondary objectives are:

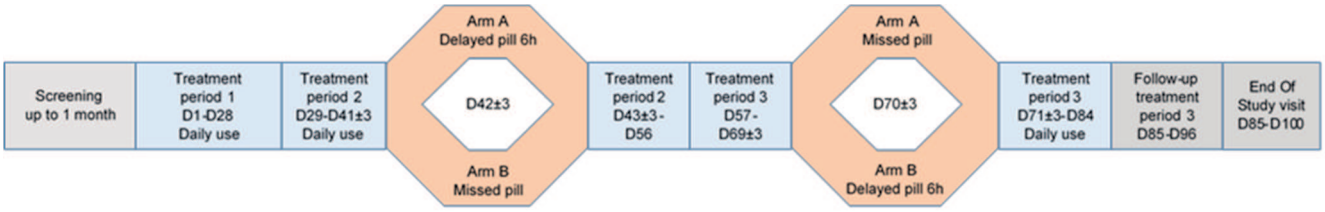
- to evaluate and compare the percentage of subjects with a protective cervical mucus score during reported perfect daily use of norgestrel 75 mcg, during a treatment period with a delayed intake of 6 hours and during a treatment period with a missed pill of norgestrel 75 mcg.
- To evaluate and compare the ovarian activity during reported perfect daily use, during a treatment period with a delayed intake of 6 hours and during a treatment period with a missed pill of norgestrel 75 mcg.
- To assess if a combination of cervical mucus score and ovarian status can be considered as a measure of protection from conception during reported perfect daily use, during a treatment period with a delayed intake of 6 hours and during a treatment period with a missed pill of norgestrel 75 mcg.
- To determine levonorgestrel pharmacokinetics after a single dose of norgestrel 75 mcg, at steady state, after a delayed intake and after a missed pill.
- To assess the safety of norgestrel 75 mcg taken daily for 12 weeks.

4. STUDY DESIGN

This is an exploratory, prospective, multi-center, randomized, cross-over study to assess the effect of norgestrel 75 mcg on cervical mucus and ovarian activity during reported perfect daily use and after a delayed intake of 6 hours and after a missed pill.

This study includes three 28-day treatment periods (approximately 3 months) with a screening period of up to 1 month to demonstrate ovulatory status prior to enrollment, a possible follow-up of 12 days to follow ovarian activity if a follicle ≥ 15 mm is observed at the end of period 3 and an end of study (EOS) visit within 5 days. Women of reproductive age (18-35 years old) who meet eligibility requirements will receive treatment for a total of three 28-day periods (84 days) but in treatment period 2 and 3, will have a 6-hour delay in pill intake or a missed pill (see Figure 2 below).

Figure 2 Design of the study



Besides the screening visit, a total of approximately 28 visits will be required for this study but up to 7 additional visits per menstrual cycle (up to 3 in treatment periods 1 & 2, up to 7 in treatment period 3) may be required if an ovarian follicle of ≥ 15mm in one dimension is visualized on TVUS.

The study is designed to evaluate cervical mucus attributes, ovarian activity and PK of LNG after daily treatment by norgestrel 75 mcg as well as the PK and PD changes that ensue with poor regimen adherence.

In the first treatment period, treatment will be installed and cervical mucus attributes and ovarian activity in the first weeks of treatment will be observed. In addition, PK profile of LNG will be determined after a single dose (Day 1) and at steady state (on week 3).

In the second and third periods of treatment, the difference on cervical mucus score and ovarian activity score between a perfect use (Day 41 ± 3 / Day 69 ± 3) and a 6-hour delayed intake (Arm A Day 42 ± 3 and Arm B Day 70 ± 3) or a missed pill (Arm B Day 43 ± 3 and Arm A Day 71) will be assessed.

5. PRINCIPAL INVESTIGATOR & RESEARCH CENTERS

Two investigational research centers located in the US will conduct the study. A complete list of investigators, sub-investigators, and coordinators will be maintained with trial documentation.

Listed here are the investigational research centers conducting this study:

- Alison Edelman, MD, MPH: Oregon Health & Science University, Portland, Oregon
- Mitchell Creinin, MD: University of California Davis Health, Sacramento, California

6. SUBJECT RECRUITMENT

Participants will be recruited from two research centers in the US. Competitive recruitment will be planned between the two centers. Each center will enroll a minimum of 20 subjects but the total number of completers should reach at least 45 subjects.

Subjects will be recruited from family planning clinics and other clinics serving reproductive-aged women for gynecologic care and reproductive health services (including the clinics' database) as well as through IRB-approved research recruitment efforts (newsletters, in-services, tear-ads, radio ads, social network ads, online form etc). Referrals from previous / ongoing participants are accepted. This study will be listed on the website ClinicalTrials.gov (see section 21.1). Subjects will be selected for the study according to the inclusion and exclusion criteria detailed in section 9.

Information collected before signature of the informed consent form (ICF), if used, will be stored in a locked office, with access limited to study staff. For subjects electing to enroll in the study, this information will become a part of their protected research record. For subjects choosing not to enroll, all protected health information (PHI) will be stored confidentially with the research study information in a locked cabinet and archived with other study-specific documents at the closure of the trial. Confidentiality of PHI will be maintained according to regulations and sites' procedures.

Women will be screened for eligibility and interest in study participation. If they meet the basic criteria and agree to participate, they will be required to provide informed written consent prior to beginning any study procedures. The protocol and patient information sheet/ ICF will be reviewed and approved by the IRB prior to initiation of the study. Information collected and created in order to conduct and oversee this research study may be stored according to regulation, sites' procedures and with the agreement of the participant.

7. STUDY DURATION

The total duration of the study for each participant is expected to be approximately 4.5 months: up to 4 weeks for screening to meet enrollment criteria, 12 weeks of treatment and a possible follow-up of 12 days to follow ovarian activity if a follicle ≥ 15 mm is observed at the end of period 3 and an EOS visit within 5 days.

Subject recruitment is expected to begin Q2 2018 and is planned to continue through the beginning of Q1 2019. However, if the enrollment rate declines, the enrollment period may be extended beyond this date. If this enrollment timeline is met, all subjects should finish active treatment by approximately the end of Q2 2019. Therefore, the total duration of the study will be approximately 15 months for each study site.

Results of the study are expected to be available Q3 2019.

8. SAMPLE SIZE/NUMBER OF SUBJECTS

Approximately 70 subjects will be screened to have at least 45 subjects who complete the study.

The primary analysis is based on the score of cervical mucus as a quantitative variable because it is expected to be the most powerful analysis. However the justification of the sample size will not be based on the primary analysis because too much information is missing such as an order of magnitude of the variance covariance matrix of the change from time point of reference. This is the reason why the sample size calculation will be based on proportions of women with no loss of protection.

A total sample size of 45 subjects should allow to detect a loss of protection that affect pertinently a substantial proportion of the population. Indeed if the difference between a cycle with a perfect use and a cycle with an infringement in the schedule is 14 % in the expected proportions of women with a loss of protection at any time and if the proportion of discordances between the 2 situations is 17% then the exact power is equal to 79.1%. If the expected difference in proportions is 15% with a rate of discordance of 18% then the exact power is 82.4% for an unconditional test. The expected difference in proportions need therefore to reach 14-15 % to get a sufficient power for detecting a significant difference. This difference in proportions is a substantial difference knowing that most of change in status (see discordance rate) are in the same direction *i.e.* from protection to loss of protection.

9. SELECTION OF SUBJECTS

9.1 Inclusion criteria:

To enroll into the clinical trial, potential subjects must:

- Be in good overall health with no chronic medical conditions that result in periodic exacerbations that require significant medical care.
- Be women between 18 and 35 years inclusive at the screening visit.
- Have a BMI< 32 kg/m².
- Have regular menstrual cycles between 21 and 35 days when not using hormonal contraception.
    - Subjects postpartum or post-abortal must have one normal menstrual cycle (2 menses) prior to enrollment.
    - Subjects previously using IUD or taking hormonal contraception (or any other hormonal treatment, except an injectable treatment) need to have at least one menstrual cycle (2 menses) without the treatment before screening.
    - Subject previously using an injectable (DMPA), must have had their last injection at least 9 months before screening.
- Not be at risk of pregnancy: not sexually active, or willing to protect all acts of intercourse with condoms, or have a sterile partner or have undergone previous tubal ligation (including validated Essure), or be in a same sex relationship.
- Be able to give informed consent form to participate in the study and in the opinion of the investigator able to follow all study requirements, use the study product and record the requested information appropriately.
- Have a negative pregnancy test at the enrollment visit.
- Have an intact uterus and both ovaries.
- Have at least one progesterone concentrations > 10 nmol/L (> 3 ng/mL) during the luteal phase of the screening period.

9.2 Exclusion criteria

To enroll into the clinical trial, potential subjects must NOT:

- Be pregnant as confirmed by positive high-sensitivity urine pregnancy test at $V1_1$ (enrollment visit)
- Trying to conceive or desire to conceive in the next 3 months
- Currently be breastfeeding, or within the last 2 months
- Have known Polycystic Ovarian Syndrome (PCOS).
- Have cancer (or past history of any carcinoma or sarcoma).
- Have known abnormal thyroid status, if in clinical judgment of the investigator it cannot be controlled during the study.
- Have known hypersensitivity to the ingredients of the test active substances or its excipients.
- Have current acute liver disease and/or benign liver tumors.
- Have vaginal or cervical infection including clinical evidence of bacterial vaginosis
- Have evidence of abnormal cervical lesion
- Have history of excisional or ablative treatment procedure on cervix (ie. Loop Electrosurgical Excision Procedure (LEEP), Cryotherapy, Cold Knife Cone)
- Have undiagnosed abnormal uterine bleeding.
- Have had prior malabsorptive-type bariatric surgery.
- Have known or suspected alcoholism or drug abuse.
- Use any hormonal contraception or IUD other than the study medication during the study.
- Use of any medications that can interfere with the metabolism of progestin-based contraceptives (e.g CYP3A4 enzymes inducers or inhibitors, etc).
- Have unstable diabetes mellitus.
- Currently participate in any other trial of an investigational medicine or participation in the past two months (or within 5 elimination half-lives for chemical entities or 2 elimination half-lives for antibodies, whichever is the longer) before start of baseline period.
- Have abnormalities in laboratory results or TVUS performed at screening visit recognized as clinically significant by the investigator
- Present conditions not suitable for frequent TVUS examinations, (e.g. virgo intacta)
- Be in custody or submitted to an institution due to a judicial order
- Be a relative, family household member of the investigator's or sponsor's staff

10. RANDOMIZATION

The study medication will be delivered only to subjects included in this study following the procedures set out in the protocol. In this study, all subjects will receive the study medication at the same dosing regimen. The randomization in this study will allocate subjects evenly to either:

- Arm A (delayed pill in treatment period 2 and missed pill in treatment period 3) or,
- Arm B (missed pill in treatment period 2 and delayed pill in treatment period 3).

Randomization will occur during the 1st visit of period 2.

11. PRIOR AND CONCOMITANT ILLNESSES AND TREATMENTS

11.1 Prior and concomitant illnesses

The subjects must not have any of the illnesses listed in the exclusion criteria at the time of inclusion.

Conditions present prior to study entry (screening) that do not worsen in severity are considered medical or surgical history, not considered AEs. Conditions identified and treated at screening, i.e. laboratory abnormalities, urinary tract infections, gynecologic infections including Chlamydia, gonorrhea, candida, bacterial vaginosis are included in medical history and are not reported as AEs.

11.2 Prior and concomitant medications

All concomitant medications, including any medication taken in the 2 weeks preceding entry into the study, will be recorded on the subject's electronic case report forms (e-CRF), including the name of the drug, start and stop dates and reason for use from the time of informed consent signature through to the end of study visit.

Other medications for the treatment of inter-current medical conditions should be permitted and recorded as detailed above unless they are part of the list of prohibited medications described in section 11.3.

11.3 Prohibited medications

The following medications are prohibited during the course of the study (refer to Appendix 1 for the complete list of excluded medicines):

- Sex hormones or other forms of hormonal contraception are exclusionary, including emergency contraception. Subjects must be educated that use of levonorgestrel- or ulipristal acetate-based emergency contraception could impact the endpoints of the study.
- Drugs that can interfere in the metabolism of hormonal contraceptives
    - CYP3A4 inducers (rifampin, barbiturates, carbamazepine, bosentan, felbamate, griseofulyin, oxcarbazepine, phenytoin, St. John's Wort, topiramate, efavirenz, etc.)
    - CYP3A4 inhibitors (clarithromycin, conivaptan, grapefruit juice, indinavir, oral azole antifungals, etc.)
- Drugs with significant evidence of fetal risks

11.4 Surgical procedures

For subjects who need to undergo unplanned surgical procedures during the study, the reason for surgery must be documented as a serious adverse event (SAE) on the e-CRF (see Section 15. Adverse Events). The surgical procedure should be documented in the "comments" section of the adverse event (AE) form in the e-CRF.

12. STUDY MEDICATION

12.1 Details of Study medication

The study medication is norgestrel 75 mcg, an oral contraceptive pill consisting of a synthetic progestin:

Drug code: Opill®
INN: norgestrel
Dosage form and strength: 1 tablet containing 75 mcg norgestrel
Packaging: blister containing 28 tablets
Manufacturer: XXX

12.2 Packaging and Labelling

All packaging and labeling of the study medication will be prepared in accordance with 21CFR, Section 312.6 and GMP by XXX. Thus, packs labelled specifically for this study will be provided to the clinical sites.

The study drug will be provided in boxes containing one blister pack of 28 tablets (75 mcg per tablet) which correspond to 28 days of study medication (1 pill per day, single dose). Study subjects will be provided with 2 boxes at the start of treatment period 1 and 1 box at the end of treatment period 1 and end of treatment period 2.

Blisters will be made of XXX sealed with an aluminium foil printed with the required information.
The study treatment labels will be in local language (English).

Information listed on the labels on the treatment boxes should comply with GCP and GMP requirements as well as local regulations. The labels will contain the following information:

- Clinical Study Number
- Site Number (space to record)
- Subject Number (space to record)
- Treatment period number (space to record)
- Product Identification : Opill® (norgestrel) Oral Contraception
- Administration Directions: Take 1 tablet by mouth every day at the same time.
- Number of dosage units (e.g. tablets) and strength
- Lot Number
- Expiry Date
- Name and address of Sponsor : HRA Pharma, 15 rue Beranger | 75003 Paris | France
- Name, adress and phone number of PI: Dr Edelman; Oregon Health & Science University, 3181 SW Sam Jackson, UHN 50, Portland, OR 97239, USA – Tel XXX or XXX
- Storage conditions: between 20-25°C (68° to 77°F) (see USP controlled temperature)
- FDA Caution Statement: CAUTION :New drug-- Limited by Federal (or United States) law to investigational use.
- For Clinical Trial Use Only.
- Keep Out of Reach of Children

12.3 Dosage schedule

The first dose will be taken at 9:00 am ± 3 hours during $V1_1$ (enrollment visit) while the subject is present at the study site.
At $V1_1$, she will also choose, with the site, her treatment time (T) starting on Day 2 for all the rest of the study (3 treatment periods).
This treatment time should be:

- same every day (± 1.5 hours) except the day of $V2_R$ and $V3_R$ (DMP period, see section 14.3.2. and 14.4.2)
- between 6:00 am and 12:00 pm
- within 3 hours of the 1st dose taken at $V1_1$

On $V2_{R-1}$ and $V3_{R-1}$, the subject will come on site to take her daily pill at 9:00 am ± 1 hour ($T2/3_{R-1}$) during the scheduled study visit. She will also come to site at $V2/3_R$ and $V2/3_{R+1}$ to take/miss her pill according to the site's instructions.

NB: at time of summer and winter time change, specific schedule has to be followed:

- If the day of time change is within 2 days before the first day of DMP period ($V2_{R-1}$ or $V3_{R-1}$), the subject will be asked to take her pill between 8:00 am and 10:00, for the two days before DMP period.
- If the day of time change is on the 2nd or 3rd day of the DMP period, the subject will take on site her pill according to the site's instructions, without taking account of the time change (i.e. at the "old" time).
- If the day of time change is any other day, the subject will take her pill between 7:00 am and 11:00 am on the day before and on the day of time change.

In case of missed study pills (with the exception to DMP periods): If one dose is missed, it should be taken as soon as it is remembered and at the latest at the time of the next dosing, thus allowing a subject to take two doses within 24 hours. The event will have to be reported to the study staff at the next visit.
If more than one consecutive dose is missed, the subject should contact the site for dosing instructions. The subject will be advised to take only the most recently missed pill, at the latest at the time of the next dosing, and to leave the other missed pills in the blister.

In any case, she will be reminded to use a non-hormonal back-up method of contraception (such as condoms or spermicides) for the next 48 hours.

In case of diarrhea and/or vomiting: if a subject has diarrhea and/or vomiting within 4 hours after taking a pill, another pill should be taken as soon as possible on the same day and the event reported to the study staff at the next visit.

In case of lost blister: if a subject loses a blister, she should call the site to be instructed either to use the extra blister she was provided with or to come back to the site for a new blister if necessary.

12.4 Treatment dispensation

Prior to dispensing the study medication, the investigator or designee will record the site number and subject's study identification number on the medication box label, and the subject's study identification number on the blister. The investigator or designee will record the amount dispensed and date of dispensation in the investigational study medication accountability log.

Subjects should be instructed to bring back both used and unused blister packs to the site at each visit so that remaining pill accountability can be performed. All unused, partially/fully used blister packs should be retained by the site at the end of each treatment period for study medication accountability.

Each participant will be provided with a total of 4 medication boxes containing 1 blister of 28 tablets each, i.e. one for each of the 3 treatment periods and one for back-up. Two boxes will be provided at the start of treatment period 1 (one to be used in treatment period 1 and one to be used as back-up if necessary), one at the end of treatment period 1, and one at the end of treatment period 2.

12.5 Investigational product accountability

Each study site is required to maintain study records of the disposition of study medication, including dates and quantities of distribution by subject ID number, and initials of the research center personnel distributing the study product. Study accountability logs will be provided for this purpose.

Study medication will be shipped to each research center after the receipt and acceptance of all necessary regulatory documents. Upon receipt of study medication, an inventory of the study medication must be completed by the Investigator (or designee). All study medication dispensed and returned must be recorded as outlined above. All dosing records must be consistent with the study accountability logs.

12.6 Storage

Study medication will be stored at the designated research sites in a dry place at the study site at room temperature (≥15^{0}C [59^{0}F] and ≤25^{0}C [77^{0}F]) under controlled and secured conditions, in a locked storage area away from sunlight to avoid temperature fluctuations. A temperature log for the investigational product storage area must be maintained for the duration of the study.

12.7 Disposal/return

At the end of the study, the monitor will complete a final accountability of all clinical supplies, including used and unused medication boxes. Once accountability is completed, remaining study product will be shipped back to the sponsor or its designee.

12.8 Compliance

Subjects will be instructed to bring their study medication pack at each visit. Compliance will be assessed by monitoring of norgestrel pill packs during these visits as well as at the end of each treatment period and by information recorded by the e-diary.

During the DMP periods, the 6-hour delayed intake will be directly observed by study staff and the missed pill will be removed from the blister by site staff and placed in a small container (clear bag, small box, etc) labeled with subject number, period, date of removal in order for the CRA to monitor the accountability.

Subjects will report pill intake (yes/no) daily and the time through e-diary.

Levonorgestrel plasma levels will be determined during the first visit of weeks 5 and 9 at the time of cervical mucus collection without informing the subject of the exact date (see section 14.Study Visit for details). Letting the subject know that they will have a blood sample to check the levonorgestrel level, at some point in the study may encourage them to stay compliant.

If a subject missed three or more consecutive pills in any treatment period or misses one pill in treatment period 2 or 3, the research center staff will discuss the matter with her and determine with the sponsor, case by case, whether she can continue moving forward in the study or if she has to be withdrawn from the study.

13. LABORATORY TESTS AND EVALUATIONS

13.1 Physical and gynecological examination

Physical and gynecological examinations (breast and pelvic examinations) will be performed at screening visit only.

13.2 Vital signs

Vital signs will be measured at screening and end of study (EOS) visits. They include systolic and diastolic blood pressure and heart rate after at minimum 2-minute rest. Height and weight will be recorded at screening only.

13.3 Laboratory parameters

Complete Blood Count (CBC) and a complete metabolic panel will be obtained at screening and then at the EOS visit. The testing will include:

- CBC: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, neutrophils (% & absolute), lymphocytes (% & absolute), monocytes (% & absolute), eosinophils (% & absolute), basophils (% & absolute)
- Electrolytes: sodium, potassium, CO2 (carbon dioxide, bicarbonate), chloride, calcium
- Metabolic panel: glucose, proteins, albumin, total protein
- Renal function: blood urea nitrogen, creatinine
- Hepatic function: alkaline phosphatase, alanine amino transferase, aspartate amino transferase, total bilirubin

Samples will be analyzed at the local certified laboratories at each study center.

The investigator or medically qualified designee must review and sign all laboratory reports; a copy of the report must be kept with each subject's chart. All out-of-range laboratory results must be assessed by the investigator or medically qualified designee for clinical significance. Any reports required from the screening assessment must be reviewed, signed and dated on or before the date/time of enrollment in order to properly document the determination of eligibility.

13.4 Hormone testing

Hormone testing (P4, E2, FSH, LH) will be performed locally at each site.

P4 will be tested at all visits up to EOS visit, with the exception of $V2_R$ and $V3_R$ during the DMP periods.

E2, FSH and LH will be tested at all regular visits, extra visits and follow-up visits until a postovulatory image is observed, with the exception of $V2_R$ and $V3_R$ during the DMP periods.

The samples will be destroyed after completion of CSR.

Point of care urine high-sensitivity pregnancy testing will be performed at $V1_1$ (enrollment visit) before dispensation of study drug and at the EOS visit.

13.5 Levonorgestrel concentrations

Blood sampling for levonorgestrel concentrations will be performed at the following visits:

- $V1_1$
- 1st visit of week 3
- 1st visit of week 5 ($V2_1$)
- $V2_{R-1}$, $V2_R$, $V2_{R+1}$
- 1st visit of week 9 ($V3_1$)
- $V3_{R-1}$, $V3_R$, $V3_{R+1}$

2K- EDTA tubes will be used for sampling. After separation of plasma, samples will be frozen at -80°C until shipment to the bioanalytical centre that will perform centralized analysis of the samples from both clinical sites. Levonorgestrel concentrations in plasma will be determined by a LC-MS/MS method.

13.6 Pap test and STI screening

A Pap test will be performed at screening for subjects with an abnormal cervical lesion detected during the gynecological examination. Subjects with high-grade lesions prior to enrollment are to be excluded.

Subjects will be screened for Chlamydia and gonorrhea by vaginal or cervical swab or urine test and results will be read on site in accordance with local standards. A wet mount should be obtained if vaginitis is suspected. Women who test positive should be treated for any infections and enrollment should be delayed until treatment has been completed.

If a non-physiologic vaginal discharge is detected, diagnosis of bacterial vaginosis will be made using wet mount and potassium hydroxide (KOH) preparation. Treatment should be instituted and completed prior to enrolment in the study for those who were diagnosed at screening. For the subjects who develop bacterial vaginosis during the treatment, oral treatment will be instituted and the subjects will remain in the study.

13.7 Transvaginal ultrasound (TVUS)

TVUS will be performed at screening, at all regular and extra visits until a postovulatory image is observed, with the exception of $V2_R$ and $V3_R$ during the DMP periods.

TVUS examinations will be performed by licensed and trained study personnel. Standard measurements will include documentation of the largest follicle's maximum measurements in 3 dimensions and average size if it is ≥10 mm, postovulatory image[1] and TVUS abnormalities. A cross-sectional picture of each ovary even if no follicles >10 mm are present will also be taken.

To maintain a high level of consistency for these evaluations, it is recommended that an experienced sonographer perform the scans on each subject, and the number be limited to the smallest group needed by the site for successful completion of the protocol.

All ultrasounds procedures should be performed using a vaginal transducer of at least 5 mHz.
The ultrasound equipment must be capable of printing the images or saving them digitally for later printing. Printed images will be placed in the source documents. All images should be clearly labeled with a subject identifier and date the TVUS was performed.

13.8 Cervical mucus

Cervical mucus will be sampled and analysed at all regular and extra visits, including all the visits during the DMP period. The cervical mucus collection will always be performed before TVUS.

A gynecologic exam is completed to assess the cervical mucus score based on the modified Insler score (WHO manual 2010). Consistency (viscosity), ferning, spinnbarkeit and cellularity will be scored on a 4-point scale (0-3), see Appendix 2 for details.
The protective effect of cervical mucus is considered as present when the score is below or equal 4.

The cervical mucus will be collected by aspiration. The cervical mucus assessment will be made by a limited amound of trained clinic personnel in order to limit variability. A centralized training will be organized to maintain a high level of consistency for these evaluations. It is recommended that an experienced physician or specifically trained nurse (whoever is available on site at the time of subject visit) perform the exam on each subject, and the number of examiners be limited to the smallest group needed by the site for successful completion of the protocol.

13.9 IMP intake and bleeding reporting (e-diary)

Every day, the subject will have to record the time of intake of study medication and the volume of bleedings if any in an e-diary:

14. STUDY VISITS

14.1 Screening visit (V0, during luteal phase)

The purpose of the screening evaluation is to obtain baseline history, physical exam, and laboratory evaluations to determine if the subject meets eligibility criteria. Prior to any screening procedure being performed, potential participants will receive information about the study, including potential risks, and patient information sheet / informed consent form, that they will sign.

Screening will include the following procedures:

- The risks, benefits, and alternative methods of contraception will be reviewed with each subject in a manner consistent with her education level.
- Each woman must sign an IRB-approved informed consent form before any of the study-related procedures can be performed. The original signed informed consent form will be kept on file by

[1] postovulatory image is defined as:
- abrupt disappearance of follicle like structure (FLS) or
- reduction in size of the leading follicle > 4 mm at two consecutive visits or
- haemorrhagic corpus luteum (FLS at least as large as the leading follicle)

the investigator with the subject's records. A copy of the executed form will be given to the subject.

- A unique subject identification number will be assigned by the site after the subject signs the informed consent form and prior to the initiation of screening assessments.
- Demographic characteristics will be collected including date of birth, ethnicity, and race.
- Previous medical, surgical and gynecological history will be collected, including history of acute and chronic medical and gynecological conditions, marijuana, illicit drug and alcohol use history, menstrual cycle history, current sexual activity, previous contraceptive use, pregnancy history and plans for future pregnancies. This includes recording the date of onset of last menstrual bleeding along with the date of last use of a method of contraception.
- Vital signs (pulse, and blood pressure) will be obtained and recorded with the subject in a sitting position after at least 2 minutes' rest. This method will be employed for all blood pressure measurements taken during the study.
- Height and weight will be recorded. BMI will be calculated in kg/m^2.
- General physical and gynecological examinations (breast and pelvic examinations) will be performed.
- A TVUS will be performed to ensure the subject has an intact uterus and both ovaries and assess endometrial thickness, endometrial appearance, presence of follicles and TVUS abnormalities.
- If indicated, a Pap test will be performed.
- Chlamydia and gonorrhea tests. A wet mount should be obtained if vaginitis is suspected.
- Wet mount and KOH preparation of vaginal fluid to confirm diagnosis bacterial vaginosis if there is presence of non-physiologic vaginal discharge.
- Blood sampling for clinical chemistry and CBC tests for safety as well as P4 to check ovulatory status.
- Women will be questioned regarding concomitant medications. Concomitant medications taken within the 2 weeks before screening and from time of consent will be reported, in addition to indications for the medications and reasons for discontinuing.
- Subject eligibility will be assessed based on all inclusion/exclusion criteria.
- Adverse events happening after signature of ICF will be recorded

The results of the routine laboratory tests, Pap and STI test results (if indicated), and remaining eligibility criteria must be reviewed by the PI/medical designee before enrolling the subject. The investigator/medical designee must review laboratory reports, which should be filed with each subject's chart. The PI/medical designee will consider an individual subject's risks regarding use of a POP. The woman will be informed by telephone/email of her screening results and, if eligible, she will be instructed to notify the study site when her next menstrual bleeding occurs in order to schedule the next visit.

If any laboratory results are abnormal, according to local lab standards and clinically significant per the investigator's judgment, the subject will be informed and excluded from the study as well as referred to her primary health care provider. At the discretion of the investigator, abnormal laboratory assessments may be repeated before a final determination of exclusion is made. Subjects who have vaginitis, or those that screen positive for Chlamydia or gonorrhea, should be treated and can then be enrolled into the trial once proof of cure is obtained. It is advisable to have partners of women who screen positive for Chlamydia or gonorrhea treated as well.

If a subject is on a moderate or strong CYP3A4 inhibitor at time of screening, and is not taking the CYP3A4 inhibitor on a chronic basis, the subject may be re-evaluated for enrollment 6 days after they complete their course of treatment. Stoppage of the inhibitor must be related to treatment completion and unrelated to the purpose of enrollment in this study.

Laboratory assessments performed >60 days prior to enrollment should be repeated. Subjects who have delayed enrollment beyond 60 days since screening should be queried regarding any changes in their medical history and the investigator will determine if there is a need to repeat the physical exam, including the gynecologic exam (breast and pelvic examinations). Vital signs (BP and pulse) and weight/BMI should be verified in accordance with exclusion criteria.

If a subject has a P4 level below 10 nmol/L during the screening visit, she will have to come back for P4 level later in the menstrual cycle. If the second level is also below 10 nmol/L, she will not be able to enroll.

Site staff should also reconfirm smoking history, drug and alcohol use, partner status, and ascertain if a subject is sexually active. CYP3A4 inducers are exclusionary.

If a subject meets all eligibility criteria, she will be invited to move forward with study treatment at $V1_1$ (enrollment). She will also be asked to fast overnight (8 hours) before $V1_1$ but water will be allowed.

14.2 Treatment period 1 ($V1_1$ to $V1_x$ – Day 1 to Day 28)

After confirmation of ovulation via an elevated P4 of 3 ng/mL (10 nmol/L) or greater in the screening cycle and fulfillment of all inclusion and exclusion criteria, eligible subjects will attend the Enrollment Visit (Visit $V1_1$ = Day 1). Treatment will be initiated during $V1_1$ which should occur within 5 days after the onset of the next menses after the Screening Visit. The subjects are allowed to delay the enrollment for one cycle if necessary.

All women will take norgestrel 75 mcg daily at the same time during treatment period 1 (28 days) as described in section 12.3.

Women will undergo twice weekly visits with blood sampling, TVUS, and cervical mucus sampling as long as follicle < 15 mm on the TVUS. If an ovarian follicle ≥ 15 mm in one dimension is visualized on TVUS, visits will be performed every other day for a maximum of 6 visits (12 days), details are provided below.

14.2.1 $V1_1$ Enrollment visit ($V1_1$ - Day 1, morning)

The visit $V1_1$ will consist of:

- Review of history and medications
- Review of inclusion & exclusion criteria
- High-sensitivity urine pregnancy test before 1st pill intake
- Blood sampling for hormone levels (P4, E2, FSH and LH)
- Blood sampling for pharmacokinetic analysis (4 samples/subject)
    - Half of subjects (subjects with even study number) will be sampled at predose, 2h ± 15 min, 6h ± 15 min, 12h ± 30 min after treatment
    - Half of subjects (subjects with odd study number) will be sampled at 1h ± 15 min, 4h ± 15 min, 8h ± 30 min, 24h ± 30 min after treatment.
- Subjects will be asked to stay fasted until 4 hours after administration (water will be allowed)
- Cervical mucus collection and analysis before treatment intake
    - *Note: at all visits where both cervical mucus analysis and TVUS are performed, the cervical mucus collection will be performed before TVUS.*
- TVUS
- Dispensation of two study medication boxes (one to be used as a back-up) and intake of the first norgestrel pill at the site at 9:00 am ± 3 hours
- Determine with subject the intake time on day 2 and advise subject of intake time of norgestrel on a daily basis and importance of compliance
- Provide instructions to the subject in case she vomits or has diarrhea within 4 hours of taking a pill, misses a pill or loses a pill (as per section 12.3 dosage schedule)
- A mobile phone for the ediary will be lent if the subject doesn't have one
- E-diary instructions: remind the subjects to complete the diary on a daily basis with bleeding data and information relative to the intake of norgestrel (dates and times)

- Concomitant medications
- Occurrence of AEs

Subjects will be allowed to leave the site between the PK samples after the 2h/4h sampling.

14.2.2 Regular twice-weekly visits ($V1_2$ to $V1_x$ – Day 1 to 28)

If an ovarian follicle ≥15 mm in one dimension is visualized on ultrasound, visits frequency will be increased to a visit every other day (see 14.2.3). The investigator will also be allowed to add another extra visit, if it is needed to follow the follicle before or between the extra visits.

Visits will always take place every 3 or 4 days, preferably during weekdays.

They will consist of:

- review of concomitant medications, occurrence of AEs
- review of diary data
- blood sampling to obtain hormone levels
    - P4 and E2
    - FSH and LH
- blood sampling for measurement of levonorgestrel plasma concentration
    - during the first visit in week 3, for steady-state pharmacokinetic analysis (1-2 samples/subject), at the following time points:
        - Half the subjects (subjects with odd study number) at predose and between 30 min and 2 h (morning visit before the administration)
        - Half the subjects (subjects with even study number) between 5 h and 9 h post-treatment (afternoon visit)
- cervical mucus collection and analysis
- TVUS
- At the last visit in treatment period 1, a new study medication box will be dispensed for the subject to be used in treatment period 2

If necessary, the investigator or study site staff member will contact the subject more frequently. E-mail, phone or text message communication may be used based on subject preference and study site assessment regarding this mode of communication with individual subjects.

14.2.3 Extra visits ($V1_2$ to $V1_x$ – Day 1 to 28)

If an ovarian follicle ≥ 15 mm in one dimension is visualized on TVUS, visits will be increased to one visit every other day for a maximum of 3 visits (6 days) before obtention of a postovulatory image[1].

The visits will consist of:

- review of concomitant medications, occurrence of AEs
- review of diary data
- blood sampling to obtain hormone levels
    - P4 and E2
    - FSH and LH
- cervical mucus collection and analysis
- TVUS

[1] a postovulatory image is defined as:

- abrupt disappearance of FLS or
- reduction in size of the leading follicle > 4 mm at two consecutive visits or
- haemorrhagic corpus luteum (FLS at least as large as the leading follicle before ovulation)

The extra visits will be stopped and the subject will go back to twice a week visits:

- when a post-ovulatory image is obtained
- if a postovulatory image is not obtained at the third extra visit

14.3 Treatment period 2 ($V2_1$ to $V2_x$ – Day 29 to 56)

14.3.1 Regular twice-weekly visits and extra visits ($V2_1$ to $V2_x$ – Day 29 to 40 ±3 days AND Day 44 ± 3 days to Day 56)

Regular and extra visits will be performed according to the same schedule as described for treatment period 1 in section 14.2 and visits will consist of the same assessments as visits described in section 14.2.2 and 14.2.3.

The exceptions to the treatment period 1 will be:

- 1st visit (study week 5):
  - Collection of box/blister of treatment period 1
  - Randomisation of the subjects to either Arm A or Arm B
  - Blood sampling for measurement of LNG plasma concentration within 30 min of mucus sampling[2]
- Delayed/missed pill (DMP) period ($V2_{R-1}$ to $V2_{R+1}$ - Day 41 ± 3 days to Day 43 ± 3 days)
  - DMP visits will take precedence over regular and extra visits (see details in section 14.3.2 below)
  - After the DMP period, subjects will go back to regular twice a week visits or extra visits every other day (if a follicule ≥ 15 mm was observed before or during the DMP period)

14.3.2 DMP period ($V2_{R-1}$ to $V2_{R+1}$ – Day 41 ± 3 days to Day 43 ± 3 days)

On 3 consecutive days (Day 41 ± 3 days to Day 43 ± 3 days), the subjects will undergo 3 visits ($V2_{R-1}$ to $V2_{R+1}$) to evaluate the effects of a delayed intake or a missed pill.

On visit $V2_{R-1}$ (Day 41 ± 3 days), the subjects will have to come to the site twice in the same day, first for the study medication intake and second for the cervical mucus collection and analysis, and PK blood sampling.

The assessments will be the same for all subjects:

- Blood sampling for hormone levels (P4, E2, FSH, LH)
- Study medication intake on site at 9:00 am ±1 hour (actual time = treatment time $V2_{R-1}$ ($T2_{R-1}$))
- Blood sampling for PK at $T2_{R-1}$ + 8 hours ± 30 min post-dose
- Cervical mucus collection and analysis at $T2_{R-1}$ + 8 hours ± 30 min post-dose
- TVUS
- Review of diary data
- Review of concomitant treatments and occurrence of AEs

On visit $V2_R$ (Day 42 ±3 days), the subjects will either delay their pill intake by 6 hours (Arm A) or not take it (Arm B). They will not be requested to stay on site between the assessments.

The assessments for **subjects randomized to group A** will consist of:

- Cervical mucus collection and analysis at $T2_{R-1}$ + 3 hours ± 15 min
- Blood sampling for PK at $T2_{R-1}$ + 3 hours ± 15 min, $T2_{R-1}$ + 5.5 hours ± 15 min
- Study medication intake on site at $T2_{R-1}$ + 6 hours ±15 min on site

[2] The blood sampling will be done for all subjects at the 1st visit of week 5, but the subjects will only be told that a blood sampling will be performed at random visits. It should encourage them to stay compliant.

- Blood sampling for PK at $T2_{R-1}$ + 7.5h ± 30 min
- Review of diary data
- Review of concomitant treatments and occurrence of AEs

The assessments for **subjects randomized to group B** will consist of:

- No study medication intake
- Blood sampling for PK at $T2_{R-1}$ + 6 hours ± 15 min
- Cervical mucus collection and analysis to be performed at $T2_{R-1}$ + 6 hours ± 15 min
- Review of diary data
- Review of concomitant treatments and occurrence of AEs

The $V2_{R+1}$ (Study Day 43 ± 3 days) visit will consist of the same assessments for all subjects:

- Blood sampling for PK within 30 min before study medication intake
- Cervical mucus collection and analysis to be performed within 30 min before study medication intake
- TVUS
- Study medication intake at $T2_{R-1}$ ± 30 min
- Blood sampling for hormone levels (P4, E2, FSH, LH)
- Review of diary data
- Review of concomitant treatments and occurrence of AEs

14.4 Treatment period 3 ($V3_1$ to $V3_x$ – Day 57 to 84)

14.4.1 Regular twice-weekly visits and extra visits ($V3_1$ to $V3_x$ – Day 57 to 68 ±3 days AND Day 72 ± 3 days to Day 84)

Regular and extra visits will be performed according to the same schedule as described for treatment period 1 in section 14.2 and visits will consist of the same assessments as visits described in section 14.2.2 and 14.2.3.

The exceptions to the treatment period 1 will be:

- 1st visit (study week 9):
  - Collection of box/blister of treatment period 2
  - Blood sampling for measurement of LNG plasma concentration within 30 min of mucus sampling[1]
- DMP period ($V3_{R-1}$ to $V3_{R+1}$ - Day 69 ± 3 days to Day 71 ± 3 days)
  - DMP visits will take precedence over regular and extra visits (see details in section 14.3.2 below)
  - After the DMP, subjects will go back to regular twice a week visits or extra visits every other day (if a follicule ≥ 15 mm was observed before or during the DMP period)
- Extra visits will continue/be initiated after Day 84 if needed (see 14.4.3)

14.4.2 DMP period ($V3_{R-1}$ to $V3_{R+1}$ – Day 69 ± 3 days to Day 71 ± 3 days)

The schedule of assessments will be the same as during treatment period 2, except that during visit $V3_R$, subjects in Arm A will not take their pill and subjects in Arm B will delay their pill intake by 6 hours.

14.4.3 Follow-up visits ($V1_2$ to $V1_x$ – Day 84 to Day 96)

If an ovarian follicle ≥ 15 mm in one dimension is visualized on TVUS between Day 72 and Day 84, extra visits may be continued/initiated after the end of treatment (Day 84). In that case, visits will be

[1] The blood sampling will be done for all subjects at the 1st visit of week 9, but the subjects will only be told that a blood sampling will be performed at random visits. It should encorage them to stay compliant.

scheduled every other day for a maximum of 6 visits (12 days), 3 before obtention of a postovulatory image[1] and 3 after.

Before a postovulatory image is obtained, the visits will consist of:

- review of concomitant medications, occurrence of AEs
- review of diary data
- blood sampling to obtain hormone levels
  - P4 and E2
  - FSH and LH
- cervical mucus collection and analysis
- TVUS

The extra visits will be stopped if:

- a postovulatory image is not obtained at the third extra visit

After a postovulatory image is observed, the visits will consist of:

- review of concomitant medications, occurrence of AEs
- review of diary data
- blood sampling to obtain hormone levels
  - P4
- cervical mucus collection and analysis

The extra visits will be stopped if:

- P4 levels rise above 30 nmol/L at one visit or 10 nmol/L for two consecutive visits, or
- after 3 additional extra visits

14.5 End of study visit (EOS) ($V4_y$ – between Day 85 and Day 100)

Subjects will be scheduled for their EOS either:

- within 5 days of taking their last dose (at the latest on day 84 of treatment) if no follow-up visits are required.
- within 5 days of their last follow-up visit if extra visits were initiated/continued after Day 84

The visit will consist of:

- Vital signs
- Blood sampling for clinical chemistry and CBC tests, for safety
- High-sensitivity pregnancy urine test
- Review of diary data and collection of mobile phone lent at screening visit, if applicable
- Review of concomitant treatments and occurrence of AEs
- Subjects will bring back medication boxe(s) including used/unused blister pack(s)

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[1] a postovulatory image is defined as:

- abrupt disappearance of FLS or
- reduction in size of the leading follicle > 4 mm at two consecutive visits or
- haemorrhagic corpus luteum (FLS at least as large as the leading follicle before ovulation)

14.6 Study flow summary

Table 2 Main study flow (not including DMP period, see Table 3)

Study periods		**Screening visit**	**Treatment phase**			**Follow up of treatment period 3** (2)	**End of study visit**
			Treatment period 1(1)	**Treatment period 2**	**Treatment period 3**		
Visits		V0	$V1_1$ to $V1_x$	$V2_1$ to $V2_x$	$V3_1$ to $V3_x$	$V4_1$ to $V4_x$	$V4_y$
Days		-	1 to 28	29 to 56	57 to 84	85 to 96	85 to 100
Norgestrel intake		-	Daily pill intake at the same time between 6:00 am and 12:00 pm			-	-
Visit frequency	if follicle < 15 mm	Within a maximum of 60 days before start of treatment phase	Regular visits - Twice a week			Not applicable	X
	if follicle ≥ 15 mm identified upon TVUS		Extra visits - Every other day For a maximum of 3 visits (6 days) before postovulatory image			Extra visits - Every other day For a maximum of 6 visits (12 days): • maximum of 3 visits before postovulatory image • maximum of 3 visits after postovulatory image	
TVUS		X	At each visit			At each visit before postovulatory image	-
Mucus analysis		-	At each visit			At each visit	-
Hormone levels		P4	P4, FHS, LH, E2 at each visit			P4, at each visit FHS, LH, E2 at each visit before postovulatory image	-
PK blood sampling		-	Day 1 (3) 1st visit week 3 (4)	1st visit week 5	1st visit week 9		-

[1] Study pill is to be started within 5 days after last menstrual period.
[2] Extra visits will be initiated /continue after Day 84 if needed[3]
[3] Half of subjects at predose, 2h, 6h, 12h and half of subjects at 1h, 4h, 8h, 24h
[4] Half of subjects at predose and between 0.5h and 2h and half of subjects between 5h and 9h

Table 3 Study flow of DMP period

Study periods		**Treatment Period 2 DMP** Visits $V2_{R-1}$ $V2_R$ and $V2_{R+1}$ should occur on 3 consecutive days.			**Treatment Period 3 DMP** Visits $V3_{R-1}$ $V3_R$ and $V3_{R+1}$ should occur on 3 consecutive days.		
Visits		**$V2_{R-1}$**	**$V2_R$**	**$V2_{R+1}$**	**$V3_{R-1}$**	**$V3_R$**	**$V3_{R+1}$**
Days		41 ± 3	42 ± 3	43 ± 3	69 ± 3	70 ± 3	71 ± 3
Norgestrel intake as per study arm	Arm A	Pill intake at 9 am ± 1 h ($T2_{R-1}$)	Pill intake at $T2_R$ = $T2_{R-1}$ + 6 h ± 15min	Pill intake at $T2_{R+1}$ = $T2_{R-1}$ ± 30 min	Pill intake at 9 am ± 1 h ($T3_{R-1}$)	No pill intake	Pill intake at $T3_{R+1}$ = $T3_{R-1}$ ± 30 min
	Arm B		No pill intake			Pill intake at $T3_R$ = $T3_{R-1}$ + 6 h ± 15min	
TVUS	Arm A	Yes	No	Yes	Yes	No	Yes
	Arm B						
Mucus analysis	Arm A	$T2_{R-1}$ +8 h ± 30 min	$T2_{R-1}$ + 3 h ± 15 min	Within 30 min before $T2_{R+1}$	$T3_R$ +8 h ± 30 min	$T3_R$ + 6 h ± 15 min	Within 30 min before $T3_{R+1}$
	Arm B		$T2_{R-1}$ + 6 h ± 15 min			$T3_{R-1}$ + 3 h ± 15 min	
Hormone Levels	Arm A	Yes	No	Yes	Yes	No	Yes
	Arm B						
PK blood sampling	Arm A	$T2_{R-1}$ +8 h ± 30 min	$T2_{R-1}$ + 3 h ± 15 min $T2_{R-1}$ + 5.5h ± 15 min $T2_{R-1}$ + 7.5h ± 30 min	Within 30 min before $T2_{R+1}$	$T3_{R-1}$ +8 h ± 30 min	$T3_{R-1}$ + 6 h ± 15 min	Within 30 min before $T3_{R+1}$
	Arm B		$T2_{R-1}$ + 6 h ± 15 min			$T3_{R-1}$ + 3 h ± 15 min $T3_{R-1}$ + 5.5h ± 15 min $T3_{R-1}$ + 7.5h ± 30 min	

15. ADVERSE EVENTS

15.1 OBLIGATIONS OF THE INVESTIGATOR REGARDING SAFETY REPORTING

15.1.1 Definitions of Adverse Events (AE), Serious Adverse Events (SAE), severity and causality assessment

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse reaction is defined as "all untoward and unintended responses to an investigational medicinal product related to any dose administered". The definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The reference document used to assess the expectedness is US Product Information of the study treatment. A copy of the document will be provided to the investigators before study start.

An event is considered **a Serious Adverse Event** (SAE), if in the view of either the investigator or sponsor, it meets the criteria as outlined in 21 CFR 312.32 (a) as per the following:
Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death,
- a life threatening adverse drug experience,

NOTE: The "life-threatening" criterion in the definition of "seriousness" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

- inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    1. routine medical treatment or monitoring or surgery in relation with the indication studied in the protocol and not associated with any deterioration
    2. planned treatment for a pre-existing condition that is unrelated to the indication of the current study and has not worsened since the start of study medication (in that case, this pre-existing condition should be mentioned in the e-CRF as patient's history or concomitant disease)
    3. Emergency consultation without any medical admission
- a persistent or significant disability/incapacity,
- or a congenital anomaly/birth defect,
- is medically important

Medical and scientific judgement should be exercised in deciding whether the case should be considered serious in other situations, such as important medical events that may not result in death, be immediately life-threatening or require hospitalization but, may jeopardize the patient or 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 development of drug dependency or drug abuse."

<u>Severity</u>
The Investigator is responsible for assessing the severity of each AE using the following definitions for severity criteria:

- Mild – events require minimal or no treatment and do not interfere with the subject's daily activities.
- Moderate – events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- Severe – events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Relationship to Investigational Product

The Investigator is responsible for assessing the relationship between the AE and the investigational product. The Investigator must determine whether there is a reasonable possibility that the investigational product caused or contributed to an AE. The relationship assessment, based on clinical judgment, often relies on the following:

- A temporal relationship between the event and administration of investigational product;
- A plausible biological mechanism for the investigational product to cause the AE;
- Another possible etiology of the AE; or
- Previous report of similar AEs associated with the investigational product or other agents in the same class.

The terms used to assess the relationship of an event to the investigational product are:

Causality Assessment	**Criteria for Assessment (note that re-challenge does not apply in this study)**
Certainly Related	The experience occurs immediately following investigational product administration, related pharmacologically (not related to underlying condition/concurrent disease or other drugs or chemicals)
Possibly Related	The experience follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the investigational product but could have been produced by other factors such as the participant's clinical state, therapeutic intervention or concomitant therapy.
Unlikely Related	Improbable temporal relationship. The experience was most probably produced by other factors such as the participant's clinical state, therapeutic intervention or concomitant therapy and does not follow a known response pattern to the investigational product.
Not Related	There is not a reasonable possibility that the AE is related to the investigational product; when an AE is assessed as not related to the investigational product, an alternative etiology, diagnosis or explanation for the AE should be provided. If new information becomes available, the relationship of any AE should be reviewed again and updated as required.

15.1.2 Adverse Events: Recording and Reporting

All AEs will be managed and reported in compliance with all applicable regulations and reported in the eCRF and in the clinical study report (CSR).

At every visit, study staff will ask each subject how she has felt since her last visit as well as directly and indirectly ask if she has experienced any AEs. A review of the subject's diary should be completed during the visit with the subject to identify any possible AEs reported through the diary.

The reporting period for AEs, regardless of seriousness or relationship to the study drug, is the period immediately following the subject signing the informed consent through the EOS. However if an AE/SAE is reported after the last visit and considered as related to the IMP, the sponsor has to be informed.

All AEs must be recorded in the subject's e-CRFs and must include the following information (when applicable):

- Specific condition or event.
    - Whenever possible, diagnosis or syndrome should be reported instead of symptoms.
    - Laboratory, vital signs or ECG parameters should be recorded as AE only if they are medically relevant (e.g.: symptomatic, leading to study drug discontinuation, requiring medical treatment).
    - Indication of whether the condition was preexisting prior to study entry or not and if yes, whether it has worsened in severity or frequency in which case it is reported as an AE. Conditions present prior to study entry (screening) that do not worsen in severity are considered medical history, not considered AEs. (Refer to Section 11.2 Prior and Concomitant Illnesses and Treatments).
- Date of occurrence.
- Date of resolution. If the event has not resolved by the end of the study-reporting period, it will be documented as still present on the case report form.
- Severity (AEs that change in intensity are recorded at the intensity level that is the most severe reported by the subject over consecutive days. If the intensity category changes over a non-consecutive period of time, then these changes should be recorded separately with distinct onset dates).
- Relationship to study medication as evaluated by the investigator (causality assessment).
- AE outcome (recovered, ongoing, etc.)
- Seriousness

The investigator should also specify actions taken with respect to the study drug(s), corrective treatment given, additional investigations performed, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the study drug(s).

15.1.3 Instructions to study participants

Participants will be provided with instructions for contacting the study site to report any untoward medical occurrences they may experience, except for possible life-threatening events, for which they will be instructed to seek immediate emergency care. Participants will be able to seek evaluation at the study site, where feasible and medically appropriate. With permission of the participant, and whenever possible, records from all non-study medical providers related to untoward medical occurrences will be obtained for review. Participants who have ongoing SAEs or related AEs at their last study visit will be followed until resolution or stabilization, or referred for additional care. If a SAE occurs after the last visit, the participant will be asked to report it to investigator, so it can be reported to the sponsor (see section 15.1.2).

15.1.4 Study reporting for SAEs

The reporting period for SAEs is the period immediately following the informed consent signature until the EOS. In case a SAE is brought to the attention of the investigator at any time after the end of the clinical trial and is considered by him to be caused by the study drug with a reasonable possibility, the SAE will be reported to the Sponsor's Pharmacovigilance Department.

SAEs must be followed until resolution, even if this extends beyond the study-reporting period. Resolution of a SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

In case of SAE, the investigator must immediately:

- Enter within 24 hours the information related to the SAE in the appropriate screen of the e-CRF.
- Attach the photocopies of all examinations carried out with the dates on which they were performed as well as the laboratory normal ranges

- All further documentation should be sent by Fax or email to the Sponsor's Pharmacovigilance Department within 1 working day of knowledge or upon request from the Sponsor Pharmacovigilance Department.
  Fax:
  E-mail:

Any additional SAE supporting documentation should be transmitted to Sponsor's Pharmacovigilance Department whenever possible (with subject identification information redacted) to verify the medical diagnosis. This includes hospital discharge summaries, lab report, death certificates/autopsy reports (where applicable), surgical procedure summaries, histology reports, and imaging reports.

As the IND holder, HRA is responsible for the appropriate recording, review and compliance with regulatory reporting requirements of SAEs to the FDA in accordance with 21 CFR 312.50.

15.1.5 Follow up

The investigator should take all appropriate measures to ensure the safety of the patient and should follow the outcome of the AE/SAE until return to normal or consolidation of the patient's condition.
Any new information should be sent by Fax or email to the Sponsor's Pharmacovigilance Department within 1 working day of knowledge:
Fax: +
E-mail:

15.1.6 Event of special interest

Pregnancy:

In case of pregnancy, the study drug will be discontinued and the investigator must immediately:
Fill in the Pregnancy Collection Form (see Appendix 6) and send it by fax or email within 1 working day to HRA Pharma's Pharmacovigilance Department:
Fax:
E-mail:

All cases of pregnancy will be recorded in the e-CRF.

The investigator should take all appropriate measures to follow the pregnancy until its final outcome (abortion, delivery or other).The Pharmacovigilance Department will contact the investigator in order to collect needed information on the pregnancy.

15.1.7 Notification of IRB of SAEs

All expedited SAEs that occur at each site must be directly reported to the IRB by the Investigator within 10 business days of the investigator's knowledge of the event. However, the death of a subject must be reported within 24 hours of discovery. The investigator should report non-expedited SAEs/AEs for their own site per their IRBs reporting guidelines.

The final adjudication of an SAE will be conducted by HRA and the final form will be sent to the principal investigator for submission to the IRB for applicable events. Investigators must also submit applicable safety information provided by HRA to their IRB.

15.2 OBLIGATIONS OF THE SPONSOR REGARDING SAFETY REPORTING

During the course of the study, the sponsor will report in an expedited manner all Suspected Unexpected Serious Adverse Reactions (SUSARs) to the Health authorities as appropriate. The sponsor should also inform investigators of SUSARs.

No specific DSMB will be set up for this trial. However, in case of pertaining safety issues emerging during the study, the independent, autonomous Data and Safety Monitoring Board (DSMB) established by the WHRU, Portland, Oregon may be used.

15.3 PREGNANCY DETERMINATION AND FOLLOW-UP

Subjects are not supposed to be at risk for pregnancy (see inclusion criteria) but If a subject becomes pregnant during the study, the investigator must inform HRA of the pregnancy within 24 hours of such determination, the subject must be discontinued from the trial, and all procedures scheduled for the EOS Visit should be performed. Additional pregnancy data will be submitted as it becomes available.

The estimated date of ovulation will be made by the investigator based upon results of the following pregnancy determination criteria, listed in order from most accurate to least accurate:

1. TVUS.
2. Estimate based on pelvic and/or abdominal examination or pregnancy outcome.
3. Daily diary information (*e.g.*, last menstrual period).
4. Quantitative β-hCG determination.
5. Investigator estimation in the absence of above criteria.

Subjects who become pregnant during the study will be informed of pregnancy options and referred for appropriate care.
All pregnancies will be monitored until outcome (i.e. 9 months follow-up or until outcome information is obtained). Information will also be collected on any maternal or fetal complications. Congenital anomalies or birth defects will be classified as SAEs. Pregnancy outcome data will be collected for analysis. Reports of pregnancy outcome and examinations during the pregnancy will be requested from the attending physician/outside clinic, if applicable. Pregnancy outcome data will include the rates of spontaneous abortion, stillbirth, live preterm, and full-term births.
If a subject has a spontaneous abortion or ectopic pregnancy this will be considered as a SAE. In addition, congenital malformations and anomalies will be recorded as SAEs and summarized.
If a subject continues with her pregnancy through childbirth, every effort will be made to maintain contact with her so that health of the baby can be evaluated at six and twelve months. Any outstanding data at the end of the study that is collected will be submitted to the FDA as a Safety Update to the NDA submission. A clinical summary of the prenatal and postnatal events will be reported separately from the case report form in narrative format in the clinical summary report.

16. STUDY CONDUCT

16.1 Deviation from the Protocol

The Investigator should not deviate from the protocol without prior notification and approval of HRA with the exception of minor visit window deviations. In the event that the investigator or the subject deviates from the protocol without a protocol waiver, notification should be provided to HRA as soon as possible detailing the circumstances of the protocol violation. Certain protocol violations may require the subject to be terminated early from the study. It is the responsibility of the research centers to report all protocol waivers and protocol violations to their IRB according to IRB policy.

16.2 Amendments to the Protocol

Neither the investigator nor the sponsor will alter this study protocol without obtaining the written agreement of the other.

Any change of the clinical trial must be written and filed as an amendment to this protocol. The Investigator(s) must submit the protocol amendment for review by their IRB and shall obtain the approval of their IRB before it is implemented.

In cases of emergency, when the protocol change or deviation is to eliminate or reduce an immediate hazard or risk to human subjects, the amendment may be implemented before review or approval by their IRB. In such cases, the investigator shall notify their IRB of the change or deviation in writing within 10 working days after implementation. Any protocol-related issues that pose an immediate or significant hazard to subjects must be reported to HRA immediately. If the protocol amendment is an administrative change, it will be sent to their IRB for information (updating of file).
All modifications of the clinical trial will be written and filed with FDA as an amendment to this protocol, maintaining original section identification. Such modifications will be made jointly by HRA, and all the Investigators with the approval of all the IRBs.

16.3 Subject Confidentiality

Subject names will not be supplied to the sponsor. Only the subject number and subject initials will be recorded in the e-CRF, and if the subject name appears on any other document, it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be told that representatives of the sponsor, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in the strictest confidence and in accordance with local data protection laws.

Subject confidentiality will be maintained by the use of coded subject ID numbers. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring by the FDA, HRA.

The investigator will maintain a personal subject identification list (subject ID numbers with the corresponding subject names) to enable records to be identified.

16.4 Discontinuing Subjects

A subject will be considered to have completed the clinical trial after she has completed the three 28-day treatment periods and completes the EOS Visit and after the final set of data has been collected and entered in the e-CRF.

Subjects **may be** discontinued prematurely for any of the following reasons:
- Emergence of AE or SAE that, in the judgment of the investigator, should result in premature discontinuation.
- Inter-current illness that, in the judgment of the investigator, should result in premature discontinuation.
- Major protocol violation as per investigator's judgment and after sponsor's approval.
- Use of prohibited medications, including any outlined in the Inclusion/Exclusion criteria
- Suspected drug interaction.
- Pathologically changed laboratory values.
- Knowledge of new risks necessitating new benefit/risk evaluation.
- Non-compliance (see section 12.8)
- Missing multiple visits
- Emergence of any of the exclusions listed above.

Subjects **must be** discontinued for any of the following reasons:
- Withdrawing their consent (e.g., due to personal reasons, experiencing AE).
- Subject lost to follow up
- Trial closed-out.
- Confirmed Pregnancy.
- Gonorrhea or Chlamydia or a pelvic-inflammatory disease diagnosis during the course of the study, except for the diagnosis being made on the initial screening test, at which time the Investigator chooses to suspend the subject's enrollment until proof of cure is obtained.
- Suspected unexpected serious adverse reaction to study medication
- Serious intercurrent problems requiring admission to the critical care unit or surgery

Subjects have the right to withdraw from the study at any stage and for any reason.

The reason for premature discontinuation will be recorded on the End of Trial form. If withdrawal from the study is due to an AE, this information will also be recorded on the Adverse Event form.
All subjects who terminate early from the trial will undergo EOS visit procedures regardless of the reason for discontinuation with the exception of those subjects who have lost contact with the research center. A subject cannot be considered lost to follow-up until the subject misses a visit and the research center performs and documents at least three (3) attempts to contact her. Documentation must include a letter sent return receipt requested to the subject instructing her to call the research center. Every effort must be made to follow-up with subjects who terminate with product-related adverse experiences, in order to determine the final outcome of AEs.

16.5 Withdrawals from Study

All efforts should be made to contact the woman when she decides to discontinue so that appropriate discontinuation data can be obtained. Such contact will not be used to dissuade any subject who wishes to terminate the study.

As far as possible, all examinations scheduled for the EOS visit must be performed on all subjects who receive study medication but do not complete the study according to protocol.

The procedures outlined for the EOS visit should be performed, whenever it occurs. Additionally, all study medication will be collected. The reasons for discontinuation will be recorded in the End of Trial CRF.

At a minimum, all subjects who discontinue study medication, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study medication. Subjects who discontinue study medication should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the subject will not return for these assessments

17. STUDY MONITORING AND DOCUMENTATION

17.1 Clinical Monitoring, Quality Control, and Quality Assurance

Monitoring and auditing procedures developed by the sponsor will be followed, in order to comply with GCP guidelines. On-site checking of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The Principal Investigator and sub-investigators will allow representatives from HRA and subcontractors direct access to all CRFs, source documents, and corresponding portions of the medical records for each participant at mutually convenient times for periodic review before, during, and after the study has been completed. The monitoring visits provide HRA Pharma and subcontractors with the opportunity to:

- Initiate the research center.
- Evaluate the progress of the study.
- Verify the accuracy and completeness of the e-CRFs.
- Ensure that all protocol requirements, applicable FDA regulations, and investigators' obligations are being fulfilled.
- Resolve any inconsistencies in the study records.
- Close out the trial at the research center.

In addition to routine monitoring, HRA or its designee may, at its discretion, perform site audits. The purpose of such audits will be to evaluate site trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements. If an audit is performed, a site must provide the auditors with direct access to all relevant records and documentation related to the study.

Regulatory authorities, the Institutional Review Board may also request access to all source documents, CRFs, and other study documentation for on-site inspection.

17.2 Administrative and Record Management and Retention of Data

All investigative site records (source documents and other subject records) will be kept in a secure and hazard free storage area. Access will be restricted to study personnel authorized to handle research documents. All records will be retained 15 years after the study completion.

HRA should be notified before destruction of any site records or transfer of oversight of the records should there be PI change at a site.

All Essential Documents as defined in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial) contained in the Trial Master File and the Investigator's File must be retained after the completion or termination of the study by the investigator and the sponsor for at least 15 years after the study completion.

However, because of international regulatory requirements, the sponsor may request retention for a longer period of time. The investigator must therefore obtain approval in writing from the sponsor prior to destruction of any records.

Throughout the study, e-CRFs and data clarification forms will be transmitted from the clinical site(s) to the sponsor or its designee and the information will be stored in an electronic database.. The final e-CRFs will be copied onto a CD-rom and sent to the site for archiving.

Data entered by subjects in e-diaries throughout the trial will be transferred at study end to the Contract Research Organization (CRO) in charge of data management..

In order to assure the accuracy of data collected into the e-CRF, it is mandatory that the sponsor (or designees), as well as representatives of regulatory agencies, have access to original source documents (e.g., patient records, patient charts, laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality.

Normally, investigator's records will be held in the investigator's archives. If the investigator is unable to meet this obligation, he or she must ask the sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

Key documents to be retained are summarized below:

	Investigator	Sponsor
• Signed informed consent documents for all subjects	Signed original	NA
• Subject identification code list, screening log (if applicable), and enrollment log	X	NA
• Record of all communications between the investigator and the IRB	Signed original	Copy
• Composition of the IRB	X	X

• Record of all communications between the investigator and sponsor (or CRO)	X	X
• List of sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant trial-related duties, together with their roles in the study and their signatures	Copy	Signed original
• e-CRFs and documentation of corrections for all subjects	Copy	Copy
• Drug accountability records	X	X
• Record of any body fluids or tissue samples retained	X	X
• All other source documents (subject records, hospital records, laboratory records, etc.)	X	NA

17.3 Study Documentation

HRA monitoring subcontractor is responsible for assuring that the essential documents maintained in the investigator site files at the research centers are accurate and complete. Essential documents in the investigator site files / trial master file will be maintained according to written SOPs.

17.4 Electronic Data Capture System

All requested information should be entered in the Electronic Data Capture (EDC) system. Prior to the start of the clinical trial, the investigator will complete an authorized signature sheet showing the signatures and handwritten initials of all individuals who are authorized to maintain study records and submit data using the EDC system.

17.5 Confidentiality and Reporting of Results

Subject names will not be entered into the EDC system; instead, unique subject identifiers will be assigned. Medical records will be kept at the research center and will be available to study staff and, HRA, site IRBs, or the FDA only. Any publications or presentations that result from this study will maintain participant confidentiality. All data will only be used for the purpose for which it has been approved. Data collected during this study and any analyses of that data will not be used in any way other than those ways already approved without further approval from HRA.

18. DOCUMENTATION AND USE OF STUDY FINDINGS

18.1 Documentation of study findings

An e-CRF will be used for each subject.

All protocol-required information collected during the study must be entered by the investigator, or designated representative, in the e-CRF. Details of e-CRF completion and correction will be explained to the investigator. If the investigator authorizes other persons to make entries in the e-CRF, the names, positions, signatures, and initials of these persons must be supplied to the sponsor.

The investigator, or designated representative, should complete the e-CRF as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

A source data location list will be prepared and updated during the study. This list will be filed in both the trial master file and the investigator study file. This list should also include identification of any data to be recorded directly on the e-CRFs and to be considered to be source data.

The completed e-CRF must be reviewed and approved by the investigator named in the study protocol or by a designated sub-investigator.

The data management CRO will provide the sponsor and the investigator with paper renditions of the e-CRF (for example, in pdf format) and / or a CD-ROM of the e-CRF at study end.

18.2 Use of study findings

All information concerning the product as well as any matter concerning the operation of HRA Pharma, such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by HRA Pharma and are unpublished, are confidential and must remain the sole property of HRA Pharma. The investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from HRA Pharma is obtained.

By signing the Investigator's declaration, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

The sponsor will prepare a final report on the study and will communicate a summary of key findings to all investigators.
Only the principal investigator will be required to sign a statement that he or she has read the report and confirms that, to the best of his or her knowledge, it accurately describes the conduct and results of the study.

Only after the study has been completed can the findings of the study be published in a scientific journal or presented at a scientific meeting. For any publication manuscript prepared by HRA Pharma, HRA Pharma reserves the right to select the investigators who will be authors and review the manuscript. HRA Pharma will allow the selected investigators 30 days for full review of the manuscript before publication. It is generally preferable that the results of the multicenter study be published together. Before submitting the results of the study for publication or presentation, the investigator will allow HRA Pharma 30 days in which to review and comment on the manuscript.

19. STATISTICAL AND ANALYTICAL METHODS

19.1 Populations

Four populations of interest will be analyzed.

- The **Intent-To-Treat** (ITT) **population** consists of all subjects who were randomized;
- The **Full Analysis Set** (FAS) or population of **evaluable women** is dependent on the question of interest.
    - It is composed of all randomized and treated women with **cervical** mucus information (mucus score) at the second or third treatment periods for the questions related to mucus and the effect of unperfect use of norgestrel.
    - It is all randomized and treated women with ovarian activity information (OAS: ovarian activity score) at the second or third treatment periods for questions related to **ovarian activity**.
    - It is all women with complete information on mucus and ovarian activity for questions related to **overall conception protection**.

  Cycles with a very early ovulation (within 10 days before the DMP period) at period 2 or 3 may be removed from the set of evaluable cycles in a sensitivity analysis or included as failure depending upon the question of interest because the effect of intake infringement cannot be assessed in these cycles. The exclusion of cycles from a given analysis, the exclusion of a woman from the FAS and the status of non evaluable cycles will be decided in a blind manner by an independent adjudication committee.
- The **per-protocol** (PP) **population** is composed of subjects from the FAS without major protocol violation/deviation and with complete cervical mucus and ovarian activity data at the three periods. Relevant protocol violation/deviation will be defined during the data review but will include at least compliance issues and early ovulation;
- The **Safety population** that consists of all subjects who took at least one dose of study medication (Opill® 75 mcg).

The ITT population will be used to describe the population and to get information on the level of compliance in a clinical trial (treatment period 1) that is expected to be better than in the real life.

The FAS or evaluable population will be used in the 'primary' analysis for assessing the effect of delayed or missed pill on mucus permeability to spermatozoids and on secondary pharmacodynamic analyses.

The PP population will be used for assessing the pharmacodynamic effect without missing data and possibly biased data due to protocol violations/deviations. This will be the "cleanest" results for assessing the effect of infringement and the PD effect at the expense of completeness of the set of randomized women and representativeness of the treated population.

The Safety set will mainly be used for safety purposes.

19.2 Description of Subjects

The number of subjects, who were screen failures, enrolled, treated, withdrawn and who completed the clinical trial will be tabulated. This will be presented in a chart called patient disposition.

Baseline demographics and characteristics will be summarized for all subjects per population. The characteristic of the ITT, FAS, PP and safety populations at entry in the study will be provided through descriptive statistics (mean, standard deviation, minimum, median, maximum and number of observations and missing cases) for quantitative variables and frequencies and percentages for categorical variables.

19.3 Efficacy analysis

19.3.1 Primary analysis

The **primary working hypothesis** states that an infringement in the schedule of intake of norgestrel 75 mcg has a negative impact on the level of conception protection of women.

The **primary objectives** of the study is to verify whether a delayed intake of 6 hours or a missed pill of norgestrel 75 mcg has an effect on cervical mucus protection and more specifically tends to increase the cervical mucus score compared to reported perfect use of norgestrel 75 mcg just before infringement.

The **primary population** of subjects is the FAS. It is composed of all randomized and treated women with cervical mucus information (mucus score) at the second or third treatment period. Subjects with a very early ovulation will be discarded from the set of evaluable cycles in the primary analysis.

The **primary treatment periods** of interest are the second and third treatment periods.

The **primary assessment criterion** of interest is the cervical mucus score during the treatment periods 2 and 3.

The symbols used in the statistical section are:

- T is the time of treatment (pill)
- TMS is the time of mucus scoring
- TMS score is the value of mucus score at the time of mucus scoring
- A or B concerns arm A or B respectively
- R denotes the day of pill intake infringement in period 2 and period 3
- R-1 denotes the day before infringement in periods 2 and 3
- R+1 denotes the day after infringement in periods 2 and 3
- V1, V2 and V3 or 1, 2 and 3 denote visits during the first, second and third periods respectively.
- $T2_{R-1}$ and $T3_{R-1}$ are times of pill intake at $V2_{R-1}$ and $V3_{R-1}$ respectively.

The **primary time points of interest** are:

- Time of mucus scoring (TMS) the day **before** infringement (delayed pill or missed pill) in period 2 and period 3 (baseline):
  - $TMS2_{R-1} = T2_{R-1}$+ 8 h ± 30 min at $\mathbf{V2_{R-1}}$ and
  - $TMS3_{R-1} = T3_{R-1}$ + 8 h ± 30 min at $\mathbf{V3_{R-1}}$.

- Time of mucus scoring the **day of infringement** in period 2 or 3:
  - Subjects belonging to arm A
    - $TMS2_{A,R} = T2_{R-1}$ +3 h ± 15 min at $\mathbf{V2_R}$ and
    - $TMS3_{A,R} = T3_{R-1}$ + 6 h ± 15 min at $\mathbf{V3_R}$
  - Subjects belonging to arm B
    - $TMS2_{B,R} = T2_{R-1}$ + 6 h ± 15 min at $\mathbf{V2_R}$
    - $TMS3_{B,R} = T3_{R-1}$ +3 h ± 15 min at $\mathbf{V3_R}$

- Time of mucus scoring the day **after** infringement (both arms):
  - $TMS2_{R+1} = T2_{R-1}$ - 30 min (before pill intake) at $V2_{R+1}$ and
  - $TMS3_{R+1} = T3_{R-1}$ - 30 min at $V3_{R+1}$.

N.B.: The **time of pill intake** the day after infringement should be the same as the day before infringement (expected around 9 am).

The **primary <u>baseline</u> time points** are:

- $TMS2_{R-1}$ = $T2_{R-1}$+ 8 h ± 30 min at $V2_{R-1}$ and
- $TMS3_{R-1}$ = $T3_{R-1}$ + 8 h ± 30 min at $V3_{R-1}$

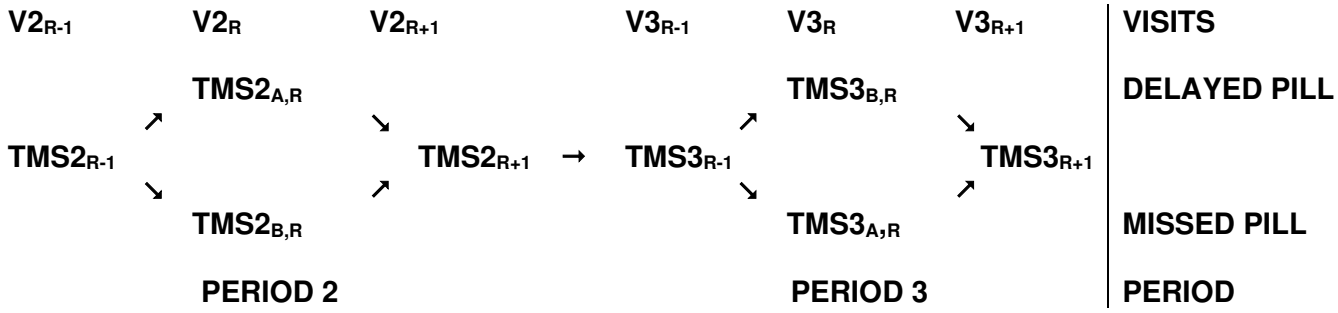
Around 8 hours after pill intake the day before infringement.

The **primary <u>response</u> time points** are:

- Arm A:
  - $TMS2_{A,R}$ = $T2_{R-1}$ + 3 h ± 15 min at $V2_R$
  - $TMS2_{R+1}$ = $T2_{R-1}$ - 30 min (before pill intake) at $V2_{R+1}$
  - $TMS3_{A,R}$ = $T3_{R-1}$ +6 h ± 15 min at $V3_R$
  - $TMS3_{R+1}$ = $T3_{R-1}$ - 30 min (before pill intake) at $V3_{R+1}$
- Arm B
  - $TMS2_{B,R}$ = $T2_{R-1}$ +6 h ± 15 min at $V2_R$
  - $TMS2_{R+1}$ = $T2_{R-1}$ - 30 min (before pill intake) at $V2_{R+1}$
  - $TMS3_{B,R}$ = $T3_{R-1}$ + 3h ± 15 min at $V3_R$
  - $TMS3_{R+1}$ =$T3_{R-1}$ - 30 min (before pill intake) at $V3_{R+1}$.

The **primary measures** of mucus are taken at the time presented in the following figure:

Figure 3 Primary measures of mucus



The **primary outcomes/endpoints** are the changes from baseline (BSL):

- Delta from BSL to $V2_R$ = Mucus score at $V2_R$ – score at $V2_{R-1}$ (period 2): change from baseline to 3 or 6 hour after infringement
- Delta from BSL to $V2_{R+1}$ = Mucus score at $V2_{R+1}$ – score at $V2_{R-1}$ (period 2): Change from baseline to just before pill intake the day after infringement
- Delta from BSL to $V3_R$ = Mucus score at $V3_R$ – score at $V3_{R-1}$ (period 3) change from baseline to 3 or 6 hour after infringement
- Delta from BSL to $V3_{R+1}$ = Score at $V3_{r+1}$ – score at $V3_{r-1}$ (period 3) Change from baseline to just before pill intake the day after infringement

The **primary model** of interest is a mixed model for repeated measures using as response delta to $V2_R$, delta to $V2_{R+1}$, delta to $V3_R$ and delta to $V3_{r+1}$. The covariates will be the period (or period effect), the intervention (type of infringement: missed pill or delayed pill), the sequence of intervention (missed pill then delayed pill and vice versa), the time and the subject. Time, period intervention type, and sequence will be considered as categorical variables. The subject as random effect (RANDOM statement of the MIXED procedure). This will permit to take into account the fact that measures from each period are derived from the same subjects. A time repeated effect (REPEATED statement of the MIXED procedure) within each combination subject* period (SUBJECT = subject* period as option of the REPEATED statement). This will permit to take into account the fact that for each subject, at each period several measures are performed over time. The proper struture of the variance covariance matrix will be retained using the best fit among unstructured matrix (UN) compound symetry (CS) and autoregressive structure (AR1).

The **primary test of interest** will be the significance of the overall mean (intercept). This will answer the question: is the overall mean change from baseline different from zero? Or does the infringement

of schedule regardless the type of infringement lead to a change in mucus score?

The **contrasts or estimates of interest** are

- the effect of infringement type: does the effect of missed pill differ from the effect of 6 hours delay? If the answer is yes then a signal of effect is detected.
- The effect of time: does the response on the day of infringement differ from the response on the day after infringement? If the answer is yes then a signal of effect of infringement is detected.

The SAP may present other models (secondary models) to answer other questions of interest or to get a more parsimonious model. For example if the sequence of intervention effect is not significant a model without this covariate can be planned in the SAP.

19.3.2 Subordinated objective

The **subordinate primary objective** is to estimate the duration of the protective effect of cervical mucus after last pill intake of norgestrel 75 mcg during reported perfect use (at the day before the infringement).

The possible increase in mucus score may have no detectable effect on conception risk depending on the level of score because it increased but remained below a threshold of good protection.

The mucus score has a value ranging from zero (not propicious for spermatozoïds progression: maximal protection) to 12 (propicious for spermatozoïds progresion: minimal protection). The **primary cut-off** for full cervical mucus protection is a cervical mucus score of 4. There is therefore a good conception protection by cervical mucus if the cervical mucus score is ≤ 4.

The **responses** of interest are:

1. The full protection by cervical mucus regardless of the use of norgestrel 75 mcg if the score was and remained at 4 or below at $V2_{R-1}$, $V2_R$, $V2_{R+1}$, $V3_{R-1}$, $V3_R$ and $V3_{R+1}$. The full protection by the mucus lasted for 2 x 3 days. The proportion of patients meeting this criterion is $p_{FP.}$
2. The absence of risk increase further to delayed intake: The score was ≤ 4 the day before infringement and remained at 4 or less the day of infringement and the day after the delayed pill intake. The protection by the mucus lasted at least up to the day after infringement. The proportion of patients fulfilling this criterion is p_{delay}.
3. The absence of risk increase further to missed pill: The score was ≤ 4 the day before infringement and remained at 4 or less the day of infringement and the day after missed pill. The protection by the mucus lasted at least up to the day after infringement.The proportion of patients fulfilling this criterion is p_{missed}.
4. The absence of risk increase due to infringement regardless of the type: The score was ≤ 4 the day before infringement and remained at 4 or less the day of infringement and the day after infringement. The protection by the mucus lasted at least up to the day after infringement. The proportion of patients fulfilling this criterion is p_{breach}.
5. The transient risk increase further to delayed intake: The score was ≤ 4 the day before infringement, exceeded 4 the day of infringement but came back to 4 or less the day after the delayed pill intake. The protection by the mucus was interrupted the day of infringement. The proportion of patients fulfilling this criterion is $p_{delay,trasient\ risk}$.
6. The transient risk increase further to missed pill: The score was ≤ 4 the day before infringement, exceeded 4 the day of infringement but came back to 4 or less the day after the delayed pill intake, The protection by the mucus was interrupted the day of infringement. The proportion of patients fulfilling this criterion is $p_{missed,transient\ risk}$.
7. The prolonged risk increase further to delayed intake: The score was ≤ 4 the day before infringement, exceeded 4 the day of infringement and the day after the delayed pill intake. The protection by the mucus was interrupted the day of infringement and at least up to the day after. The proportion of patients fulfilling this criterion is $p_{delay,\ prolonged\ risk,}$.

8. The prolonged risk increase further to missed pill: The score was ≤ 4 the day before infringement, exceeded 4 the day of infringement and the day after the missed pill. The protection by the mucus was interrupted the day of infringement and at least up to the day after. The proportion of patients fulfilling this criterion is $p_{missed, prolonged risk, }$.
9. Other definitions can be added in the SAP to get a detailed picture of the effect of infringement and its duration.

Comparison between the missed pill and the delayed pill can easily be performed and tested through a stratified McNemar test (stratification on the site, CMH option in SAS). The SAS glimmix procedure for repeated measures was not retained for decision making test because convergence issues in fitting the model are too frequent. The first null hypothesis is H_0: Proportion of protected women at baseline (R-1) is equal to the proportion of protected women after schedule infringement and more specifically at Day R (27 hours and 30 hours post treatment). The second null hypothesis is the equality of proportions at baseline (R-1) and at Day R+1 (48 hours post treatment).

19.3.3 Secondary analyses

Cervical mucus protection in each type of treatment period

The aim of this secondary objective is to assess the level of cervical mucus protection during reported perfect use, during a treatment period with a delayed pill intake of 6 hours and during a treatment period with a missed pill of norgestrel 75 mcg.

The time frames are:

- reported perfect use: all the visits of the period 1 before a postovulatory image is obtained
- delayed pill intake: all the visits of the period 2 for Arm A and all the visits of period 3 for Arm B before a postovulatory image is obtained
- missed pill: all the visits of the period 2 for Arm B and all the visits of period 3 for Arm A before a postovulatory image is obtained.

The assessment criterion is the cervical mucus score. The cut off is a cervical mucus score of 4. There is conception protection by cervical mucus if the cervical mucus score is ≤ 4.

The endpoints are:

- The percentage of subjects with cervical mucus score ≤ 4, between 5 and 8, and ≥ 9 in reported perfect use period
- The percentage of subjects with cervical mucus score ≤ 4, between 5 and 8, and ≥ 9 in delayed pill intake periods
- The percentage of subjects with cervical mucus score ≤ 4, between 5 and 8, and ≥ 9 in missed pill periods
- The percentage of subjects with cervical mucus score ≤ 4 in all periods

Other analyses based on other endpoint of interest can be in the SAP.

Ovarian Activity in each type of treatment period

The aim of this secondary objective is to describe the distribution of the ovarian status among the subjects, during reported perfect use, during a treatment period with a delayed pill intake of 6 hours and during a treatment period with a missed pill of norgestrel 75 mcg.

The time frames are:

- reported perfect use: all the visits of the period 1
- delayed pill intake: all the visits of the period 2 for Arm A and all the visits of period 3 for Arm B

- missed pill: all the visits of the period 2 for Arm B and all the visits of period 3 for Arm A

The assessment criterion is the OS as defined in Appendix 3[1].
The OS are ranked depending on the risk of conception: $OS_{nlp} > OS_{alp} > OS_a > OS_q$.
For each treatment period the most risky OS will be considered.

The endpoints are:

- The percentage of subjects with OSq, OSa, OSa/OSalp and OSnlp in reported perfect use period
- The percentage of subjects with OSq, OSa, OSa/OSalp and OSnlp in delayed pill intake periods
- The percentage of subjects with OSq, OSa, OSa/OSalp and OSnlp in missed pill periods
- The percentage of subjects with OSnlp in all periods

19.3.4 Other secondary analyses

Protection from conception based on cervical mucus score and OS (binary and ternary analyses))

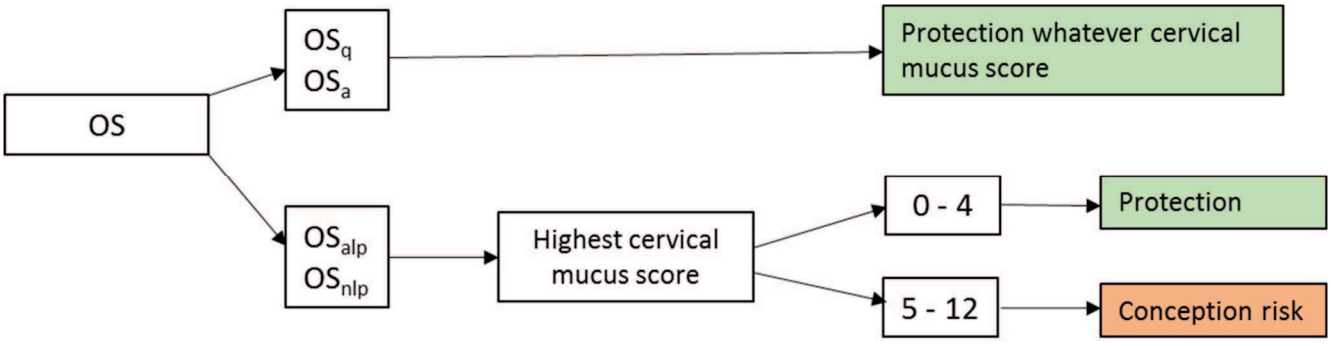
Based on cervical mucus score and OS only, the aim of these exploratory analyses are to assess if a combination of cervical mucus score and ovarian status can be considered as a measure of protection from conception or not and the level of protection, during reported perfect use of norgestrel 75 mcg and after a delayed intake/missed pill.

For both analyses, the assessment criteria will be the OS and the highest cervical mucus score during the 3 visits before a postovulatory image is obtained including the visit when the postovulatory image is obtained[2].
For the OS, the risk of conception is ranked depending on the OS: $OS_{nlp} > OS_{alp} > OS_a > OS_q$ and for each treatment period the most risky OS will be considered.

<u>Binary analysis</u>

The aims of this analysis is to determine whether a subject is protected on not, according to the algorithm presented in Figure 4

Figure 4 Conception protection based on OS and cervical mucus score (binary analysis)



The endpoints will be, for each treatment period, the distribution of subjects:

[1] The ovarian status are:
OSq = quiescence defined as a OAS ≤ 3
OSa = ovarian activity defined as a OAS = 4 or 5
OSalp = ovulation with abnormal luteal phase defined as a OAS = 6 at only one visit
OSnlp = ovulation with normal luteal phase as a OAS = 6 at two consecutive visits or OAS = 7

[2] The number of visits considered for the evaluation of the mucus score may be modified by the adjudication committee (see section 20).

- considered as protected: OS_q or OS_a OR cervical mucus score ≤4
- considered as at risk of conception: OS_{alp} or OS_{nlp} AND cervical mucus score ≥ 5

Ternary analysis

The aims of this analysis is to determine the level of protection for a subject, according to Table 4 presented below.

Table 4 Conception protection based on OS and cervical mucus score

		Ovarian Status			
		OS_q	OS_a	OS_{alp}	OS_{nlp}
Highest Mucus score	0-4	maximum	maximum	maximum	maximum
	5-8	maximum	maximum	medium	medium
	9-12	maximum	maximum	medium	minimum

The endpoints will be, for each treatment period, the distribution of subjects with:

- Minimum protection or unlikely to be protected: OS_{nlp} and cervical mucus score ≥ 9
- Medium protection or likely to be protected: OS_{nlp} and cervical mucus score comprised between 5 and 8 or OS_{alp} and cervical mucus score ≥ 5
- Maximum protection or highly likely to be protected: OS_q or OS_a or a cervical mucus score ≤ 4

Pharmacokinetics of LNG and PK/PD analysis

The PK profile of LNG after administration of norgestrel 75 mcg will be assessed at different times during the study.

The PK profile of LNG will first be assessed at Day 1 after the first administration of norgestrel 75 mcg in fasted conditions.

All the subjects will be sampled at different time points after administration as presented in the table below:

Table 5 PK sampling schedule at Day 1

	Sampling times							
	predose	1h	2h	4h	6h	8h	12h	24h
Odd #		X		X		X		X
Even #	X		X		X		X	

During the first visit of the 3rd week of treatment, the pharmacokinetics of LNG at steady state will be assessed.
All the subjects will be sampled at different times points. If the visit is in the morning, they will be sampled predose and between 0.5h and 2h post administration. If the visit is in the afternoon, they will be sampled between 5h and 9h post administration.
The plasma concentration(s) for each subject will be reported with the nominal time of sampling.

The pharmacokinetics of LNG will also be assessed during the DMP period. The sampling schedule will depend on the arm the subjects had been randomized in (see Table 6 below).

Table 6 PK sampling schedule during the DMP period

	DMP 2						DMP 3					
	$V2_{R-1}$	$V2_R$				$V2_{R+1}$	$V3_{R-1}$	$V3_R$				$V3_{R+1}$
	$T2_{R-1}$ + 8h	$T2_{R-1}$ + 3h	$T2_{R-1}$ + 5.5h	$T2_{R-1}$ + 6h	$T2_{R-1}$ + 7.5h	$T2_{R-1}$ - 0.5h	$T3_{R-1}$ + 8h	$T3_{R-1}$ + 3h	$T3_{R-1}$ + 5.5h	$T3_{R-1}$ + 6h	$T3_{R-1}$ + 7.5h	$T3_{R-1}$ - 0.5h
Arm A	X	X	X		X	X	X			X		X
Arm B	X			X		X	X	X	X		X	X

The mean plasma concentration for each time point will be calculated:

- $V2/3_{R-1}$: $C2/3_{R-1,8h}$ (Arm A + Arm B)
- $V2/3_R$: $C2_{R-1,27h}$ (Arm A), $C3_{R-1,27h}$ (Arm B), $C2_{R-1,29.5h}$ (Arm A), $C3_{R-1,29.5h}$ (Arm B), $C2_{R-1,30h}$ (Arm B), $C3_{R-1,30h}$ (Arm A), $C2_{R,1.5h}$ (Arm A), $C3_{R,1.5h}$ (Arm B)
- $V2/3_{R+1}$: $C2/3_{R+1,-0.5h}$ (Arm A + Arm B)

The concentration of LNG will also be determined in all subjects during the 1st visit of study week 5 ($V2_1$) and 9 ($V3_1$). The sample will be drawn within 30 minutes of the mucus analysis.
The concentrations will be reported as $C2_1$ and $C3_1$.

A population pharmacokinetic model will be developed using a dedicated software for nonlinear mixel model. The model will be developed using a sparse sampling scheme. This model will be used to estimate population PK parameters such as clearance and volume of distribution as well as derived PK parameters (C_{24h}, C_{max} and AUC). Complete details of all PK analyses and methods will be provided in a separate analysis plan finalized before the database lock (DBL).

A PK/PD analysis, describing the relationships between pharmacokinetic and pharmacodynamic data will be performed; details will be provided in a separate analysis plan finalized before database lock.

19.3.5 Presentation of pharmacodynamic data

PD effect will be evaluated by cervical mucus analysis and ovarian activity during the three treatment periods.

- Cervical mucus score: the time course of the mucus score will be presented for each period graphically along with summary statistics.
- TVU largest follicle diameter measurement: The time course of the diameter will be presented graphically along with summary statistics. The time series will be truncated after a postovulatory image has been obtained
- P4, E2, FSH and LH measurement. The time course of each parameter will be presented for each period graphically along with summary statistics.

19.4 Safety analysis

Safety data will be collected by querying subjects about AEs and vaginal bleeding patterns and by performing safety laboratory parameters at screening and the EOS visit. Subjects will report bleeding data and drug intake using a e-diary every day.

Evaluation of the bleeding patterns will be based on the subjects responses in the e-diary and validated during clinic visits. Vaginal bleeding in between expected menstrual periods will be categorised as breakthrough bleeding and spotting based on the bleeding intensity recorded in the e-diary. Amenorrhea or absence of bleeding for two menstrual cycles or more than 60 days in subjects who took the medication as prescribed will also be noted.

Safety will be evaluated by incidence of premature discontinuation and AEs. Summaries will be provided for all AEs reported, and separately for AEs leading to study discontinuation. Serious Adverse Events (SAEs) will be listed separately and described by narrative.

19.4.1 Incidence of Adverse Events

The number (percentage) of subjects with at least one AE will be presented in a frequency table. Summaries will also be presented by relationship to study medication ("relationship" is defined as not related, unlikely related, possibly, or definitely related to study medication) and intensity of AE).

19.4.2 Discontinuation Due to Adverse Events

Subjects who are discontinued due to one or more AEs will be listed, and specific information about the AEs leading to discontinuation will become part of the final clinical study report.

19.4.3 Serious Adverse Events

Subjects with SAEs will be listed and the following variables included: SAE description (as reported by investigator), MedDRA "lowest level" term, MedDRA "preferred" term, MedDRA system-organ class (based on the "included" term), start and stop dates relative to the admission, maximum intensity, relationship to the investigational product (according to the investigator), action taken, and outcome. Subject SAE narratives will be part of the final clinical study report.

19.4.4 Deaths

Subjects who died during the study will be listed and the following variables will be included: main reason(s) for death (as reported by the investigator), diagnosis of the SAE contributing to the death, date of death relative to the first day of product use, and relationship to study drug according to the Investigator. Subject SAE narratives, including information regarding the death, will be part of the final clinical study report.

20. ADJUDICATION COMMITTEE

An adjudication committee will be implemented for the study. Experts in the cervical mucus assessment and ovarian activity who are not affiliated with either of the study sites will comprise the committee. The committee will gather at study end, after the data review meeting.

Its responsibilities will be to review data regarding IMP intake and TVU, hormonal and mucus measurements, to make decisions for each subject on compliance (for the analysis of the data), and reach agreement on ovarian activity score, ovarian status and cervical mucus score. They will also define the set of evaluable cycles. The adjudication committee will work in a blinded manner (see section 19.1).

A separate charter will be drawn to provide the details.

21. ETHICAL CONSIDERATIONS AND LEGAL ASPECTS

21.1 Good Clinical Practice

The study will be conducted in accordance with legal and regulatory requirements including FDA's applicable Code of Federal Regulations, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996 incl rev6), and the Declaration of Helsinki (World Medical Association 2013).
In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonization (ICH) guideline on GCP, and applicable local regulatory requirements and laws.

This study will be listed on the website ClinicalTrials.gov by HRA Pharma, before the first subject is enrolled.

21.2 Study without direct benefit to individual subjects

No direct benefit to individual subjects is expected from this study. Because participation is on a voluntary basis, subjects will be remunerated for their time spent in the study and travel expenses at the end of the study and on a prorated basis in the event of early discontinuation. Details of remuneration will be listed in the participant's information sheet approved by the IRB.

21.3 Delegation of investigator responsibilities

The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the study medication, and their trial-related duties and functions.
The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

21.4 Interactions with Institutional Review Boards

This protocol and any protocol amendments, together with the required documents will be submitted by the sponsor to the responsible IRB according to the applicable requirements at the site. The study will commence at each participating site only after their IRB has granted full approval. Investigators/institutions will permit trial related monitoring, audits, IRB review and regulatory inspection(s) providing direct access to source data/documents.

Study medication can only be supplied to the investigator after documentation on all ethical and legal requirements for starting the study has been received by the sponsor. This documentation must also include a list of the members of the IRB and their occupation and qualifications. If the IRB will not disclose the names of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. Formal approval by the IRB should preferably mention the study title, study code, study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member.

Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB and, if applicable, the authorities must be informed of all subsequent protocol amendments, in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The investigator must keep a record of all communication with the IRB and, if applicable, between a coordinating investigator and the IRB. This also applies to any communication between the investigator (or coordinating investigator, if applicable) and the authorities.

21.5 Ongoing information for IRB

The site will notify the sponsor at the time of IRB submission.
If required by legislation or the independent IRB, the sponsor must verify that the following is submitted to the IRB:

- Information on serious or unexpected AEs as soon as possible
- Periodic reports on the progress of the study

21.6 Informed Consent

Under informed consent, the subject shall understand that she is authorizing access to medical records as required for monitors, auditors, IRBs and regulatory authorities. Subjects that agree to participate in the study must sign the informed consent form (ICF) prior to study-specific procedures. The ICF will be HIPAA compliant.

It is the investigator's responsibility to assure that each subject is provided an explanation of the details contained in the informed consent statement and other locally required documents prior to the individual signing the ICF certifying voluntary participation in the trial and prior to study participation.
The document must be in a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician. If not required by local law, another appropriately trained and qualified healthcare professional, other than a physician, is acceptable.

After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions.

The subjects will be informed of their right to privacy and the fact that personal information will be treated as strictly confidential and will not be publicly available in accordance with HIPAA regulations. They will also be informed that HRA Pharma and the FDA have the right to inspect and possibly photocopy their medical records to verify the accuracy and completeness of the clinical trial results.

Prior to study participation, all study candidates will:

- Be informed of the nature and purpose of the study.
- Be given an explanation of the procedures to be followed in the study.
- Be given a description of any attendant discomforts and risks reasonably to be expected from the study, as well as from the study product.
- Be given an opportunity to ask any questions concerning the study.
- Be instructed that consent to participate in the study may be withdrawn at any time; and that the participant may discontinue participation in the study without prejudice.
- Be given a copy of an ICF.
- Be given the opportunity to decide to consent or not to consent to the study without coercion.
- Be informed of alternative contraceptive methods available.
- Be given information for whom to contact if there are questions about the research, participant rights, or to report research-related injury.

21.7 Conflicts of Interest

Investigators will be affiliated with their study sites and report any conflicts of interest in accordance with their employer. They will receive support for this clinical study but will not profit from results, either positive or negative, with regard to the product being evaluated. HRA, the study sponsor, could profit from the successful development of this product.

21.8 Confidentiality

The information on individual subjects arising from this study is to be considered confidential and transmitted to the sponsor only in a form that will not permit identification of the individual. The information obtained from the subjects that can be identified with the subject will remain confidential within the research team. Regulatory and sponsoring agencies may request access to the study records and related medical records of each participating subject; the subject's identity will remain confidential to the extent permitted by the applicable laws and regulations. The results of the research will be released to public agencies including regulatory agencies, clinical investigators, and research organizations without reference to items identifiable to a particular subject. The results will be published such that the identity of the subjects will not be disclosed and cannot be ascertained. National and international agencies and sponsoring agencies may request access to the medical records of each participating subject, and if requested, the subject's identity will remain confidential. All records will be kept in a secure storage area with limited access.

21.9 Premature closure of the study

The sponsor may decide to close this study at any time. As far as possible, this should occur after consultation with the investigator. The IRB must be informed.
Should the study be closed prematurely, all study materials (study medication, lab equipment, etc.) must be returned to the sponsor, as if the study had been completed.

21.10 Liability and insurance

The sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the study protocol as well as with applicable law and professional standards.

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APPENDICES

Appendix 1: List of Exclusionary Medications

Interfere with the metabolism of hormone contraceptives:	
Isotretinoin	Modafinil
barbiturates	Oxcarbazepine
Primidone	Griseofulvin
Topiramate	Primidone
Phenylbutazone	anticonvulsants
Ritonavir	
Certain antibiotics can interfere with metabolism of hormone contraceptives: **Please request an approval from HRA for specific antibiotics**	
Liver enzyme inducers:	
Carbamazepine	Rifampin
Lansoprazole	Rifabutin
phenobarbital	Herbal preparations containing St. John's Wort (hypericum perforatum)
Phenytoin	Efavirenz
Bosentan	

FDA List of CYP3A4 Inhibitors	
STRONG:	
Boceprevir	Clarithromycin
Conivaptan	Grapefruit juice
Indinavir	Itraconazole
Ketoconazole	Lopinavir/Ritonavir
Mibefradil	Nefazodone
Nelfinavir	Posaconazole
Ritonavir	Saquinavir
Telaprevir	Telithromycin
Voriconazole	
MODERATE:	
Amprenavir	Aprepitant
Atazanavir	Ciprofloxacin
Darunavir/Ritonavir	Diltiazem
Erythromycin	Fluconazole
Fosamprenavir	Grapefruit juice
Imatinib	Verapamil

Drugs with significant evidence of fetal risks should not be allowed in our study.

The following list includes some of the common drugs that contraindicate study participation. Please note that this **list is NOT exhaustive**; drugs not on the list should be researched by the study center staff.

- Clarithromycin (Biaxin)
- Most anticonvulsant drugs including: divalproex sodium (Depakote), primidone (Mysoline), carbamazepine (Tegretol, Carbatrol), gabapentin (Neurontin), phenytoin (Dilantin), benzodiazepines (see below), etc.
- Benzodiazepines, including: diazepam (Valium), alprazolam (Xanax), clonazepam (Klonopin), clorazepate (Tranxene), temazepam (Restoril), triazolam (Halcion), etc.

- Warfarin (Coumadin)
- Lithium
- Isotretinoin (Accutane)
- Ribavirin
- Measles, mumps, varicella, and rubella vaccination (within 3 months after vaccination)
- High dose vitamin A (topical Retin-A is OK)
- Thalidomide
- Diethylstilbestrol (DES)
- Misoprostol (Cytotec)
- Lipid-lowering statin drugs, including: atorvastatin (Lipitor), lovastatin (Mevacor), simvastatin (Zocar), Pravastatin (Provachol), etc.
- Azathioprine (Imuran)
- ACE inhibitors including benazepril (Lotensin), captopril (Capoten), Enalapril, Fosinopril (Monopril), Lisinopril (Zestril; Prinivil), Moexipril (Univasc), Perindopril (Aceon), Quinapril (Accupril), Ramipril (Altace), and Trandolapril (Mavik)
- Paroxetine (Paxil)
- Tetracyclines (Emtet, Panmycin, Sumycin, Tetra 250)
- All chemotherapeutic agents.

Appendix 2: Cervical mucus sampling and scoring

Cervical mucus will be sampled and assessed according to the methodology described in the WHO Laboratory Manual for the Examination and Processing of Human Semen. Fifth edition 2010 and provided in the next pages.

Volume will not be assessed.

Viscosity is scored as follows:
0 = thick, highly viscous, premenstrual mucus
1 = mucus of intermediate viscosity
2 = mildly viscous mucus
3 = watery, minimally viscous, mid-cycle (preovulatory) mucus

Ferning is scored as follows:
0 = no crystallization
1 = atypical fern formation
2 = primary and secondary stem ferning
3 = tertiary and quaternary stem ferning

Spinnbarkeit is scored as follows:
0 = <1 cm
1 = 1–4 cm
2 = 5–8 cm
3 = 9 cm or more

The rank scores for cells are:
0 = >20 cells per HPF or >1000 cells per µL
1 = 11–20 cells per HPF or 501–1000 cells per µL
2 = 1–10 cells per HPF or 1–500 cells per µL
3 = 0 cells

APPENDIX 5 Cervical mucus

A5.1 Introduction

Spermatozoa within cervical mucus are suspended in a fluid medium. The interaction of spermatozoa with the secretions of the female reproductive tract is of critical importance for their survival and functioning. There is at present no practical method of evaluating the effects of human uterine and tubal fluids on spermatozoa. However, cervical mucus is readily available for sampling and study.

The epithelium of the human cervix comprises different types of secretory cells, and the nature and abundance of secretory granules vary in different parts of the cervix. Secretions from these cells contribute to the cervical mucus. Ovarian hormones regulate the secretion of cervical mucus: 17β-estradiol stimulates the production of copious amounts of watery mucus and progesterone inhibits the secretory activity of the epithelial cells. The amount of cervical mucus secreted shows cyclical variations. In women of reproductive age with a normal menstrual cycle, the daily mucus production varies from 500μl at mid-cycle to less than 100μl at other times. Small amounts of endometrial, tubal and possibly follicular fluids may also contribute to the cervical mucus pool. In addition, leukocytes and cellular debris from the uterine and cervical epithelia are present.

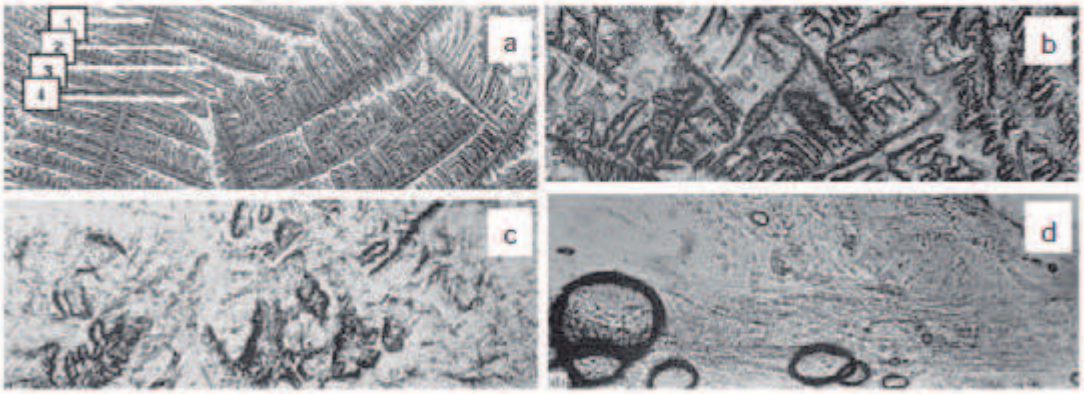
Cervical mucus is a heterogeneous secretion containing over 90% water. It exhibits a number of rheological properties:

- Viscosity (consistency) is influenced by the molecular arrangement and by the protein and ionic concentrations of the cervical mucus. Mucus varies during the cycle from highly viscous (often cellular) just before menstruation to watery at mid-cycle just before ovulation. By the time ovulation is completed, the viscosity of the mucus has already begun to increase again.
- Spinnbarkeit is the term used to describe the fibrosity, the "threadability", or the elasticity characteristics of cervical mucus.
- Ferning refers to the degree and pattern of crystallization observed when cervical mucus is dried on a glass surface (see Fig. A5.1).

Cervical mucus is a hydrogel comprising a high-viscosity component and a low-viscosity component made up of electrolytes, organic compounds and soluble proteins. The high-viscosity component is a macromolecular network of mucin, which influences the rheological properties of the mucus. Cervical mucin is a fibrillar system consisting of subunits made of a peptide core and oligosaccharide side-chains. Cyclical alteration in the constituents of cervical mucus influences the ability of spermatozoa to penetrate and survive. Spermatozoa can penetrate human cervical mucus from approximately the ninth day of a normal 28-day cycle; penetrability increases gradually to reach a peak just before ovulation. Sperm penetration then begins to diminish before large changes in mucus properties are apparent. Individual variations in timing and degree of sperm penetrability are common. Motile spermatozoa may be guided by strands of cervical mucus to the cervical crypts, where they may be retained and released slowly into the uterus and Fallopian tubes.

Fig. A5.1 Examples of fern formation in cervical mucus air-dried on a glass slide

(a) Ferning: 1, primary stem; 2, secondary stem; 3, tertiary stem; 4, quaternary stem (score 3); (b) mainly primary and secondary stems (score 2) but some tertiary stems also present; (c) atypical fern crystallization (score 1); (d) no crystallization (score 0). The round structures are air bubbles. See section A5.3.3 for explanation of scoring.



Comment: It is important to evaluate sperm–cervical mucus interaction as part of any complete investigation of infertility. A finding of abnormal sperm–cervical mucus interaction may be an indication for artificial insemination or other forms of assisted reproduction.

A5.2 Collection and preservation of cervical mucus

A5.2.1 Collection procedure

Expose the cervix with a speculum and gently wipe the external os with a cotton swab to remove the external pool of vaginal contaminants. Remove the exocervical mucus with the swab or with forceps. Collect cervical mucus from the endocervical canal by aspiration with a mucus syringe, tuberculin syringe (without needle), pipette or polyethylene tube. The manner in which suction pressure is applied to the collection device should be standardized. Advance the tip of the device approximately 1 cm into the cervical canal before applying suction. Then maintain suction as the device is withdrawn. Just before the device is completely withdrawn from the external cervical os, release the suction pressure. It is then advisable to clamp the catheter to protect against accumulation of air bubbles or vaginal material in the collected mucus when the device is removed from the cervical canal. Whenever possible, the quality of the mucus should be evaluated immediately on collection. If this is not possible, the mucus should be preserved (see Section A5.2.2) until it can be tested.

When cervical mucus is to be collected other than at mid-cycle, its production can be increased by the administration of 20–80 μg of ethinyl estradiol each day for 7–10 days before collection. This procedure will produce a more hydrated, and therefore less viscous, mucus secretion (Eggert-Kruse et al., 1989). While this approach may be useful in assessing sperm–mucus interaction in vitro, it will not necessarily reflect the in-vivo situation for the couple when hormones are not administered.

A5.2.2 Storage and preservation

Mucus can be preserved either in the original collection device or in small test-tubes sealed with a stopper or with self-sealing laboratory film to avoid dehydration. Care should be taken to minimize the air space in the storage container. The samples should be preserved in a refrigerator at 4 °C for up to 5 days. If possible, mucus specimens should be used within 2 days of collection; the interval between collection and use should always be noted. Rheological and sperm penetration tests should not be performed on mucus specimens that have been frozen and thawed.

A5.3 Evaluation of cervical mucus

Evaluation of the properties of cervical mucus includes assessment of spinnbarkeit, ferning (crystallization), viscosity and pH. Appendix 6 contains a sample form for scoring and recording these cervical mucus properties according to the system devised by Moghissi (1976), based on an original proposal by Insler et al. (1972). The score is derived from the volume of cervical mucus collected (see Section A5.3.1) and the four variables (see Sections A5.3.2 to A5.3.5) describing its characteristics and appearance. The pH of the mucus is not included in the total cervical mucus score, but should be measured as an important determinant of sperm–mucus interaction (Eggert-Kruse et al., 1993). The maximum score is 15. A score greater than 10 is usually indicative of good cervical mucus favouring sperm penetration; a score of less than 10 may mean that the cervical mucus is unfavourable to sperm penetration.

A5.3.1 Volume

The viscosity of mucus makes accurate measurement of volume difficult. It can be estimated from the length of the mucus within catheter tubing of known diameter (see Box A5.1).

Box A5.1 Determining the volume of mucus collected

The volume of a mucus preparation (V, μl = mm^3) is obtained by multiplying the cross-sectional area of the tubing (A, mm^2) by the length (L, mm) containing mucus: $V = A \times L$. The cross-sectional area $A = \pi r^2$, where π is approximately 3.142 and r is the radius of the tubing. Thus a 10 cm (100 mm) length of mucus in 2 mm diameter tubing ($A = 3.142 \times 1 \times 1 = 3.142\ mm^2$) has a volume of $A \times L = 3.142 \times 100 = 314\ mm^3$ = 314 μl or 0.31 ml.

Volume is scored as follows:

0 = 0 ml
1 = 0.01–0.10 ml or approximately 0.1 ml
2 = 0.11–0.29 ml or approximtely 0.2 ml
3 = >0.3 ml or approximately 0.3 ml or more

A5.3.2 Viscosity (consistency)

The viscosity of cervical mucus is the most important factor influencing sperm penetration. There is little resistance to sperm migration through the cervical mucus in mid-cycle, but viscous mucus—such as that observed during the luteal phase—forms a more formidable barrier.

Viscosity is scored as follows:

0 = thick, highly viscous, premenstrual mucus
1 = mucus of intermediate viscosity
2 = mildly viscous mucus
3 = watery, minimally viscous, mid-cycle (preovulatory) mucus

A5.3.3 Ferning

Ferning (see Fig. A5.1) is scored by examination of cervical mucus that has been air-dried on glass microscope slides. Such preparations reveal various patterns of crystallization, which may have a fern-like appearance. Depending on the composition of the mucus, the "ferns" may have only a primary stem, or the stem may branch once, twice or three times to produce secondary, tertiary and quaternary stems. Several fields around the preparation should be observed, and the score expressed as the highest degree of ferning that is typical of the specimen.

Fern types can be very variable, depending on, for example, the thickness of the preparation and the number of cells present. A preparation may display more than one stage of ferning: sometimes all stages can be found in one preparation.

Ferning is scored as follows:

0 = no crystallization
1 = atypical fern formation
2 = primary and secondary stem ferning
3 = tertiary and quaternary stem ferning

A5.3.4 Spinnbarkeit

Place a drop of cervical mucus on a microscope slide and touch it with a coverslip or a second slide held crosswise; then gently lift the coverslip or second slide. Estimate the length of the cervical mucus thread stretched between the two surfaces.

Spinnbarkeit is scored as follows:

0 = <1 cm
1 = 1–4 cm
2 = 5–8 cm
3 = 9 cm or more

A5.3.5 Cellularity

It is recommended that all cell counts be expressed in cells per μl. An estimate of the number of leukocytes and other cells in the cervical mucus is traditionally based on the number counted per high-power microscope field (HPF) (see Box A5.2).

Box A5.2 Volume observed per high-power field in a 100-μm-deep mucus preparation

The volume of mucus observed in each microscope field depends on the area of the field (πr^2, where π is approximately 3.142 and r is the radius of the microscopic field) and the depth of the chamber (here 100 μm). The diameter of the microscope field can be measured with a stage micrometer or can be estimated by dividing the diameter of the aperture of the ocular lens by the magnification of the objective lens.

With a ×40 objective and a ×10 ocular of aperture 20 mm, the microscope field has a diameter of approximately 500 μm (20 mm / 40). In this case, r = 250 μm, r^2 = 62 500 μm^2, πr^2 = 196 375 μm^2 and the volume is 19 637 500 μm^3 or about 20 nl.

Thus, a count of 10 cells per HPF is approximately equivalent to 10 cells per 20 nl, or 500 cells per μl. As the number of cells counted is low, the sampling error is high; a replicate count of 10 has a sampling error of 22% (see Table 2.2), so the value could lie anywhere between 280 and 720 cells per μl.

The rank scores for cells are:

0 = >20 cells per HPF or >1000 cells per μl
1 = 11–20 cells per HPF or 501–1000 cells per μl
2 = 1–10 cells per HPF or 1–500 cells per μl
3 = 0 cells

A5.3.6 pH

The pH of cervical mucus from the endocervical canal should be measured with pH paper, range 6.0–10.0, in situ or immediately following collection. If the pH is measured in situ, care should be taken to avoid touching the exocervical mucus, which always has a pH lower (more acidic) than that of mucus in the endocervical canal. Care should also be taken to avoid contamination with secretions of the vagina, which have a low pH.

Spermatozoa are susceptible to changes in pH of the cervical mucus. Acid mucus immobilizes spermatozoa, whereas alkaline mucus may enhance motility. Exces-

250 APPENDIX 5 Cervical mucus

sive alkalinity of the cervical mucus (pH greater than 8.5), however, may adversely affect the viability of spermatozoa. The optimum pH value for sperm migration and survival in the cervical mucus is between 7.0 and 8.5, which is the normal pH range of mid-cycle cervical mucus. Although a pH value between 6.0 and 7.0 may be compatible with sperm penetration, motility is often impaired below pH 6.5 and sperm–cervical mucus interaction tests are often not performed if the pH of mucus is below 7.0.

In some cases cervical mucus may be substantially more acidic. This can be due to abnormal secretions, the presence of a bacterial infection, or contamination with vaginal fluid.

References

Eggert-Kruse W et al. (1989). Prognostic value of in-vitro sperm penetration into hormonally standardized human cervical mucus. Fertility and Sterility, 51:317–323.

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Insler V et al. (1972). The cervical score. A simple semiquantitative method for monitoring of the menstrual cycle. International Journal of Gynaecology and Obstetrics, 10:223–228.

Moghissi KS (1976) Postcoital test: physiological basis, technique and interpretation. Fertility and Sterility, 27:117–129.

Appendix 3: Determination of Ovarian Activity Score (OAS) and Ovarian Status (OS)

Table 7 Determination of Ovarian Status

Ovarian Activity Score	Activity	Size FLS / sonographic image	Estradiol (nmol/L)	Progesterone (nmol/L)	Ovarian Status[1]
1	**No activity**	≤ 10 mm	Independent of E2 level	≤ 5	OSq
2	**Potential activity**	> 10 and ≤ 13 mm	Independent of E2 level	≤ 5	OSq
3	**Non-active follicle like structure (FLS)**	> 13 mm	≤0.1[2]	≤ 5	OSq
4	**Active follicle like structure (FLS)**	> 13 mm	>0.1[2]	≤ 5	OSa
5	**Postovulatory, low P level**	Postovulatory image[2]	>0.1[2]	≤ 10	OSa
6	**Postovulatory, intermediate P level**	Postovulatory image[3]	> 0.1[2]	> 10 and ≤ 30	Only 1 P > 10 and ≤ 30 → OSalp 2 consecutive P > 10 and ≤ 30 → OSnlp
7	**Postovulatory, high P level**	Postovulatory image[3]	> 0.1[2]	> 30	OSnlp

[1] The ovarian status are:

- OSq = quiescence defined as a OAS ≤ 3
- OSa = ovarian activity defined as a OAS = 4 or 5
- OSalp = ovulation with abnormal luteal phase defined as OAS = 6 at only one visit
- OSnlp = ovulation with normal luteal phase as a OAS = 6 at two consecutive visits or OAS = 7

[2]~27.24 pg/mL

[3] A postovulatory image will be defined as follows:

- Image observed after abrupt disappearance of FLS OR
- Image observed after reduction in size of the leading follicle > 4 mm at two consecutive visits OR
- Haemorrhagic and cystic corpus luteum (FLS at least as large as the leading follicle before ovulation)

Appendix 4: Helsinki Declaration

Ethical Principles for Medical Research Involving Human Subjects Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

GENERAL PRINCIPLES

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician

or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

RISKS, BURDENS AND BENEFITS

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

VULNERABLE GROUPS AND INDIVIDUALS

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs and priorities of this group and the research cannot b carried out in a non-vulnerable group. In

addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

RESEARCH ETHICS COMMITTEES

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any SAEs. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

PRIVACY AND CONFIDENTIALITY

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

INFORMED CONSENT

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent,

preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect with the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impractical to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

USE OF PLACEBO

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention(s), except in the following circumstances:

- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable;

Or

- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

- And the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

POST-TRIAL PROVISIONS

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 5: Serious Adverse Event Report Form

Appendix 6: Pregnancy Collection Form