Protocol 151042-002
NCT03585712

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

Statistical Analysis Plan
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STATISTICAL ANALYSIS PLAN APPROVAL

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
BMI	Body Mass Index
BSL	Baseline
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
FASM	Full Analysis Set – Cervical Mucus
FASO	Full Analysis Set – Ovarian Activity
FASC	Full Analysis Set – Overall Conception Protection
FSH	Follicle-Stimulating Hormone
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
ITT	Intent-To-Treat
LC-MS/MS	Liquid Chromatography with double Mass Spectrometry
LH	Luteinizing Hormone
LNG	Levonorgestrel
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
PD	Pharmacodynamics
PK	Pharmacokinetic(s)
POP	Progestin Only Pill
PP	Per-Protocol
SAF	Safety
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
$T2_{R-1}$/$T3_{R-1}$	Time of treatment intake on the day before delayed intake/missed pill per randomization arm, in treatment period 2/3
TMS	Time of Mucus Scoring
TVUS	TransVaginal Ultrasound
WHO	World Health Organization

1.0 INTRODUCTION

This statistical analysis plan (SAP) was developed after review of the 151042-002 study protocol version 1.0 26FEB2018 and case report forms (e-CRFs) version 2.0 06JUN2018, but before any analysis of the data had begun. Detailed information is given to aid in the production of the statistical output and the statistical section of the Final Study Report. This document gives a summary of the protocol and describes the populations that will be analyzed. All subject characteristics and efficacy and safety parameters that will be evaluated, along with the specific statistical methods, are described.

2.0 PROTOCOL SUMMARY

2.1 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.

Opill® (norgestrel (NG) 75 mcg) is a 2nd generation synthetic progestin-only oral contraceptive 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).

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 the light of limited PK and PD data on NG and POPs in general that supports the clinical guidance of taking it every day 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.

2.2 Objectives

The primary objectives of the study are:

- 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[1] of norgestrel 75 mcg
- to estimate the duration of the protective effect of cervical mucus after last pill intake of norgestrel 75 mcg during reported perfect use[1] (The protective effect of cervical mucus is considered as present when the score is below or equal 4.)

[1] defined as the day before the delayed intake or the missed pill

The secondary objectives of the study are:

- to evaluate and compare the percentage of subjects with a protective cervical mucus score during reported perfect daily use of norgestrel 75 mcg[2], 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[2], 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[2], 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.

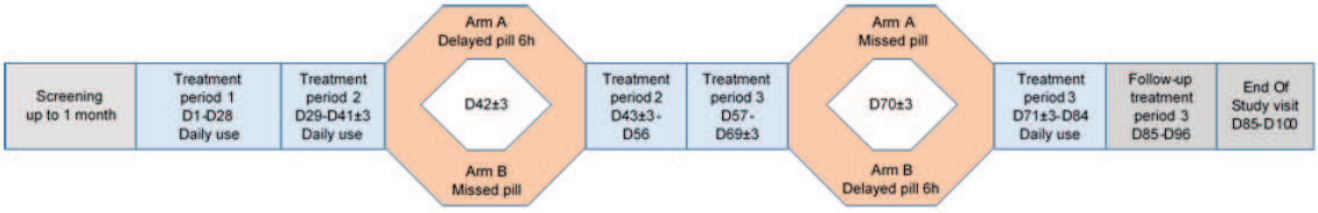
- to assess the safety of norgestrel 75 mcg taken daily for 12 weeks.

2.3 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.

Women of reproductive age (18-35 years old inclusive) who meet eligibility requirements will be recruited for this study. This study has a screening period of up to 1 month to demonstrate ovulatory status prior to enrollment followed by three 28-day treatment periods (approximately 3 months) and a possible follow-up of 12 days if ovarian activity shows a follicle ≥ 15 mm is observed at the end of period 3 and an end of study (EOS) visit within 5 days. During the treatment period 2 the subjects will be randomized into two arms: Arm A will have a delayed pill intake of 6 hours on D42 (± 3 days) and Arm B will have a missed pill (24-hour delayed pill intake on D42 (± 3 days). In the next treatment period, these subjects will cross-over meaning Arm A will have a missed pill (24-hour delayed pill intake) on D70 (± 3 days) and Arm B will have a delayed pill intake of 6 hours on D70 (± 3 days) (see Figure 1 below).

Figure 1: Design of the Study



[2] defined as treatment period 1

2.4 Study Endpoints

2.4.1 Primary Endpoint

The primary outcomes/endpoints are the changes from baseline (BSL), where baseline is the day before the infringement. Abbreviations for visits are defined in section 3.7.1.

- Delta from BSL to $V2_R$ (Day 42±3) = Mucus score at $V2_R$ - score at $V2_{R-1}$ (Day 41±3): change from baseline to 3 (delayed pill period) or 6 hour (missed pill period) after infringement

- Delta from BSL to $V2_{R+1}$ (Day 43±3) = Mucus score at $V2_{R+1}$ - score at $V2_{R-1}$ (Day 41±3): Change from baseline to just before pill intake the day after infringement

- Delta from BSL to $V3_R$ (Day 70±3) = Mucus score at $V3_R$ - score at $V3_{R-1}$ (Day 69±3): Change from baseline to 3 (delayed pill period) or 6 hour (missed pill period) after infringement

- Delta from BSL to $V3_{R+1}$ (Day 71±3) = Score at $V3_{R+1}$ - score at $V3_{R-1}$ (Day 69±3): Change from baseline to just before pill intake the day after infringement

The subordinate primary endpoint is the proportions of subjects with "protective effect of cervical mucus" the missed pill period and the delayed pill period for the following categories[3]:

- Full protection by cervical mucus regardless of the use of norgestrel 75 mcg
- Absence of risk increase further to delayed intake
- Absence of risk increase further to missed pill
- Absence of risk increase due to infringement regardless of the type
- Transient risk increase further to delayed intake
- Transient risk increase further to missed pill
- Prolonged risk increase further to delayed intake
- Prolonged risk increase further to missed pill

2.4.2 Secondary Endpoints

Cervical Mucus

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

The perfect use period is all visits in period 1 of the study. The worst (meaning highest) cervical mucus score in the period will be used for the analyses.

[3] see section 3.7.1 for definitions of each risk category

Ovarian Activity

- The percentage of subjects with OS_q, OS_a, OS_{alp} and OS_{nlp} in reported perfect use period
- The percentage of subjects with OS_q, OS_a, OS_{alp} and OS_{nlp} in delayed pill intake periods
- The percentage of subjects with OS_q, OS_a, OS_{alp} and OS_{nlp} in missed pill periods
- The percentage of subjects with OS_{nlp} in all periods

The perfect use period is all visits in period 1 of the study. The worst (meaning most risk of ovulation) ovarian activity category in the period will be used for the analyses.

Conception Protection

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

- 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
- 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 (inclusive) 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

- PK parameters including C_{24h}, C_{max} and AUC

Safety

- incidence of adverse events
- bleeding patterns by cycle

A summary of the **efficacy** objectives and endpoints for the study is below:

Efficacy Objective	**Efficacy Endpoint**	**Statistical Test**	**Table Number**
Effect on cervical mucus score	Mucus score at $V2_R$ - score at $V2_{R-1}$ (Day 41±3): change from baseline to 3 (delayed pill period) or 6 hour (missed pill period) after infringement	Repeated measures mixed model	14.2.1
	Mucus score at $V2_{R+1}$ - score at $V2_{R-1}$ (Day 41±3): Change from baseline to just before pill intake the day after infringement	Repeated measures mixed model	14.2.1
	Mucus score at $V3_R$ - score at $V3_{R-1}$ (Day 69±3): Change from baseline to 3 (delayed pill period) or 6 hour (missed pill period) after infringement	Repeated measures mixed model	14.2.1
	Score at $V3_{R+1}$ - score at $V3_{R-1}$ (Day 69±3): Change from baseline to just before pill intake the day after infringement	Repeated measures mixed model	14.2.1
Duration of the protective effect of cervical mucus	Full protection by cervical mucus regardless of the use of norgestrel 75 mcg	McNemar	14.2.3
	Absence of risk increase further to delayed intake	McNemar	14.2.3

Efficacy Objective	Efficacy Endpoint	Statistical Test	Table Number
	Absence of risk increase further to missed pill	McNemar	14.2.3
	Absence of risk increase due to infringement regardless of the type	McNemar	14.2.3
	Transient risk increase further to delayed intake	McNemar	14.2.3
	Transient risk increase further to missed pill	McNemar	14.2.3
	Prolonged risk increase further to delayed intake	McNemar	14.2.3
	Prolonged risk increase further to missed pill	McNemar	14.2.3
Percentage of subjects with a protective cervical mucus score	The percentage of subjects with cervical mucus score ≤ 4, between 5 and 8 (inclusive), and ≥ 9 in reported perfect use period	McNemar	14.2.6
	The percentage of subjects with cervical mucus score ≤ 4, between 5 and 8 (inclusive), and ≥ 9 in delayed pill intake periods	McNemar	14.2.6
	The percentage of subjects with cervical mucus score ≤ 4, between 5 and 8 (inclusive), and ≥ 9 in missed pill periods	McNemar	14.2.6
	The percentage of subjects with cervical mucus score ≤ 4 in all periods	McNemar	14.2.6
Ovarian activity	The percentage of subjects with OS_q, OS_a, OS_{alp} and OS_{nlp} in reported perfect use period	McNemar	14.2.9
	The percentage of subjects with OS_q, OS_a, OS_{alp} and OS_{nlp} in delayed pill intake periods	McNemar	14.2.9
	The percentage of subjects with OS_q, OS_a, OS_{alp} and OS_{nlp} in missed pill periods	McNemar	14.2.9
	The percentage of subjects with OS_{nlp} in all periods	McNemar	14.2.9
Combination of cervical mucus score and ovarian status	Percentage of subjects in each period considered as protected: OS_q or OS_a or cervical mucus score ≤4	None	14.2.10
	Percentage of subjects in each period considered as at risk of conception: OS_{alp} or OS_{nlp} and cervical mucus score ≥ 5	None	14.2.10
	Percentage of subjects in each period with minimum protection or unlikely to be protected: OS_{nlp} and cervical mucus score ≥ 9	None	14.2.10
	Percentage of subjects in each period with medium protection or likely to be protected: OS_{nlp} and cervical mucus score comprised	None	14.2.10

Efficacy Objective	Efficacy Endpoint	Statistical Test	Table Number
	between 5 and 8 (inclusive) or OS_{alp} and cervical mucus score ≥ 5		
	Percentage of subjects in each period with maximum protection or highly likely to be protected: OS_q or OS_a or a cervical mucus score ≤ 4	None	14.2.10

2.5 Sample Size Consideration

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 based on the consistent mechanism of action of norgestrel on cervical mucus. However the justification of the sample size will not be based on the primary analysis as there is no basis provided by published data on this parameter, such as 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 who complete the study should allow to detect a loss of protection that would demonstrate a pertinent effect on a substantial proportion of the population. Indeed if the difference between a cycle (or day) with a perfect use and a cycle (or day) 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 are in the same direction i.e. from protection to loss of protection.

3.0 STATISTICAL METHODS

3.1 Statistical Handling Policy and Analysis Conventions

This section details general policies to be used for the statistical analyses. Departures from these general policies may be given in the specific detailed sections of this SAP. When this situation occurs, the rules set forth in the specific section take precedence over the general policies. The following policies will be applied to all data presentations and analyses.

- All statistical tests will use a significance level of $\alpha = 0.05$. Two-tailed tests will be performed for all analyses that use statistical testing.

- All p-values will be rounded to 3 decimal places. All p-values that round to 0.000 will be presented as '<0.001' and p-values that round to 1.000 will be presented as '>0.999'. Any

p-value ≤ 0.05 will be considered statistically significant and will be marked with one asterisk (e.g., 0.025*).

- Summary statistics will consist of the number and percentage of responses in each category for discrete variables, and the mean, median, standard deviation (SD), minimum, and maximum for continuous variables.

- All mean values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Median values will be formatted to same decimal place as the measured values when that is possible without losing accuracy; otherwise, they will be formatted to one more decimal place than the measured values.

- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses. The denominator for percentage calculations will be the number of non-missing observations.

- All listings will be sorted for presentation in order of site number, subject number, and date of procedure or event.

- All analysis and summary tables will have the population sample size (n and % (% will not be shown in the column header if the table also presents means)) for each treatment group in the column heading.

- Calculating change from baseline to a visit will be done as follows: Change = Visit – Baseline.

- Baseline is defined as the last data point before the day of infringement (i.e. $V2_{R-1}$ or $V3_{R-1}$).

- Version 9.4 of SAS® or higher will be the statistical software package used to produce all summaries, listings, statistical analyses, and graphs.

3.2 Subject Disposition

Subject disposition will be summarized for the All Enrolled population (see Section 3.4 for Analysis Population definitions). The following data will be presented:

- The number and percentage of subjects who completed or discontinued prematurely from the study by each treatment phase (reported perfect use, delayed pill intake and missed pill) will be presented. The number and percentage of subjects who discontinued for each reason will also be summarized.

- A listing of subjects that discontinued prematurely from the study. The listing will include site number, subject number, age, number of days on drug, and reason for discontinuation. The number of days on drug will be calculated using the reported dosing days based on diary data.

- The number and percentage of subjects at each scheduled visit for all subjects.

The End of Trial (DS) CRF will be used to determine who discontinued prematurely from the study.

3.3 Protocol Deviations

The number and percentage of subjects with each protocol violation and the total will be tabulated for all subjects for the Intent-to-Treat population.

3.4 Analysis Populations

All Enrolled – This population includes all successfully screened subjects enrolled in the study. AE will be primarily used for baseline and demographics tables including disposition.

Safety (SAF) – This population consists of all subjects who took at least one dose of study medication.

The Safety (SAF) set will be used for safety purposes including adverse events, intermenstrual bleedings and labs data, but also to describe the population and to summarize and describe the level of compliance based on daily intake.

Intent-to-Treat (ITT) – This population consists of all subjects who were randomized. ITT will be the primary population used for sensitivity analyses.

The ITT population will be used in the primary sensitivity analysis for assessing the effect of delayed or missed pill on cervical mucus scores and on secondary pharmacodynamic analyses.

Full Analysis Set – This population consists of all **evaluable subjects.** These are subjects who have complete (including mitigated) data on cervical mucus and ovarian activity for the adjudication committee to assess evaluability of a cycle. They will be classified into 3 analysis populations depending on the question of interest. There are 3 full analysis sets defined: Cervical Mucus, Ovarian Activity and Conception Protection. Full analysis set requires at least one evaluable treatment cycle.

- Full Analysis Set – Cervical Mucus (FASM) – This population is composed of all randomized and treated subjects with **cervical mucus** information (mucus score) at the second or third treatment periods for the questions related to mucus on the effect of unperfect use (delayed and missed intake) of norgestrel.

- Full Analysis Set – Ovarian Activity (FASO) – This population consists of all randomized and treated subjects with ovarian activity information (OAS: ovarian activity score) at the second or third treatment periods for questions related to **ovarian activity**.

- Full Analysis Set – Conception Protection (FASC) – This population consists of all randomized and treated subjects with 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 assessment of evaluable cycles, the exclusion of cycles from a given analysis and the exclusion of a subject from the FASM/FASO/FASC will be decided in a blinded manner by an independent adjudication committee.

The FASM, FASO and FASC (or evaluable populations) will be used in the primary analysis for assessing the effect of delayed or missed pill on cervical mucus scores and on secondary pharmacodynamic analyses.

Per-protocol (PP) – This population consists of all subjects from the FASM/FASO/FASC without major protocol violation/deviation and with complete cervical mucus and ovarian activity data for all the three treatment periods. Relevant protocol violation/deviation will be defined during the data review. This will include pill intake compliance issues and early ovulation.

The PP population will be used for assessing the efficacy and PK results 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 number of subjects in each population will be summarized for all subjects.

3.5 Subject Demographics and Pre-Treatment Characteristics

Subject demographics will be summarized for the All Enrolled and Full Analysis Set – Cervical Mucus populations. Pre-treatment characteristics will be summarized for the All Enrolled population. The demographics and pre-treatment characteristics will be summarized for all subjects.

3.5.1 Demographics

The summary of demographics will include age, race, ethnicity, weight and height at screening and BMI. The summary will be done for the All Enrolled and FAS Cervical Mucus populations and will include:

- The number and percentage of subjects within each category of race and ethnicity.

- The sample size, mean, median, SD, minimum, and maximum values for age, weight, height and BMI. Age will be calculated (with the INTCK function) using the Screening Visit Date and the Date of Birth.

3.5.2 Contraceptive History

The number and percentage of subjects reporting contraceptive history for each contraceptive method will be summarized. For those subjects not at risk of pregnancy, the reasons why not at risk will also be summarized.

3.5.3 Gynecological History

The summary of gynecological history will include average cycle length, usual flow duration, heaviest volume of flow, history of irregular periods, yeast infection history and bacterial vaginosis history. The summary will include:

- The number and percentage of subjects within each category of heaviest volume of flow, history of irregular periods, yeast infection history and bacterial vaginosis history.

- The sample size, mean, median, SD, minimum, and maximum values for average cycle length and usual flow duration.

3.5.4 Pregnancy History

The summary of pregnancy history will summarize the following endpoints:

- The number and percentage of subjects within each category of complications during pregnancy, complications with baby, any pregnancy planned within the next 4 months and breastfeeding history and current status.

- The sample size, mean, median, SD, minimum, and maximum values for number of times pregnant and number of live births.

3.5.5 Substance Use History

The summary of substance use will summarize the number and percentage of subjects for the following categories:

- Alcohol use
- Marijuana use
- Illicit drug use

The sample size, mean, median, SD, minimum, and maximum values quantify use of these substances will also be presented.

3.5.6 Physical Examination

Physical examinations will be performed at screening. Each body system will be categorized as normal or abnormal. The number and percentage of subjects in each category will be given for each body system.

3.5.7 Gynecological Examination

Gynecological examinations will be performed at screening. Each body system will be categorized as normal or abnormal. The number and percentage of subjects in each category will be given for each body system.

3.5.8 Gynecological Assessments

The summary of gynecological assessments will summarize the number and percentage of subjects for the following categories:

- Chlamydia test type
- Chlamydia test results
- Chlamydia treated (positive test results only)
- Gonorrhea test type
- Gonorrhea test results
- Gonorrhea treated (positive test results only)
- Vaginitis test results
- Vaginosis test results
- Vaginosis treated (positive test results only)
- PAP smear required?
- PAP smear results

3.5.9 Medical History

The number and percentage of subjects reporting a medical history for each body system will be summarized.

3.5.10 Pre-Treatment Signs and Symptoms

Pre-treatment signs and symptoms will be coded using MedDRA 21.0. The number and percentage of subjects reporting each pre-treatment sign and symptom will be summarized by system organ class and preferred term for the Safety population. The number and percentage of subjects reporting any pre-treatment signs and symptoms will also be reported.

If a subject reports the same pre-treatment sign or symptom more than once, then that subject is only counted once for the summary of that pre-treatment sign or symptom, using the most severe intensity.

3.5.11 Prior and Concomitant Medications

Summaries for prior and concomitant medications will be done for the Safety population. Each summary below will be done for all subjects:

- Prior Medications – Prior medications are considered to be any medication that was stopped prior to the date of the first dose of study drug.

- Concomitant Medications – Concomitant medications are considered to be any medication that was taken on or after the date of the first dose of study drug.

All medications recorded on the CRF will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug classifications. The WHO Drug dictionary version used for this study will be March 2018.

Each summary will give the number and percentage of subjects who took medications that were coded to each generic drug name and therapeutic drug class, as well as the number and percentage of subjects that took any medication at all. If the start of end date of the medication is a partial date (or completely unknown) then the medication will be classified as a concomitant medication unless the partial end date is clearly before the first dose of study drug.

3.5.12 Screening Transvaginal Ultrasound

The endometrial stripe thickness and endometrium appearance at the screening transvaginal ultrasounds will be summarized for all subjects using the Safety population.

3.6 Treatment Compliance

Compliance will be summarized for the Safety and FASM populations.

Compliance = 100 * (total # pills indicated as taken on diary entries) / (date last pill taken – date first pill taken +1 – number of planned missed doses). The compliance calculation will be different for each treatment group, as based on treatment schedule. The reported perfect use period (treatment period 1) and the delayed pill period have 0 planned missed doses while the missed pill period has 1 planned miss dose.

The following information will be presented for each treatment group for compliance:

Summary statistics (sample size, mean, median, SD, minimum, and maximum) for treatment compliance

The number and percentage of subjects in each of the following categories of compliance: <75%, 75% - <85%, 85% - <95%, 95% - <100%, and 100%.

Compliance will also be summarized for the Safety population for treatment periods 1 and 2 combined as well as for all treatment periods combined.

3.7 Efficacy Analysis

All efficacy analyses will be done for the appropriate FAS, PP and ITT populations unless otherwise specified.

3.7.1 Primary Efficacy 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 FASM. It is composed of all randomized and treated women with cervical mucus information (mucus score) at the second or third treatment period.

A sensitivity analysis using the ITT population will be done to compare to the primary analysis on the FASM population. Additionally, the analysis will be performed for the PP population.

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 intake)
- TMS is the time of mucus evaluation/scoring
- TMS score is the value of mucus score at the time of mucus evaluation
- 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 treatment 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 $V3_{R+1}$.

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

The **primary baseline 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 $V3_{R-1}$

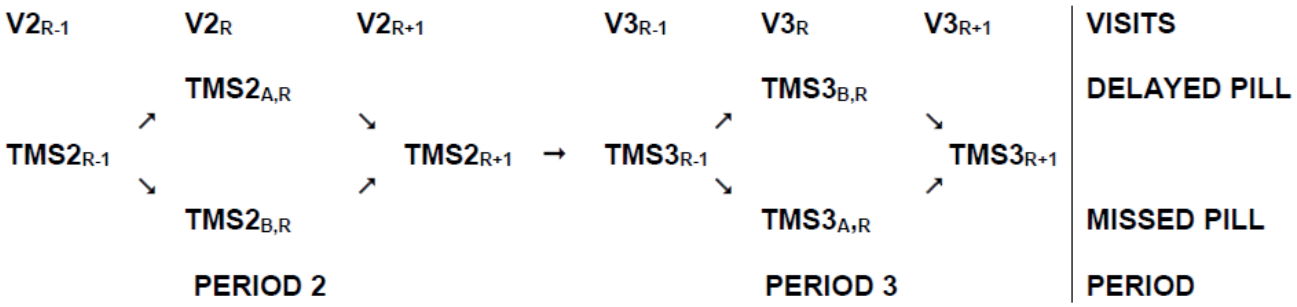
Around 8 hours after pill intake the day before infringement.

The **primary response 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:



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 (visit) 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 structure of the variance covariance matrix will be retained using the best fit among unstructured matrix (UN) compound symmetry (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 **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. If the cervical mucus was too thick to be collected (and thus a cervical mucus score could not be obtained) the analyses using the **FASM, ITT and PP populations** will use the following approach:

Baseline Mucus Score	Post-Baseline Mucus Score	Mucus Score Used in Analysis
0-4	Too thick to collect	Score equal to baseline
>4	Too thick to collect	Post-baseline score =4
Too thick to collect	Any observed mucus score	Baseline score =0
Too thick to collect	Too thick to collect	Change from baseline = 0

A sensitivity analysis using the FASM population will also be done and if the cervical mucus was too thick to be collected (and thus a cervical mucus score could not be obtained) the mucus score will be assigned using multiple imputation.

The SAS code for the 2 primary contrasts of interest are:

```
PROC MIXED DATA=MUCUS;
CLASS VISIT PERIOD INTERVENTION SEQUENCE;
MODEL MUCUS_CHG = PERIOD INTERVENTION VISIT SEQUENCE / S;
RANDOM SUBJ_ID;
REPEATED  / SUBJECT=SUBJ_ID*PERIOD;
ESTIMATE 'EFFECT OF INFRINGEMENT' INTERVENTION 1 -1 ;
ESTIMATE 'EFFECT OF TIME' VISIT 1 -1 1 -1;
RUN;
```

Subordinated Primary 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 progression: 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. If the cervical mucus was too thick to be collected (and thus a cervical mucus score could not be obtained) the subordinate primary objective analysis will consider the sample to have good contraception protection and have a cervical mucus score ≤ 4. Otherwise if the cervical mucus score is missing the subject will not be included in the analysis for the missing endpoint.

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 $p_{delay,transient\ risk}$.

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 $p_{missed,\ prolonged\ risk}$.

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 (which is only performed for the missed pill arm) is the equality of proportions at baseline (R-1) and at Day R+1 (48 hours post treatment).

3.7.2 Secondary Efficacy Analyses

3.7.2.1 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 FASM population will be used for the analysis and a sensitivity analysis will be done using ITT and PP.

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 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

If the cervical mucus was too thick to be collected (and thus a cervical mucus score could not be obtained) the analysis will consider the sample to have good contraception protection and have a cervical mucus score ≤ 4. Otherwise if the cervical mucus score is missing the subject will not be included in the analysis. A period must have at least 7 cervical mucus assessment to be included in the summaries. A stratified McNemar test (stratification on the site, CMH option in SAS) will be used to compare the distribution of cervical mucus scores in the perfect use period to the delayed and missed pill periods (pairwise vs perfect use).

The worst (meaning highest) cervical mucus score in the period will be used for the analyses.

3.7.2.2 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 adjucation committee will evaluate whether cycles should be excluded from analyses (including period 1 cycles if low compliance of taking study drug). The details for the review process will be defined in a separate document prepared for the adjudication process. The FASO population will be used for the analysis and a sensitivity analysis will be done using ITT and PP.

The time frames are:

- reported perfect use period: all the visits of the period 1
- delayed pill intake period: all the visits of the period 2 for Arm A and all the visits of period 3 for Arm B
- missed pill period: 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 5.4.

The OS are ranked depending on the risk of conception: $OS_{nlp} > OS_{alp} > OS_a > OS_q$. The OS classification will be determined by the adjudication committee.

For each treatment period the most risky OS will be considered.

The endpoints are:

- The percentage of subjects with OS_q, OS_a, OS_a/OS_{alp} and OS_{nlp} in reported perfect use period
- The percentage of subjects with OS_q, OS_a, OS_a/OS_{alp} and OS_{nlp} in delayed pill intake periods
- The percentage of subjects with OS_q, OS_a, OS_a/OS_{alp} and OS_{nlp} in missed pill periods
- The percentage of subjects with OS_{nlp} in all periods

A stratified McNemar test (stratification on the site, CMH option in SAS) will be used to compare the distribution of ovarian activity classification in the perfect use period to the delayed and missed pill periods (pairwise vs perfect use). The worst (meaning most risk of ovulation) ovarian activity category in the period will be used for the analyses.

3.7.2.3 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. The FASC population will be used for the analysis and a sensitivity analysis will be done using ITT and PP.

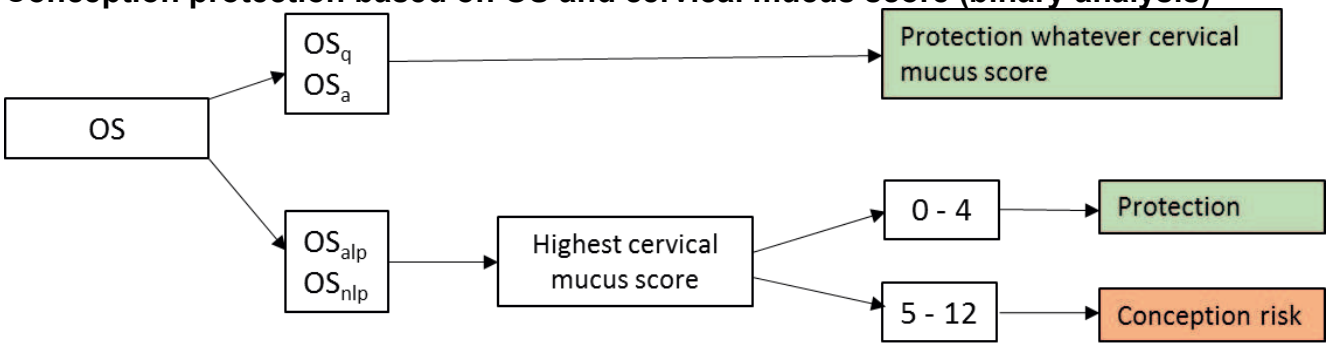
For both analyses, the assessment criteria will be the OS and the highest cervical mucus score during the 3 visits before a postovulatory image is obtained including the visit when the postovulatory image is obtained.

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.

Binary analysis

The aims of this analysis is to determine whether a subject is protected on not, according to the algorithm presented below:

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



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

- 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 aim of this analysis is to determine the level of protection for a subject, according to the table below.

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 classification of OS (and thus conception protection level also) will be determined by the adjudication committee.

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

3.7.2.4 Cervical Mucus

Details on cervical mucus score calculations are in Section 5.3. The following information will be summarized for all subjects in the Safety population using descriptive statistics.

- Was cervical mucus too thick to be collected?
- Was cervical mucus collected prior to TVUS?
- Viscosity score
- Ferning score
- Spinnbarkeit score
- Cellularity score
- Total cervical mucus score

A plot of the total cervical mucus score by visit will be done for the Safety population.

3.7.2.5 Transvaginal Ultrasound and Hormones

Transvaginal ultrasound (TVUS) examinations will be summarized at all assessed visits for the Safety population. The following endpoints will be summarized for the screening visit, each of the 3 treatment periods, delayed pill period and missed pill period:

- Was postovulatory image seen?
- Right Ovary
    - Presence of follicles
- Left Ovary
    - Presence of follicles
- Any abnormalities found?

For each of the 3 treatment periods subjects will be counted as having the outcome (e.g, had a postovulatory image seen) if the outcome happens at least once during the treatment period. Summaries will also be done by infringement type.

TVUS largest follicle diameter measurement: The time course of the diameter will be presented graphically along with P4 and E2 (see below) at each visit.

<u>Hormones</u>

Profile graphs for each subject will be prepared for P4 and E2 and will include largest follicle diameter (largest diameter for each day) also.

3.8 Pharmacokinetics

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:

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, 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.

During the DMP period, the sampling schedule will depend on the arm the subjects had been randomized in (see table below).

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 $C3_1$.

LNG concentrations at each timepoint will be summarized in a table presenting summary statistics (sample size, mean, median, SD, minimum, and maximum) for all treatment periods for the PP population. A figure will be created to display the mean concentrations at each timepoint for all treatment periods.

3.9 Safety Analysis

All safety analyses will be done for the Safety population.

All laboratory data will be presented in the conventional United States (US) units, as reported by the central laboratory, including normal ranges, and if an abnormal result triggers an AE reporting or not.

Final evaluation is defined to be the last evaluation performed after the first dose of study drug was taken.

3.9.1 Treatment Exposure

Treatment exposure will be calculated using the following formula:

Exposure = Last Date of Dosing – First Date of Dosing + 1.

The number of days of treatment exposure will be summarized using descriptive statistics.

3.9.2 Adverse Events

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. Incidence of adverse events will be summarized for each treatment group by system organ class and preferred term. The number and percentage of subjects with each system organ class and preferred term will be presented for all subjects. Tables to summarize the incidence rates will be created for each of the following groups:

- Adverse events
- Serious adverse events
- Adverse events leading to premature discontinuation
- Adverse events by intensity
- Adverse events by relationship to study drug
- Adverse events presented in descending order of frequency by preferred term (no system organ class shown)

If a subject reports the same adverse event more than once, then that subject is only counted once for the summary of that adverse event, using the most severe intensity. The only exception to this will be for the summary by relationship to study drug. For that summary, if a subject reports the same adverse event more than once, then that subject is only counted once for the summary of that adverse event, using the most severe relationship to study drug. The same principle will be applied at the body system level summary.

If relationship to study drug are unknown then the adverse event will be summarized in the highest category of relationship to study drug. However every effort should be made to assess the relationship to the study drug before the data review. If intensity is unknown for any AEs the summary table will present the unknown category. If the start date of the adverse event is a partial date (or completely unknown) then the adverse event will be included in the summary tables (i.e. assumed to be treatment-emergent) unless the partial start date is clearly before the first dose of study drug.

Adverse events that led to premature discontinuation from the study will be listed. Serious adverse events will also be listed. These listings will contain details about the adverse event such as intensity, seriousness (only for AE leading to discontinuation) and relationship to study drug. Other supportive data, such as the subject's age, BMI, last menstrual period (for pregnancy reports) will be given.

All adverse events will be coded with MedDRA 21.0 and subsequent versions.

3.9.3 Hematology and Chemistry

Hematology and chemistry mean changes from screening to the end of study visit will be summarized. The summary will present data for the screening visit and the mean change from screening to the end of study visit. The sample size, mean, SD, median, minimum, and maximum values for each treatment will be presented for each parameter.

A summary of shifts from screening to the end of study visit will be given for each parameter. The normal range for each parameter will be used to create categories of low, normal, or high. Any result that is higher (lower) than the upper (lower) limit of normal will be categorized as high (low) and any result within the lower and upper limits of normal will be categorized as normal.

Hematology and chemistry data will be located in separate tables.

3.9.4 Vital Signs

Vital signs and weight mean changes from screening to the end of study visit will be summarized. Vital sign measurements will include systolic blood pressure, diastolic blood pressure and sitting heart rate. The summary will present data for the screening visit and the mean change from screening to the end of study visit. For each visit, the sample size, mean, SD, median, minimum, and maximum values will be presented for each parameter.

3.9.5 Vaginal Bleeding and Spotting

Vaginal bleeding and spotting will be recorded daily by subjects in the diary. The total number of bleeding or spotting days for each subject at each treatment period will be summarized. Menstrual bleeding, intermenstrual bleeding and spotting will be summarized separately. No imputation of missing data will be performed. The number of days with diary data recorded in each treatment period will be summarized.

3.9.6 Listing of Pregnancies

A listing of any pregnancies that occur will be created and will include the last menstrual period date as well as details the estimated date of conception and the methods used to estimate the date of conception. The listing will also indicate which treatment period the estimated date of conception occurred.

4.0 REFERENCES

HRA Pharma Protocol 151042-002: 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, version 1.0 26FEB2018.

5.0 APPENDICES

5.1 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)	
				$V2_{N-1}$	$V2_NA$	$V2_NB$	$V2_{N+1}$		$V3_{N-1}$	$V3_NA$	$V3_NB$	$V3_{N+1}$		
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

(a) Only if follicle ≥ 15 mm is observed after Day 73 AND the criteria for stopping the extra-visits were not fulfilled 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) Randomization 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

5.2 Adjudication Committee

An adjudication committee will be convened for this 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 before the database lock to review the data.

Its responsibilities will be to review data regarding IMP intake in relation to TVU results, hormonal levels and mucus scores. They will define the set of evaluable treatment cycles. They will make decisions for each subject and reach agreement on cervical mucus score and ovarian activity score/ovarian status.

A separate charter will be created to provide the details on this committee.

5.3 Cervical mucus sampling and scoring

General information on cervical mucus sampling and scoring is given below. See Appendix 5 in protocol for additional details.

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.

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

5.4 Determination of Ovarian Activity Score (OAS) and Ovarian Status (OS)

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)

5.5 Table of Contents for Data Displays

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Listing Number	Listing Title	Population
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