STATISTICAL ANALYSIS PLAN

Sponsor : HRA Pharma

Clinical trial protocol : 2914-012

Title: Prospective Observational Study to Assess Clinical Follow-up and Outcomes of Pregnancies Exposed to ella® (ellipse II)

Reference PAS/L/15/0012 Version 1.1

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Signature Page

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Summary

LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
CI	Confidence intervals
EMA	European Medicine Agency
FDA	Food and Drug Administration
FU	Follow-Up
HCP	Health Care Providers
LMP	Last Menstrual Period
QC	Quality Control
RR	Risk Ratio
SAP	Statistical Analysis Plan
TLF	Tables, Listings and Figures
UPA	Ulipristal acetate
WHO	World Health Organisation

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1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the different statistical analyses which will be conducted on the study data, in conformity with the final version amended n°8.0 of the protocol 2914-012, dated the 30th March, 2015.

Any additional details or amendments will be discussed and included in a revised version of the SAP. The SAP will be finalised before database lock.

2. DESCRIPTION OF THE STUDY

2.1 Study rationale

ella®/ellaOne® (ulipristal acetate 30 mg tablet) is a selective progesterone modulator with antagonistic and partial agonist effects at the progesterone receptor. Ulipristal acetate [17alpha-acetoxy-11beta-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20 dione] was initially developed at the US National Institutes of Health. The compound has been tested in an extensive battery of non-clinical and clinical studies and was approved for marketing at the dose of 30 mg (tablet) for emergency contraception up to 120 hours (5 days) under the Tradename ellaOne® in the European Union (EU/1/09/522/001) and ella® in the United States of America (NDA 022474), in May 2009 and August 2010 respectively. Initially approved as a Prescription drug, EllaOne® has been approved in Europe for marketing without prescription since January 2015.

During the evaluation process of the ella®/ellaOne® registration dossier, the EMA (European Medicines Agency) and FDA (Food and Drug Administration) requested additional information on the potential effects of ella® exposure on pregnancy course and outcome. The approval of NDA 022-474 included two post-marketing requirements (PMR 1673-1 and PMR 1673-2) as a condition of approval. PMR 1673-1 was to conduct a prospective, observational pregnancy outcome study to include fetal and neonatal outcomes and maternal pregnancy complications following a pregnancy exposed to UPA. PMR 1673-2 was to conduct a case-control study of pregnancy loss complications if a signal of concern was identified in PMR 1673-1 study. Although there were no safety signals related to pregnancy exposure to ella® from the completed phase III trials, these PMR were required by the FDA at the time of approval because there were not a sufficient number of pregnancies exposed to ella® to evaluate whether there is any fetal, neonatal or maternal risk following exposure to ella® in early pregnancy in case of emergency contraception failure or inadvertent exposure.

HRA Pharma committed to collecting information on clinical follow-up and outcomes of pregnancies that began following ella® failure as well as pregnancies inadvertently exposed to ella® by putting in place an observational study (Ellipse I), targeting 1000 investigators in Europe and the USA (Study 2914-012, Ellipse I). The main objective of the study Ellipse I was to estimate the rates of outcomes of specific events of pregnancies exposed to ella®. The secondary objectives were to collect data on birth complications of pregnancy loss in pregnancies exposed to ella® and to assess adverse events (AE) during the course of pregnancies exposed to ella®.

Recruitment of sites was very slow and difficult in the Ellipse I study and it became evident that only a limited number of pregnancies would be reported. Between 2011 and 2013; out of 219 sites initiated in Europe only 8 pregnant women were recruited. In Europe, it was decided to redirect efforts from the observational study Ellipse I towards improving the existing online European pregnancy registry. EMA thus agreed that no additional sites would be initiated and that data collection would be stopped once the improved web-based pregnancy registry would be launched.

In parallel, as per FDA requirement, decision was also taken to continue data collection in the US through the Ellipse I study and to amend the ellipse I protocol into an Ellipse II protocol (2914-012 Ellipse II) to include the web-based enrolment and prospective data collection. Pregnant Women in the US, who have been exposed to ella® during the menstrual cycle in which the pregnancy started or at any time during pregnancy will be directly enrolled in the study using a website interface that will be accessible to Health Care Professionals (HCP) and women themselves. Enrolling an exposed woman

in the study will involve completing an online questionnaire either by the HCP or directly by the woman.

In the USA, at the time of the study initiation the use of ella® was very low and limited to family planning clinics [Planned Parenthood Family planning of America (PPFA)] which typically do not follow-up women after they become pregnant. It has thus been decided to identify high-volume abortion PPFA clinics where women might have used ellaOne® to avoid a pregnancy. At these sites, such prospective studies can be performed as ultrasound reports at the time of abortion can establish living, normally-appearing pregnancies and accurate gestational age before an induced abortion taking place weeks after exposure to ellaOne®.

A total of 9 PPFA affiliates consisting of 32 abortion clinics thus accepted to participate in the Ellipse II study.
In parallel, the Ellipse II website was constantly accessible to other Health Care Professional and to any pregnant woman who has been exposed to ella® during the menstrual cycle in which the pregnancy started or at any time during pregnancy.

2.2 Study objectives

2.2.1 Primary objective

The primary objective of this observational study is to assess the nature and rates of pregnancy outcomes for pregnancies exposed to ella® (whether due to failure of the emergency contraception or to inadvertent exposure during pregnancy).

2.2.2 Secondary objectives

The secondary objective is to assess the nature and prevalence of maternal complications in ella®-exposed pregnancies

2.3 Description of the overall study design and plan

2.3.1 Study design

The ellipse II study is a prospective, observational study to assess clinical follow-up and outcomes of pregnancies exposed to ella®.
Enrolment will be made directly through the Website either directly by the woman or a Health Care Provider. There will be 2 different accesses: either a web-interface directly accessible by the woman for self-enrolment or an eCRF only accessible by Health Care Providers.

2.3.2 Study plan

	Enrolment in the study	**Pregnancy Course**	**End of pregnancy**	**4 months FU[3]**
Written informed consent	X			
Inclusion criteria	X			
Pregnancy diagnosis	X			
ella® exposure	X			
Prior and concomitant medications	X	X	X	
Recreational drug use (tobacco, alcohol, illicit drugs)	X	X	X	
Serology and prenatal tests results	X			
Medical history	X			
Maternal and fetal pregnancy complication	X	X	X	
Pregnancy outcome			X	
Live birth follow-up				X

2.4 Definition of populations analysed

Pregnancy outcomes will be described for pregnancies with known outcome (patients with missing outcomes, patients with ongoing pregnancies and patients lost to follow-up will be excluded). The proportion of patients with outcomes and lost to follow-up (or missing outcome) will be reported.

3. STUDY ENDPOINTS AND ASSESSMENT METHOD

3.1 Primary outcomes

Outcomes to be evaluated as primary endpoints are:

- Live birth outcomes
  - Healthy baby
  - Congenital anomaly: a baby born with a congenital anomaly
  - Neonatal death: a newborn who died during the first 28 days of life
  - Preterm birth: a baby born at less than 37 weeks of gestational age
- Pregnancy loss outcomes
  - Ectopic pregnancy: implantation of the fertilized egg and pregnancy development in a location outside the uterus and attempt to develop in this location
  - Spontaneous abortion:
    - early fetal death (i.e. < 20 completed weeks of gestation)
    - missed abortion (blighted ovum)
    - not specified: all spontaneous abortions which are not early fetal death and not missed abortions
  - Fetal death:
    - intermediate fetal death (between > 20 and <28 completed weeks of gestation)
    - late fetal death (≥ 28 completed weeks of gestation)
  - Induced abortion can be either:
    - an induced abortion for non-medical reason
    - an induced abortion for medical reasons (termination of pregnancy for fetal anomaly, other pregnancy or maternal health complications)
  - Maternal death
- Gestational age: age of the embryo or fetus based ultrasound examination
- Normal-appearing pregnancy: medical assessment based on analysable ultrasounds results.

3.2 Secondary outcomes

Outcomes to be evaluated as secondary endpoints are defined as follows:

- Maternal health complications of pregnancy are health problems of the pregnant woman that adversely affect her pregnancy, including maternal death.
- Proportion of women with ella®-exposed pregnancy complication
- Proportion of women with bleeding
- Proportion of women with infection
- Proportion of women with a need for surgical management

3.3 Endpoints derivation

3.3.1 Primary endpoints

The different outcomes presented above will be derived as well:

✓ Live Birth outcomes

Live births outcomes	Derivation
Proportion of live births among all pregnancy outcomes	Number of live births/total number of pregnancies
Proportion of healthy babies among live births	Number of healthy babies / number of live births
Live birth prevalence of congenital anomalies	Number of live births with congenital anomalies / number of live births
Live birth prevalence of other neonatal morbidity	Number of live births with neonatal morbidity (excluding congenital anomaly)/number of live births.
Total prevalence of congenital anomalies	Total number of congenital anomalies (terminations of pregnancy for fetal anomaly, fetal deaths, live births with congenital anomalies) / total number of births (live births + fetal deaths/stillbirths)
Proportion of neonatal deaths	Number of neonatal deaths / number of live births
Proportion of preterm births	Number of preterm births / number of live births

✓ Pregnancy loss outcomes

Pregnancy loss outcomes	Derivation
Proportion of normal-appearing pregnancies (with analysable ultrasound results) before induced abortion	Number of normal-appearing pregnancies with ultrasound results compatible with normal growth and development / number of pregnancies with analysable ultrasound results which terminated by induced abortion (due to an anomaly detected, other medical reason, non-medical reason)
Proportion of ectopic pregnancies	Number of ectopic pregnancies / total number of pregnancies
Proportion of spontaneous abortions	Number of spontaneous abortions / total number of pregnancies
Proportion of fetal deaths	Number of fetal deaths/total number of pregnancies
Proportion of intermediate fetal deaths	Number of intermediate fetal deaths/total number of pregnancies
Proportion of late fetal deaths	Number of late fetal deaths/total number of pregnancies
Proportion of all induced abortions	Number of induced abortions / total number of pregnancies
Proportion of induced abortions for medical reason	Number of induced abortions for medical reason / total number of pregnancies
Proportion of induced abortion for non-medical reason	Number of induced abortions for non-medical reason / total number of pregnancies
Proportion of maternal deaths	Number of maternal deaths / total number of pregnancies

3.3.2 Secondary endpoints

- Proportion of women with ella®-exposed pregnancy complication = number of complications / number of pregnancies)
- Cumulative incidence of excessive bleeding episodes = number of excessive bleeding episodes / number of pregnancy losses during the study .

3.3.3 Other demographic and clinical variables

- Patient's age = (date of ella® intake – date of birth) / 365.25

  If date of ella® intake is missing or incomplete, date of LMP will be taken into account only. If data of LMP is missing or incomplete, the date of diagnosis will be taken into account. If date of diagnosis is missing, the date of ultrasound will be taken into account. If all these dates are missing the date of pregnancy outcome (birth, induced abortion for non-medical reason, induced abortion for medical reason) or any date of examination during pregnancy (rubella test, toxoplasmosis test, prenatal test
  If all these dates are missing or incomplete then age won't be recalculated and will be considered as missing.

- Time from last menstrual period (LMP) to exposure = Date of 1st ella® intake – Date of first day of LMP (=date of last menstrual period)

- Exposure (repeated doses) = 1 if at least one row in the "Additional intake of ella® during pregnancy ", else = 0

- BMI = weight (kg) / height (m²)

4. STUDY POPULATION

The current study targets any ella®-exposed pregnant women in the US. Nevertheless, as the majority of women who become pregnant despite using an emergency contraception are attempting to avoid pregnancy, the Ellipse II study mostly targets ella®-exposed women seeking abortion services at Planned Parenthood affiliates.
The study is still ongoing until PMR fulfilment. This analysis concerns all reported pregnancies from first women included in the study through the 22nd December 2015 cut-off date and a final report will be provided at the end of study. All reported cases are included in a pooled analysis with other sources in which a single 30mg or greater doses of UPA were administered by women.

5. STATISTICAL METHODS

Given the method of patient selection for this study, the vast majority of the outcomes contained in the data base will be induced abortions for non-medical reasons. Hence, given the limited sample size for essentially all outcomes of interest, no inferential statistics will be conducted. Only descriptive statistical analyses will be performed and point estimates with 95% confidence intervals will be given for the proportions of outcomes.

Additional statistical analyses may be considered, in particular if initial results suggest that they may be feasible and necessary.

For descriptive purposes, the following statistics will be presented

Table 5.1: Descriptive statistics summary

Demographic characteristics	**Categorical data**	Number of subjects, number of missing data, percentage of subjects Percentages are calculated based on documented data for each outcome (non-missing observations)
	Continuous data	Number of observations, number of missing data, mean, standard deviation, median, 1st and third quartiles, range (minimum and maximum).
Primary endpoint		Proportions (prevalence) Percentages are calculated based on documented data for each outcome
Secondary endpoint	**Categorical data**	Proportions (prevalence) Percentages are calculated based on documented data
	Continuous data	Number of observations, number of missing data, mean, standard deviation, median, 1st and third quartiles, range (minimum and maximum)..

5.1 Methodological approach for demographic characteristics

The following baseline characteristics data of enrolled and completed cases will be described:

- Age, as a continuous variable in years or categorical (<35 years or >=35 years groups)
- Weight in kilograms, height in meters and BMI (kg/m²)
- Sac > 20 mm (Yes, No)
- Intra-uterine pregnancy which is normal-appearing for gestational age (Yes, No, Unknown)
- Gestational age at ultrasound (weeks)
- Number of 30mg tablets of ella®
- Time from intercourse to ella® intake (hours)
- Pregnancy status before ella® intake (pregnant/not pregnant)

- Pregnancy stage at ella® exposure (Before pregnancy / 1st trimester / 2nd trimester / 3rd trimester)
- How was the pregnant stage at ella® exposure determined (Ultrasound / LMP / Other)?
- time from LMP to exposure in days
- Multiple ella® intakes since LMP
- History of pregnancy (Yes, No)
- Number of previous pregnancies
- Number of live infants
- History of spontaneous abortion (miscarriage) (Yes, No)
- Number of spontaneous abortions (miscarriage)
- History of fetal death (Yes, No)
- Number of fetal deaths
- History of induced abortions for non-medical reason (Yes, No)
- Number of induced abortions for non-medical reason
- History of induced abortions for medical reason (Yes, No)
- Number of induced abortions for medical reason
- History of birth defects (Yes, No)
- Number of birth defects

Demographic characteristics of patients with known pregnancy outcome (excluding lost to follow-up patients and missing outcomes) will be described as well as those of patients where the pregnancy outcome is missing.
Patients with missing outcomes are defined as those with no pregnancy outcome ticked.

Statistical description as shown on Table 5.1 will be produced for each of these demographic characteristics.

Frequency of exposure to other drugs (other than ella®) received during pregnancy will be calculated by ATC code and drug name according to WHODRUG dictionary.

Narratives will be written for the lost follow up patients.
Moreover, baseline demographic characteristics will be presented by Pregnancy stage at ella® exposure.

In addition to these analyses, number and percent of enrolled women in each region and affiliate will be calculated on patients with known pregnancy outcome, patients with unknown pregnancy outcome and overall.

5.2 Methodological approach for primary endpoints

Each pregnancy outcome will be described by proportions (prevalence), as described in Table 5.1.
These proportions (prevalence) of outcomes will be calculated for the overall sample.

5.3 Methodological approach for secondary endpoints

The numbers of maternal and pregnancy complications will be calculated.

These analyses will be performed for the overall sample.

The nature and incidence of complications of pregnancies exposed to ella® will be assessed. An individual listing will report all these individual results.
Statistical description as shown on Table 5.1 will be produced for fetal loss complications.

5.4 Significance level

No inferential statistical analysis will be performed.

5.5 Missing data

No imputations will be performed.

5.6 Statistical software

The programming of the statistical analyses will be performed by SAS® software version 9.2 or later.

5.7 QC plans

Two staff members are involved in the Quality Control (QC) process:

- the reviewer statistician
- the programmer

To check the quality of the analyses and programs, manual checks will be performed by reviewer.

The process for reviewer actions is the following for each Tables, Listings and Figures (TLF):

- Check of the input data base
- Manual review of SAS scripts
- Re-run of SAS scripts
- Manual check of the SAS log
- Manual check of the SAS outputs
- Manual comparison of the SAS outputs with the TLF produced by the programmer
- QC document filling (see below)

The QC document's structure is the following:

TLF name	Status	Comment	Correction
T001			
T002			
T003			
T004			
T005			

At the end of the process:

- If there is no issue with a TLF: *Comment* and *Correction* columns are missing and *Status* column is filled with “OK”.
- If there is an issue with a TLF: *Correction* column is missing and a comment explaining the nature of the issue is written in the *Comment* column. *Status* is filled at “NOK”.

The QC document will be stored on SOLADIS server. Reviewer and programmer can share this document.

When reviewer considers it necessary to update some programs to resolve issue(s) (not necessarily after each TLF), he sends an e-mail to the programmer to adjust programs to solve the issue identified by the reviewer.
When done, the programmer filled the *Correction* column to “Done”.
Programmer then sends an e-mail to the reviewer who re-runs the whole process for the updated TLF(s).
If the issue is solved, the reviewer fills the QC document, updating *Status*, *Comment* and *Correction* columns.

6. REPORTING CONVENTIONS

6.1 General Reporting Conventions

- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (*e.g.*, μ, α, β).
- All date values will be presented as DD/MMM/YYYY (*e.g.*, 29/AUG/2001) format. A four-digit year is preferred for all dates.

6.2 Rounding

- Age as continuous variable will be truncated to become an integer variable. Example: 28.8 years -> 28 years.
- Integer variables (mostly duration variables) will be described with 1 decimal for mean and standard deviation estimations and no decimal for median, range and quartiles.
- Descriptive statistics for continuous variables (such as BMI) and percentages calculated for qualitative items and the various endpoints will be noted with 1 decimal.
- P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as “<0.001”.

7. SUMMARY TABLES AND LISTINGS

7.1 Tables of demographic characteristics

Table 7.1.1: Baseline demographic – all Patients

	Patients with known pregnancy outcome (TOTAL=###)	Patients with unknown pregnancy outcome (TOTAL =###)
Age (years)		
N	###	###
Missing	###	###
Mean (SD)	##.# (#.##)	##.# (#.##)
Median	##.#	##.#
Min; Max	##.#; ##.#	##.#; ##.#
Age : n (%)		
<35 years	## (##.#)	## (##.#)
>=35 years	## (##.#)	## (##.#)
Missing	## (##.#)	## (##.#)
Weight (kg)		
N	###	###
Missing	###	###
Mean (SD)	##.# (#.##)	##.# (#.##)
Median	##.#	##.#
Min; Max	##.#; ##.#	##.#; ##.#
Height (m)		
N	###	###
Missing	###	###
Mean (SD)	##.# (#.##)	##.# (#.##)
Median	##.#	##.#
Min; Max	##.#; ##.#	##.#; ##.#
BMI (kg/m²)		
N	###	###
Missing	###	###
Mean (SD)	##.# (#.##)	##.# (#.##)
Median	##.#	##.#
Min; Max	##.#; ##.#	##.#; ##.#

n: number of subjects fulfilling the item listed
N: number of subjects with available data for the relevant endpoint

Table 7.2.2: Baseline demographic by pregnancy stage at ella® exposure – all Patients

	Before pregnancy (treatment failure) **(TOTAL=###)**	1st trimester (inadvertent exposure) **(TOTAL =###)**	2nd trimester (inadvertent exposure) **(TOTAL =###)**	3rd trimester (inadvertent exposure) **(TOTAL =###)**	Unknown (TOTAL=###)
Age (years)					
N	###	###	###	###	###
Missing	###	###	###	###	###
Mean (SD)	##.# (#.##)	##.# (#.##)	##.# (#.##)	##.# (#.##)	##.# (#.##)
Median	##.#	##.#	##.#	##.#	##.#
Min; Max	##.#; ##.#	##.#; ##.#	##.#; ##.#	##.#; ##.#	##.#; ##.#
Age : n (%)					
<35 years	## (##.#)	## (##.#)	## (##.#)	## (##.#)	## (##.#)
>=35 years	## (##.#)	## (##.#)	## (##.#)	## (##.#)	## (##.#)
Missing	## (##.#)	## (##.#)	## (##.#)	## (##.#)	## (##.#)
Weight (kg)					
N	###	###	###	###	###
Missing	###	###	###	###	###
Mean (SD)	##.# (#.##)	##.# (#.##)	##.# (#.##)	##.# (#.##)	##.# (#.##)
Median	##.#	##.#	##.#	##.#	##.#
Min; Max	##.#; ##.#	##.#; ##.#	##.#; ##.#	##.#; ##.#	##.#; ##.#
Height (m)					
N	###	###	###	###	###
Missing	###	###	###	###	###
Mean (SD)	##.# (#.##)	##.# (#.##)	##.# (#.##)	##.# (#.##)	##.# (#.##)
Median	##.#	##.#	##.#	##.#	##.#
Min; Max	##.#; ##.#	##.#; ##.#	##.#; ##.#	##.#; ##.#	##.#; ##.#
BMI (kg/m²)					
N	###	###	###	###	###
Missing	###	###	###	###	###
Mean (SD)	##.# (#.##)	##.# (#.##)	##.# (#.##)	##.# (#.##)	##.# (#.##)
Median	##.#	##.#	##.#	##.#	##.#
Min; Max	##.#; ##.#	##.#; ##.#	##.#; ##.#	##.#; ##.#	##.#; ##.#

n: number of subjects fulfilling the item listed
N: number of subjects with available data for the relevant endpoint

Table 7.3.3: Baseline demographic by pregnancy stage at ella® exposure – all Patients

	Patients with known pregnancy outcome (TOTAL=###)	Patients with unknown pregnancy outcome (TOTAL =###)	All patients (TOTAL =###)
Region : n (%)			
Region 1	## (##.#)	## (##.#)	## (##.#)
Region 2	## (##.#)	## (##.#)	## (##.#)
…			
Missing	##	##	##
Affiliate: n (%)			
Region 1	## (##.#)	## (##.#)	## (##.#)
Region 2	## (##.#)	## (##.#)	## (##.#)
…			
Missing	##	##	##

n: number of subjects fulfilling the item listed
N: number of subjects with available data for the relevant endpoint

7.2 Tables of history of pregnancy

Table 7.2.1. History of pregnancy – All patients

	Patients with known pregnancy outcome (TOTAL=###)	Patients with unknown pregnancy outcome (TOTAL =###)
History of pregnancy : n (%)		
Yes	## (##.#)	## (##.#)
No	## (##.#)	## (##.#)
Number of previous pregnancies		
1	## (##.#)	## (##.#)
2	## (##.#)	## (##.#)
3	## (##.#)	## (##.#)
4	## (##.#)	## (##.#)
5	## (##.#)	## (##.#)
6	## (##.#)	## (##.#)

Table 7.2.2. History of Spontaneous abortion – All patients
Same template as Table 7.2.1

Table 7.2.3. History of Fetal death – All patients

Same template as Table 7.2.1

Table 7.2.4. History of induced abortions for non-medical reason abortion – All patients
Same template as Table 7.2.1

Table 7.2.5. History of induced abortions for medical reason – All patients
Same template as Table 7.2.1

Table 7.2.6. History of birth defect – All patients
Same template as Table 7.2.1

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7.3 Tables of characteristics of Ella® intake

Table 7.3: Ella® intake – all Patients

	Patients with known pregnancy outcome (TOTAL=###)	Patients with unknown pregnancy outcome (TOTAL =###)
Number of 30mg tablets of ella®		
N	###	###
Missing	###	###
Mean (SD)	##.# (#.##)	##.# (#.##)
Median	##.#	##.#
Min; Max	##.#; ##.#	##.#; ##.#
Time from intercourse to ella® intake (in hours)		
N	###	###
Missing	###	###
Mean (SD)	##.# (#.##)	##.# (#.##)
Median	##.#	##.#
Min; Max	##.#; ##.#	##.#; ##.#
Time from intercourse to ella® intake (women not pregnant before ella® intake) (in hours)		
N	###	###
Missing	###	###
Mean (SD)	##.# (#.##)	##.# (#.##)
Median	##.#	##.#
Min; Max	##.#; ##.#	##.#; ##.#
Time from intercourse to ella® intake (women pregnant before ella® intake) (in hours)		
N	###	###
Missing	###	###
Mean (SD)	##.# (#.##)	##.# (#.##)
Median	##.#	##.#
Min; Max	##.#; ##.#	##.#; ##.#
Pregnancy status before ella® intake : n (%)		
Pregnant	## (##.#)	## (##.#)
Not pregnant	## (##.#)	## (##.#)
Unknown	## (##.#)	## (##.#)
Pregnancy stage at ella® exposure : n (%)		
Before pregnancy (treatment failure)	## (##.#)	## (##.#)
1st trimester (inadvertent exposure)	## (##.#)	## (##.#)
2nd trimester (inadvertent exposure)	## (##.#)	## (##.#)
3rd trimester (inadvertent exposure)	## (##.#)	## (##.#)
Unknown	## (##.#)	## (##.#)
How was the pregnant stage at ella® exposure determined : n (%)		
Ultrasound	## (##.#)	## (##.#)

LMP	## (##.#)	## (##.#)
Other	## (##.#)	## (##.#)
Time from LMP to exposure (in days)		
N	###	###
Missing	###	###
Mean (SD)	##.# (#.##)	##.# (#.##)
Median	##.#	##.#
Min; Max	##.#; ##.#	##.#; ##.#
Time from LMP to exposure (women not pregnant before ella® intake) (in days)		
N	###	###
Missing	###	###
Mean (SD)	##.# (#.##)	##.# (#.##)
Median	##.#	##.#
Min; Max	##.#; ##.#	##.#; ##.#
Time from LMP to exposure (women pregnant before ella® intake) (in days)		
N	###	###
Missing	###	###
Mean (SD)	##.# (#.##)	##.# (#.##)
Median	##.#	##.#
Min; Max	##.#; ##.#	##.#; ##.#
Multiple ella® intakes since her LMP : n (%)		
Yes	## (##.#)	## (##.#)
No	## (##.#)	## (##.#)
Missing	## (##.#)	## (##.#)

n: number of subjects fulfilling the item listed

7.4 Tables of characteristics of pregnancies

Table 7.4 Characteristics of pregnancies at outcome – all patients

	Patients with known pregnancy outcome (TOTAL=###)	Patients with unknown pregnancy outcome (TOTAL =###)
Gestational age at ultrasound (in weeks)		
N	###	###
Missing	###	###
Mean (SD)	##.# (#.##)	##.# (#.##)
Median	##.#	##.#
Min; Max	##.#; ##.#	##.#; ##.#
Sac > 20 mm: n (%)		
Yes	## (##.#)	## (##.#)
No	## (##.#)	## (##.#)
Missing	## (##.#)	## (##.#)
Intra-uterine pregnancy which is normal-appearing for gestational age: n (%)		
Yes	## (##.#)	## (##.#)
No	## (##.#)	## (##.#)
Unknown	## (##.#)	## (##.#)

7.5 Table of patients lost to follow-up

Table 7.5: Patients lost to follow-up – all patients

	n/N	Proportion
Lost to follow-up	xx/xx	xx.x%

7.6 Results for primary endpoints: Pregnancy outcomes

7.6.1 Table for the global population

Table 7.6: Primary endpoints – Patients with known pregnancy outcome

	Primary outcome	n/N	Missing	Proportion
Live Birth	Proportion of live births	xx/xx	xx	xx.x%
	Proportion of healthy babies	xx/xx	xx	xx.x%
	Live births prevalence of congenital anomalies	xx/xx	xx	xx.x%
	Live births prevalence of other neonatal morbidity	xx/xx	xx	xx.x%
	Total prevalence of congenital anomalies	xx/xx	xx	xx.x%
	Proportion of neonatal deaths	xx/xx	xx	xx.x%
	Proportion of preterm births	xx/xx	xx	xx.x%
Pregnancy loss	Proportion of ectopic pregnancies	xx/xx	xx	xx.x%
	Proportion of spontaneous abortions	xx/xx	xx	xx.x%
	Proportion of intermediate fetal deaths	xx/xx	xx	xx.x%
	Proportion of late fetal deaths	xx/xx	xx	xx.x%
	Proportion of normal-appearing pregnancies (with analysable ultrasound results) before induced abortion	xx/xx	xx	xx.x%
	Proportion of all induced abortions	xx/xx	xx	xx.x%
	Proportion of induced abortions for non-medical reason)	xx/xx	xx	xx.x%
	Proportion of induced abortions for medical reason	xx/xx	xx	xx.x%
	Proportion of maternal deaths	xx/xx	xx	xx.x%

7.7 Results for secondary endpoints

7.7.1 Table for the overall population

Table 7.7.1.1: Secondary endpoints – Healthy babies

	Healthy babies (TOTAL=###)
Birth weight (kg)	
N	###
Missing	###
Mean (SD)	##.# (#.##)
Median	##.#
Min; Max	##.#; ##.#
Delivery method : n (%)	
Vaginal	## (##.#)
Cesarean	## (##.#)
Missing	## (##.#)
APGAR score at 1 minute	
N	###
Missing	###
Mean (SD)	##.# (#.##)
Median	##.#
Min; Max	##.#; ##.#
APGAR score at 5 minutes	
N	###
Missing	###
Mean (SD)	##.# (#.##)
Median	##.#
Min; Max	##.#; ##.#

Table 7.7.1.2: Secondary endpoints - Patients with known pregnancy outcome

Secondary outcome	n/N	Missing	Proportion
Maternal and pregnancy complications	xx/xxx	xx	xx.x%

Table 7.7.1.3: Secondary endpoints - Fetal loss complications

	Pregnancy loss (TOTAL=###)
Vaginal Bleeding : n (%)	
Yes	## (##.#)
No	## (##.#)
Missing	## (##.#)
Type of bleeding : n (%)	
Spotting	## (##.#)
Regular	## (##.#)
Heavy	## (##.#)
Missing	## (##.#)
Excessive bleeding : n (%)	
Yes	## (##.#)
No	## (##.#)
Missing	## (##.#)
Duration of bleeding (days)	
N	###
Missing	###
Mean (SD)	##.# (#.##)
Median	##.#
Min; Max	##.#; ##.#
Blood transfusion performed : n (%)	
Yes	## (##.#)
No	## (##.#)
Missing	## (##.#)
Curettage performed : n (%)	
Yes	## (##.#)
No	## (##.#)
Missing	## (##.#)
Curettage performed : n (%)	
Following the usual protocol	## (##.#)
Because doctor was worried about excessive bleeding	## (##.#)
Missing	## (##.#)
Gestational age (weeks)	
N	###
Missing	###
Mean (SD)	##.# (#.##)
Median	##.#
Min; Max	##.#; ##.#
Infection : n (%)	
Yes	## (##.#)
No	## (##.#)
Missing	## (##.#)
Infection is a complication of pregnancy loss: n (%)	

Yes	## (##.#)
No	## (##.#)
Unknown	## (##.#)
Other complication: n (%)	
Yes	## (##.#)
No	## (##.#)
Unknown	## (##.#)

7.8 Results for concomitant medications

7.8.1 Table for the overall population

Patients with at least one Concomitant medication		N (%)
ATC code 1		
	ATC code 2	N (%)

7.9 Individual listings

Listing 7.1. Listing of all pregnancies

Subject Identifier for the Study	Age	BMI	Gestational age at ultrasound	Date of ultrasound	Date of diagnosis	Date of LMP	Expected delivery date	Number of tablets taken	Date of 1st ella® intake	Cycle day at 1st ella® intake	Date of 2nd ella® intake	Cycle day at 2nd ella® intake

Listing 7.2 : Listing of patients with healthy babies

Subject Identifier for the Study	Age calculated	Pregnant at ella® intake	Date of conception	Pregnancy term (weeks)	Number of babies born	Baby gender	Birth weight (kg)	Delivery method	APGAR score at 1 min	APGAR score at 5 min
ID1	xxxxx	xx	DD/MMM/YYYY	xx	xxx	Female	xx	xxxx	xx	xx
						Male	xx	xxxx	xx	xx

1 baby per row

Listing 7.3. Pregnancy information for pregnancies resulting in induced abortion for non-medical reason

Subject Identifier for the Study	Age calculated	Gestational age at ultrasound	Date of 1st ella® intake	Date of induced abortion for non-medical reason	Time between ella® intake and outcome (days)	Placenta pathology examination performed	Examination date	Examination result	Pregnancy term at time of fetal loss	Number of fetus(es)	Factors that may have had an impact on fetal loss	Other comments

Listing 7.4. Induced abortions for medical reason

Subject Identifier for the Study	Age calculated	Gestational age at ultrasound	Date of 1st ella® intake	Date of induced abortion for medical reason	Time between ella® intake and outcome (days)	Placenta pathology examination performed	Examination date	Examination result	Pregnancy term at time of fetal loss	Number of fetus(es)	Factors that may have had an impact on fetal loss	Other comments

Listing 7.5. Pregnancy information for pregnancies resulting in ectopic pregnancy

Subject Identifier for the Study	Age calculated	Gestational age at ultrasound	Date of 1st ella® intake	Time between ella® intake and outcome (days)	Placenta pathology examination performed	Examination date	Examination result	Pregnancy term at time of fetal loss	Number of fetus(es)	Factors that may have had an impact on fetal loss	Salpingitis or known tubal anomaly	Previous ectopic pregnancy	Previous tubal surgery	Other comments

Listing 7.6. Pregnancy information for pregnancies resulting in spontaneous abortion

Subject Identifier for the Study	Age calculated	Gestational age at ultrasound	Date of 1st ella® intake	Time between ella® intake and outcome (days)	Placenta pathology examination performed	Examination date	Examination result	Pregnancy term at time of fetal loss	Number of fetus(es)	Factors that may have had an impact on fetal loss	Other comments

Listing 7.7: Neonatal deaths - Patients with known pregnancy outcome

Subject Identifier for the Study	Outcome	Pregnancy term	Delivery method	Medically confirmed	Age calculated	Pregnant at ella® intake	Number of babies born	Age of neonate at death (days)	Cause of death	Relationship to ella® intake	Autopsy performed	Birth weight (kg)	Gender	APGAR score at 1 min	APGAR score at 5 min

1 baby per row

Listing 7.8: Fetal loss complications - Patients with known pregnancy outcome

Subject Identifier for the Study	Outcome	Medically confirmed	Age calculated	Pregnant at ella® intake	Any vaginal bleeding?	Type of bleeding	Duration of bleeding	Bleeding clinically excessive	Blood transfusion performed	Curettage performed	Any infection	Location of infection	Infectious agent	Treatment given	Infection= complication of pregnancy loss	Any other complication	Any other complication description

Listing 7.9. Listing of concomitant medications

Subject Identifier for the Study	Pregnancy outcome	Date of outcome	Date of 1st ella® intake	ATC code*	Drugname*	Indication	Intake during the cycle of conception	Period of exposure

*resulting from coding with WHO Drugs dictionary

Listing 7.10. Listing of hormonal contraception after Ella® intake in the same menstrual cycle

Subject Identifier for the Study	Pregnancy outcome	Date of outcome	Date of 1st ella® intake	Medication Name	Date of first intake after ella® intake	Route of administration

*resulting from coding with WHO Drugs dictionary

Listing 7.11: Congenital anomalies - Patients with known pregnancy outcome

Subject Identifier for the Study	Medically confirmed	Age calculated	Pregnant at ella® intake	Pregnancy term	Outcome	Date of conception	Date of 1st ella® intake	Date of 2nd ella® intake	Date of 3rd ella® intake

Subject Identifier for the Study	Age calculated	Delivery method	Number of babies born	List of Congenital anomalies	Relationship to ella® intake	Possible cause	Gender	Birth weight	APGAR score at 1 min	APGAR score at 5 min

Listing 7.12: Maternal history - Patients with known pregnancy outcome

Subject Identifier for the Study	Outcome	Age calculated	History of pregnancy	Number of previous pregnancies	Number of live infants	History of spontaneous abortion (misacarriage)	Number of spontaneous abortions	History of fetal death	Number of fetal deaths	History of induced abortions for non-medical reason	Number of induced abortions for non-medical reason

Subject Identifier for the Study	History of induced abortion for medical reason	Number of induced abortions for medical reason	History of birth defects	Number of infants with birth defects	Specify birth defects	Description of any maternal family history of congenital anomaly	Description of any other significant family history

Listing 7.13: Recreational drug use - Patients with known pregnancy outcome

Subject Identifier for the Study	Outcome	Age calculated	Drug	Y/N	Estimated weekly intake	Route of administration	1st trimester period consumption	2nd trimester period consumption	3rd trimester period consumption	consumption throughout pregnancy	Unknown consumption
ID1	xxxxx	xx	Tobacco	X	xx	xxxx	x	x	x	x	x
			Alcohol	X	xx	xxxx	x	x	x	x	x
….											

Listing 7.14: Medical condition(s) during pregnancy - Patients with known pregnancy outcome

Subject Identifier for the Study	Outcome	Age calculated	Record	Condition	Start date	Ongoing	Stop date

Listing 7.15: Initial serology tests - Patients with known pregnancy outcome

Subject Identifier for the Study	Outcome	Age calculated	Rubella test performed	Date of test	Result	Toxoplasmosis test performed	Date of test	Result

Listing 7.16: Prenatal tests - Patients with known pregnancy outcome

Subject Identifier for the Study	Outcome	Age calculated	Prenatal tests done	Ultrasound	Ultrasound record	AFP/serum markers	Amniocentesis	Reason for Amniocentesis	Cordocentesis	Reason for Cordocentesis	Other test, type	Other test, reason

Subject Identifier for the Study	Outcome	Test date	Evidence of a structural defect from one or more of the prenatal tests	Specify if other	Placenta pathology examination performed	Placenta pathology examination Date	Placenta pathology examination Result	Autopsy performed	Autopsy Date	Autopsy result

Listing 7.17: Congenital anomaly detected since birth - Patients with known pregnancy outcome

Subject Identifier for the Study	Outcome	Number of babies born	Baby age (months)	Baby height (cm)	Baby weight (kg)	Congenital anomaly	Relationship to ella® intake	Diagnosis date	Possible causes

1 baby per row

Listing 7.18: Late development detected since birth - Patients with known pregnancy outcome

Subject Identifier for the Study	Outcome	Number of babies born	Baby age (months)	Baby height (cm)	Baby weight (kg)	Details of late development detected since birth	Relationship to ella® intake	Diagnosis date	Possible causes

1 baby per row

Listing 7.19: Baby deaths - Patients with known pregnancy outcome

Subject Identifier for the Study	Outcome	Number of babies born	Baby age at deaths (days)	Cause of death	Relationship to ella® intake	Autopsy performed	Other comments

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8. REFERENCES

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