OBSERVATIONAL STUDY PROTOCOL

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

Protocol 2914-012
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PROTOCOL SYNOPSIS

Title

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

Phase

IV

Indication

Emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure (Marketing Authorization NDA 022474 dated 13 August 2010).

Objectives

Primary objective:
To assess the rates of occurrence of outcomes of pregnancies exposed to ella® (whether due to failure of the emergency contraception or inadvertent exposure during pregnancy). Data analysed will come from this prospective observational study, other studies and pharmacovigilance reporting.

Secondary objectives:
To collect data on fetal and neonatal outcomes, birth and maternal complications in case of pregnancies exposed to ella®.
To assess the nature and incidence of complications of pregnancy loss in pregnancies exposed to ella®.

Design

Prospective observational study.

Population

Pregnant women in the USA, who have been exposed to ella®:
- during the menstrual cycle in which the pregnancy started or
- at any time during pregnancy.

Women will be directly enrolled in the study using a website interface that will be accessible to Health Care Professionals (HCP) and women themselves.

Sample size

A sample size of 400 pregnancies with known outcome was chosen as it provides 80% power to detect a two-fold increase (Risk Ratio=2) for events with a proportion of 3% and a three-fold increase (RR=3) for events with a proportion of 1% (e.g., approximately equivalent to the total prevalence of congenital heart defects).

Data collection

Detailed clinical data on ella® exposure, pregnancy course and pregnancy outcomes, including fetal and neonatal outcomes, maternal pregnancy complications, medical history and use of other medications will be collected online using the study website.

Statistical analyses

The data collected in this study will be pooled with all reports of pregnancies collected by the Sponsor which include outcome information. Additional data sources include other clinical trials and Pharmacovigilance reporting. Pregnancy outcomes will be analyzed on the pooled dataset.

Baseline characteristics data of enrolled and completed cases will be described: age, pregnancy status at time of ella® exposure, dates of unprotected intercourse, last menstrual period, and ella® intake.

Each pregnancy outcome will be described as a proportion of pregnancies, with 95% exact confidence intervals.

Birth, maternal and pregnancy complications will be evaluated for each individual case, and the relationship with ella® exposure will be assessed according to the standard Pharmacovigilance process.

Proportions of adverse outcomes of ella®-exposed pregnancies will be compared with those from a suitable general reference population that would comprise essentially all non-exposed pregnancies, e.g. for congenital anomalies, population would be based on data from registries for congenital anomalies, notably members of the European Surveillance of Congenital Anomalies, EUROCAT.

Sponsor's pharmacovigilance responsibilities

All cases will be managed according to the sponsor's Pharmacovigilance processes, in line with the applicable legislation.

Whenever applicable, individual case safety reports (ICSRs) will be submitted to Health Authorities on an expedited basis according to current regulations.

Progress status updates will be given in each Periodic Safety Update Report (PSUR) and Development Safety Update Report (DSUR) if applicable.

Additionally, a descriptive analysis of the data collected will be provided annually in the PSUR.

Study duration and dates

Recruitment of women will be done using a website access. Implementation of the website is planned for the second quarter of 2014 and website will be in place during the whole course of the study.

STUDY SCHEDULE

Period of pregnancy / Study procedures	Enrolment in the study	Pregnancy Course	End of pregnancy	4 months FU[3]
Written[1] 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[2]			X	
Live birth follow-up[3]				X

[1]: Signed ICF will be collected according to local regulations. When completed by the HCP, prior starting the questionnaire completion, the ICF will be downloaded from the website and a print-out copy signed by the woman. When completed by the woman, prior starting the questionnaire completion, an electronic signature will be requested on the ICF module and the woman will be requested to save and/or print the ICF for her records.
[2]: Possible pregnancy outcomes are: Live birth (healthy baby, congenital anomaly or other neonatal diagnosis, or neonatal death); pregnancy loss (spontaneous abortion or ectopic pregnancy or induced abortion, premature stillbirth)
[3]: In case of live birth, the period of observation of the study will last for 4 months post-delivery to access possible congenital anomalies that may not be detected at birth.

ABBREVIATIONS AND DEFINITIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AFP	Alpha-Fetoprotein
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organization
DMB	Data Monitoring Board
DSUR	Development Safety Update Report
EC	Emergency Contraception
EUROCAT	European Surveillance of Congenital Anomalies
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research
ICF	Informed Consent Form
ICSR	Individual Case Safety Report
EMA	European Medicines Agency
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
LMP	Last Menstrual Period
NDA	New Drug Authorization
PI	Prescribing Information
PL	Patient Leaflet
PSUR	Periodic Safety Update Report
RR	Risk Ratio
SAE	Serious Adverse Event
TOPFA	Terminations Of Pregnancy for Fetal Anomaly
UPA	Ulipristal Acetate
USA	United States of America

1 INTRODUCTION AND STUDY RATIONALE

ella® (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. HRA Pharma acquired the license rights of the compound in 2000 and has been developing it ever since. The compound has been tested in an extensive battery of non-clinical and clinical studies and was approved for marketing New Drug Authorization (NDA) at the dose of 30 mg (tablet) for emergency contraception up to 120 hours (5 days) in the European Union (EU/1/09/522/001) and the United States of America (NDA 022474), in May 2009 and August 2010 respectively.

During the clinical development phase, only a small number of pregnancies have occurred following administration of ella®. During the evaluation process of the ella® 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.

HRA Pharma committed to collecting information on clinical follow-up and outcomes of pregnancies that begin following ella® failure as well as pregnancies inadvertently exposed to ella® by putting in place:

- A voluntary web-based pregnancy registry available in all European countries where the product is launched and accessible to all ella® prescribers;
- An observational study, targeting 1000 investigators in the Europe and the USA (ellipse).

After several months of efforts to conduct the observational study required in PMR 1673-1 (ellipse), HRA Pharma came to the conclusion that it was highly unlikely that it would ever be able to recruit the target site prescribers and that, also due to the very low rate of ella® failure, the number of reported pregnancies would remain extremely limited.

Indeed, the process of selection of investigators began in May 2011 in the European Union. At that time, over 6,000 healthcare providers (HCPs) were contacted. Due to a disappointing response rate, an additional 3,700 providers were contacted started in September 2011. The first site was initiated in June 2011 and 219 sites had been initiated in Europe by end 2012. Eight pregnant women have been identified, and actions have been undertaken to increase the number of selected sites in Europe. In the US, finding investigational sites has found to be even more difficult since the use of ella® is very low and limited to family planning clinics which typically do not follow-up women after they become pregnant. Several institutions providing emergency contraception were contacted from December 2010. In September 2011, in order to reach a larger number of HCPs in the USA, an information document was prepared for distribution during 10 medical congresses held in October and November throughout the territory. About 2,600 attendees were expected to participate in these congresses. No feedback from HCPs has ever been received. At this time, no US site has been able to or interested in participating in the study.

There was therefore a clear need to change the way pregnancy data are obtained in order to collect information on pregnancy outcomes after ella® exposure.

Following consultation with European authorities (EMA), it was decided to redirect efforts from the observational study towards improving the existing online pregnancy registry. The EMA agreed that no additional sites would be initiated in the observational study and that data collection would be stopped once the improved web-based pregnancy registry was launched. The ellipse study progress was also discussed with the FDA during a Type C meeting held on November 15, 2012 and it was decided to amend the ellipse protocol to include the web-based enrollment and data collection.

2 STUDY OBJECTIVES

2.1 Primary objective

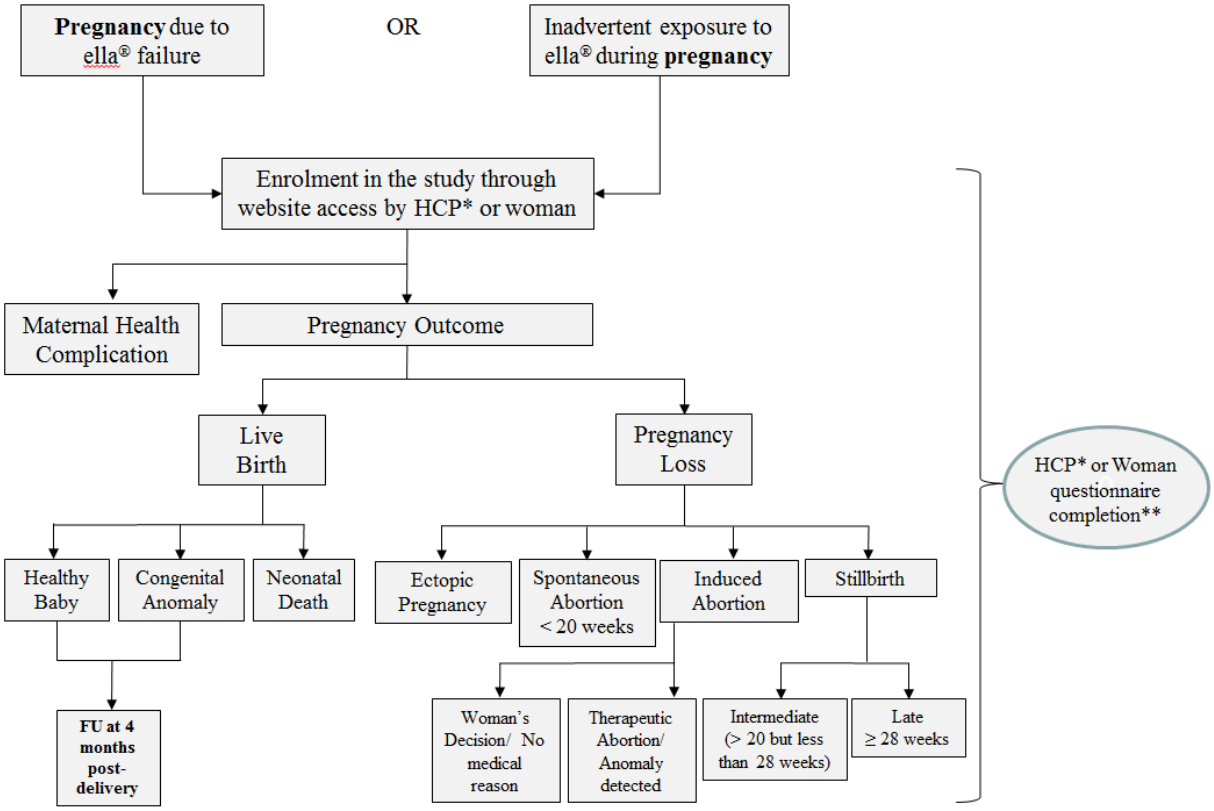
The primary objective of this observational study is to assess the rates of occurrence of outcomes of pregnancies exposed to ella® (whether due to failure of the emergency contraception or inadvertent exposure during pregnancy). Data analyzed will come from this prospective observational study, other studies and pharmacovigilance reporting.

2.2 Secondary objectives

The secondary objectives of this observational study are:

- To collect data on fetal and neonatal outcomes, birth and maternal complications in pregnancies exposed to ella®;
- To assess the nature and incidence of complications of pregnancy loss in pregnancies exposed to ella®.

3 STUDY DESIGN AND SCHEMATIC REPRESENTATION OF THE OUTCOMES



* Women who do not want to provide her HCP contact details, will have the option to contact a referent physician who will be commissioned to follow-up directly with the woman.

** Questionnaire may be completed on-line either by the woman or the HCP at any time from pregnancy diagnosis up to known pregnancy outcome. For live birth (except for neonatal death), woman or the HCP will be requested to complete a follow-up questionnaire 4 months after the delivery date.

4 SELECTION OF WOMEN

4.1 Number of women

As per rationale detailed in section 9.1, a total of 400 ella®-exposed pregnancies with known outcomes will be analysed.

4.2 Enrolment process

Enrolling an exposed woman in the study will involve completing an online questionnaire either by the HCP or directly by the woman (see also section 8.1 Description of Study Steps).

4.2.1 Completion of HCP on-line questionnaires by the HCP

There will be a specific on-line questionnaire to be completed by the HCP where data on pregnancy diagnosis and exposure to ella® will first be collected. Once the pregnancy outcome is known, the HCP will be requested to complete the rest of the questionnaire.

For live birth, HCP will be requested to complete follow-up forms 4 months after the delivery date (**4-month Follow-Up HCP Form**).

4.2.2 Completion of the Woman on-line questionnaires by the woman

There will be one online questionnaires to be completed by women, which will be different from that for HCPs.
A single questionnaire will be completed by the woman, where data on pregnancy diagnosis, exposure to ella®, and if known at the time of the questionnaire completion, the pregnancy outcome. If not known at the time of the first completion, the woman will have the option to get back to the questionnaire and continue its completion when the outcome will be known.

For live birth, woman will also be requested to complete a follow-up questionnaire 4 months after the delivery date (**4-month Follow-Up Woman Form**).

The language of the woman questionnaire will be further adapted to facilitate understanding and format will have functional ergonomics that are permitted by online data entry such as linked questions, drop-down menus, and agenda for fill in dates. In addition, some of the questions will integrate a specific tutorial for helping the declarant to enter appropriate answers. Contents of the information requested in the woman questionnaires are detailed in a specific distinct document submitted to the IRB for its approval prior to implementation.

Women who do not want to provide their HCP contact details, will have the option to contact a referent physician who will be commissioned to follow-up directly with the women. Referent physician will be able to answer their questions and guide them through the questionnaire completion process. The referent physician will not be able to complete the woman questionnaire on their behalf.

4.2.3 Enrolment enhancement

In addition to changing the way the study is conducted, the following actions will be carried out to enhance the enrolment of ella®-exposed pregnant women in the USA:

- A dedicated website will provide a complete description of the study for Ella®-exposed women and HCP as well as access to reporting forms.
- HCP and ella®-exposed pregnant women will primarily be made aware of this study through information in the Product Labelling [Prescribing Information (PI) / Patient Leaflet (PL)]. Introduction of the website address in PI and PIL will help HCP and women to have direct access to the on-line study.
- Promotional information for HCP will include a reminder on the existence of the pregnancy study.
- Links to the study website will be made from the product and company websites.
- A reminder to HCP about the existence of the study could also be done at the following occasions:
    - Information to HCP by sales representatives;
    - Local, national and international scientific meetings/conferences/congresses;
    - Continuing education sessions for medical professionals;
    - Contacting relevant professional organizations;
    - Registering the study on pregnancy registry website (such as the FDA Office of Women's Health (OWH) pregnancy registry website).

4.3 Inclusion criteria

Women meeting all the following criteria will be considered for admission to the study:

- Pregnant women in the USA, exposed to ella® during the menstrual cycle in which the pregnancy started (treatment failure) or at any time during pregnancy (inadvertent exposure during pregnancy)
- Written informed consent provided:
    - When the questionnaire is completed by the HCP, the ICF will be downloaded from the website and 2 print-out copies signed by the woman. One signed copy will be given to the woman for her records.
    - When completed by the woman, an electronic signature will be requested on the ICF module and the woman will be requested to save and/or print-out the ICF for her records.

5 INFORMATION ON ella® SUPPLY

HRA Pharma will not supply any medication. Women will be enrolled after having taken commercially available ella®.

6 MEDICAL HISTORY

Maternal medical history related to previous pregnancies or any other relevant medical history will be reported by the HCP or woman questionnaire.

Family history of hereditary or other birth defect will also be collected.

7 PRIOR AND CONCOMITANT MEDICATIONS

Any relevant medication (prescription or non-prescription), including hormonal contraceptive, taken from the Last Menstrual Period (LMP) and up to pregnancy outcome will be collected in the HCP or woman questionnaire.

HRA Pharma's Pharmacovigilance department may contact the reporter to collect additional relevant information needed for the appropriate evaluation of a case.

8 STUDY PROCEDURES AND SCHEDULE

8.1 Overview of safety data

Pregnancy information
Date of diagnosis, date of LMP, date and results of ultrasound (if applicable) and expected delivery date.

Exposure to ella®
Data on exposure to ella® include date of ella® intake and number of tablets taken, time from intercourse to ella® intake; pregnancy stage at ella® exposure, pregnancy status before ella® intake.

Outcomes
All outcomes and the data collected to assess them are:

- Live birth – gender, birth weight, gestational age, delivery method and Apgar scores will be collected in all cases. For healthy babies and those with congenital anomalies or other neonatal diagnosis, the study observation period will last until 4 months after delivery;
    - Congenital anomaly or other neonatal diagnosis – description of anomaly and possible causes will be additionally collected;
    - Neonatal death (from birth through to 28 completed days of age*)– age at death, possible etiology and result of autopsy if performed will be additionally collected.

- Pregnancy loss – gestational age, possible etiology of pregnancy loss and any complications (vaginal bleeding, need for curettage, infection) will be collected in all cases.
    - Spontaneous abortion (or early fetal death i.e. < 20 completed weeks of gestation*)
    - Ectopic pregnancy
    - Induced abortion (no medical reason – woman's elective choice, elective abortion with fetal defects, or maternal health complications)
    - Stillbirth:
        - Intermediate fetal death (more than 20 completed weeks of gestation but less than 28*)
        - Late fetal death (≥ 28 completed weeks of gestation*).

Maternal health complications of pregnancy

In all cases, relationship of the outcome observed with the exposure to ella® will be assessed by the HCP and according to the standard pharmacovigilance process.

* According to the WHO International Classification of Disease (ICD)

Prior and concomitant medications
Prior and concomitant medications will be collected in the HCP or women questionnaires. Collection period covers the pregnancy duration from LMP to the end of pregnancy.

Other
Maternal family history; recreational drug use (tobacco, alcohol, illicit drugs) and serological and prenatal tests.

8.2 Description of study steps

Depending upon the questionnaire (HCP or woman), the following information will be collected through the questionnaires' completion either directly from the woman or by the HCP.

8.2.1 Completion of the on-line questionnaire by the HCP

Depending upon the outcome, there will be different forms to be completed on-line by the HCP and for live birth only, 4-month Follow-Up HCP Forms will have to completed as well.

8.2.1.1 Website access and registration

At the first website access, the HCP will be requested to:

- Register on the website, a user identifier and a password (to be changed at the first login) will be sent by e-mail to the HCP. HCP will be requested to use this login to access the on-line questionnaire;
- Complete the on-line training;
- Fulfil administrative steps: download and acknowledge Confidentiality Agreement reading, as well as the Study protocol.

8.2.1.2 Enrolment Steps

Prior to enroll a woman, the HCP will have to:

- Download the Information Sheet from the website, to be given to the woman during the consultation;
- Download the ICF and the HIPAA Authorization agreement from the website and print it out;
- Enroll the woman by collecting her signature on the ICF and HIPAA agreement and give her a copy of the signed documents.

After enrolment, the HCP will access the on-line questionnaire and will be asked to:

-Collect the woman contact details to ensure future follow-up of the pregnancy outcome (first 3 characters of the last name and first character of the first name,), date of birth, weight and height. If applicable, the contact details of the clinician/midwife in charge of pregnancy follow-up should also be collected (see also section 8.3 Participant follow-up)

-Collect information on pregnancy [including date of diagnosis, date of LMP, date and results of ultrasound (if applicable), expected delivery date]

-Collect data on ella® exposure (date of ella® intake, number of tablets taken, time from unprotected intercourse to ella® intake, pregnancy stage at exposure and pregnancy status before ella® intake)

-Collect relevant current or prior medication during the pregnancy, including hormonal contraception or folic acid at the time of conception

-Collect any relevant medical condition (including maternal health complications) observed preceding or during pregnancy

-Save and submit the questionnaire

8.2.1.3 Completion of the Pregnancy Outcome Forms

When the outcome of the pregnancy is known*, the HCP will be asked to fill-in the Pregnancy Outcome forms.

-Access the website with the HCP unique user ID and password

-Start the Pregnancy Outcome Form completion

-Collect the pregnancy outcome observed [live birth (i.e. healthy baby, congenital anomaly, neonatal death) including pregnancy complications, pregnancy loss (including spontaneous abortion, ectopic pregnancy, therapeutic abortion, intermediate or late fetal death), maternal health complications]

-Collect recreational drug use (tobacco, alcohol, illicit drugs), if any

-Collect relevant maternal and family medical history, including history related to previous pregnancies, including congenital birth defects

-Collect serology and prenatal tests (type, date, results)

-Collect relevant concomitant medications

-Save and submit the forms.

8.2.1.4 Completion of the 4-month Follow-Up HCP Forms

In case of live birth and 4 months after the delivery, the HCP be reminded to re-access the website. The HCP will be asked to:

-Access the website with the HCP unique user ID and password

-Collect the age, height and weight of the baby

-Collect congenital anomaly detected since birth, if applicable

-Collect late development detected since birth, if applicable

-Collect death data, if applicable.

8.2.2 Completion of the on-line questionnaire directly by the woman:

Up to three questionnaires will be completed by the woman: the first two ones including Pregnancy and Outcome Forms, and one for live birth only, a 4-month Follow-up Form.

* In case a woman completed the questionnaire on her own, she should be reminded to bring her unique patient number to allow the HCP to provide further information on the pregnancy if requested.

8.2.2.1 Website access and enrolment

- Access the website
- Download the Information Sheet from the website, read it and acknowledge its reading and understanding
- Download the ICF from the website, acknowledge its reading and understanding by signing it electronically
- Read inclusion criteria and get enrolled by saving or printing-out the signed ICF, to be kept for the woman's records
- By signing and saving and/or printing out the ICF, the woman will be considered as enrolled in the study.

8.2.2.2 Completion of the Pregnancy and Outcome Forms

- Access the on-line questionnaire
- Provide first 3 characters of her last name and first character of her first name, date of birth, e-mail address (which will be blinded to the sponsor), her weight and height
- Provide information on pregnancy [including date of diagnosis, date of LMP, date and results of ultrasound (if applicable), expected delivery date]
- Provide data on ella® exposure (date of ella® intake, number of tablets taken, time from unprotected intercourse to ella® intake, pregnancy stage at exposure, additional ella® intake)
- Provide relevant concomitant medications taken during the pregnancy, including hormonal contraception or folic acid at the time of conception
- Report any relevant medical condition preceding or during pregnancy (e.g. diabetes, hypertension)
- Provide the pregnancy outcome observed [live birth (including healthy baby, congenital anomaly, neonatal death), pregnancy loss (including spontaneous abortion, ectopic pregnancy, therapeutic abortion, intermediate or late fetal death)]
- Provide recreational drug use (tobacco, alcohol, illicit drugs), if any
- Provide HCP details*. If the woman is not willing to provide her HCP details, she will be invited to contact a referent physician for assistance in the completion of the questionnaire
- Save and submit the questionnaire
- A unique patient number will be sent by e-mail to the woman, to be used for further access to the website. The woman will be able to further access her file at any time by using her unique patient number and continue the questionnaire completion when additional follow-up data is known.

8.2.2.3 Completion of the 4-month Follow-Up Woman Form

In case of live birth and four months after the delivery, the woman will receive an e-mail asking to re-access the website.

- Access the website and re-enter the unique file number provided by e-mail at the time of the Pregnancy and Outcome Forms submission

* Ideally the HCP in charge of the pregnancy follow-up (for e.g. midwife, obstetrician,…)

- Provide the age, height and weight of the baby
- Provide any congenital anomaly detected since birth, if applicable
- Collect late development detected since birth, if applicable

8.3 Participant follow-up

Reporters (HCP or women) will be asked to carefully keep either their user ID and password or the unique patient number they received.

Reporters, mainly the HCP can be contacted by the Sponsor's drug safety department to obtain medical follow-up information on women included in the study or on baby(ies)'s health 4 months after the delivery date (for life births only).
However, as stated earlier, if the reporter is a woman who did not provide contact details of an HCP the system will generate an e-mail to the woman to request further information. Note that the woman email address will be kept blinded to the sponsor.

Additionally, each HCP having enrolled a woman before the pregnancy outcome was known will be contacted by the Sponsor's drug safety department at 20 weeks of the pregnancy and at the scheduled delivery date and will be asked to complete the online questionnaire accessible on the website.

This contact will be done via e-mail within 15 days after the presumed date of delivery. If no answer is received within 30 days, the HCP will be contacted again twice with 1 month interval.

8.4 Methods of data collection

Online questionnaires for data collection will be available on a dedicated and secured website. Once submitted, these questionnaires will be received by the Sponsor's drug safety department.

Specific questionnaires may be completed on-line either by the HCP or directly by the woman at any time from pregnancy diagnosis up to known pregnancy outcome.

There will be a specific on-line questionnaire to be completed by the HCP where data on pregnancy diagnosis and exposure to ella® will first be collected. Once the pregnancy outcome is known, the HCP will be requested to complete the rest of the questionnaire.
For live birth only (except for neonatal death), HCP will be requested to complete a follow-up questionnaire 4 months after the delivery date (**4 month Follow-Up HCP Form**).

When completed directly by the woman, the woman will have to complete a simplified questionnaire where data on pregnancy diagnosis, exposure to ella®, and if known at the time of the questionnaire completion, the pregnancy outcome.
For live birth only (except for neonatal death), the woman will be encouraged to fill in a 4-month Follow-Up Form around 4 months after the delivery date (**4 month Follow-Up Woman Form**).

The on-line questionnaires together with instructions will be available in English for the HCP and in both English and Spanish for the woman.

9 STATISTICAL PROCEDURES

9.1 Sample size justification

As described below, a sample size of 400 pregnancies with known outcomes was chosen as it provides 80% power to detect a two-fold increase (Risk Ratio=2) for events with a proportion of 3% and a three-fold increase (RR=3) for events with a proportion of 1% (e.g., approximately equivalent to the total prevalence of congenital heart defects) (refer to Annex 1).

Sample size and confidence interval calculations were done using Stata (version 11, Statacorp) and EpiInfo (CDC, Atlanta, GA) software programs.

Estimates for sample size requirements were performed with the goal of detecting a signal, if one exists, of an increase in the proportion of adverse pregnancy outcomes for pregnancies exposed to ella® compared to a given reference population. For these calculations, it is assumed that event rates / proportions would be comparable for an unexposed population and its corresponding source population, as by far most (essentially all) pregnancies in the source population would be unexposed to ella®.

Sample size calculations were performed assuming a type-I (alpha) error rate of 0.05, two-sided tests and a ratio of exposed to unexposed group of 1:10. Higher ratios (e.g., 1:6 or 1:4) would require somewhat higher sample sizes for the exposed group (detailed calculations are not shown) but the difference would be relatively small as the main determinant of study power will be the number of pregnancies exposed to ella®.

Pregnancies exposed to ella® will come from various population sources. In this context, stratified analyses for country-specific (or regional) outcomes may be helpful but would pose substantial limits as to the power for detecting the statistical significance of any observed differences.

Various sources of data may be found for large numbers of (essentially all) unexposed pregnancies for different adverse pregnancy outcomes (e.g. for congenital anomalies, population-based data from registries for congenital anomalies, notably members of the European Surveillance of Congenital Anomalies, EUROCAT).

The term proportion is being used here as the measure of the frequency of adverse outcomes (e.g., preterm delivery / intrauterine growth restriction) and/or a specific adverse event (e.g., stillbirths, congenital anomalies). This may represent a cumulative incidence or in case of congenital anomalies the total or live birth prevalence of an anomaly (prevalence is the accepted term in the field of congenital anomalies to take into account early / unrecognized pregnancy loss, which precludes a true calculation of an incidence rate for congenital anomalies in the general population).

Table 1 (Annex 1) presents the sample size requirements for comparisons of proportions of adverse outcomes in pregnancies exposed to ella® versus those in the general population (essentially all unexposed). In summary, a sample size of approximately 50 and 100 pregnancies exposed to ella® can provide sufficient power to detect a two-fold increase [Risk Ratio (RR) = 2] in the risk of an adverse event with a baseline frequency of 20 (such as miscarriage) and 10%, respectively [such as intrauterine growth restriction as defined at birth (i.e. Small for Gestational Age)]; for a 50% increase (RR=1.5), the corresponding sample sizes would be approximately 160 and 375, respectively. A sample size of approximately 200 would provide a power of 80% to detect a two-fold increase for an adverse pregnancy event with a proportion of 5% in the general population (such as preterm birth). A sample size of approximately 400 would provide 80% power to detect a two-fold increase (RR=2) for events with a proportion of 3% and a three-fold increase (RR=3) for events with a proportion of 1% (e.g., approximately equivalent to the total prevalence of congenital heart defects [1],[2],[3]). For rarer events (e.g., those noted in Table 2 – Eurocat data) with a proportion of 0.1% (e.g., oro-facial clefts with a

prevalence of approximately 1 per 1000) or 0.05% (e.g., major specific congenital anomalies such as spina bifida which has a baseline total prevalence of about 4-5 per 10,000), sufficient power to detect even a ten-fold increase (RR=10) would require, respectively, almost 500 and 1000 pregnancies exposed to ella®; detection of a three-fold increase (RR=3) would require approximately 4000 pregnancies exposed to ella® and 40,000 unexposed pregnancies.

Confidence intervals are also provided for proportions of adverse outcomes that may be obtained for a given number of pregnancies exposed to ella® (Table 3, Annex 1). These confidence intervals will be used to evaluate the precision of estimates for assessing the frequency of various adverse pregnancy outcomes in the pregnancies exposed to ella®.

In addition, for sample sizes of 50, 100, 400 and 1000, one-sided 97.5% binomial exact confidence intervals were calculated for the proportion of adverse outcomes assuming that zero adverse events are observed for a given sample. The upper bounds of these confidence intervals (the lower bound is fixed at zero) can be used as an approximate indication of what may be the highest event rates that would be missed because of a limited sample size. In particular, these confidence intervals can be used to assess to what extent rare outcomes (e.g., specific congenital anomalies) may be missed given the (highest) sample sizes that may be feasible to collect.

In summary, sample size calculations described above and presented in detail in Table 1 (Annex 1) show that for relatively frequent events, e.g., spontaneous abortions, or a composite index of different adverse outcomes (e.g., intrauterine growth retardation, preterm delivery and congenital anomalies) with a baseline proportion of 20% and 10%, sample sizes of 50 and 100, respectively, can provide sufficient power to detect a two-fold increase in the risk of adverse events associated with exposure to ella®. For events with a baseline proportion of 5 and 3% in the population, the corresponding sample sizes would be 200 and 400, respectively. For rare outcomes such as specific congenital anomalies (Table 2, Annex 1), only very high increases in the risk (Table 1, Annex 1) may be detectable given feasibility considerations.

Taking into account the above calculations and feasibility considerations, a sample size of 400 pregnancy outcomes was chosen for the study.

9.2 Statistical analyses

9.2.1 Study Population

The data collected in this study will be pooled with all reports of pregnancies collected by the Sponsor which include information on pregnancy outcome. Additional data sources include other past and current clinical trials and spontaneous pharmacovigilance reporting. Pregnancy outcomes will be analyzed on the pooled dataset.

9.2.2 Statistical analysis

All planned analyses will be detailed in the statistical analysis plan.

9.2.2.1 Descriptive analysis

Descriptive statistics (mean, standard deviation, 95% confidence interval for mean, minimum, median, maximum, and number of observations and missing cases) for quantitative variables, and proportions (cumulative incidence or prevalence) for categorical variables will be calculated with binomial or Poisson exact confidence intervals. The proportion of cases that are lost to follow-up will be described.

Baseline characteristics data of enrolled and completed cases will be described: age, pregnancy status at time of ella® exposure, time from unprotected intercourse to exposure in case of treatment failure, or time from LMP to exposure in case of inadvertent use as well as multiple ella® intakes since her LMP.

9.2.2.2 Primary Objective Assessments

The primary objective of this observational study is to estimate the rates of occurrence of outcomes of pregnancies exposed to ella® in order to detect a possible signal of concern for adverse outcomes related to exposure to ella®.

Each pregnancy outcome will be described by proportions (cumulative incidence/prevalence) with exact 95% confidence interval.

For each pregnancy outcome, data from all sources (past and current clinical trials, registry, spontaneous pharmacovigilance reporting) will be used. Outcomes to be evaluated are defined as follows:

<u>All Induced abortions (due to a medical/non-medical reason)</u>:
Proportion of normal-appearing pregnancies (with analysable ultrasound results) before induced abortion = number of normal-appearing pregnancies with ultrasound compatible with normal growth and development/ number of pregnancies with analysable ultrasound results.

<u>Therapeutic abortion (medical indication)</u>
Proportion of therapeutic abortions = number of therapeutic abortions / number of pregnancies

<u>Birth outcomes</u>

Proportion of live births = number of live births/ total number of births

Proportion of healthy babies = number of live births without any anomaly (healthy babies) / number of deliveries

Total live birth prevalence of congenital anomalies = number of live births with congenital anomalies / number of live births

Proportion of neonatal deaths = number of neonatal deaths / number of live births

<u>Congenital anomalies:</u>

Total prevalence of congenital anomalies = total number of congenital anomalies (terminations of pregnancy for fetal anomaly (TOPFA), stillbirths, live births with congenital anomalies / total number of births (live births + stillbirths)

<u>Pregnancy loss outcomes</u>

Proportion of spontaneous abortions (or spontaneous abortion cumulative incidence) = number of spontaneous abortions / number of pregnancies

Proportion of intermediate fetal deaths* = number of intermediate fetal deaths / number of pregnancies

Proportion of stillbirths (or stillbirth cumulative incidence) = number of stillbirths / number of pregnancies

* more than 20 completed weeks of gestation but less than 28, according to the WHO fetal death classification.

Proportion of ectopic pregnancies (or ectopic pregnancy cumulative incidence) = number of ectopic pregnancies / number of pregnancies with known outcomes reported

These proportions (cumulative incidence) of adverse events and their 95% confidence intervals will be calculated for the overall sample as well as by country, in order to assess potential differences due to variations in clinical practice regarding the management of pregnancies and pregnancy complications. Results will also be presented by age.

9.2.2.3 Secondary Objective Assessments

The secondary objectives of this observational study are to:

- Collect data on pregnancy, birth and maternal complications in case of pregnancies exposed to ella®.

  In addition to statistical analysis, pregnancy, birth and maternal complications will be described with a case by case approach, and the relationship with ella® intake (certain / probable / possible / unlikely / not related / unknown) will be assessed by pregnancy data monitoring board (DMB).

- Assess the nature and incidence of complications of pregnancy loss in pregnancies exposed to ella®.

Complications of pregnancy loss are of special interest, in particular excessive and prolonged bleeding events.
Duration of bleeding events will be described in terms of descriptive statistics (mean, standard deviation, median, range).
The cumulative incidence of excessive bleeding episodes (considered as excessive by the HCP) will be calculated by dividing their occurrence by the number of pregnancy losses during the study.

Cumulative incidence of maternal heath complications related to pregnancy loss will also be calculated by dividing the number of complications by the number of pregnancy losses.

These proportions (cumulative incidence) of adverse events and their 95% confidence intervals will be calculated for the overall sample as well as by country, in order to assess potential differences due to variations in clinical practice regarding the management of pregnancies and pregnancy complications. Results will also be presented by age.

9.2.2.4 Statistical testing and multi-variable analysis

Given an appropriate reference population, the usual tests for statistical significance: chi-square or Fischer's exact test for the proportions or t-tests for continuous (interval-scale) variables (such as birth weight) will be used to evaluate the statistical significance of differences in event rates between pregnancies exposed to ella® versus those in the reference group (unexposed) pregnancies. Given a sufficiently large sample size for pregnancies exposed to ella®, multi-variable models (multiple linear and logistic regression for continuous and binary outcomes, respectively) will be used to assess the effects of risk factors for adverse outcomes in pregnancies exposed to ella®. This will be helpful in part for evaluating whether any particular adverse events in pregnancies exposed to ella® are due to known risk factors for these events or to suggest groups of women who may be at high risk for certain adverse events to determine whether precautionary measures (close surveillance / relative contra-indications) may be indicated for certain groups of women.

10 SPONSOR PHARMACOVIGILANCE RESPONSIBILITIES

Whenever applicable, Individual Case Safety Reports will be reported to Health Authorities on an expedited basis according to current regulation [i.e. in no case later than 15 calendar days from receipt (see GVP Module VI EMA/873138/201 and 21 CFR for the USA).

This includes:

- Reports of congenital anomalies or development delay in the fetus or in the baby
- Reports of fetal death and spontaneous abortion.
- Reports of suspected adverse reactions (ADRs) in babies that are classified as serious.
- Reports of pregnancies resulting from ella® failure reported as required in GVP module VI for reports of lack of therapeutic efficacy for contraceptive.

Unintended pregnancy reports (i.e. reports of pregnancies inadvertently exposed to ella® without outcome data or with normal outcome) are considered as not serious by the company.

Reports of the aggregate data concerning pregnancies will be compiled and submitted to Health Authorities via Periodic Safety Update Reports (PSUR).

11 DATA MONITORING BOARD

An independent board of experts will evaluate outcomes of exposed pregnancies reported to the Sponsor's Pharmacovigilance department. All pregnancies entered in the pharmacovigilance database (all clinical studies, European registry, spontaneous pharmacovigilance reporting) will be reviewed and assessed by the board. It is a multidisciplinary and multinational board including the following medical specialties:

- 1 Obstetrics–Gynaecology/Reproductive Endocrinology specialist;
- 1 Dysmorphologist specialized in congenital anomalies;
- 1 Paediatrician specialized in neonatology;
- 1 Statistician with a sub-specialty in epidemiology.

This group will serve as an autonomous independent pregnancy Data Monitoring Board (DMB) reviewing all reported pregnancies from all sources (all past and current clinical trials including the ellipse II study, European registry and spontaneous pharmacovigilance case reports) periodically reviewing the reported outcomes of all pregnancies exposed to ella® by batches of 50. Moreover if specific safety issues are detected, a DMB meeting may be called by HRA Pharma.

11.1 Assessment of pregnancy outcome

According to the following information provided (date of last menstrual period, date of ella® intake, associated risks factors), the DMB will review all pregnancy outcomes and determine for each pregnancy complication whether it could be linked to ella® intake.

11.2 DMB assessment

Following data review, the DMB will prepare a synopsis report stating that it performed a review and giving conclusions as follows:

Conclusions on the case evaluated:

1. *There is no relationship between ella® intake and the outcome observed.*

2. *The relationship between ella® intake and the outcome observed is unknown.*
3. *It is unlikely that the outcome reported is due to ella® intake.*
4. *It is possible that the outcome reported is due to ella® intake.*

For any of the conclusions, the DMB chair will provide a copy of the written synopsis including the conclusions made during the meetings as well as supplementary comments as applicable to HRA Pharma within 15 days after the DMB meeting.

11.3 DMB working procedures

Prior to the first review, the sponsor will provide the DMB with written standard operating procedures describing the list of members, their CVs, the frequency of review, the list of data to be reviewed, the list of conclusions applicable to evaluated cases and the list of records to be archived.

12 ETHICAL AND LEGAL ASPECTS

12.1 Women information and informed consent

Women must consent in writing (hand-writing or electronic signature) prior to start completing the on-line questionnaire, and after the nature, scope and information that should be collected have been explained in a form understandable to them.

In the USA, the woman must consent in writing (hand-writing or electronic signature) after having read the ICF and a copy (paper copy or electronic record) of the signed informed consent should be retained by the participant woman. Informed Consent Form (ICF) contains all required items and HRA Pharma requirements (see Annex 2).

When the questionnaire will be completed by the HCP, HCP will download the Informed Consent form from the website and print it to enable the woman to sign and date the ICF. Signing and dating the IFC will trigger her enrolment in the study and a copy of the written ICF will be given to the woman.

For women completing the questionnaire online, in the absence of the HCP, they will have to read the ICF, acknowledge they have read and understood it by ticking the appropriate box in the questionnaire and insert their electronic signature. Acknowledging and signing electronically this form will enable the generation of a printable version of the consent and trigger her enrolment in the study. Signed ICF will have to be saved or printed-out and kept by the woman.

In all cases, the system will not allow for any data collection for the observational study if no valid electronic/or hand writing signature has been obtained from the woman and a printed version generated to allow copy retention by the woman.

12.2 Confidentiality and data protection

Women's names or e-mail details will not be supplied to the sponsor. Only the women's initials (first characters of first name/first 3 characters of last name) and age will be recorded in the reporting questionnaires, and if the woman's name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. All data (initials age and the e-mail address if the woman agrees to provide it) will allow the HPC/referent physician to identify correctly the women during the contacts with HRA Pharma.

Study findings stored on a computer will be stored in accordance with local data protection laws. As per European directive 95/46/EC requirements and Health Insurance Portability and Accountability Act (HIPAA) of 1996 Privacy Rule on data protection, women and HCP/referent physician will be informed of their right to access and amend the information collected by the Sponsor in the framework of this observational study. If a woman states such a request, the HCP/referent physician should promptly inform HRA Pharma.

12.3 Observational study approval

Before the start of the study in the USA, the study protocol will be submitted to FDA within the sponsor IND application in accordance with HRA Pharma's post-marketing commitment, and submitted to Institutional Review Board (IRB) for approval.

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

The authorities and institutions will be informed of all subsequent protocol amendments, in accordance with local regulations.

12.4 Ongoing information for IRB

If required by legislation or the IRB, HRA Pharma must verify that the following is submitted to the IRB:

- Information on suspected Serious and Unexpected Adverse Drug Reactions as soon as possible

- Periodic reports on the progress of the study and safety reports (at least annually).

13 MONITORING

No routine on site monitoring activity will be performed in the framework of this observational study. The only communication which may occur will be done by the sponsor's drug safety department in case of safety queries on the pregnancy outcomes, including in person visit.

14 DOCUMENTATION AND USE OF STUDY FINDINGS

14.1 Documentation of study findings

The reporting forms will be completed electronically either by the HCP or directly by the woman.

The HCP should complete forms as soon as possible after the pregnancy or its outcome is known.

In case partial information was collected (outcome not known at the time of the questionnaire completion by the HCP) and to ensure that the information on pregnancy course and outcome is correctly received, the HCP will be contacted by the Sponsor or its representative until known pregnancy outcome is obtained, according to the following schedule:

1. First contact at the time of initial declaration receipt
   HCP will be reminded that they must complete information on pregnancy outcome
2. Second contact at approximately 20 weeks of woman's pregnancy

To collect potential information on outcome, if no information was received in the meantime

3. Third contact at the scheduled delivery date
   If the pregnancy outcome was not known at the second contact and no information was received in the meantime
4. Fourth contact 3 months after the date scheduled for delivery
   If no information was available at the third contact and no information was received in the meantime

5 In case of live birth (except for neonate death), HCP/referent physician or the woman (wherever applicable) will be contacted by the Sponsor's drug safety department for safety follow up 4 months after the delivery date.

14.2 Use of study findings

The sponsor has full ownership of the original data completed as part of the study.

The HCP agrees that the results of the study may be used for the purposes of national and international publications, and information for medical and pharmaceutical professionals.

The sponsor will prepare a final report on the study and will communicate a summary of key findings to all HCP.

The sponsor intends to publish the results of the study within 24 months after completion of the study. If the sponsor publishes the results of the study during such 24-month period, the principal investigator, on behalf of the ella® observational study group, may elect to serve as co-authors of such publications, and following publication, will be permitted to present the results of such publications in symposia.

A progress report of the study will be included in ella® PSUR and DSUR sent to Health Authorities every year.
Additionally, a descriptive analysis of the data collected will be provided annually in the PSUR submitted yearly.

15 STUDY DURATION AND DATES

Recruitment will be done through website access. Implementation of the website is planned for the second quarter 2014. Website will be in place during the whole course of the study.

ANNEX 1: REFERENCES AND STATISTICAL TABLES

References:

[1] Jentink J, Dolk H, Loane MA, Morris JK, Wellesley D, Garne E, de Jong-van den Berg LT for the EUROCAT Antiepileptic Study Working Group. Intrauterine exposure to carbamazepine and specific congenital malformations: systematic review and case-control study BMJ. 2010; 341.

[2] Dolk H, Loane M, Garne E; European Surveillance of Congenital Anomalies (EUROCAT) Working Group. Congenital heart defects in Europe: prevalence and perinatal mortality, 2000 to 2005. *Circulation*. 2011 Mar 1; 123(8):841-849.

[3] Khoshnood B, Lelong N, Houyel L, Thieulin AC, Jouannic JM, Magnier S, Delezoide AL, Magny JF, Rambaud C, Bonnet D, Goffinet F on behalf of the EPICARD Study Group. Prevalence, timing of diagnosis and mortality of newborns with congenital heart defects: A population-based study. *Heart* 2012, Nov, 98 (22): 1667-73.

Table 1. Sample size calculations for comparison of adverse pregnancy outcomes for pregnancies exposed to ella® versus those unexposed (or in the general population)

Pregnancies												
	Proportion of adverse outcomes in the unexposed population (%)											
	20,0	20,0	10,0	10,0	5,0	5,0	3,0	1,0	1,0	0,1	0,1	0,05
	Proportion of adverse outcomes in the exposed population (%)											
	30,0	40,0	15,0	20,0	7,5	10,0	6,0	2,0	3,0	0,3	1,0	0,5
Risk Ratio	1,5	2,0	1,5	2,0	1,5	2,0	2,0	2,0	3,0	3,0	10,0	10,0
	Sample sizes											
Ella exposed	164	46	375	108	798	232	398	1225	392	3978	479	959
Unexposed / general population	1640	460	3750	1080	7980	2320	3980	12250	3920	39780	4790	9590

**Notes: Event rates / proportions would be comparable for an unexposed population vs. the corresponding source population as essentially all would be unxposed to ella ®. All calculations assume a type-I (alpha) error rate of 0.05, two-sided tests and a ratio of exposed to unexposed group of 1:10. Higher ratios (e.g., 1:6 or 1:4) would require somewhat higher sample sizes for the exposed group but the difference would be relatively small as the main determinant of study power will be the number of exposed pregnancies. Furthermore, notwithstanding the caveats for selection of reference population(s) or a comparison group(s), various sources of data may be found for large numbers of (essentially all) unexposed pregnancies for different adverse pregnancy outcomes (e.g., population-based registries for congenital anomalies).*

Table 2. Total and live birth prevalence of congenital anomalies - overall and for certain major groups / specific anomalies - EUROCAT data* (2006-2010)

Congenital anomalies	Total prevalence* (per 10,000)	Live birth prevalence* (per 10,000)
All	208	176
Congenital heart defects	66	55
Oro-facial clefts	13	13
Neural tube defects	8	2
Ventricular septal defect	29	27
Atrial septal defects	19	11
Transpoistion of great arteries	3	3
Tetralogy of Fallot	3	3
Co-arctation of aorta	3	3
Cleft lip with or without palate	8	8
Anencephaly	3	0
Spina bifida	4	2
Abdominal wall defects	5	5
Esophageal atresia with or without trachea-esophageal fistula	2	2

** Data for total prevalence correspond to the period 2006-2010 (source: http://www.eurocat-network.eu/) and for live birth prevalence 2010 (source: Eurocat Special Report : Congenital Anomalies are a Major Group of Mainly Rare Diseases: http://www.eurocat-network.eu/content/Special-Report-Major-Group-of-Mainly-Rare-Diseases.pdf)*

Table 3. Confidence intervals for estimates of the proportions of adverse pregnancy outcomes based on the number of pregnancies exposed to ella®

i) 50 pregnancies

Proportion of adverse outcomes in the ella exposed population (%)	20,0	10,0	6,0	4,0	2,0
Number of events	10	5	3	2	1
95% binomial exact confidence intervals	10.0 - 33.7	3.3 - 21.8	1.3 - 16.5	0.5 - 13.7	0.05 - 10.6

ii) 100 pregnancies

Proportion of adverse outcomes in the ella exposed population (%)	20,0	10,0	6,0	4,0	2,0	1,0
Number of events	20	10	6	4	20	10
95% binomial exact confidence intervals	12.7 - 29.2	4.9 - 17.6	2.2 - 12.6	1.1 - 9.9	0.2 - 7.0	0.03 - 5.4

iii) 400 pregnancies

Proportion of adverse outcomes in the ella exposed population (%)	**20,0**	**10,0**	**6,0**	**4,0**	**2,0**	**1,0**	**0,5**	**0,3**
Number of events	**80**	**40**	**24**	**16**	**8**	**4**	**2**	**1**
95% binomial exact confidence intervals	**16.2 - 24.3**	**7.2 - 13.4**	**3.9 - 8.8**	**2.3 - 6.4**	**0.9 - 3.9**	**0.3 - 2.5**	**0.06 - 1.8**	**0.006 - 1.4**

One-sided 97.5% binomial exact confidence intervals in case of zero adverse events observed (e.g., for rare outcomes such as a specific congenital anomaly)

	Number of exposed pregnancies			
	N = 50	N = 100	N = 400	N = 1000
97.5% one-sided confidence intervals for the proportion (%) of adverse events	0 - 7.1	0 - 3.6	0 - 0.9	0 - 0.4

ANNEX 2: PARTICIPANT CONSENT FORM AND HIPAA AUTHORIZATION AGREEMENT

Participant Consent Form

Prospective Observational Study to Assess Clinical Follow-up and Outcomes of Pregnancies Exposed to ella®

(Protocol #: 2914-012)

Sponsor:	**HRA Pharma**
Principal Investigator:	**Paul Fine, M.D.**
Telephone:	**713-831-6553 (24 Hour)**
Address:	**Planned Parenthood Gulf Coast, Inc.** **4600 Gulf Freeway** **Houston, TX 77023**

This study is sponsored by HRA Pharma. It is aimed at collecting medical information about pregnancy in women who have taken the emergency contraceptive ella®, in order to gain more information on the effect of ella® on pregnancy.

You can be enrolled in this observational research study if you became pregnant right after taking ella® or if you have taken ella® since your pregnancy began. Enrollment in this study will involve completing on line questionnaire(s) either by your doctor or directly by yourself.

If you participate in this study, you will be asked about your use of ella®, any medical problems you may have had in the past and about your current health. If applicable, you will also be asked for the contact details of the doctor who prescribed you ella® and/or the doctor/midwife who will look after you during your pregnancy. Information about your pregnancy will be collected including: any medication you may take; any medical conditions you may have; the results of any tests you may have performed and if applicable, your baby's health after birth and 4 months later*. This study will not interfere with your medical follow-up during your pregnancy, as you will neither be asked to come in for any additional visits nor have any extra medical examinations performed. If you have decided to complete the questionnaire(s) on your own but do not wish to provide your doctor's details, you will also have the option to contact a referent physician who will be able to guide you through the online questionnaire completion. You will be asked to sign a separate form to allow your physician or a referent physician to release your (and, if applicable, your baby's) health information to this registry.

Your identity will remain strictly confidential. Personal data collected are limited to your initials (first letter of first name and first 3 letters of last name), age and e-mail address to allow accurate follow-up of your information by your doctor or the referent physician who has been commissioned to assist you in the completion of this questionnaire. Also note that your e-mail address will never be seen by HRA Pharma.

Only appropriate personnel within HRA Pharma and Health Authorities will have access to the data collected in this study.

Your participation in this study as well as any information communicated to HRA Pharma is entirely voluntary. You remain free to stop taking part in the study at any time if you wish to without affecting your care now or in the future. You will not be paid for taking part in this study. Also you will not benefit directly from this study, but it is hoped that your participation will help others in the future.

Answering questions about your pregnancy may be upsetting. You can talk to the study staff at the number on the first page of this form if you have any concerns.

If you have any questions or complaints about your rights as a research participant, contact Chesapeake IRB by emailing adviser@chesapeakeirb.com. Reference Pro00009605 An IRB is a group of people who review research studies to protect the rights and welfare of research participants.

A description of this study will be available on http://www.clinicaltrials.gov/, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at anytime.

If you have any questions about this study, please contact the study staff at the telephone number listed on the first page of this form.

If you agree to take part, please provide your name and initial the relevant boxes below.

I the participant …… (name, first name) agree to participate in the study and:

☐ I agree to provide to my referent-doctor or my doctor all information requested, related to my health during pregnancy, the outcome of my pregnancy and my baby's health.

☐ *(Please initial box)*

☐ If he/she requests it, I agree to provide to my referent-doctor or my doctor the contact details of the person who prescribed ella® to me.

☐ *(Please initial box)*

☐ If I do not plan to be followed by my doctor during my pregnancy, I agree to provide to my doctor the contact details of the doctor/midwife in charge of my pregnancy follow-up, in order to allow the collection of the information mentioned above.

☐ *(Please initial box)*

Click HERE to print this form for your records.

HIPAA Authorization Agreement

Permission to Review, Use and Release Information about You for 2914-012

INTRODUCTION

You are being asked to read, review, and sign this authorization agreement as a result of a federal law on the privacy of identifiable health information. The law is called the federal Health Insurance Portability and Accountability Act (HIPAA). It requires that research subjects get written notification about the collection, use and disclosure (sharing) of health information that can identify them. In addition, it requires researchers like the Health Care Provider(s) you have contacted/visited for your ella®-exposed pregnancy (it can be your General Practitioner, your Obstetrician/Gynecologist, your Midwife, Pediatrician,…) to ask research subjects for permission to use and disclose identifiable health information for the purpose of this research study.

Signing this authorization agreement authorizes your Health Care Provider you have visited for your pregnancy to collect health information that can identify you and to use and disclose this information to the parties specifically named in this authorization agreement.

EXPLANATION OF AUTHORIZATION

Information used and disclosed may include your own research record or your baby(ies)'s medical record(s), supporting information from your/your baby's medical records, results of laboratory, diagnostic or other tests, results of tests on samples (blood, urine or tissue) that have been stored, and clinical observations made during your participation in the research study.

As part of this study, the Health Care Provider will record health information about you that contains your name and other items that can be used to identify you. The health information identifying you will remain in the Health Care Provider's research records indefinitely. In addition, authorized representatives of HRA Pharma, Chesapeake Research Review, Inc. (a Research Ethics Review Board that reviews this study), the Food and Drug Administration (FDA) and other US governmental agencies, and possibly governmental agencies of other countries, will be given access to these records on request and may copy them. Copies of your medical records that do not include your name but may be traced back to you may be given to HRA Pharma and Chesapeake Research Review, Inc. The sponsor may send a copy of the records to the FDA or other regulatory agencies such as governmental agencies in other countries. By signing this form you are authorizing this use and disclosure.

Because of the need to release information to these and other parties, absolute confidentiality cannot always be guaranteed. After its release, information that can identify you may no longer be protected by federal privacy rules. However, information will be collected and shared following professional standards of confidentiality.

This Authorization is valid once it is signed and dated by you. This Authorization has no expiration date, unless governed by state law, which requires a specific date of expiration. If state law applies, the authorization will expire December 31, 2061.

Information and results from this study may be presented at meetings or published in journals. Your name, and information that can easily be traced back to you, will not be included in presentations and publications.

SUSPENSION OF YOUR RIGHT TO ACCESS PERSONAL INFORMATION

Under federal privacy rules you have a right to inspect and obtain a copy of your personal health information, including personal health information maintained in the study medical records.
If there is a medical need during your participation, study medical records may be made available to you, or to medical professionals who are caring for you, as needed for your care.

VOLUNTARY PARTICIPATION

Your authorization to use and disclose your identifiable health information for the purpose of this research study is voluntary. However, if you do not provide your written authorization for the use and disclosure of your identifiable health information, you cannot participate in this research study.

In addition, your participation in the overall research study is entirely voluntary. You may refuse to participate or may quit at any time during the study. All you have to do is tell the your Health Care Provider.

If you decide to stop participating in the research study, you may also end your authorization allowing the researchers to collect, use and disclose any additional health information that could identify you. To end your authorization, you must notify your Health Care Provider of your decision in writing. If you end your authorization, no new health information that can identify you will be gathered from you or your existing medical records. However, information that is in your study records at the time that your authorization is ended cannot be removed.

You may freely ask questions about this authorization agreement now or at any time. If anything causes you concern, or you have questions you may contact your Health Care Provider.

STATEMENT OF AUTHORIZATION

I have read this authorization agreement and its contents were explained. My questions have been answered. I voluntarily authorize my Health Care Provider to collect, use and disclose my health information as specified in this authorization agreement. I will receive a signed and dated copy of this authorization agreement for my records. By signing this authorization agreement I am not giving up any of my legal rights.

_____ ____/____/____
Signature of Research Subject Date

_____
Printed Name of Research Subject

STATEMENT OF PERSON EXPLAINING AUTHORIZATION (EXCEPT FOR SELF-ENROLMENT PROCESS)

I have carefully explained to the subject the nature and purpose of the authorization agreement. I have been available to answer any questions that the subject has regarding this authorization agreement.

_____ ____/____/____
Signature of Person Explaining Authorization Date

_____
Printed Name of Person Explaining Authorization