HRA Pharma

ELLA® ACTUAL USE TRIAL PROTOCOL

Title:	A Multi-Center, Open-**L**abel Trial **I**nvestigating **B**ehavior **R**elated to **ella**® Use in a Simulated OTC Environment (LIBRella)
Compound:	ulipristal acetate 30 mg
Phase:	Phase IV
Protocol Number:	151032-001
Protocol Version / Date:	Final v3.1 / 5 May 2017
Sponsor's Name and Address:	Laboratoire HRA Pharma 15 rue Beranger 75003 PARIS France
Pharmacovigilance Contact Information	HRA Pharma Pharmacovigilance 15 rue Béranger 75003 PARIS, fax: + 33 1.42.77.03.52 e-mail : pharmacovigilance@hra-pharma.com
24-Hour Adverse Event Reporting Number	1-800-530-3680

Signatures

Authors:

Russell D. Bradford, MD, MSPH
Vice President, Medical Affairs
PEGUS Research, Inc.

Russell D. Bradford
Digitally signed by Russell D. Bradford
DN: cn=Russell D. Bradford, o=PEGUS Research, Inc., ou, email=bradfordr@pegus.com, c=US
Date: 2017.05.16 08:55:34 -06'00'

Signature _____ Date _____

Approval:

Sarah Farnsworth, PhD
Vice President, Scientific Affairs
PEGUS Research, Inc.

Sarah Farnsworth
Digitally signed by Sarah Farnsworth
DN: cn=Sarah Farnsworth, o=PEGUS Research, Inc., ou=VP, Scientific Affairs, email=FarnsworthS@pegus.com, c=US
Reason: I am approving this document
Date: 2017.05.16 08:54:37 -06'00'

Signature _____ Date _____

Christine Adelbrecht
Clinical Trial Manager
Laboratoire HRA Pharma

Signature _____ Date 16 May 2017

Virna Gamalinda
Senior Medical Officer,
Women's Health
Laboratoire HRA Pharma

Signature _____ Date 16 May 2017

Document History

Document	Version / Date	Summary of Changes
Final protocol	Final v1.0_22Dec2016	n/a
Amended protocol	Final v1.1_26Jan2017	In response to IRB review: Schedule of Activities updated to include specification on timing and method of subject study drug payment reimbursement. Section 3.3.1 Inclusion Criteria was updated to add “Seeking the use of emergency contraception”. Section 5.2.2 and Section 12.3 clarification added that assent of adolescent subjects will be gathered where state or local laws do not allow for waiver of parental consent. Section 5.5 Flow chart of activities revised to include explicit consent to gather sensitive data. Section 12.3 Subject Information and Consent updated to specify retention of anonymous study data from screen fail, disqualified to participate and non-consented subjects. Sections 12.2 and 12.3 removed references to waiver of parental consent. Removed reference to birth date as an example of PII collected and clarified that PII collected will be for compensation and follow-up purposed only. Sponsor decision throughout, revised number of health clinics from approximately 20 to approximately 25 thereby increasing total investigative sites to approximately 35.

Amended Protocol	Final v2.0_06Mar2017	The following changes were made in response to feedback received from FDA in a teleconference on 24Feb2017: Added breastfeeding as an exclusion criterion to participate in Use Phase Added premenarchal status as an exclusion criterion to participate in Use Phase Urine-based pregnancy testing at enrollment was added as a study procedure to confirm pregnancy status prior to allowing subjects to purchase (as pregnancy is an exclusion criterion to participate in Use Phase). Section 5.5 Flow chart of activities revised to include new exclusion from Use Phase following positive pregnancy test at enrollment.
Amended Protocol	Final v3.0_27Apr2017	The following changes were made in response to written comments received from FDA on 03-Apr-2017, reference ID 4078573: Secondary Endpoint D reworded to reflect that breastfeeding was added as an exclusion criterion to the Use Phase in v2.0. Added Secondary Endpoint I Section 2.3: Additional relevant DFL messages added for Secondary Endpoint D. Secondary Endpoint I and rationale added Section 3.1 Added clarifying text that study staff will not answer subject questions about the IP, but will redirect them to the labeling. Section 3.3: Sample size increased to 175 for adolescents, with approximately 50 under the

		age of 15 and 125 ages 15-17. Supplemental rationale for active recruitment of adolescents was added. Section 4.3.2: Rationale for maximum purchase of 9 packages of IP added. Section 5.5 Flow chart of activities revised to reflect revised approach to adolescent recruitment Section 6.3: Rationale for not imposing a low literacy quota in the study was added. Section 8.4.2: Complete definitions of Correct, Acceptable, and Incorrect Selectors added Section 8.4.3: Process for physician mitigation added. Section 9.3: Added a secondary analysis by subject rather than dosing instance for relevant endpoints. Section 9.3.3.1: Clarified analysis for Secondary Endpoint D Section 9.3.3.3: Clarified that other proportions will be presented with self-selection endpoints, such as [(cell A + cell D) / (cell A + cell B + cell C + cell D)] and [cell D/ (cell B + cell D)].
Amended Protocol	Final v3.0_27Apr2017	In response to IRB review: References to adolescent recruitment changed from “targets” to “goals,” in the setting of capping enrollment for adults (to allow room for an adolescent subgroups of FDA-requested size).

Protocol Summary

Study Title	A Multi-Center, Open-**L**abel Trial **I**nvestigating **B**ehavior **R**elated to **ella**® Use in a Simulated OTC Environment (LIBRella)
Phase	Phase IV
Background and Rationale	ella® (ulipristal acetate) is proposed for a prescription to over-the-counter (Rx-to-OTC) switch. This actual use trial (AUT) will be conducted to demonstrate appropriate consumer behavior when using the product in the absence of a physician or other learned intermediary. This study will be conducted to obtain measurements of consumer behaviors related to the actual use of the product, in particular the compliance with key communication messages presented in the Drug Facts Label (DFL).
Objective and Endpoints	The objective of this study is to evaluate the adequacy of the proposed OTC labeling to guide appropriate consumer behavior by measuring pre-specified endpoints. The determination of the following primary endpoints and other measures is based on the potential clinical consequences of a consumer failing to heed each key label instruction and the concerns the United States Food and Drug Administration (US FDA) has raised with regard to the potential for misuse of the product in an OTC setting. Endpoints are designated either as Actual Use endpoints or Self-Selection endpoints. <u>Primary Endpoints</u> A. Actual Use: Proportion of dosing instances among user population taken within 120 hours (5 days) of most recent episode of unprotected sex. B. Actual Use: Proportion of dosing instances among user population in which no more than one tablet was taken. C. Self-Selection: Proportion of female selectors who are not pregnant at the time of selection decision. <u>Secondary Endpoints</u> D. Self-Selection: Proportion of female selectors who are not breastfeeding at the time of selection decision. E. Self-Selection: Proportion of self-selection population who make a correct selection decision. F. Actual Use: Proportion of dosing instances among user population in which hormonal birth control (HBC) is not taken for 5 days after taking ella®. G. Actual Use: Proportion of dosing instances among user population associated with use of hormonal contraceptives in the same cycle after taking ella® in which subject reports using a condom (or other barrier method) every time they have sex until their next menstrual period. H. Actual Use: Proportion of user population who do not use

	the study product more than once in the same menstrual cycle. I. Self-Selection/Actual Use: Proportion of self-selection population taking one of the "ask a doctor or pharmacist before use" products who do not select, who select but do not use or who report contacting a healthcare provider or pharmacist. <u>Other Measures</u> J. Actual Use: Proportion of user population who used a HBC method sometime during the previous two months. K. Actual Use: Proportion of user population who use any EC on more than one occasion within the study period. L. Actual Use: Proportion of user population who report becoming pregnant within the study period.
Study Design	This is an observational open-label, multicenter, 6-week study designed to mimic an OTC-like environment in which subjects will use ella® after making a self-selection and purchase decision about the product based only on their reading of the DFL and other information on the package. The study will increase understanding regarding how subjects will use the medication in an OTC-like environment.
Number of Subjects	A total of approximately 950 subjects will be allowed to purchase the study medication. Assuming that about 80% of those who purchase will both use the study medication and participate in at least one follow up telephone call, that will yield an actual use population among which to evaluate the primary endpoints of 760 subjects. In order to allow for a subgroup of adolescent users, adult purchasers will be constrained to no more than 775, allowing for an adolescent subgroup of approximately 175 (or more, should a higher proportion naturally occur). Among adolescents, enrollment will be further broken down to include approximately 50 purchasers under the age of 15 and approximately 125 purchasers ages 15-17.
Methods	The nature of the indication (emergency contraception, EC) makes recruitment for the trial challenging. By definition a woman does not know in advance that she will need EC, and when she does need it (i.e., after she has had unprotected sex), she needs to take it very quickly. Therefore, a typical passive advertising campaign aimed at consumers interested in the indication (the approach typically used in AUTs) is unlikely to be effective in this study. Subjects will be recruited at the point of OTC-like sale in women's health clinics and in retail pharmacy study sites. Sites will be chosen which currently sell EC in an OTC or OTC-like setting and which have enough EC sales to meet recruitment goals. Approximately 35 sites will be used, composed of approximately

	25 women's health clinics and 10 retail pharmacy research sites. In order to be as representative as possible of the OTC EC-seeking population, when potential subjects come to a site looking to purchase EC, they will be offered the opportunity to participate in the study. Potential subjects will be directed to study staff for a face-to-face interview and screened for initial study inclusion criteria. Subjects who meet the initial screening inclusion criteria for the study will be given an (empty) ella® package and will be allowed as much time as they need to review the information on the outside of the entire package. Subjects will be asked to make a selection decision regarding whether the product is appropriate for them to use or not. Reasons for selection and deselection will be recorded. Those that select the product will then be told the cost of the investigational product and will be asked if they would like to purchase it for their own use. Reasons for any non-purchase and purchase decisions will be recorded. Following the purchase decision, subjects will provide demographic information and limited medical history. The Rapid Estimate of Adult Literacy in Medicine (REALM)[1] or Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen)[2] will then be administered. Subjects will be asked to sign the informed consent and then provide information about current medication use. Subjects who sign consent will provide a urine sample for pregnancy testing. Subjects with a positive pregnancy test result will be informed that the test was positive, will be asked the selection and purchase question again to better assess their self-selection decision, and then excluded from further study participation. Qualified subjects will be allowed to purchase the study product and told they may return to the site at any time to resupply. Subjects will not be allowed to purchase more than 3 one-dose packages at a time or more than 9 one-dose packages during the study period (although this will not be communicated to the subjects unless they attempt to purchase more than that). While any request for more will be denied, the request will be recorded. Subsequent contact will be by up to two telephone interviews conducted by trained nurses (interviewers) at a central research site. Subjects will be contacted by phone at Week-2 (Day 14 with an allowable window of ±3 days) and at Week-6 (Day 42±4 days) to gather information on if, how and when the subject took the product, any adverse events (AEs), concomitant medications, and other actions the subject may have taken related to the use of the product. Results of the End-of-Study pregnancy test will be reported by subjects and recorded. Once all steps of the final telephone interview are completed, the subject will be instructed to return leftover study medication, if any, and empty packaging to PEGUS and will exit the study.

Statistical Analysis	A summary of the disposition of subjects (including responders, self-selection population, purchasers and users) and reasons for exclusion from these populations will be provided. Demographic characteristics, medical history and other background information will be summarized for the responder, self-selection, purchaser, and user populations. Frequencies and percentages will be presented for categorical data, mean, standard deviation (SD); median, and range will be presented for numerical data. Frequencies, percentages and 2-sided 95% confidence intervals (CIs) will be calculated for the primary and secondary endpoints using the exact method. For the primary endpoints, it will be concluded that the established target threshold is reached if the lower limit of the CI of the point estimate is equal to or exceeds the value of the pre-determined threshold. Endpoints and demographics will be presented for subgroups of interest, with subjects dichotomized on the corresponding variables, which include (but are not necessarily limited to) literacy, gender, age (adolescent vs. adult women), and history of hormonal birth control use. Several of the endpoints are based on dosing instance, rather than by subject, as subjects have the potential to take more than one dose over the course of the study. Correctness of selection or behavior can only be evaluated at the time of use, rather than at the time of purchase. However, for each of those endpoints, a secondary analysis by subject will also be presented. A more detailed description of planned data analysis procedures will be found in the Statistical Analysis Plan (SAP) which will be approved and signed before the database is locked.
Study Duration	The duration of this study is expected to be around 6 months (from first subject enrolled in the study until last subject last visit), with subject recruitment proposed to start mid-Q2 2017 and end in Q4 2017. The actual overall study duration or subject recruitment period may vary.
CRO	PEGUS Research, Inc. 331 South Rio Grande, Suite 100 Salt Lake City, UT 84101
Date	27 April 2017

Schedule of Activities

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and

ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Visit Procedure	Intercept Recruitment	Enrollment Visit / First Purchase[a]	Week 2	Week 6	End of Study / Early Termination[e]
		Day 1	14±3 Days	42±4 Days	
Invitation to participate	X				
Review screening / study inclusion criteria		X			
Subject reviews outer packaging and makes selection and purchase decision		X			
Collect demographics and relevant medical history		X			
Administer REALM or REALM-Teen test[c]		X			
Study exclusion/inclusion criteria assessed for eligibility to continue		X			
Subject signs informed consent		X			
Urine pregnancy test performed[h]		X			
Collect current/regular relevant medications and associated conditions[b]		X			
Purchase transaction conducted[d]		X			
Telephone interviews			X	X	X
End-of-study telephone interview					X
Record End-of-study pregnancy test results[f]					X
Concomitant medications		X	→	→	X
Adverse Events		X	→	→	X
Reimbursement for cost of study medication (After all subjects complete the study) [g]					X

Abbreviations: → = ongoing/continuous event; REALM = Rapid Estimate of Adult Literacy in Medicine; REALM-Teen = Rapid Estimate of Adolescent Literacy in Medicine

a. Day relative to first purchase of study medication (Day 1).
b. Subjects will be asked to provide a list of any conditions they have and any medications they are taking. Females only.
c. REALM or REALM-Teen will be conducted for all subjects who participate in the enrollment interview regardless of self-selection/purchase decision.
d. Subjects will be allowed to purchase any amount of study medication up to 3 packages at the baseline visit, or return to the site at any time during their use phase and purchase the maximum amount (up to 9 packages) allowed during subsequent treatment weeks (6 weeks).
e. Early termination interview will be conducted during the study if the subject is discontinued or withdraws consent prior to Week 6.
f. Subjects are provided with a urine pregnancy test at enrollment and asked to keep it until directed to use it at the end of study.
g. After study closeout, subjects are reimbursed the purchase price paid for any study drug.The subjects are not notified of this when enrolling in the study in order to maintain an OTC-like environment for selection/purchase of the study drug. Subjects will be notified of and provided with the reimbursement via mail following study closeout.
h. Subjects with a positive pregnancy test will be asked to make a selection decision again to better assess self-selection and then will be excluded from the use phase.

Glossary and Abbreviations

AE	Adverse Event
AUT	Actual Use Trial
CI	Confidence Interval
CIL	Consumer Information Leaflet
CRF	Case Report Form
CRO	Contract Research Organization
DCI	Data Collection Instrument
DFL	Drug Facts Label
DMP	Data Management Plan
EC	Emergency Contraceptive
EDC	Electronic Data Capture
EDP	Exposure During Pregnancy
EOS	End-of-Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBC	Hormonal Birth Control
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
LCS	Label Comprehension Study
MedDRA	Medical Dictionary for Regulatory Activities
OTC	Over-the-Counter
PBOS	Plan B One Step
PHI	Personal Health Information
PII	Personal Identifiable Information
POP	Progestin-Only Pill
PT	Preferred Term
PV	Pharmacovigilance
REALM	Rapid Estimate of Adult Literacy in Medicine
REALM-Teen	Rapid Estimate of Adolescent Literacy in Medicine
Rx	Prescription
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class

SOP	Standard Operating Procedure
SSS	Self-Selection Study
SUSAR	Suspected Unexpected Serious Adverse Reaction
UPA	Ulipristal Acetate
US	United States
USPS	United States Postal Service

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1 INTRODUCTION

ella® (ulipristal acetate) is proposed for a prescription to over-the-counter (Rx-to-OTC) switch. This study is designed to assess whether consumers will use the product in a manner consistent with the labeling. A Drug Facts Label (DFL) for the nonprescription version of ella® has been drafted and evaluated in a pivotal label comprehension study (LCS). This protocol describes the next stage of the development program, a pivotal self-selection (SS) and actual use trial (AUT), which will provide measures of how and when consumers select to use and use the product in an OTC-like setting.

1.1 Indication

The proposed labeled "Purpose" for nonprescription ulipristal acetate 30 mg is "Emergency contraceptive." The proposed labeled "Use" for nonprescription ulipristal acetate 30 mg is "for women to reduce chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)."

1.2 Background and Rationale

This AUT is designed to demonstrate that consumers will select and use ella® in a manner consistent with the labeling.

2 STUDY OBJECTIVE AND ENDPOINTS

2.1 Objective

The objective of this study is to evaluate the behavior of subjects in an OTC-like setting when selecting and using ella®.

2.2 Endpoints

The determination of primary and secondary endpoints has been made based on the potential clinical consequences of a consumer failing to heed each key label instruction and the expressed concerns of the United States Food and Drug Administration (US FDA) about the potential for misuse of the product in an OTC setting. The rationale behind selection and prioritization of endpoints is summarized below in Section 2.3. The appropriateness of behaviors will be assessed by measuring the endpoints as per the endpoint analysis listed in Section 9.3.

2.2.1 Primary Endpoints

A. Actual Use: Proportion of dosing instances among user population taken within 120 hours (5 days) of most recent episode of unprotected sex.
B. Actual Use: Proportion of dosing instances among user population in which no more than one tablet was taken.
C. Self-Selection: Proportion of female selectors who are not pregnant at the time of selection decision.

2.2.2 Secondary Endpoints

D. Self-Selection: Proportion of female selectors who are not breastfeeding at the time of selection decision

E. Self-Selection: Proportion of self-selection population who make a correct selection decision.
F. Actual Use: Proportion of dosing instances among user population in which hormonal birth control (HBC) is not taken for 5 days after taking ella®.
G. Actual Use: Proportion of dosing instances among user population associated with use of hormonal contraceptives in the same cycle after taking ella® in which subject reports using a condom (or other barrier method) every time they have sex until their next menstrual period.
H. Actual Use: Proportion of user population who do not use the study product more than once in the same menstrual cycle.
I. Self-Selection/Actual Use: Proportion of self-selection population taking one of the "ask a doctor or pharmacist before use" products who do not select, who select but do not use or who report contacting a healthcare provider or pharmacist

2.2.3 Other Measures

J. Actual Use: Proportion of user population who used a HBC method sometime during the past two months.
K. Actual Use: Proportion of user population who used any emergency contraceptive (EC) on more than one occasion within the study period.
L. Actual Use: Proportion of user population who report becoming pregnant within the study period.

2.3 Rationale for Designation of Study Endpoints

The determination of endpoints and designation as primary or secondary endpoints has been made based on the potential clinical consequences of a consumer failing to heed each key label instruction and FDA's concerns regarding potential product misuse. Each endpoint is listed in Table 1 below, with the DFL messages relevant to the endpoint, followed by the rationale underlying the classification as a primary or secondary endpoint. Note that the "Other Measures" listed above in Section 2.2.3 are not endpoints. Rather, they are descriptive only, and will be used to help characterize the study population in the analysis.

Table 1 Endpoint Rationale for Primary and Secondary Endpoints

Endpoints		Relevant DFL Message(s)
Primary		
A	Actual Use: Proportion of dosing instances among user population taken within 120 hours (5 days) of most recent episode of unprotected sex.	Directions: Take one tablet as soon as possible and no later than 120 hours (5 days) after unprotected sex.

Rationale: The Sponsor proposes to test this message as a primary endpoint because it communicates directions for effective use of ella®, and the limited time-window for its effective use. Use of ella® after 5 days diminishes the product's efficacy, although it is not expected to introduce any drug-related risks. This

endpoint will allow confirmation that consumers do not take ella® later after unprotected intercourse than recommended in the product label.

B	Actual Use: Proportion of dosing instances among user population in which no more than one tablet was taken.	Directions: Do not take more than one tablet.

Rationale: The Sponsor proposes to test this message as a primary endpoint in the context of FDA's recommendation to demonstrate in an AUT whether consumers misuse ella® with intake of more than the recommended dose. This is proposed as a primary endpoint despite the fact that, while taking one tablet is essential to effectiveness of the product, dose-finding studies using up to 200 mg of ulipristal acetate (UPA) (more than 6 times the intended 30 mg dose) demonstrated no safety concerns (HRA2914-503), suggesting it is likely that taking more than the recommended dose is likely to impose little or no additional risk in women.

C	Self-Selection: Proportion of female selectors who are not pregnant at the time of selection decision.	Warnings: Do not use if you are already pregnant (because it will not work)

Rationale: The Sponsor proposes to test this message as a primary endpoint as it would allow the study to confirm that consumers do not select or take ella® if they are already pregnant, although the available safety data are reassuring for pregnant women exposed to ella®.

Secondary

D	Self-Selection: Proportion of female selectors who are not breastfeeding at the time of selection decision.	Warnings: Do not use if you are breastfeeding

Rationale: While it has been shown that UPA and its metabolite are both excreted in breastmilk over the first 120 hours after administration, UPA is unlikely to have any detrimental effects on the newborn infant if ingested in breast milk, given the mechanism of action of UPA and the fact that there is no role for progesterone in the newborn infant. To date, no safety signal has been identified in newborns breastfed by women who have taken UPA 30mg.

Because breastfeeding is not a contraindication for use of ella® in the prescription setting (though it is not recommended because of a lack of clinical data), this has been designated as a secondary endpoint in this AUT.

E	Self-Selection: Proportion of self-selection population who make a correct	• Do not use if you are already pregnant

	selection decision.	• Do not use for regular birth control • Do not use more than once in the same menstrual cycle • Do not use if you are breastfeeding • Use: for women to reduce chance of pregnancy after unprotected sex • Allergy alert: Do not use if you have ever had an allergic reaction to any of the ingredients

Rationale: The main goal of the AUT is to assess actual use of ella®. Given that potential clinical consequence of incorrect selection is unlikely to be serious, the Sponsor proposes to test correct self-selection of potential consumers as a secondary endpoint.

F	Actual Use: Proportion of dosing instances among user population in which HBC is not taken for 5 days after taking ella®.	Directions: After taking this product; users of birth control pills, patch or vaginal ring after use of this product: Do not use birth control pills, patch or vaginal ring for 5 days after taking this product. If you do, it may block the ability of both this product and your birth control to work.

Rationale: The concern about starting HBC within 5 days after taking ella® relates to a theoretical decrease in the efficacy of ella® resulting from an interaction between ella® and progestins in HBC products. In reality it is uncertain to what extent the efficacy of ella® is affected or, indeed whether it is affected at all.

The recommendation to delay starting HBC after taking ella® stems from a single study by Brache et al published in 2015[3]. The study was designed to explore a possible interaction between ella® and HBC, when HBC was started immediately after taking ella®. It was a small study of just 49 women who were not using HBC prior to using ella®, and who took ella® when an ovarian follicle had reached at least 14 mm in diameter and so were soon to ovulate; that is, at the point in the menstrual cycle when ovulation was already most likely to occur. The following day, half of the women started an HBC (a progestin-only pill, POP) while the others started a placebo. The key finding was that 44% of women who started HBC ovulated within 5 days of taking ella® while only 10% of women in the placebo group ovulated in that time frame. Notably, over 50% of women who started HBC after ella® did not ovulate and so were not at risk of pregnancy. Nevertheless, the theoretical concern was that starting HBC immediately after ella® use might reduce the efficacy of ella®.

This was a small pharmacodynamic study of just 49 women, and the recommendation to delay the start or restart of HBC is based on observing just 11 women ovulating. Most importantly, the study was not designed with pregnancy as

an endpoint. Nevertheless, the Sponsor took a conservative and cautious position in changing the prescription ella® label to reflect this theoretical concern, hence the advice to wait 5 days before starting or restarting HBC. However, because of all the limitations of the Brache study, the medical community cannot agree whether or not this recommendation is important. In Europe, this instruction has not been added to the ella® label and the failure rate of ella® remains low.

The situation pertaining to use of ella® followed by HBC under OTC conditions is different. In the Brache study, the women had not taken HBC prior to using ella® and they took ella® in the presence of a large pre-ovulatory follicle, i.e., on the verge of ovulating. In the OTC situation, the recommendation to delay starting HBC applies only to women who have already been taking HBC prior to using ella® (since to acquire a new supply of HBC will require a prescription). Thus these ella® users are likely to be women who are seeking EC because they have missed pills. Unlike the women in the Brache study, these women are at very low risk of pregnancy. HBC use suppresses ovarian activity and it takes time for the ovary to recover when the pill is stopped. In a Cochrane review of the effect of missed pills on fertility, Zapata et al[4] reviewed a number of pharmacodynamic studies in which pills were deliberately missed. They concluded that even after missing up to 14 days of HBC (pills) ovulation is uncommon. In 207 women who missed pills for between 8 and 11 days, there were no ovulations and in women who did ovulate (usually following missed pills for longer intervals) the cycle was not normal, follicles were small, progesterone levels were low and cervical mucus hostile.

So, in conclusion, if a woman buys ella® over the counter and has a supply of HBC, which she wants to restart after ella® use, should she fail to follow the instructions to delay restarting HBC, she is highly unlikely to get pregnant. Accordingly, the Sponsor proposes that the percentage of women who delay re/start of the HBC for 5 days after ella® intake be a secondary endpoint in this study.

G	Actual Use: Proportion of dosing instances among user population associated with use of hormonal contraceptives in the same cycle after taking ella® in which subject reports using a condom (or other barrier method) every time they have sex until their next menstrual period.	Directions: After taking this product; users of birth control pills, patch or vaginal ring after use of this product: Use condoms (or another barrier method) every time you have sex until your next menstrual period.

Rationale: This secondary endpoint is intended to address the hypothetical risk of pregnancy resulting from unprotected intercourse after use of ella® due to the potential risk of delayed ovulation in users of hormonal contraceptives. However, as described above in Secondary Endpoint F, risk of pregnancy for these women is minimal, and therefore this endpoint is also designated a secondary endpoint in this AUT. While women who start HBC with a 5-day delay can further decrease the slim chance of pregnancy from an act of unprotected sex in that short interval

by using condoms, once again, this was a very cautious position since the chance of pregnancy in that interval, even without use of a condom, is extremely low. Furthermore, all women (not just those starting/restarting HBC after ella® use) having unprotected sex after using any method of EC (i.e., ella® or EC containing LNG including Plan B) and before their next menses should ideally use condoms as back up to reduce the risk of pregnancy, but labeling to that effect is not present on other EC products in the OTC marketplace.

H	Actual Use: Proportion of user population who use the study product more than once in the same menstrual cycle.	Directions: Do not use more than once in the same menstrual cycle.

Rationale: While data has been collected that demonstrates that using ella® more than once during a menstrual cycle does not pose any safety risk, the direction not to use ella® more than once in a menstrual cycle is still on the prescribing information. For this reason, as well as feedback from the FDA, this will therefore be tested as a secondary endpoint.

I	Self-Selection/Actual Use: Proportion of self-selection population taking one of the "ask a doctor or pharmacist before use" products who do not select, who select but do not use or who report contacting a healthcare provider or pharmacist	Consumer Information Leaflet: Talk to a healthcare professional or your pharmacist before taking ella® if you are taking certain drugs to treat: • seizures (barbiturates, carbamazepine, felbamate, oxcarbazepine, phenytoin, topiramate) • tuberculosis (rifampin) • fungal infections (griseofulvin) • HIV or AIDS • pulmonary hypertension (bosentan) • St. John's Wort (or any herbal products containing hypericum perforatum)

Rationale: *In vitro* studies indicate that ella® is predominantly metabolized by CYP3A4, suggesting that CYP3A4 inducers may decrease the plasma concentration of ella® if administered concomitantly, as it was shown with rifampicin. However, no clinical studies have demonstrated a potential increased risk of pregnancy among women treated with CYP3A4 inducers and there is no data indicating that increasing the dose of UPA may have an impact on a theoretical risk of pregnancy. Additionally, similar drug-drug interactions exist for levonorgestrel and CYP3A4 inducers, the only other readily available option for emergency contraception.

Unintended pregnancy is particularly undesirable in women taking many of these drugs since they are used to treat serious conditions many of which pose significant risks to the fetus. ella® is not contraindicated in these circumstances, rather the potential concern is that emergency contraception (including

levonorgestrel) may be less effective if used with concomitant medication. An emergency contraceptive which *may* be slightly less effective is arguably preferable to no emergency contraception for this particular group of women.

Given that the clinical impact of concomitant use of a CYP3A4 inducer with ella® use is unclear, that there are no recommendations precluding the use of ella® under these circumstances, and that the only other available option for oral EC has similar interactions (despite no drug interactions listed in the OTC labeling), this endpoint is designated as secondary.

3 STUDY DESIGN

This is an observational open-label, multicenter, 6-week study designed to create as much as possible an OTC-like environment in which subjects will make a self-selection and purchase decision about ella® based only on their reading of the outside of the package including the DFL. Qualified subjects who choose to purchase the study medication will do so, then leave the study site and use the product on their own. The study is designed to assess if, when and how subjects use the medication in an OTC-like environment.

It is important to note that subject characteristics and how they might be related to behaviors directed by the DFL that are gathered at screening, enrollment, or during the 6-week study period will not be discussed directly with subjects until the end of study interview.

3.1 Naturalistic Design

This trial is a multi-center trial conducted in a naturalistic environment. Study characteristics and procedures were designed to make it as naturalistic as possible. Some of the key naturalistic elements include the following:

- There are minimal study exclusionary criteria imposed on subjects, making this trial nearly an all-comers study to mimic the likely OTC population.
- The study will be conducted in women's health clinics and pharmacies, representing typical locations where consumers now commonly purchase EC in an OTC-like setting.
- The proposed OTC packaging and labeling is the only product information provided to subjects during the study. Subjects will only review the outer packaging at the initial visit. Study staff will not provide any additional information or encouragement regarding product selection at that visit. Staff will not answer subject questions but will redirect them to the outer package.
- After purchasing the study product, subjects will take the package with them when they leave the site; the package will include the outer packaging and, inside the package, the consumer information leaflet (CIL) and study medication.

3.2 Study Sites

Approximately 25 women's health clinics and 10 retail pharmacies will be chosen for this study as they provide an environment that is considered typical of those from which consumers may expect to find this product following approval, and which represent the places women currently go to seek EC in an OTC-like setting. The women's health clinics sell currently available OTC EC in an OTC-like manner without the requirement to see a clinician. These clinics typically have a window or a front desk area where women purchase EC by requesting it from non-clinical staff, in a manner similar to consumers purchasing an OTC product in a pharmacy.

Study sites will be selected to provide geographic and demographic diversity. They will be selected from approximately eight geographic regions in the US. Each site has a private office or a suitable semi-private area where the study will be carried out privately and without distraction. The study area will also have all of the necessary computer equipment and a high-speed Internet connection to accommodate the electronic data capture system (EDC).

It is expected that subjects enrolled through health centers are likely to be younger on average and have higher prevalence of low literacy than subjects who might respond to recruitment for a more typical AUT.

3.2.1 Site Training and Procedural Integrity

PEGUS Research will select sites and train the site staff after approval by the Sponsor and the Institutional Review Board (IRB). All study staff will receive study-specific training. All training will be documented and retained in the study files.

3.3 Subject Selection

Actual use trials are designed to determine how well the general population of consumers is able to apply the information in nonprescription drug labeling to guide their own behavior. Subjects should therefore represent a wide range of demographic characteristics.

In order to mimic the OTC marketplace as much as possible, subject selection will be self-driven by response to an invitation to participate in the study issued at the point of sale for women seeking EC. In general, that will mean intercepting women who are self-pay or who are willing to be self-pay for the purposes of the study, and who present for EC only. Consumers who are purchasing EC for someone else's use will not be invited to participate, as they cannot give consent on behalf of the actual user.

Given that adolescents are an important subgroup in the study, adult subjects will be constrained to no more than 775 subjects, allowing for an adolescent subgroup number of approximately 175. Further, the group of older adolescents (age 15 and older) will be constrained to 125, to allow for approximately 50 subjects under the age of 15. If adolescent recruitment lags significantly behind adult enrollment, as a backup recruitment method, clinicians within the health center will be allowed to invite adolescents to participate in the study if the subject identifies a need for EC in the context of a clinical visit. In those cases, clinicians will not instruct subjects how to use

the study product; they will simply acknowledge the need for EC and extend the invitation to participate.

While it is unusual in an actual use trial to allow for active recruitment on the part of clinicians, the FDA-requested goals for adolescent enrollment are very likely to make supplemental recruitment measures necessary, particularly for those under age 15. Should recruitment via clinicians for adolescent subjects be necessary, in order to minimize the potential for bias, clinicians will be trained not to counsel potential adolescent subjects about the use of EC in general, nor will they give specific counseling about the study product. This supplemental mechanism of recruitment, if used because needed to meet adolescent recruitment goals, is unlikely to have any impact on the primary endpoints of the study. The usual concern about active clinician recruitment is that it may bias self-selection. There are three factors to consider regarding this theoretical concern. First, consumers' ability to self-select for emergency contraception as a whole in the OTC market has already been established. Second, self-selection for this product is very similar to already available OTC emergency contraceptives. Third, any potential bias affecting self-selection would be in the negative direction as subjects may indeed select the product mistakenly thinking that the clinician has recommended it, when, in fact, the product is not right for them. In order to estimate any impact of clinician referral on self-selection endpoints, data will be presented separately for adolescent subjects recruited in this manner.

3.3.1 Inclusion Criteria: Self-Selection Phase

In order to enroll a sample as representative as possible of the likely OTC consumer, the study inclusion criteria are defined as broadly as it is feasible. Subjects must meet the following initial screening inclusion criteria in order to begin the enrollment interview:

1. Able to read, speak and understand English
2. Can see well enough to read information on the label
3. Another member of the respondent's family has not participated in this study
4. Consumer or someone else in the household does not work for a market research or advertising company, public relations firm, news organization, pharmacy or pharmaceutical company, medicine manufacturer, as a healthcare professional, or as part of a health care practice, managed care or health insurance company, trained or worked as a healthcare professional or market research professional (eliminated for reasons of confidentiality and increased awareness of medicines and their labels)
5. Has not participated in a health-related market research or product label study in the past 12 months
6. Has not participated in a clinical trial in the past 12 months
7. Has never participated in a study about EC
8. Seeking the use of emergency contraception

Additionally, subjects must meet all of the following inclusion criteria to be eligible for enrollment into the use phase of the study:

- Evidence of a personally signed and dated informed consent form indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.
- Willing and able to comply with the initial visit and planned phone calls and other study procedures.

3.3.2 Exclusion Criteria: Use Phase

All subjects who agree to participate at the site will be asked to make a selection decision. Subjects presenting with any of the following will not be included in the use phase of the study (i.e., will not be allowed to purchase and use study medication):

1. Unwilling to purchase study medication.
2. Unwilling to provide written informed consent.
3. Unwilling or unable to provide contact information.
4. Unwilling to state that the product is for their own use and no one else's.
5. Pregnant, by self-report or by a urine pregnancy test.
6. Male.
7. Known allergy to ulipristal acetate or inactive ingredients.
8. Currently breastfeeding.
9. Premenarchal (have not experienced a first menstrual cycle).

Subject eligibility will be reviewed and documented by the Investigator or his/her designee before subjects are allowed to purchase and begin the use phase of the study.

3.3.3 Recruitment Methods

The nature of the indication (emergency contraception) makes recruitment for the trial challenging. By definition a woman does not know in advance that she will need EC, and when she does need it (because she has had unprotected sex), she needs it quickly. Therefore, a passive advertising campaign aimed at consumers interested in the indication (the approach typically used in AUTs) is unlikely to be effective for this study. Similarly, it would be inappropriate to make a woman who has had unprotected sex and is in need of EC as soon as possible wait for a scheduled appointment at the study site and potentially delay her taking the EC that she needs to take within a limited timeframe. This is particularly true because an approved OTC option is available to her outside the study.

Therefore, subjects will be actively recruited at the point of OTC-like sale in women's health clinics and in the retail pharmacy study sites. Sites which currently sell EC in an OTC or OTC-like setting and which have enough EC sales to meet recruitment goals will be chosen. They will also be chosen to ensure geographic and demographic diversity, and to be as representative of literacy in the general population as possible. When a subject presents asking for EC, they will be offered the opportunity to participate in the

study. Additionally, posters advertising the study may be placed strategically within the sites to attract potential subjects who are there considering a purchase of EC. In the event that adolescent recruitment significantly lags behind adult recruitment, as a supplementary method of recruitment, clinicians within the health centers will be allowed to invite adolescent subjects who, during the course of a clinical visit, have identified the need for EC. In those cases, the clinician will be instructed not to give instructions on how EC generally or the product specifically is to be used. Potential subjects recruited in this way then will be routed to the study staff for the face-to-face enrollment interview. See Section 3.3 for more information.

3.4 Randomization

There is no randomization in this study.

3.5 Data Collection

Data will be collected in structured one-on-one interviews using a standardized questionnaire either in-person (at the initial enrollment visit) or by telephone (in two follow-up interviews). The interviews will be administered by a trained interviewer using an internet-based Electronic Data Capture (EDC) application in which the interviewer will read the introductory scripts and the questions from the screen and will enter the responses directly into the study database. As a precaution, a paper version of the questionnaire will be available at each site should there be a loss of internet connection while using the EDC system during the course of an interview. This will allow the interviewer to complete the enrollment process for that subject; interviews will not be started on a paper DCI. Data from any interviews completed on paper will be entered into the EDC system as soon as possible after access is restored, and the paper questionnaires will be retained as source documents in the study files.

The questionnaires will include primarily open-ended questions. Question types will include direct questions and follow-up questions for clarification. No multiple-choice questions will be used. To facilitate the accurate capture of responses, open-ended questions will have pre-coded answer alternatives. It is important to note that these response alternatives will not be read to the subjects, nor will subjects be able to see them on the screen. Where close-ended questions are used (e.g., yes/no, or ok/not ok), subjects will be asked to explain their answers so behavior can be adequately assessed. When interviewers must type in open-ended question responses, they will capture short responses verbatim, and will accurately summarize longer responses.

During the self-selection interview at the initial visit, the ella® outer package including DFL will remain in front of the subject and the subject will be informed they can refer to the label at any time. However, the subject will neither be encouraged nor discouraged from referring to the package in response to any specific question.

All data will be collected via standardized, predesigned questionnaires in a one-on-one setting either in person or by telephone. For this study, no daily diary will be used. In the context of an AUT, a daily diary has the potential to influence subject behavior, making it much less naturalistic. In the case of a daily or frequent use medication, the advantages of a diary for the purposes of measuring the key endpoints may outweigh those

disadvantages. However, in the context of a single use product for EC, subject recall of when they took the product relative to unprotected sex and/or enrollment is expected to be quite good, as it is a singular, unique event with strong anchoring to context and timeline.

3.6 Test Materials

At the initial site visit, subjects will be provided with an empty ella® package that will display the proposed DFL (Appendix 18.1); they will review that package/box when making a self-selection and purchase decision.

The product purchased and taken home for use will include the exact same outer package, but the study medication and a CIL will be in the package.

Subjects who enter the use phase will also be provided with an administrative study information card (to include subject number, the central telephone number for any inquiries and direction to call to report any changes in health [AEs] experienced during the study). The administrative study information card will serve as a memory tool for subjects, and will not be returned to PEGUS. Subjects will also receive a self-administered urine pregnancy test to use at the end of the study and a pre-paid envelope to mail back unused study product or empty packaging.

3.7 Study Administrative Structure

Laboratoire HRA Pharma is the Sponsor for this study. PEGUS Research is the contract research organization (CRO) responsible for the development of the study materials, training interviewers, fielding of the study, coding of open-ended responses, analysis of the data, and preparation of the study report.

4 STUDY TREATMENTS

4.1 Allocation to Treatment

All subjects enrolled in the use phase of this open-label study will be given the opportunity to purchase and take 30 mg of ulipristal acetate.

4.2 Breaking the Blind

Not applicable to this study.

4.3 Drug Supplies

4.3.1 Formulation and Packaging

Tablets for oral administration contain 30 mg ulipristal acetate and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, and povidone.

ella® is available as a 30 mg tablet, packaged in a carton containing a blister card with a single tablet, constituting one dose.

4.3.2 Preparation and Dispensing

All subjects who use study medication will take ulipristal acetate 30 mg. Subjects are to use the investigational product (IP) based on their understanding of the directions on the outer packaging including DFL and inside the product packaging (in the CIL).

Subjects will be allowed to purchase the study product at the study site. Subjects will not be allowed to purchase more than 9 single-count packages during the entire study period. They will be allowed to purchase up to 3 packages at a time (on any one calendar day) during their first visit to the site and may return to the study site at any time to purchase additional medication, up to a total of 9 packages, during the following 6 weeks. These purchase limits will not be disclosed to subjects unless they try to purchase more than 3 packages in a day or more than 9 packages over the course of the study. Any such requests that exceed the purchase limits will be recorded.

It is typical to allow participants in an actual use trial to purchase more IP than they would use under usual conditions, in order to allow for the observation and measurement of overuse/misuse of the product, should it occur. In this case, as there is no true “typical use” for EC because the product is used under unusual circumstances (in instances of unprotected sex), purchase limits were chosen to allow for reasonable behavior on the part of subjects, even if beyond the label directions, without allowing for larger scale misuse. While the expectation is that the vast majority of subjects will purchase a single package of the IP, it would be reasonable for subjects to purchase additional doses for advance provision. The daily limit was set at three to account for this. Again, while the expectation is that very few subjects will return for resupply, in order to observe overuse or misuse should it occur, repurchase will be allowed. Indeed, given FDA’s expressed concern about the potential for misuse of this product, in previous interactions FDA agreed with the planned purchase limits as these limits would allow the AUT to estimate the likelihood of potential misuse when the product is available OTC.

4.3.3 Drug Storage and Accountability

The Investigator will ensure that the IP is stored under recommended storage conditions at the site and in accordance with the drug label (store at controlled room temperature 20°C to 25°C [68°F to 77°F]; see United States Pharmacopeia [USP]).

The IP must be stored as indicated on the package. Deviations from the storage requirements, including any actions taken, must be documented and reported to the monitor by the sites. Deviations outside of the range of 20°C to 25°C [68°F to 77°F], but between 15°C and 30°C [59°F and 86°F], will be documented and reported to the Sponsor by the monitors and IP will continue to be used. If a deviation is identified outside of the range 15°C to 30°C [59°F to 86°F], the deviation must be reported upon discovery and the IP must be quarantined and not used until the Sponsor provides documentation of permission to use the IP. The Investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the IP(s).

At the end of the trial, subjects will be asked to return any unused study medication and empty packaging. Subjects will be provided with a pre-paid, pre-addressed United States Postal Service envelope to send any unused study medication and empty packaging to

PEGUS Research. If PEGUS Research has not received the return unused medication or empty packaging within three business weeks after the subject exits the study, one follow-up telephone call will be placed requesting that the subject return any unused study medication and empty packaging.

The Sponsor will provide instructions as to disposition of any unused and returned IP.

4.4 Drug Administration

Subjects who use the IP are to use it based on their understanding of the labeling.

Because use of the IP is not driven by protocol, there are no medication errors involving subject exposure to the IP, though there may be potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject. Any such medication error will be reported to the HRA pharmacovigilance (PV) department. If applicable, any associated adverse event(s) (AE(s)) will be documented via the mechanism for spontaneous AE reports.

4.4.1 Compliance

There is no protocol-directed use of the study product and subjects will use the product at their own discretion based on their understanding of the DFL and other material on or in the package. The subjects will report on their use of the product in the two follow-up telephone interview(s).

4.5 Concomitant Medication(s)

The IP packaging (the CIL) will contain information about the use of other medications when taking ella®. Subjects will be queried at enrollment about medications that they are currently taking. During the two study telephone interviews, subjects will be queried about any new medications that they have begun taking since the start of the study.

4.6 Rescue/Escape/Salvage Therapy

Not applicable for this study.

4.7 Batch Recall

In case a batch recall is required during the course of this protocol, site monitors will be responsible for communicating with research sites and for organizing and following-up on the logistics of the recall, in collaboration with the sponsor and research sites.

At the end of the process, the site monitors will ensure that the total number of IPs returned to the PEGUS matches the total number of IPs delivered to all sites. Any discrepancy must be explained.

5 STUDY PROCEDURES

5.1 Pre-Interview Activities

Potential subjects who spontaneously present to one of the study sites seeking EC in an OTC or OTC-like setting will be invited by clinic or pharmacy staff to participate in the

study. Potential subjects who are interested will be immediately routed to study staff trained to do the enrollment procedures.

5.2 Study Period

5.2.1 Enrollment Visit, Self-Selection/Purchase Decision

At the enrollment/self-selection visit (constituting Study Day 1), which takes places at the women's health clinic or pharmacy, initial inclusion criteria will be reviewed and potential subjects will be shown the ella® package and given as much time as needed to review the information on the outer package. After reviewing the outer package, they will be asked whether the product is okay or not okay for them to use and if they want to purchase the product for their own use. Reasons for selection/non-selection and purchase/non-purchase will be recorded.

5.2.2 After Purchase Decision and Before Use Phase

The purpose of this study is to see how the subject complies with the labeled directions; therefore, the date of the use of study medication is determined by the subject. Study Day 1 will be defined as the day the product is dispensed to the subject. On Study Day 1, subjects will complete the enrollment interview including associated medical conditions and demographic information. Subjects will also be asked to complete the REALM[1] or REALM-Teen[2] test to establish reading ability.

Study exclusion criteria will be assessed and only qualified subjects who decide to purchase the product will continue on to the study use phase. Subjects will provide informed consent. Parental consent and subject assent will be obtained where required based on applicable local laws and regulations. See Section 12.3 for further information on parental consent of adolescent subjects.

After consent, all subjects will provide a urine sample for the study staff member to conduct a urine-based dip pregnancy test. Subjects with a positive pregnancy test will be asked to make a selection and purchase decision again with the new information regarding pregnancy and then excluded from the use phase of the study.

Qualified subjects will be required to provide contact information (for the purposes of conducting telephone follow-up interviews) and information regarding any medications they are currently using. Subjects who choose to will then purchase the IP and site study staff will complete the electronic product accountability form. While it is expected that most subjects will purchase a single package of ella®, subjects will be allowed to purchase up to 3 boxes in any one day, and will be allowed to return to the study site at any time during the use phase to purchase additional medication. Subjects will not be allowed to purchase more than 3 single dose packages in a single day, or more than 9 single-dose packages during the study period although this will not be communicated to the subjects unless they attempt to purchase more than that. Any requests for purchase more than the limits will be recorded.

Subjects will also be informed that study and End-of-Study (EOS) phone interviews will be conducted at Week 2/Day 14 (with an allowable window of ±3 days) and at Week 6/Day 42 (±4 days). Subjects who have purchased the product will be dispensed the product to use how and when they see fit.

Subjects also will be provided with a self-administered urine pregnancy test and given instructions to use the test at the end of the study period. Results will be recorded in the database in the End-of-Study interview.

5.3 Use Phase

5.3.1 Unscheduled Study Site Visits

During any unscheduled visit to a study site for purposes of subjects obtaining additional IP, the study staff contact with the subjects will be limited to:

1. Dispensing additional IP with no questions asked or answered or directions given about the use of the IP by the study staff.
2. Appropriately documenting the IP dispensed.
3. Assisting any subject presenting self-reported AEs by immediately having the subject contact PEGUS Research.

5.3.2 Telephone Interviews

The two scheduled phone interviews will be conducted by PEGUS Research clinical staff (usually nurses) to collect information regarding AEs and concomitant medications. During the 6 weeks of the study, subjects will be contacted by phone on Days 14 (with an allowable window of ±3 days) and 42 (±4 days) to answer phone interview questions and provide information on AEs and concomitant medication (and, in the end of study interview, about pregnancy test results).

In addition, several non-leading questions will be asked about behavior at the two phone interviews. Information will be asked for during both phone interviews in a masked manner to avoid influencing future behavior (e.g., “Besides taking the medication, is there anything else you have done to prevent pregnancy since we last spoke?”).

Subjects will be compensated for their time and effort to enroll and participate in the study at designated intervals during the study.

5.3.2.1 Week 2 Interview

The intent of the week 2 interview is to collect information about the initial use of the product. Because subjects in this study will be invited to participate after independently presenting to the clinic or the pharmacy seeking EC (and not in response to advertising), it is expected that most subjects will be purchasing EC for immediate use (because they have very recently had an episode of unprotected sex), rather than solely for advanced provision. The interview at 2 weeks is intended to ascertain whether the subject took the IP, and if so, to collect information about when she took ella® in relation to her enrollment visit (and in relation to their most recent episode of unprotected sex) and measure other behaviors in the period immediately surrounding taking the product. Timing of this interview is expected to be long enough after enrollment to allow for capturing of use within or outside of the 5-day window and resumption or starting of hormonal contraception use in the 5 or more days after ella® intake, but also to be soon enough that recall should not be problematic. Information about AEs and changes to concomitant medications will also be collected.

5.3.2.2 Week 6 Interview

Timing of the Week 6 interview is intended to allow for most women to have had at least one menstrual period after enrollment. Questions will be designed to collect information about behaviors related to EC use outside of the immediate period after use, as well as responses to a missed period. Information about AEs and changes to concomitant medications will also be collected.

5.3.2.3 End-of-Study Interview

In most cases, the EOS interview will take place in conjunction with the 6-week telephone call together with the week 6 interview. However, it is conceptualized as a separate interview in order to allow for collection of key end of study measures in cases where subjects elect to withdraw before the 6-week telephone call. The end-of-study interview will collect information from the subject regarding the use of other forms of contraception, including other uses of EC (if any) within the study period, and the timing of such use. Subjects will also be asked about possible pregnancy, and will be asked to report the results of their EOS pregnancy test. This interview allows for direct questions about the rationale behind any behaviors that are not consistent with the DFL and CIL, without concern about biasing the subject's subsequent behavior.

5.4 Subject Withdrawal (Early Termination)

An EOS interview will be conducted with any subject who discontinues or withdraws consent prior to Week 6, unless the subject withdraws consent for disclosure of future information. This interview will attempt to collect the EOS information and the reasons for the subject's early termination. If the subject withdraws from the study between days 1 and 17 (day 14+3), the clinical interviewer will attempt to complete the Week 2 and EOS interviews and gather EOS pregnancy test results. If the subject withdraws between days 17 and 46 (day 42+4), the clinical interviewer will attempt to complete the Week 6 and EOS interviews and gather EOS pregnancy test results. See Sections 6.4, 6.5, and 6.6 for more detailed information on the interviews.

Subject participation may be terminated by an investigator during the study for any of the following reasons:

- Significant protocol violation;
- AEs, including SAEs;
- Pregnancy;
- Physician decision;
- Subject's request;
- At the discretion of the Investigator or designee if s/he feels that study discontinuation is necessary to protect the subject, or that there are unmanageable factors that will interfere significantly with the study procedures and/or the interpretation of results.

Any such subjects will be asked to return any unused study medication and empty packaging and will be precluded from purchasing additional study medication, but earlier

collected data will be used and ongoing data collection will be allowed, unless the subject requests otherwise.

Subjects may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor (or Sponsor designee) for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

If a subject refuses contact for scheduled follow-up calls, any efforts made to contact the subject will be documented. In any circumstance, every effort will be made to document subject outcome, if possible. The investigator will inquire about the reason for withdrawal, request the subject to return all unused IP(s) and empty packaging, request the subject to participate in a final telephone interview, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations will be performed, and no additional data will be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

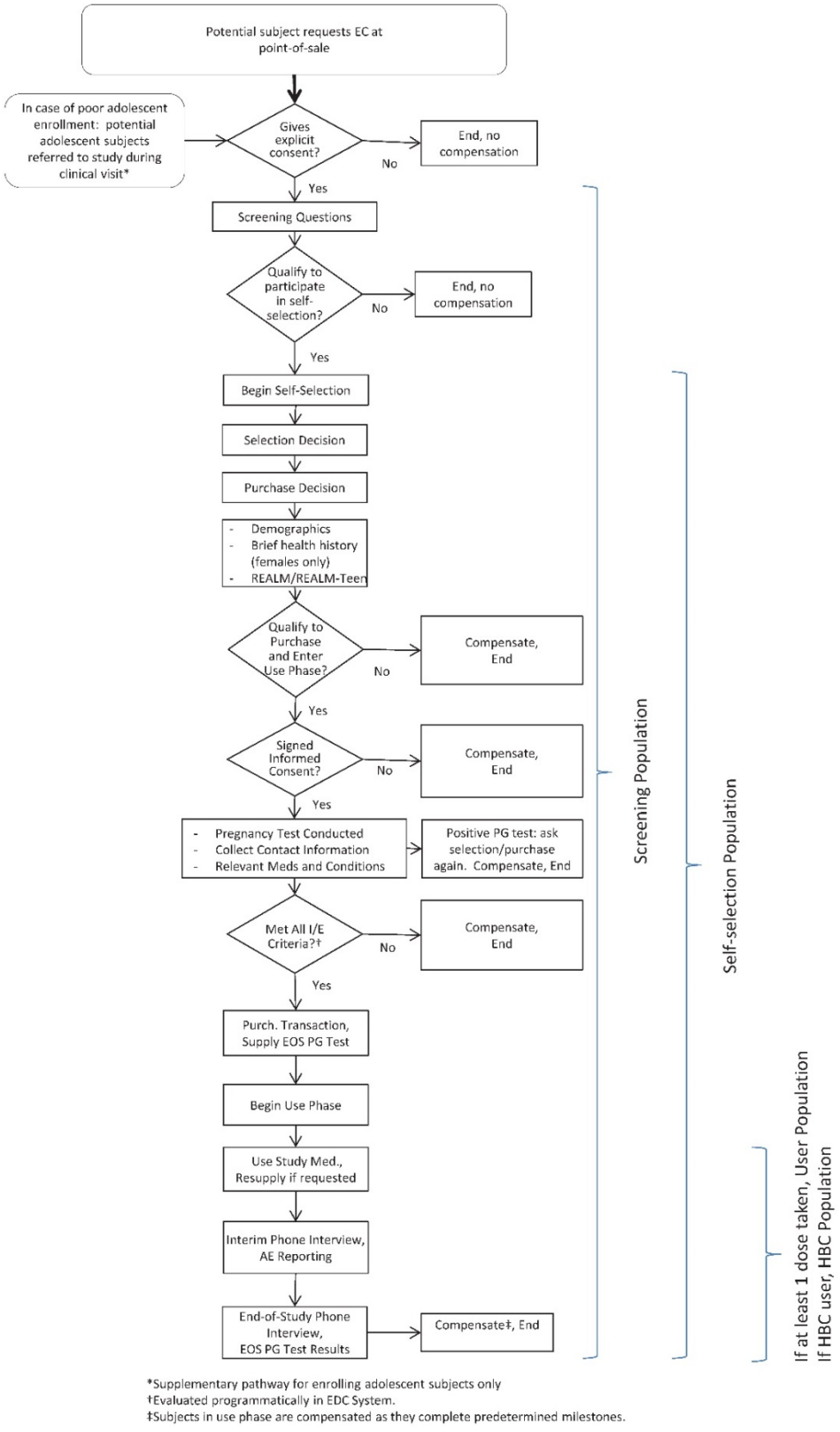
A subject may be declared lost to follow-up if, during the study, the available contact information is determined to be incorrect and no other information is available. Every attempt will be made to contact lost to follow-up subjects, including three phone call attempts and a United States Postal Service (USPS) letter. Subjects whose status is withdrawn, lost to follow-up, withdrawal due to an AE or withdrawal from the study for other reasons will be recorded in the case report form (CRF).

If a subject wishes to discontinue his or her participation in the study, the Investigator/interviewer will document the reason for withdrawal, ask the EOS questions where possible and follow-up with the subject regarding any new or unresolved AEs and collect or make arrangements to collect all IP provided to the subject. Data collected up to the point of withdrawal will be retained and used as appropriate in the data analysis.

5.5 Study Flow

Study procedures are represented in a flow chart in Figure 1 below.

Figure 1 Study Procedures Flowchart



*Supplementary pathway for enrolling adolescent subjects only
†Evaluated programmatically in EDC System.
‡Subjects in use phase are compensated as they complete predetermined milestones.

6 ASSESSMENTS

Every effort will be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time, there may be circumstances outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible.

The study team will be informed of these incidents in a timely fashion. All data will be collected using an Electronic Data Capture Data Collection Instrument (DCI).

6.1 Screening Assessment

Subjects will be screened during the initial visit to determine those individuals who will be included or excluded from the trial.

6.2 Enrollment Interview

Subjects will be shown the ella® outer package and allowed to make a decision about whether the product is appropriate for them to use, and whether to purchase ella® for their own use. Subsequent questions will be asked to gather limited medical and medication history as it pertains to use of the product.

6.3 Reading Level Assessment

The REALM[1] (for adults) or the REALM-Teen[2] (for adolescents) test will be used to measure reading grade level and will be the measure of literacy used for this study. The REALM score corresponds to four grade-equivalent reading levels as shown in Table 2 below, while the REALM-Teen score corresponds to 5 grade-equivalent reading levels as shown in Table 3 below. A REALM score of 60 or less (a reading level of 8th grade or lower) defines the low literacy subgroup among adult subjects.

The REALM-Teen test does not have a 9th grade reading level cutoff, so a cutoff score of 60 or lower will be used to define the low literacy cohort for the adolescent group as well (which is the midpoint of the 8th - 9th grade-equivalent reading level). This allows for a somewhat more conservative requirement to be classified as low literacy among the adolescent cohort in comparison to the cutoff for 10th grade-equivalent reading level.

The REALM-Teen will be used to demonstrate (along with demographics) that adolescent subjects represent a diversity of age, race, educational attainment, and reading ability. However, given the relatively small absolute number of low literacy adolescents expected (if 25% of the sample of 175 adolescents meet the criteria, this would yield approximately 44 low-literacy adolescents), low literacy adolescents will be included with low literacy adult subjects to comprise the overall low literacy subgroup.

Table 2 REALM Test Grade-Equivalent Reading Levels

REALM[1] Score	Grade-equivalent Reading Level	Included as Low-literacy	Included as Normal-literacy
0-18	3rd	X	
19-44	4th to 6th	X	
45-60	7th to 8th	X	
61-66	9th and above		X

Table 3 REALM-Teen Test Grade-Equivalent Reading Levels

REALM-Teen[2] Score	Grade-equivalent Reading Level	Included as Low-literacy	Included as Normal-literacy
0-37	3rd	X	
38-47	4th - 5th	X	
48-58	6th - 7th	X	
59-62	8th - 9th	≤ 60	≥ 61
63-66	10th and above		X

Given that literacy (as measured by the REALM or REALM-Teen) is not known in advance and cannot be directly used in screening in an actual use trial, recruitment targets for low literacy are not set. In self-selection and actual use studies that recruit in the typical manner, the proportion of low literacy subjects typically ranges from 12-18%. In contrast with label comprehension studies, whose samples are meant to be approximately representative of the general population and therefore controlling for factors of interest like literacy is potentially justified, one of the overarching goals of an actual use trial is to enroll a sample based on individuals who present seeking the product, and this approximates the likely OTC user population. Actual use trials seek to enroll subjects who seek out the product as they are those most likely to use the product when available OTC. In this case, forcing a certain percentage of low-literacy enrollment would compromise the representativeness of the sample in a manner that is inappropriate. While it is inappropriate to force a specified proportion of low literacy subjects in an AUT, it is still important to have a sample of low literacy participants of sufficient size to allow for conclusions to be drawn as to performance of study endpoints among subjects of low literacy. The total sample size of this study was selected to ensure that the absolute size of the subgroup of low literacy participants will be large enough to evaluate the endpoints among those of low literacy. If 15% of 950 subjects are classified as low literacy by the REALM or REALM-Teen, the cohort of low literacy subjects will be approximately 143 subjects, representing a low literary subgroup of sufficient size. As an illustration, the 95% confidence interval (exact) around a point estimate of 85% for 143 subjects is +/-7%.

6.4 Interim Follow-Up Telephone Interviews

During the course of the study, all subjects will be contacted twice via telephone by a trained nurse (Interviewer) who will ask a series of questions related to the use of the study medication, as well as collect information related to medications and AEs.

The answers to these questions will be part of the study database and used to determine the performance of the endpoints. There will be a total of 2 phone interviews, one at day 14 (with an allowable window of ±3 days) and one at day 42±4 days, during which the nurses will limit the dialogue with the subjects to the interview script.

6.5 End-of-Study/Early Termination Telephone Interview

The EOS interview will occur at the end of the study (typically this will be in conjunction with the 6-week call), or upon early termination from the study. All subjects will be contacted via telephone by a trained nurse (Interviewer) who will ask a series of questions related to the use of the study medication, as well as collect information related to medications and AEs.

As participation for that subject will then be complete, and therefore the risk of biasing future behavior irrelevant, this end-of-study interview will include direct questions about how the product was used. The answers to these questions will be part of the study database and used to determine the performance of some of the endpoints.

Typically, the EOS interview will be conducted during the 6-week telephone call immediately following the 6-week interim follow-up interview. However, in cases where subjects may withdraw earlier for any reason, the EOS interview will be conducted at that time.

6.6 Pregnancy Testing

All subjects will be asked directly if they are currently pregnant in the enrollment interview. Any subject that reports being pregnant will be disqualified from participation in the use phase. Subjects that sign consent will provide a urine sample for the study staff member to conduct a urine-based pregnancy test. Subjects with a positive result will be informed of the result, asked the selection and purchase question again, and then excluded from participating in the use phase. Subjects with a negative result will not be provided with the test result, unless they specifically request this information. The concern is that a woman who has had recent unprotected sex and seeks EC might erroneously interpret a negative pregnancy test as an indication that she does not need EC. To minimize this risk, the consent form will contain an explanatory note that pregnancy testing cannot detect a pregnancy that may occur as a result of recent unprotected sex. At the end of the enrollment interview, subjects who are proceeding into the use phase will be given a home pregnancy test (with the instructions to use it) to take home and use at the end of the study. Nurse interviewers will inquire about the results of the pregnancy test during the EOS interview. An additional call will be placed at 7 days ±3 days following the EOS interview to collect that information if the subject reported at the EOS interview that they had not yet used the test. This allows for shipping time if the subject requires an additional pregnancy test to be sent. In addition, at the time a subject withdraws from the study, nurse interviewers will inquire if the subject would be willing to take the pregnancy test and report the results.

7 ADVERSE EVENT REPORTING

7.1 Adverse Events

All observed or volunteered AEs regardless of suspected causal relationship to the IP(s) will be reported as described in the following sections. This study includes only one treatment group.

While responsibility for collection, recording, and reporting of all AEs will be assumed by PEGUS Research, study staff at the study sites will identify any spontaneous reporting of AEs to the site staff and facilitate the reporting to the centralized clinical nurse interviewers. All site staff and subjects will be provided with a 24-hour toll-free number to report any adverse events or other issues. Note that for this section “Investigator” refers to the central principal investigator at PEGUS Research who oversees this process.

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE. The Investigator is required to assess causality. Follow-up by the Investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and the Sponsor concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious AE that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical trial.

7.2 Reporting Period

For SAEs, the active reporting period to the Sponsor or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject’s participation in the use phase of the study, ie, prior to undergoing any study-related procedure and/or receiving IP, through and including 28 calendar days after the last administration of the IP. SAEs occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the Investigator becomes aware of them; at a minimum, all SAEs that the Investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

For non-serious AEs the reporting period begins from the time the subject has taken at least 1 dose of study treatment through last subject visit.

7.3 Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation wherein subjects are administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;

- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

7.4 Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or,
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or,
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or,
- Test result is considered to be an AE by the Investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

7.5 Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life threatening (immediate risk of death);

- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Is a medically important event.

Medical and scientific judgement is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

7.5.1 Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see Section on SAE Reporting Requirements).

7.6 Hospitalization

AEs reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);

- Administrative admission (e.g., for yearly physical exam);
- Protocol specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

7.7 Severity Assessment

If required on the AE CRFs, the Investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

7.8 Causality Assessment

The Investigator’s assessment of causality must be provided for all AEs (serious and non-serious). The Investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An Investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. If the Investigator does not know whether or not investigational product caused the event, then the event will be handled as “related to investigational product” for reporting purposes, as defined by the Sponsor. If the Investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the Investigator determines an SAE is associated with study procedures, the Investigator must record this causal relationship in the source documents and CRF,

as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

7.9 Exposure During Pregnancy

For IPs and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or being exposed (e.g., due to treatment or environmental exposure) or after discontinuing or having been directly exposed to the IP;
- A male has been exposed (e.g., due to treatment or environmental exposure) to the IP prior to or around the time of conception or is exposed during his partner's pregnancy.

If a study subject becomes or is found to be pregnant during the study subject's treatment with the IP, the Investigator must submit this information to the Sponsor as an EDP, regardless of whether an SAE has occurred. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information for all pregnancy reports with an unknown outcome. The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify the Sponsor of the outcome as a follow up to the initial pregnancy report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (i.e. ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion.

Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the Investigator assesses the infant death as related or possibly related to exposure to IP.

Additional information regarding the EDP may be requested by the Investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

7.10 Withdrawal Due to Adverse Events

Withdrawal due to AE should be distinguished from withdrawal due to insufficient response, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined herein.

7.11 Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs during all phone interviews.

7.12 Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

7.12.1 Serious Adverse Event Reporting Requirements

If an SAE occurs, the Sponsor is to be notified within 24 hours of study staff awareness of the event. In case of SAE, the investigator must immediately complete the SAE data collection form and send it by fax or by email within 24 hours to the Sponsor's Pharmacovigilance Department:

Fax: +33 1 42 77 03 52

Email: pharmacovigilance@hra-pharma.com

In particular, if the SAE is fatal or life-threatening, notification to the Sponsor must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy.

In the rare event that the Investigator does not become aware of the occurrence of an SAE immediately (e.g., if an outpatient study subject initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the Investigator is obligated to pursue and provide information to the Sponsor in accordance with the time frames for reporting specified above. In addition, an Investigator may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or its designated representative.

7.12.2 Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

7.12.3 Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting to regulatory authorities, including suspected unexpected serious adverse reactions (SUSAR) is the responsibility of the Sponsor PV department and will be carried out in accordance with applicable local regulations by the Sponsor.

8 DATA MANAGEMENT

8.1 EDC System

Information collected during the subject interviews will be entered directly into an EDC application (DATATRAK ONE, DATATRAK International, Inc.). Automatic data checks will alert users of discrepancies and inconsistencies, where applicable. In the event of a data entry error, users will have the ability to correct information previously entered. Data Management will review the information entered as defined in this protocol.

All users will have a unique login user name and password, and system access privileges will be strictly controlled and documented. Whenever data is modified after the initial data entry process, a computer-generated audit trail entry will be created. The audit trail, user access privilege processes, and electronic signatures collected by the system will be compliant with 21 CFR Part 11 requirements.

If an internet connection is not available, the interview will not be started. If the internet connection is lost during the course of an interview, a paper copy of the electronic forms will be available to complete the interview. When the Internet connection is restored, study staff at the site will enter the data from the paper forms into the EDC system. If this were to occur, the completed paper copy of the electronic forms is the source document. Otherwise, the electronic record is the source.

8.2 Data Management Plan

A detailed Data Management Plan (DMP) will describe procedures to ensure the proper management and quality of study data and additional PEGUS Standard Operating Procedures (SOPs) specify the activities performed to ensure the quality, accuracy and reliability of the statistical analysis and the final study report.

8.3 Conceptual Approach to Self-Selection

This is not a dedicated self-selection study, however every AUT has some component of self-selection, and, in fact, one of the secondary endpoints in this study is the typical self-selection metric.

Conceptually, the self-selection decision can be characterized as a 2x2 table (Table 4 below) where the subject's decision to select or not select the study product for use is

crossed with whether or not it is appropriate for subject to use, based on subject's self-reported health status and clinical characteristics.

Table 4 Self-Selection Decision Outcomes

Subject's Selection Decision	Appropriate to Use: YES	Appropriate to Use: NO
YES (selectors)	**Cell A** Correct Decision	**Cell B** Incorrect Decision
NO (non-selectors)	**Cell C** Incorrect Decision	**Cell D** Correct Decision

The four cells in the self-selection matrix can be characterized as follows.

Cell A: Subjects who say the study product is right for them to use and based on their self-reported medical and demographic information, the study product is right for them to use.

Cell B: Subjects who say the study product is right for them to use and based on their self-reported medical and demographic information, the study product is not right for them to use.

Cell C: Subjects who say the study product is not right for them to use and based on their self-reported medical and demographic information, the study product is right for them to use.

Cell D: Subjects who say the study product is not right for them to use and based on their self-reported medical and demographic information, the study product is not right for them to use.

8.4 Classification Activities

In order to evaluate subjects for the relevant endpoints, each subject will be classified on two key variables: (1) the selection decision and (2) the appropriateness of use given the selection decision, in order to populate the typical 2x2 self-selection table (Table 4 above). Subjects will be classified on these two variables as described in Sections 8.4.1 and 8.4.2 below.

8.4.1 Selection Decision

The selection phase of the interview consists of the self-selection question and the purchase question, with accompanying neutral follow-up questions. All subjects who go on to actually purchase the study product will be categorized as selectors. Even subjects who do not eventually complete the purchase of the product will be classified as a selector or a non-selector on the basis of the initial selection and purchase questions. However, all information recorded during the selection phase of the interview will be considered in the classification of subjects as selectors or non-selectors. Subjects who offer modifying information in open-ended responses to neutral probing will be re-

categorized accordingly. Please note that for this study, subjects are offered the opportunity to enroll when they present for purchase of EC. That is, these are subjects who came to the site having already determined they need EC and expecting to purchase EC.

A subject who initially indicates that they would select and purchase the product, but who independently and unprompted changes their purchase decision during the selection phase of the interview would be categorized as a non-selector. For the majority of subjects, any information offered once the interview proceeds beyond the selection phase of the interview will not be considered during selection classification. However, for subjects that self-report not being pregnant, sign consent and then receive a positive result from the enrollment pregnancy test, the selection questions will be asked again and used to classify the subject as a selector or non-selector. Financial and cost-related reasons for saying no to the purchase question will not be used as rationale for re-classifying subjects who would otherwise be selectors.

The selection decision for each subject will be examined on a case-by-case basis, taking into account all the information gathered during the selection phase of the interview. Two independent coders will evaluate the available data and indicate whether the subject is a selector or a non-selector. Discrepancies will be resolved by a third coder (as described in Section 8.4.3).

8.4.2 Appropriate to Use

Non-selectors will be classified on the variable Appropriate for Use as follows:

> **Yes:** meets the label criteria for use, representing those who could have selected appropriately, but did not (**Cell C**).
>
> **No:** does not meet the label requirements for use, and appropriately did not select (**Cell D**). This includes those subjects who otherwise might have met the strict criteria for appropriate use according to the DFL, but who give a medically appropriate rationale for their non-selection decision. For example, if a subject who otherwise meets the labeled criteria for use does not select the product and for example cites the desire to use another EC product so they can restart hormonal contraception immediately as their reason for not selecting, that subject will be re-classified from Cell C to Cell D. A physician will review the casebook for each subject who falls into Cell C to determine if any subjects meet that criterion.

Selectors will be classified on the variable Appropriate for Use as follows:

> **Yes:** either meets the strict label criteria for use (1-Correct Selectors) or reported and measured characteristics justify the selection decision (2-Acceptable Selectors), representing those who chose to use the product who made a clinically acceptable decision despite not meeting the strict label criteria for use (**Cell A**).
>
> **No:** does not meet strict label criteria and reported and measured characteristics do not justify the selection decision (3-Incorrect Selectors), representing those who chose to use the product, but should not have (**Cell B**).

Complete definitions of Correct, Acceptable, and Incorrect Selectors follow:

1) Correct Selectors. Subject meets the strict criteria of the Drug Facts label, including:
    a) No contraindications (not pregnant or breastfeeding, no known allergy to any of the ingredients, no previous use of ella® within the same menstrual cycle, no use as regular birth control)
    b) Is a woman of childbearing potential. This would include all women who do not report any of the following: surgical sterilization (tubal ligation, hysterectomy, or bilateral oophorectomy) or postmenopausal for at least one year
    c) Has had unprotected sex in the 5 days prior to use of the product
2) Acceptable Selectors. Subject does not meet the strict criteria of the DFL, but selection is classified as appropriate because they are judged clinically (see Section 8.4.3) to be an appropriate selector. This group is expected to be quite small.
3) Incorrect Selectors. This group includes selectors who are not correct or acceptable, including having any of the following:
    a) A contraindication to the product (are pregnant or breastfeeding, or has an allergy to one of the ingredients, previously used ella® within the same menstrual cycle, or use as regular birth control)
    b) Is a man
    c) Is a woman without childbearing potential. This would include all women who report any of the following: surgical sterilization (tubal ligation, hysterectomy, or bilateral oophorectomy) or postmenopausal for at least one year
    d) Has not had unprotected sex in the 5 days prior to use of the product

Please note, for the purposes of this study, for all subjects who qualify to purchase the product, self-selection will be evaluated at the time of use, rather than time of purchase, and each instance of use will be independently evaluated for the self-selection endpoints. For example, if a subject purchases two packages of the study product, using one immediately and one four weeks later, each of those use instances will be evaluated for appropriateness. Because the timing of the most recent episode of unprotected sex is one of the elements of appropriate use, behavior surrounding each dosing instance must be the basis for self-selection evaluation.

Subjects who are either pregnant or breastfeeding and who select the product will be precluded from purchasing, and will be classified as incorrect selectors.

8.4.3 Physician Mitigation

Subjects occasionally make a decision to select a product for use that according to the strict DFL-defined algorithm appears to be an incorrect decision, but, when examined clinically, is acceptable. This review and clinical judgement will be done by three physicians working independently, evaluating the entire casebook for each Incorrect Selector (as defined above in Section 8.4.2) for evidence that the subject made a clinically justifiable selection decision. Their assessments are then compared, and any discrepancies resolved by a majority rule.

Each physician reviewer will review the entire casebook for every subject who falls into Cells B or C of the self-selection table. For subjects in Cell B, physicians will make an assessment of whether the use instance was acceptable based on clinical judgement of the subject's behavior and her stated reasons for those actions. If yes, each physician's complete rationale for mitigation will be recorded and the subject will be reclassified from Cell B to Cell A. For subjects in Cell C, physicians will make an assessment of whether the non-selection decision was based on a reasonable medical rationale. If yes, each physician's complete rationale for mitigation will be recorded and the subject will be reclassified from Cell C to Cell D.

8.4.4 Coding of Open-ended Responses

The responses to open-ended questions will be coded to make them amenable to numeric analysis and display. Coding procedures will follow PEGUS Research SOP DAT:008. Once data for at least 50% of subjects has been collected, listings of individual responses for each question will be created. The listings will be reviewed to discover the underlying conceptual structure suggested by the data, and a coding frame (a list of categories, each of which is assigned a one or two-digit number) will be created for each question. The coding frames will be reviewed and revised as necessary when 100% of the data is collected and cleaned. When the coding frame is finalized, reviewed and approved, coding may be performed.

Coding will be done using data from the final, clean data set. Two coders working independently will code each question with a significant number of responses (e.g. >25). Their code assignments will then be compared and the Coding Supervisor will resolve any discrepancies. Multiple codes (typically no more than seven) may be assigned to elements of one response. Once coded, these data will be displayed in standard frequency tables. For these tables, the unit of analysis, and thus the denominator, changes to become the number of responses rather than the number of subjects.

9 DATA ANALYSIS/STATISTICAL METHODS

A detailed methodology for the statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be finalized prior to database lock. The SAP may modify the plans outlined in the protocol; however, any major modifications to the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

This is a naturalistic, observational trial to assess use patterns from the prospective OTC population in a simulated OTC setting. The analyses will largely employ descriptive statistics including frequencies, percentages and appropriate summary statistics.

9.1 Sample Size Determination

For the purposes of this AUT, sample size has been set for practical and logistical reasons at approximately 950 purchasers. Given that subjects are recruited after independently seeking EC, most of those who enter the self-selection phase are expected to purchase, and most purchasers are expected to actually use the product during the study. If approximately 75% of subjects pass the screening criteria, self-select

and both qualify and agree to purchase and enter the use phase, it is expected that up to 1270 subjects will need to be interviewed to yield 950 purchasers.

Assuming approximately 950 purchasers, if 80% of those purchasers use the product within the study period, that would yield a user population of 760. Estimating approximately 40% of users will have had recent hormonal contraceptive use would yield a recent hormonal contraceptive users population of 305. Allowing for a further 20% loss to follow-up yields a user population of approximately 608 and a recent hormonal contraceptive user population of 245.

Because actual use trials are not hypothesis-testing comparative trials, study sample size is designed to allow for adequate evaluation of key endpoints across all subjects and among several subgroups. As the analysis of actual use trials typically focuses on estimating the proportion (and associated 95% confidence intervals) of individual endpoints, sample size is most often based on the number of subjects needed to constrain the confidence interval (CI) to a limited range. For this study, assuming 85% correct response (the confidence interval depends on the actual point estimate), a sample of 608 subjects would constrain the CI to ±3.1%. For purposes of illustration, Table 5 provides the 2-sided exact 95% confidence interval for various sample sizes around a point estimate of 85%.

Table 5 Two-sided 95% CIs for Various Sample Sizes Around 85% Point Estimate

	N=760[a]	N=608[b]	N=245[c]	N=143[d]
95% CI around a point estimate of 85%	±2.7%	±3.1%	±5.1%	±7.0%

[a] User population (maximum)
[b] User population (allowing for loss-to-follow up)
[c] Recent hormonal contraceptive users
[d] Low literacy subjects

9.2 Analysis Populations

The populations of interests are defined as follows:

- Responder Population: Subjects who accept the invitation to participate and begin the screening process (including those who do not meet screening criteria for proceeding to the self-selection phase).
- Self-Selection Population: Subjects who accept the invitation to participate and meet study inclusion criteria, participate in a face-to-face interview at the study site and make a self-selection and purchase decision.
- Purchasers: Subjects who meet study enrollment criteria and purchase the study medication.
- User Population: Subjects who take at least one dose of study medication during the study.
- Recent hormonal contraceptive users: Subjects in the user population who also report recent hormonal contraceptive use (i.e., use of a hormonal contraceptive within the previous two months).

9.3 Endpoint Analysis

A summary of the disposition of subjects (including responders, self-selection population, purchasers and users) and reasons for exclusion from these populations will be provided. Demographic characteristics, medical history and other background information will be summarized for the responder, self-selection, purchaser, and user populations.

Frequencies and percentages will be presented for categorical data, mean, standard deviation (SD); median, and range will be presented for numerical data.

Frequencies, percentages and 2-sided 95% CI will be calculated for the primary and secondary endpoints using the exact method. For the primary endpoints, it will be concluded that the established target threshold is reached if the lower limit of the CI of the point estimate is equal to or exceeds the value of the pre-determined threshold.

Several of the endpoints are based on dosing instance, rather than by subject, as subjects have the potential to take more than one dose over the course of the study. Correctness of selection or behavior can only be evaluated at the time of use, rather than at the time of purchase. However, for each of those endpoints a secondary analysis by subject will also be presented.

Endpoints and demographics will be presented for subgroups of interest, with subjects dichotomized on the corresponding variables, which include (but are not necessarily limited to) literacy, gender, age (adolescent vs. adult women), and history of HBC use.

A more detailed description of planned data analysis procedures will be found in the SAP which will be approved and signed before the database is locked.

9.3.1 Primary Endpoint Analysis

Frequencies, percentages and two-sided exact 95% confidence intervals will be calculated for the three primary endpoints for the entire study population and for selected subgroups.

9.3.1.1 A: Actual Use: Proportion of dosing instances among user population taken within 120 hours (5 days) of most recent episode of unprotected sex.

The first primary endpoint is the proportion in which the denominator includes all dosing instances of the IP and the numerator includes all dosing instances of the IP which were taken within 120 hours (5 days) of the subject's most recent episode of unprotected sex.

9.3.1.2 B: Actual Use: Proportion of dosing instances among user population in which no more than one tablet was taken.

The second primary endpoint is the proportion in which the denominator is all discrete dosing instances of the IP and the numerator includes all dosing instances where no more than one tablet was taken.

9.3.1.3 C: Self-Selection: Proportion of female selectors who are not pregnant at the time of selection decision.

The third primary endpoint is the proportion in which the denominator includes all females who selected to use the product (regardless of whether they purchased/used) and the numerator includes all female selectors who were not pregnant at the time of the selection decision. In the case of subjects that report not being pregnant, sign consent and then receive a positive result on the pregnancy test, the second selection decision will be used for analysis of this endpoint.

9.3.2 Target Thresholds

The threshold for the three primary endpoints is 90%. The objective will be considered met for these endpoints if the lower bound of the 2-sided 95% CI for each endpoint meets or exceeds the established threshold.

- *A: Actual use: Proportion of dosing instances among user population taken within 120 hours (5 days) of most recent episode of unprotected sex.*

The Sponsor proposes to test this message as a primary endpoint because it communicates directions for effective use of ella®, and the limited time-window for its effective use. Use of ella® after 5 days diminishes or abolishes the product's efficacy, although it is not expected to introduce any drug-related risks. Despite the fact that this label language is almost identical to the label language tested, approved, and in-market for Plan B One-Step (PBOS) (which is "Take as soon as possible and no later than 3 days (72 hours) after unprotected sex"), the Sponsor will test this as a primary endpoint.

Testing it as a primary endpoint would test whether the longer time window (5 vs 3 days) during which consumers may benefit from ella® use is well-followed. This would also allow us to confirm that consumers do not take ella® later after unprotected intercourse than recommended in the product label.

A performance threshold of 90% is proposed because while taking the product within the 5-day window is very important to maximize effectiveness, taking it outside of the 5 days window is not expected to introduce any serious drug-related risks.

- *B: Actual Use: Proportion of dosing instances among user population in which no more than one tablet was taken.*

The Sponsor proposes to test this message as a primary endpoint in the context of FDA's recommendation to demonstrate in an AUT whether consumers misuse ella® and one of the potential misuse scenarios would be the intake of more than the recommended dose, which would be assessed through this endpoint.

A threshold of 90% was designated despite the fact that dose-finding studies using up to 200 mg of UPA (more than 6 times the intended 30 mg dose) demonstrated no safety concerns (HRA2914-503). Accordingly, it is likely that taking more than the recommended dose is likely to impose little or no additional risk in women.

- *C: Self-Selection: Proportion of female selectors who are not pregnant at the time of selection decision.*

The Sponsor proposes to test this message as a primary endpoint as it would allow the study to confirm that consumers do not select ella® if they know they are already pregnant.

Of important note, the caution against use if already pregnant is on the approved and marketed PBOS DFL that uses the exact same language as that proposed on the ella® DFL ("Do not use if you are already pregnant (because it will not work)". The ella® LCS demonstrated that consumers understand this warning extremely well. Moreover, data suggest use of ella® in pregnancy is safe. For ella®, the analysis of the global pregnancy safety database conducted in the context of the Ellipse II study has been specifically intended to assess the occurrence rates of outcomes of pregnancies exposed to ella® due either to failure of the EC or inadvertent exposure during pregnancy, including fetal and neonatal outcomes and maternal pregnancy complications. Data from the collected UPA-exposed pregnancies did not reveal a negative signal on the course of the pregnancy, its outcome, or the growth and development of the embryo and the fetus.

Despite the fact that the available safety data are reassuring were a pregnant woman to take ella®, this has been designated as a primary endpoint in this AUT with a 90% threshold.

9.3.3 Secondary Endpoint Analysis

9.3.3.1 D: Self-Selection: Proportion of female selectors who are not breastfeeding at the time of selection decision.

The first secondary endpoint is the proportion in which the denominator includes all females who selected to use the product (regardless of whether they purchased/used) and the numerator includes all female selectors who were not breastfeeding at the time of the selection decision.

9.3.3.2 E: Self-Selection: Proportion of self-selection population who make a correct selection decision regarding use of the product.

This endpoint is the proportion of those subjects making the self-selection decision who make a correct decision about whether the product is right for them to use, as outlined below.

9.3.3.2.1 Populating the Self-Selection Table

Each subject will be classified on two key variables: (1) the selection decision and (2) the appropriateness of use given the selection decision, in order to populate the typical 2x2 self-selection table.

Selection Decision: The selection phase of the interview consists of the self-selection and purchase questions, with accompanying neutral follow-up questions. All subjects who go on to actually purchase the study product will be categorized as selectors. Even

subjects who do not eventually complete the purchase of the product will be classified as a selector or a non-selector primarily on the basis of the initial self-selection and purchase questions, or in the case of a positive enrollment pregnancy result, the second self-selection and purchase question. However, all information recorded during the selection phase of the interview will be considered in the classification of subjects as selectors or non-selectors. Subjects who offer modifying information in open-ended responses to neutral probing will be re-categorized accordingly.

Appropriate to Use:

Non-selectors will be classified on the variable Appropriate for Use as follows:

> **Yes:** meets the label criteria for use, representing those who could have selected appropriately, but did not (**Cell C**).
>
> **No:** does not meet the label requirements for use, and appropriately did not select (**Cell D**). This includes those subjects who otherwise might have met the strict criteria for appropriate use according to the DFL, but who give a medically appropriate rationale for their non-selection decision. For example, if a subject who otherwise meets the labeled criteria for use does not select the product and cites the fact that they are taking a medicine for Human Immunodeficiency Virus (HIV) as their reason for not selecting (which otherwise does not disqualify a subject from using, but rather suggests that they talk to a doctor), that subject will be re-classified from Cell C to Cell D. A physician will review the casebook for each subject who falls into Cell C to determine if any subjects meet that criterion.

Selectors will be classified on the variable Appropriate for Use as follows:

> **Yes:** either meets the strict label criteria for use (1-Correct Selectors) or reported and measured characteristics justify the selection decision (2-Acceptable Selectors), representing those who chose to use the product who made a clinically acceptable decision despite not meeting the strict label criteria for use (**Cell A**).
>
> **No:** does not meet strict label criteria and reported and measured characteristics do not justify the selection decision (3-Incorrect Selectors), representing those who chose to use the product, but should not have (**Cell B**).

Complete definitions of Correct, Acceptable, and Incorrect Selectors follow:

> 4) Correct Selectors. Subject meets the strict criteria of the Drug Facts label, including:
>
> a) No contraindications (not pregnant or breastfeeding, no known allergy to any of the ingredients, no previous use of ella® within the same menstrual cycle, no use as regular birth control)
>
> b) Is a woman of childbearing potential. This would include all women who do not report any of the following: surgical sterilization (tubal ligation, hysterectomy, or bilateral oophorectomy) or postmenopausal for at least one year
>
> c) Has had unprotected sex in the 5 days prior to use of the product

5) Acceptable Selectors. Subject does not meet the strict criteria of the Drug Facts label, but selection is classified as appropriate because they are judged clinically (see Section 8.4.3) to be an appropriate selector. This group is expected to be quite small.
6) Incorrect Selectors. This group includes selectors who are not correct or acceptable, including having any of the following:
    a) A contraindication to the product (are pregnant or breastfeeding, has an allergy to one of the ingredients, previously used ella® within the same menstrual cycle, or use as regular birth control)
    b) Is a man
    c) Is a woman without childbearing potential. This would include all women who report any of the following: surgical sterilization (tubal ligation, hysterectomy, or bilateral oophorectomy) or postmenopausal for at least one year
    d) Has not had unprotected sex in the 5 days prior to use of the product

9.3.3.2.2 Analyzing the Self-Selection Table

Cell A represents a correct decision, namely consumers for whom the study product is right to use who choose to use it, and therefore presents very little potential adverse clinical consequences.

Cell C, while not technically correct, is a decision that accrues no health risk, but rather is a missed opportunity to use the drug. Thus, these subjects are considered neither correct nor incorrect and are usually left out of the primary self-selection analysis.

The most critical self-selection decision is made by subjects who, based on their health status, should not use the study drug (cells B and D). Unlike an incorrect decision by consumers for whom this product is appropriate (cell C), an incorrect decision (cell B) by these consumers has potential efficacy or safety implications.

Because it is expected that very few subjects will be inappropriate for use, this endpoint will be measured by the following proportion, taken from the self-selection table [(cell A + cell D)/(cell A + cell B + cell D)]. Again, note that this does not take into account cell C, as those subjects could have chosen to use the product, but did not (for whatever reason).

Other proportions will also be presented, including the total correct selectors as described by the equation [(cell A + cell D) / (cell A + cell B + cell C + cell D)] and the typical self-selection metric, namely the proportion described by the equation [cell D/(cell B + cell D)]. This proportion represents a correct non-selection decision. In other words, this is the proportion of those who should not select the product who correctly do not select it.

9.3.3.3 F: Actual Use: Proportion of dosing instances among user population in which HBC is not taken for 5 days after taking ella®

This secondary endpoint is the proportion in which the denominator includes all dosing instances of the IP and the numerator includes all dosing instances in which there is no reported use of HBC for at least 5 days.

9.3.3.4 G: Actual Use: Proportion of dosing instances among user population associated with use of hormonal contraceptives in the same cycle after taking ella® in which subject reports using a condom (or other barrier method) every time they have sex until their next menstrual period.

This secondary endpoint is the proportion in which the denominator includes all dosing instances of the IP among those who start or restart hormonal contraception in the same menstrual cycle and the numerator includes dosing instances where the subject reports using condoms every time they have sex during the remainder of that menstrual period.

9.3.3.5 H: Actual Use: Proportion of user population who do not use the study product more than once in the same menstrual cycle.

This secondary endpoint is the proportion in which the denominator includes all subjects who take at least one dose of the product (user population) and the numerator includes all subjects who do not use more than one dose(s) of the study product within the same menstrual cycle after taking the initial dose of ella®.

9.3.3.6 I: Self-Selection/Actual Use: Proportion of self-selection population taking one of the “ask a doctor or pharmacist before use” products who do not select, who select but do not use or who report contacting a healthcare provider or pharmacist.

This secondary endpoint is the proportion defined by the denominator including all subjects who participate in the self-selection interview who report taking one of the “ask a doctor or pharmacists before use” compounds (including barbiturates, carbamazepine, felbamate, oxcarbazepine, phenytoin, topiramate, rifampin, griseofulvin, a prescription drug to treat HIV/AIDS, bosentan, or a supplement containing St. John’s Wort) and the numerator is all such subjects who either do not select or use or who report talking with a doctor or pharmacist about it use during the course of the study.

9.3.4 Other Measures Analysis

The other measures are all simple proportions where the user population represents the denominator.

J. Proportion of user population who use a HBC method sometime during the past two menstrual cycles.
K. Proportion of user population who used any EC on more than one occasion within the study period.

L. Proportion of user population who report becoming pregnant within the study period.

9.4 Safety Analysis

Adverse event (AE) analyses will include all events which initially occurred, or worsened following treatment. Adverse events will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) and classified according to their severity (mild, moderate, or severe) and relationship (related or not related) to study product. For the summary by severity, subjects who have multiple occurrences of the same AE will be classified according to the worst reported severity of the AE. Similarly, for the summary by relationship to the study product, the AE will be classified according to the worst relationship.

9.5 Interim Analysis

There will be no interim analysis for this study

9.6 Missing Data

All missing data will be considered missing and no statistical procedures will be employed to estimate or impute missing data.

9.7 Open-ended Data

Verbatim responses will be coded as described in Section 8.4.4 above, with coded responses presented within individual question tables. For all verbatim responses (including those which were coded), listings will be generated and presented.

10 DATA HANDLING AND RECORD KEEPING

10.1 Data Collection Instruments / Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to a paper data record, an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

Each investigator has ultimate responsibility for the collection and reporting of all the clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) that pertain to his or her phase of the study (enrollment interview and purchase for site investigators, follow up interviews and AE reports for the central investigator). Each investigator is responsible for ensuring that data collected are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents

must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the CRF, or part of the CRF, will also serve as source documents. In these cases, a document should be available at the investigator's site as well as at the Sponsor and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

Data for this study will be entered directly into a validated EDC system. This system will provide a complete audit trail, which includes information about the initial data entry and all changes and deletions. When the data collection form is saved, data edits will check entries in each field and provide immediate notification to the interviewer of data that is unacceptable (a different value must be entered) or questionable (the data field must be checked and if left intact, an explanation must be given). Using this system, the interviewer will be able to correct entries or make clarifications while the subject is still being interviewed.

All users will have a unique login user name and password, and system access privileges will be strictly controlled and documented. The audit trail, user access privilege processes, and electronic signatures collected by the system will be compliant with 21 CFR Part 11 requirements.

If the internet connection fails during the course of an interview, data collection will be completed on a paper copy of the electronic forms. When the internet connection is restored, study staff at the site will enter the data from the paper forms into the EDC system. If this were to occur, the completed paper copy of the electronic forms is the source document. Otherwise, the electronic record is the source.

10.2 Study Documentation

PEGUS Research will maintain accurate and complete records of the study. Study files and critical documents will be maintained at PEGUS Research throughout the study period, and will be retained or transferred to the Sponsor at its direction.

10.3 Confidentiality of Study Documents and Electronic Records

PEGUS Research holds all study-related documents and communications in the strictest confidence. PEGUS Research will ensure that the subject's anonymity is maintained. On documents submitted to the Sponsor, subjects will not be identified by name or other personally identifiable information, but by numerical identification code.

11 QUALITY CONTROL AND QUALITY ASSURANCE

The procedures described herein pertaining to the conduct, evaluation and documentation of this study are designed to ensure that the Sponsor and study personnel abide by Good Clinical Practice (GCP) guidelines. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

SOPs from PEGUS Research will be followed to ensure quality. PEGUS staff will train and approve prospective interviewers prior to their work on the study. PEGUS Research

is responsible for selecting sites and training study personnel. Training will consist of an overview of the purposes and design of the study as well as detailed instructions on the methods, including subject recruitment, proper administration of the questionnaire, use of the EDC application and guidelines for correctly capturing and entering responses. A study-specific interviewer-training guide will be developed to serve as the basis for training. All training will be documented.

Regulatory authorities, the Institutional Review Board / Independent Ethics Committee, and / or the sponsor's or CRO's clinical quality assurance group may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

12 ETHICS

The study will be carried out in keeping with applicable local law(s) and regulation(s).

12.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment posters, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC will be retained in the investigator file. Copies of IRB/IEC approvals will be forwarded to the Sponsor.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and the Sponsor in writing immediately after the implementation.

12.2 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2013).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonization (ICH) guideline on GCP, and applicable local regulatory requirements and laws.

PEGUS Research will oversee the process for the approval of all Investigators, trial protocol, informed consent forms and other relevant trial documents. All correspondence with the IRB will be retained in the trial files for each site. All records identifying subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Subject names will be collected for compensation and follow-up purposes only and will not be linked to any study data. This information will not be supplied to the Sponsor or any other entity. No personally

identifiable information (PII) will be captured in the study database. In accordance with the Federal Privacy Standard, a Notice of Information Practices, which describes how subjects' health information will be used and disclosed and how they can obtain access to this information, will be made available, if applicable.

12.3 Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law. Explicit permission to gather sensitive data will be sought and documented prior to any data collection. No PHI will be collected for subjects that screen fail, do not qualify for the use phase of the study, or choose not to sign consent. Any data collected after explicit permission is granted will be retained as anonymous study data for use by the sponsor.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed by the Sponsor, approved by the IRB/IEC before use, and available for inspection.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before dispensing of study medication. The investigator will retain the original of each subject's signed consent document.

Adolescents recruited in this study, as some may not have a high degree of parental involvement and since requirement of parental consent might introduce risk in some circumstances, are NOT children for the purposes of this study. This is allowed for in 45 CFR 46.408 (c) "…*if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements… provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition*." Since adolescents are presenting to the research sites seeking emergency contraceptives on their own accord, they meet the criteria for a mature minor in most states. Moreover, in most cases, adolescents seeking emergency contraception would not need parental consent for treatment and reproductive services in most states, and may not meet the definition of "children" in § 50.3(o) and thus would not be subject to the requirements of 21 CFR 50 subpart D. The definition provided is "*Children means persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted*." However, depending on the age of the adolescent enrolling in the study, some state laws and regulations may preclude the adolescent from receiving contraceptive services without parent consent (i.e., under age 12 in many states). Where

state and local laws require, parental consent and adolescent subject assent will be documented.

All records identifying subjects will be kept confidential, and to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Subject names will be collected for compensation and follow-up phone calls only. No personal identifiable information (PII) will be stored in the study database. This information will not be supplied to the Sponsor or any other entity. In accordance with the Federal Privacy Standard, a Notice of Information Practices, which describes how subjects' health information will be used and disclosed and how they can obtain access to this information, will be made available, if applicable.

Subjects' implicit consent will be obtained prior to collecting any personally-identifiable contact information. Explicit verbal consent to gather sensitive data will be requested and documented prior to collecting any health or other sensitive information.

Subject names, contact information, and other identifiable data will be maintained entirely separate from the study database. All parties will ensure protection of subject personal data and will not include subject names on any data forms, reports, publications, or in any other disclosures, except where required by laws. Personally-identifiable data will be replaced by a numerical code consisting of a numbering system generated by the EDC system in order to de-identify the study subject. In case of data transfer, PEGUS will maintain high standards of confidentiality and protection of subject personal data.

12.4 Liability and Insurance

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

12.5 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the IP, the Sponsor should be informed immediately.

In addition, the investigator will inform the Sponsor immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

12.6 Mandatory Reporting

There will not be questions in the interview addressing personal sexual experience and it is not expected that subjects will spontaneously disclose information that would trigger mandatory reporting requirements. However, interviewers will be trained in the mandatory reporting conditions in each state where the interviews are conducted and to

identify such conditions if they are reported by subjects. Subjects will be informed in the introduction to the study that confidentiality will be strictly guarded, except for circumstances requiring reporting to authorities.

13 SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of ella® at any time.

If a study is prematurely terminated or discontinued, the Sponsor will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the participating pharmacy and health center study sites. As directed by the Sponsor, all study materials must be collected and all CRFs completed to the greatest extent possible.

14 PUBLICATION OF STUDY RESULTS

14.1 Communication of Results by the Sponsor

The Sponsor fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov) and/or the European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations.

15 EMERGENCY CONTACTS

In emergency situations, the investigator should contact PEGUS Research Inc. by telephone on the number listed on the title page of the protocol.

16 STUDY DURATION AND DATES

The duration of this study is expected to be around 6 months (from first subject enrolled in the study until last subject last visit), with subject recruitment proposed to start mid Q2 2017 and end in Q4 2017. The actual overall study duration or subject recruitment period may vary.

17 REFERENCES

1. Murphy, Peggy W.; Davis, Terry C.; Long, Sandra W.; Jackson, Robert H.; Decker, Barbara C. Rapid Estimate of Adult Literacy in Medicine (REALM): a quick reading test for patients. *Journal of Reading* 1993 Oct; 37(2):124-30.

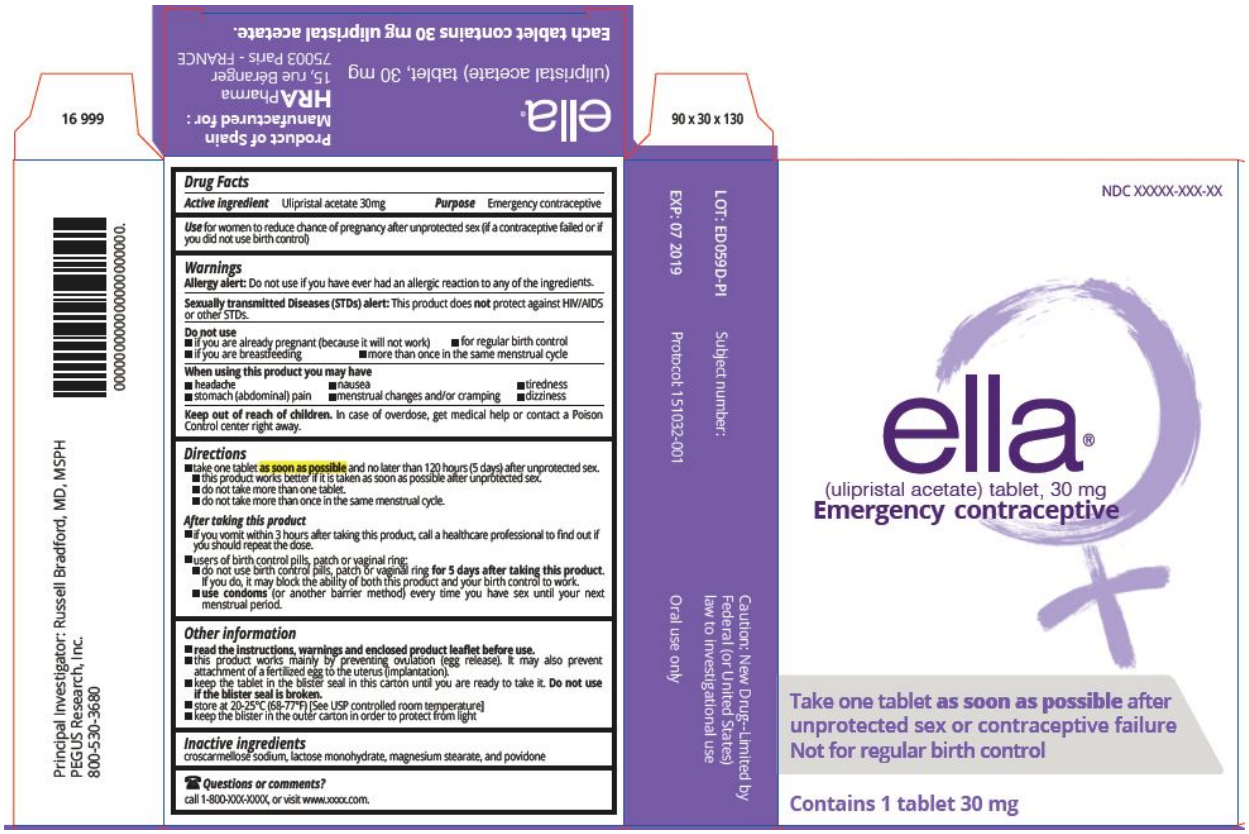
2. Davis TC, Wolf MS, Arnold CL, Byrd RS, Long SW, Springer T, Kennen E, Bocchini JA. Development and validation of the Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen): a tool to screen adolescents for below-grade reading in health care settings. Pediatrics. 2006 Dec 1;118(6):e1707-14.

3. Brache et al. A prospective randomised pharmacodynamic study of quick-starting a desogestrel progestin-only pill following ulipristal acetate for emergency contraception. Human Reproduction 2015; 30 (12) 2785-93.

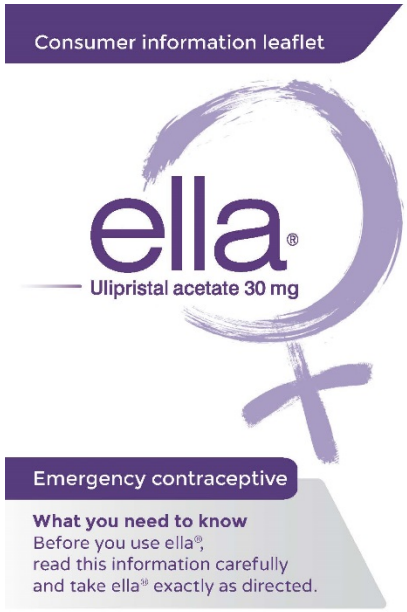
4. Zapata LB, Steenland M, Brahami D, Marchbanks PA, Curtis K. Effect of missed hormonal contraceptives on contraceptive effectiveness: a systematic review. Contraception 2013;87 (5): 685-700.

18 APPENDICES

18.1 Mock Package and Drug Facts Label



18.2 Consumer Information Leaflet



Before taking ella®

WHAT IS ella®?

- ella® is an emergency "back-up" contraceptive that helps **prevent pregnancy** when taken **after** unprotected sex.

  Unprotected sex is when you either didn't use any form of birth control, or you used your birth control method incorrectly or it failed (for example, the condom slipped or broke).

- ella® is **not** a regular birth control method.

  You should not use ella® as your routine birth control because it is not as effective as regular birth control methods, such as birth control pills or condoms.

  If you are sexually active and want to prevent pregnancy, you should consistently use a regular birth control method. Talk to a healthcare professional if you need help deciding what method is best for you.

WHEN AND HOW SHOULD I TAKE ella®?

- Take one tablet **as soon as possible** and no later than 120 hours (5 days) after unprotected sex.
  - Do not take more than one tablet.
  - Do not use more than once in the same menstrual cycle.

The sooner you take ella® after unprotected sex, the better it will work.

- If you vomit within 3 hours of taking ella®, call a healthcare professional to find out if you should repeat the dose.
- You can take ella® with or without food.

WHEN SHOULD I NOT TAKE ella®?

- If you **know** you are **already pregnant**, do not take ella® because it will not work. ella® can only prevent a pregnancy from happening and it is not known how ella® might affect a developing fetus.
- If you are breastfeeding, do not take ella® because ella® passes into breast milk and it is not known how ella® might affect the baby.

  If you are breastfeeding and had unprotected sex, there are other options for emergency contraception available in pharmacies or from a healthcare professional.

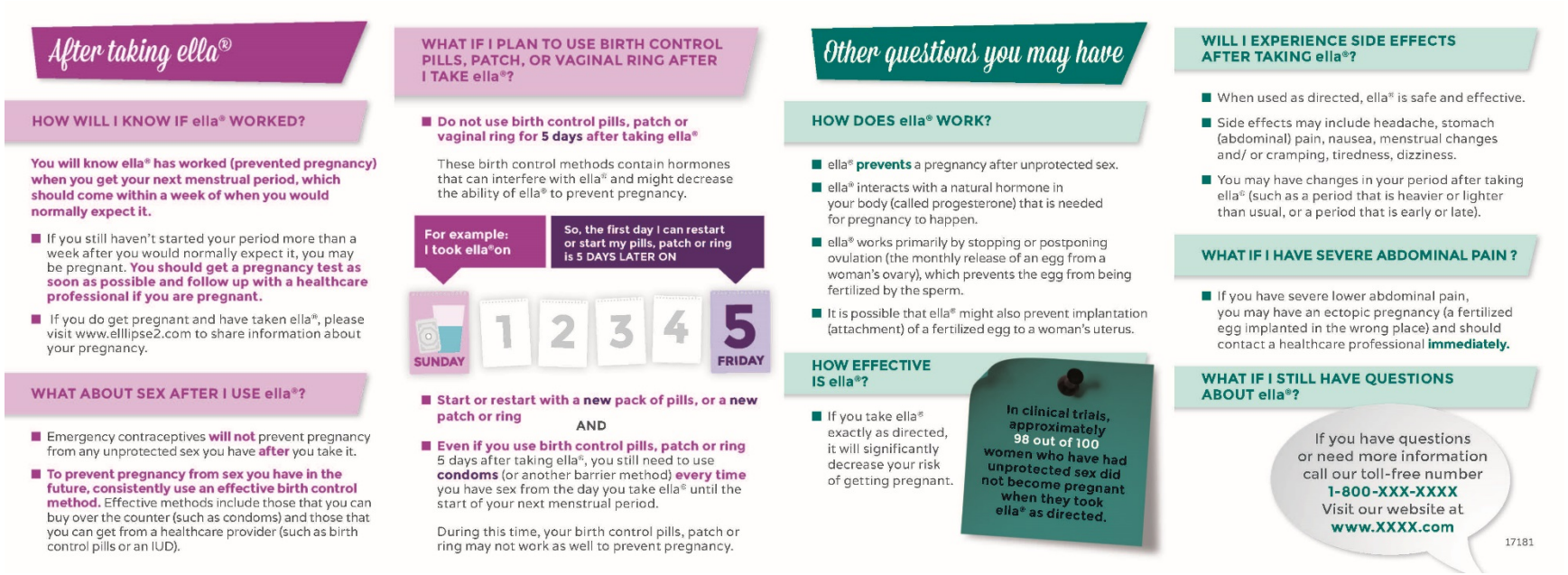
- Do not use ella®, more than once in the same menstrual cycle (use of ella® more than once in a cycle has not been studied).

WHAT SHOULD I DO IF I AM TAKING OTHER MEDICINES AND WANT TO USE ella®?

There are some prescription medicines and herbal products that may make ella® less effective.

Talk to a healthcare professional or your pharmacist before taking ella® if you are taking certain drugs to treat:

- seizures (barbiturates, carbamazepine, felbamate, oxcarbazepine, phenytoin, topiramate)
- tuberculosis (rifampin)
- fungal infections (griseofulvin)
- HIV or AIDS
- pulmonary hypertension (bosentan)
- St. John's Wort (or any herbal products containing hypericum perforatum)



After taking ella®

HOW WILL I KNOW IF ella® WORKED?

You will know ella® has worked (prevented pregnancy) when you get your next menstrual period, which should come within a week of when you would normally expect it.

- If you still haven't started your period more than a week after you would normally expect it, you may be pregnant. **You should get a pregnancy test as soon as possible and follow up with a healthcare professional if you are pregnant.**
- If you do get pregnant and have taken ella®, please visit www.elllipse2.com to share information about your pregnancy.

WHAT ABOUT SEX AFTER I USE ella®?

- Emergency contraceptives **will not** prevent pregnancy from any unprotected sex you have **after** you take it.
- **To prevent pregnancy from sex you have in the future, consistently use an effective birth control method.** Effective methods include those that you can buy over the counter (such as condoms) and those that you can get from a healthcare provider (such as birth control pills or an IUD).

WHAT IF I PLAN TO USE BIRTH CONTROL PILLS, PATCH, OR VAGINAL RING AFTER I TAKE ella®?

- **Do not use birth control pills, patch or vaginal ring for 5 days after taking ella®**

These birth control methods contain hormones that can interfere with ella® and might decrease the ability of ella® to prevent pregnancy.

For example: I took ella® on SUNDAY

So, the first day I can restart or start my pills, patch or ring is 5 DAYS LATER ON FRIDAY

1 2 3 4 5

- **Start or restart with a new pack of pills, or a new patch or ring**

AND

- **Even if you use birth control pills, patch or ring** 5 days after taking ella®, you still need to use **condoms** (or another barrier method) **every time** you have sex from the day you take ella® until the start of your next menstrual period.

During this time, your birth control pills, patch or ring may not work as well to prevent pregnancy.

Other questions you may have

HOW DOES ella® WORK?

- ella® **prevents** a pregnancy after unprotected sex.
- ella® interacts with a natural hormone in your body (called progesterone) that is needed for pregnancy to happen.
- ella® works primarily by stopping or postponing ovulation (the monthly release of an egg from a woman's ovary), which prevents the egg from being fertilized by the sperm.
- It is possible that ella® might also prevent implantation (attachment) of a fertilized egg to a woman's uterus.

HOW EFFECTIVE IS ella®?

- If you take ella® exactly as directed, it will significantly decrease your risk of getting pregnant.

In clinical trials, approximately 98 out of 100 women who have had unprotected sex did not become pregnant when they took ella® as directed.

WILL I EXPERIENCE SIDE EFFECTS AFTER TAKING ella®?

- When used as directed, ella® is safe and effective.
- Side effects may include headache, stomach (abdominal) pain, nausea, menstrual changes and/ or cramping, tiredness, dizziness.
- You may have changes in your period after taking ella® (such as a period that is heavier or lighter than usual, or a period that is early or late).

WHAT IF I HAVE SEVERE ABDOMINAL PAIN ?

- If you have severe lower abdominal pain, you may have an ectopic pregnancy (a fertilized egg implanted in the wrong place) and should contact a healthcare professional **immediately.**

WHAT IF I STILL HAVE QUESTIONS ABOUT ella®?

If you have questions or need more information call our toll-free number **1-800-XXX-XXXX**
Visit our website at **www.XXXX.com**

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