HRA Pharma

OPILL® ACTUAL USE TRIAL PROTOCOL

Title:	A Multi-Center **O**ral Contraceptive **P**ill Use **T**rial Conducted **I**n an **O**TC **N**aturalistic Environment (OPTION)
Compound:	Norgestrel 0.075 mg
Protocol Number:	151042-001
Protocol Version / Date:	Final v. 1.2 / 15 Dec 2017
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Document History

Document	Version / Date	Summary of Changes
Final protocol	Version 1.0	N/A
Amended protocol	Version 1.1	Incorporated IRB Recommendations. General wording and flow changes of the document to better clarify study procedures. Section 1.2: Dosing information about norgestrel 0.075 and how it is currently a prescription medication. Section 3.3: Information regarding that subjects must personally enroll in this study, and certify that they are seeking the study product for their own use. Representative buyers (such as family members and/or male partners, etc.) will not be allowed. Section 5.3.2: Information regarding the “Mock Purchase” of the study and how that pertains to potential subjects specifically adolescents. Section 12.3: Informed consent documents will be presented electronically, and signatures gathered digitally, however, all consent procedures (including obtaining informed consent from a parent or legal guardian, if necessary) will be conducted in person. An archived copy of the signed informed consent document will be made available to subjects digitally.

Amended Protocol	Version 1.2	Section 3.3, 3.3.1: Revised to incorporate exclusion of subjects younger than 12. Section 3.6: Clarify the rationale for when CIL and reminder card are available to subjects. Section 4.3.3: Revised to clarify that subjects will return study materials, any unused IP and empty packaging to the study site. Sections 5.3.3, 5.4.3.2, 6.4, 6.5, 8.2 : Text revised to reflect that the results of the end of study home pregnancy test will be recorded in the online medication use / electronic diary Section 5.4.1: Text revised to allow for sites to collect relevant details around an AE and report back to PEGUS Research staff. Section 5.4.2: Text added to clarify that subjects without easy access to the internet will be provided a device for use in the study. Sections 5.4.4, 6.8: Clarified that subjects who fail to return for an end of study visit will be contacted and reminded. Section 9.3.3.6: Clarified timeframe for pregnancy determination. Section 10.1: Clarified that interviews will not be conducted in the absence of an active internet connection. Section 12.3: Clarified that PII will not be retained for subjects who do not pass screening or who do not qualify for use phase, and clarified language outlining consent procedures for minors who are not

		"children" according to local law and regulation. Section 12.4: Addition of language describing the ability of subjects to opt in for future contact if there are related research opportunities.

Protocol Summary

Study Title	A Multi-Center **O**ral Contraceptive **P**ill Use **T**rial Conducted **I**n an **O**TC **N**aturalistic Environment (OPTION)
Background and Rationale	Opill® (norgestrel 0.075 mg) is proposed for an Rx-to-OTC switch. This combined Self-Selection (SS) / Actual Use Trial (AUT) will be conducted to demonstrate appropriate consumer selection and use behavior as guided by OTC labeling when using the product in the absence of a physician or other learned intermediary. This study will be conducted to obtain measurements of self-selection and consumer behaviors related to the actual use of the product compliance with key communication messages presented in the Drug Facts Label (DFL).
Objectives and Endpoints	The objective of this study is to evaluate the adequacy of the proposed OTC labeling to guide appropriate consumer selection and use behavior by measuring pre-specified endpoints. The designation of the following endpoints as primary or secondary endpoints or other measures is based on the potential clinical consequences raised if a consumer were to fail to heed the label instructions. Endpoints are designated either as Self-Selection endpoints or Actual Use endpoints. <u>Primary Endpoints</u> A. Self-Selection: Proportion of self-selection population who make a correct selection decision regarding use of the product B. Actual Use: Use of the study medication every day C. Actual Use: Use of the study medication at the same time of day D. Actual Use: Use of the study medication without an extended break or any break between packs <u>Secondary Endpoints</u> A. Actual Use: Proportion of user population who do not use study medication together with another form of hormone-containing birth control B. Actual Use: Proportion of user population who report using a barrier method of contraception (or abstaining from intercourse) for the first 48 hours after starting to use the study medication C. 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 (and cite that as the reason for not selecting), who select but do not use (and cite that as the reason for not using), or who report contacting a healthcare provider or pharmacist about use of the product

	D. Self-Selection/Actual Use: Proportion of self-selection population who report having liver problems who either do not select (and cite that as the reason for not selecting), who select but do not use (and cite that as the reason for not using), or who report contacting a healthcare provider about use of the product E. Actual Use: Proportion of user population who experience one of the "Talk to a doctor" conditions listed within the "When using this product" or "Stop use and ask a doctor" sections of the label who report contacting a healthcare provider and/or stop use as directed by the label F. Actual Use: Number of pregnancies reported during the course of the study <u>Other Measures</u> A. Actual Use: Character and frequency of adverse events as reported by the user population B. Actual Use: Patterns of use, including discontinuation rates and reasons for discontinuation C. Actual Use: Proportion of user population who experience severe vomiting or diarrhea within 4 hours of taking their daily pill who report using a barrier method of contraception every time they have sex (or abstain from intercourse) for the next 48 hours D. Actual Use: Characterize healthcare seeking behavior among subjects
Study Design	This is an observational open-label, multi-center, 16-week study designed to mimic an OTC-like environment in which consumers will make a selection (and purchase decision, in the case of pharmacy sites) about the product based on their reading of the DFL and other information on the outer package, and then, if they choose to, take Opill® home and use the product aided by the OTC labeling (DFL, Consumer Information Leaflet (CIL) and reminder card). The study will increase understanding regarding how consumers will use the medication in an OTC-like environment.
Number of Participants	A total of approximately 900 subjects will be allowed to proceed to the use phase of the study. Assuming that about 80% of those who proceed to the use phase will both use the study medication and participate in at least one follow-up telephone call that will yield an actual use population of approximately 720 subjects among which to evaluate the primary endpoints. In an effort to achieve an adequate subgroup of adolescent users (age 12-17), adult purchasers will be constrained to no more than 725. Efforts will be made to enroll an adolescent subgroup of approximately 175 use phase participants (or more, should a higher proportion naturally occur). Additionally, among adolescents, a sample of 50 use phase subjects age 12-15 will be sought.

Methods	Subjects will be primarily recruited via passive recruiting methods, such as in-store posters, newspaper advertisements, direct mail postcards, and digital space advertising. Respondents to advertisements will either call PEGUS Research or visit a study website for initial screening (during which data regarding age, gender, and minimal study exclusion criteria will be collected) and scheduling of an in-person enrollment visit at a local participating research site. Approximately 46 sites will be used, comprising retail pharmacy research sites and women's health clinics or adolescents' clinics in geographically diverse locations. Challenging goals for enrollment of adolescent subjects have been established. Experience suggests that the methods of advertising that are typically used in an AUT will not be sufficient to enroll a large enough cohort of adolescents. The requirement to recognize that a study advertisement could apply to them and to respond, schedule an appointment, and actually show up for that appointment often proves to be beyond what most adolescents will do (particularly among adolescents that are seeking the product without a parent's involvement). Because enrolling a sufficient number of adolescents in the study is important, a small number of women's health clinics or adolescent clinics (approximately 10 in total) will be included as study sites. In those clinics, active recruitment will be implemented, wherein clinic staff will offer adolescents who are seeking oral contraception the opportunity to participate in the study. During the face-to-face enrollment visit, potential subjects who meet the inclusion and exclusion criteria for the study will be given an (empty) Opill® package and will be allowed as much time as they need to review the information on the outside of the entire package (including the DFL). Subjects will then be asked if the product is OK or not OK for them to use. For subjects at pharmacy sites, those who report that it is OK for them to use will 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 decision will be recorded. For subjects at clinic sites, those who report that it is OK for them to use will be asked if they would like to obtain it for their own use. Following the selection decisions, in response to a structured questionnaire, subjects will provide limited medical history, current medication use, and demographic information. 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. Subjects that sign consent will take a urine-based pregnancy test. Qualified subjects then will be allowed to purchase (pharmacy sites) or be given (clinic sites) the study product to take home and told they may return to the site at any time for resupply. Subjects will be allowed to purchase/obtain up to eight 28-count (four-week supply) packages during the study period, although that limit will

	not be communicated to subjects unless they attempt to purchase/obtain more than that. While any request for more than 8 packages will be denied, the request and reason for it will be recorded. Subjects will record their use of the product using an online medication use diary. Subsequent contact will be via four telephone interviews conducted by trained nurse interviewers working from a central research site at weeks 4, 8, 12, and 16. Interviewers will contact subjects by telephone to conduct scripted interviews 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. Once all steps of the final telephone interview are completed, the subject will be asked to take a self-administered urine-based home pregnancy test and record the results in their electronic diary. Subjects will then be prompted to return to the study site for an additional end-of-study pregnancy test and to return any unused study medication or empty packaging. If the subject does not complete a home pregnancy test but does return to the site for the end of study visit and associated pregnancy test, no additional follow-up will be done. If the subject does not record the end of study home pregnancy test and fails to return to the site for the end of study visit, a nurse interviewer will follow up and request that they complete a self-administered urine-based pregnancy test at home, report the results in their electronic diary, and return to the site for the end of study visit.
Statistical Analysis	A summary of the disposition of subjects (including responders, self-selection population, use phase subjects 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 self-selection, use phase 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. A more detailed description of planned data analysis procedures will be found in the Statistical Analysis Plan which will be approved and signed before the database is locked.
Study Duration	The duration of this study is expected to be approximately 10 months (from first subject enrolled in the study until last subject last visit), with subject recruitment proposed to start in Q1 2018 and end in Q3 2018. 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	15 Dec 2017

Schedule of Activities

The schedule of activities table below 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 Identifier	**Recruitment**	**Enrollment Visit / First Purchase[a]**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**End of Treatment / Early Termination[f]**	**End of Study Visit**	**After Study Completion**
		Day 1	**28±4 Days**	**56±4 Days**	**84±5 Days**	**112±5 Days**			
Initial screening and scheduling	X								
Review screening / study inclusion criteria		X							
Subject reviews outer packaging and makes selection and purchase decision		X							
Collect demographics		X							
Collect current/regular relevant medications and associated conditions[b]		X							
Administer REALM or REALM-Teen test [c]		X							
Study exclusion/inclusion criteria assessed for eligibility to continue		X							
Subject signs informed consent		X							
Enrollment pregnancy test[d]		X							
Purchase transaction[e]/Product dispensed		X							
Subject uses study diary		X	→	→	→	→	X		
Interim telephone interviews			X	X	X	X			
End-of-study telephone interview							X		
Concomitant medications		X	→	→	→	→	X		
Adverse Events		X	→	→	→	→	X		

Visit Identifier	Recruitment	Enrollment Visit / First Purchase[a]	Week 4	Week 8	Week 12	Week 16	End of Treatment / Early Termination[f]	End of Study Visit	After Study Completion
		Day 1	28±4 Days	56±4 Days	84±5 Days	112±5 Days			
Self-administered end-of-study pregnancy test								X	
Return study drug and materials								X	
Site-administered end-of-study pregnancy test							X		
Reimbursement for cost of study medication (after all subjects complete the study)									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 medical conditions they have and any medications they are taking. Females only.

c. REALM[1] or REALM-Teen[2] test will be conducted for all subjects regardless of self-selection and purchase decision.

d. Subjects with a positive pregnancy test at enrollment will be asked to make a selection decision again to better assess self-selection and then will be excluded from the use phase.

e. Subjects will be allowed to purchase or be dispensed any amount of study medication up to a total of 8 packages at any time during their use phase.

f. Early termination interview will be conducted during the study if the subject is discontinued or withdraws consent prior to Week 16.

Glossary and Abbreviations

AAFP	American Academy of Family Physicians
ACCP	American College of Clinical Pharmacy
ACOG	The American Congress of Obstetricians and Gynecologists
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
AMA	American Medical Association
APHA	American Public Health Association
ASRM	American Society for Reproductive Medicine
AUT	Actual Use Trial
CFR	Code of Federal Regulations
CI	Confidence Interval
CIL	Consumer Information Leaflet
CIOMS	Council for International Organizations of Medical Sciences
COC	Combined Oral Contraceptive
CRF	Case Report Form
CRO	Contract Research Organization
DCI	Data Collection Instrument
DFL	Drug Facts Label
DMP	Data Management Plan
EDC	Electronic Data Capture
EDP	Exposure During Pregnancy
EOS	End of Study
FDA	Food and Drug Administration
FD&C	Food, Drug and Cosmetics (US Federal act)
GCP	Good Clinical Practice
HBC	Hormonal Birth Control
HIV	Human Immunodeficiency Virus
HPO	Hypothalamic-Pituitary-Ovarian
HRT	Hormone Replacement Therapy
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IP	Investigational Product
IUD	Intrauterine Device
LCS	Label Comprehension Study
LNG-IUS	Levonorgestrel-releasing Intrauterine System
MedDRA	Medical Dictionary for Regulatory Activities
NHANES	National Health and Nutrition Examination Survey

OTC	Over-the-Counter
PHI	Personal Health Information
PII	Personally Identifiable Information
POC	Progestin Only Contraceptive
POP	Progestin Only Pill
PT	Preferred Term
PV	Pharmacovigilance
RCT	Randomized Control Trial
REALM	Rapid Estimate of Adult Literacy in Medicine
REALM-Teen	Rapid Estimate of Adolescent Literacy in Medicine
Rx	Prescription
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SLE	Systemic Lupus Erythematosus
SOC	System Organ Class
SOP	Standard Operating Procedure
SSS	Self-Selection Study
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
US / USA	United States / United States of America
US SPR	US Selected Practice Recommendations for Contraceptive Use
USPS	Unites States Postal Service
USMEC	United States Medical Eligibility Criteria (for Contraceptive Use)
WHO	World Health Organization

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1 INTRODUCTION

Opill® (norgestrel 0.075 mg; currently approved as Ovrette®, with the new proposed proprietary name Opill®) is proposed for a prescription to over-the-counter (Rx-to-OTC) switch. This study is designed to assess whether consumers in a simulated OTC environment will self-select and use the product in a manner consistent with the OTC labeling. A Drug Facts Label (DFL) for the nonprescription version of Opill® has been drafted and evaluated in pivotal label comprehension studies (LCS). This protocol describes the next stage of the development program, a pivotal self-selection study (SSS) 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 norgestrel 0.075 mg is “Daily Birth Control Pill”. The proposed labeled “Use” for nonprescription norgestrel 0.075 mg is “for daily use by women to prevent pregnancy”.

1.2 Dose

Norgestrel 0.075 mg (previously marketed under the tradename Ovrette®), taken daily, is an approved prescription progestin-only oral contraceptive pill (POP). The current prescription formulation and dose is proposed for the Rx-to-OTC switch. The safety and efficacy of the study product at that dose were established with the initial approval of the product for prescription use.

1.3 Background and Rationale

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

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

The objective of this study is to evaluate the adequacy of the proposed OTC labeling to guide the behavior of subjects in an OTC-like setting when selecting and using Opill®.

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. The rationale behind selection and prioritization of endpoints is summarized below in Section 2.3 (a full detailed rationale for primary endpoints is presented in Section 9.3.2). The appropriateness of behaviors will be assessed by measuring the endpoints as per the endpoint analysis described in Section 9.3.

2.2.1 Primary Endpoints

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

B. Actual Use: Use of the study medication every day
C. Actual Use: Use of the study medication at the same time of day
D. Actual Use: Use of the study medication without an extended break or any break between packs

2.2.2 Secondary Endpoints

A. Actual Use: Proportion of user population who do not use study medication together with another form of hormone-containing birth control.
B. Actual Use: Proportion of user population who report using a barrier method of contraception (or abstaining from intercourse) for the first 48 hours after starting to use the study medication.
C. 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 (and cite that as the reason for not selecting), who select but do not use (and cite that as the reason for not using), or who report contacting a healthcare provider or pharmacist about use of the product.
D. Self-Selection/Actual Use: Proportion of self-selection population who report having liver problems who either do not select (and cite that as the reason for not selecting), who select but do not use (and cite that as the reason for not using), or who report contacting a healthcare provider about use of the product.
E. Actual Use: Proportion of user population who experience one of the "Talk to a doctor" conditions listed within the "When using this product" or "Stop use and ask a doctor" sections who report contacting a healthcare provider and/or stop use as directed by the label.
F. Actual Use: Number of pregnancies reported during the course of the study.

2.2.3 Other Measures

A. Actual Use: Character and frequency of adverse events as reported by the user population.
B. Actual Use: Patterns of use, including discontinuation rates and reasons for discontinuation.
C. Actual Use: Proportion of user population who experience severe vomiting or diarrhea within 4 hours of taking their daily pill who report using a barrier method of contraception every time they have sex (or abstain from intercourse) for the next 48 hours.
D. Actual Use: Characterize healthcare seeking behavior among subjects.

2.3 Rationale Underlying Selection and Prioritization of Study Endpoints

The determination of endpoints and prioritization as primary, secondary or other measures has been made based on the potential clinical consequences of a consumer failing to heed each key label instruction. Each endpoint is listed in Table 1 below, with the DFL messages relevant to the endpoint, followed by the rationale underlying the classification as primary, secondary or other measure. Please note that the rationale in the table below describe the reasons for measuring each endpoint and their classifications. Descriptions of how each endpoint is calculated is found in Section 9.3.

Table 1 Endpoint Rationale

Endpoints	Relevant DFL Message(s)
Primary	
A Self-Selection: Proportion of self-selection population who make a correct selection decision regarding use of the product	Use For daily use by women to prevent pregnancy Allergy alert: Do not use if you are allergic to this product or any of its ingredients. Do not use ● if you are male ● if you have ever had any cancer ● if you are already pregnant or think you may be pregnant ● as an emergency contraceptive (to prevent pregnancy after unprotected sex)

Rationale: This endpoint measures the ability of subjects to make a correct self-selection decision based on their own medical profile and history and the label inclusion and exclusion criteria. This is important to the extent that data about safe and effective use of the product are linked to the elements inherent to correct selection (or non-selection). Therefore, general self-selection is designated as primary endpoint.

Please note that the criteria upon which initial selection is judged include the absolute contraindications, as translated from the prescription labeling contraindications section to the proposed DFL. Two conditional contraindications from the prescription labeling are presented in other sections of the DFL to reflect their conditional nature, namely, unexplained intermenstrual bleeding and liver problems. Evaluation of the instructions regarding those two messages is evaluated individually based on subject behavior in discrete endpoints.

B Actual Use: Use of the study medication every day	Directions ● Take 1 tablet at the same time every day ● this product will work best to prevent pregnancy when taken exactly as directed ● if you are more than 3 hours late taking your tablet or miss taking your tablet on 1 or more days: ● take 1 tablet immediately, as soon as you remember that you missed it ● then go back to taking your daily tablet at your usual time ● use a condom (or another barrier method) every time you have sex during the next 2 days (48 hours), because it takes 2 days for Opill® to start working again

Rationale: This endpoint is designed to measure the extent to which subjects comply with the instruction to take one tablet every day. This endpoint is relevant to several key messages from the DFL which are directly related to efficacy of the product. A woman who does not follow the instructions to take one tablet every day and is engaging in sexual

intercourse may put herself at risk of unintended pregnancy. Therefore, adherence to this message is designated as a primary endpoint.

C	Actual Use: Use of the study medication at the same time of day	Directions ● Take 1 tablet at the same time every day ● this product will work best to prevent pregnancy when taken exactly as directed ● if you are more than 3 hours late taking your tablet or miss taking your tablet on 1 or more days: ● take 1 tablet immediately, as soon as you remember that you missed it ● then go back to taking your daily tablet at your usual time ● use a condom (or another barrier method) every time you have sex during the next 2 days (48 hours), because it takes 2 days for Opill® to start working again

Rationale: This endpoint is designed to measure the extent to which subjects comply with the instruction to take the product at the *same time* every day. While it is not clear the extent to which failure to heed this instruction is *clinically* relevant, pharmacodynamics of other progestin only pills (POPs) suggest that they may be most efficacious if taken no more than 3 hours after the time of day the previous day's dose was taken. Therefore, adherence to this message is designated as a primary endpoint.

D	Actual Use: Use of the study medication without an extended break or any break between packs	Directions ● Take 1 tablet at the same time every day ● Never skip your daily tablet ● to prevent pregnancy, take this product every day, even when you bleed or have spotting ● When you finish this pack, start the next one the following day without a break

Rationale: This endpoint is intended to ensure that women understand that this product is taken daily, without any breaks, and adhere to that instruction. The endpoint assesses whether users understand not to take breaks between pills as it is important that consumers do not miss several days in a row for any reason. It is being assessed in part because, some consumers may be accustomed to or familiar with the pattern of use for some combined oral contraceptives (COCs) where pills containing active ingredients are taken for 21 (or more) days followed by a pill-free break of 4-7 days (or 4-7 days of inactive pills). If a woman fails to heed the instructions not to skip pills, to take the product every day even if they bleed or have spotting, or to start the next pack the day after finishing a pack, and takes breaks in her use of the product, she may, if sexually active, put herself at risk of unintended pregnancy. Therefore, adherence to this message is designated as a primary endpoint. Please note that all cases of missed pills at any time will be captured in primary endpoint B above, so that this endpoint represents a special case in which multiple pills are missed in a row or pills are missed in between packs.

Secondary

A	Actual Use: Proportion of user population who do not use study medication together	Do not use

	with another form of hormone-containing birth control	● together with another birth control pill, vaginal ring, patch, implant, injection or an IUD (intra-uterine device)

Rationale: This endpoint measures whether subjects use the study product concomitantly with another hormone-containing birth control method. This is designated as a secondary endpoint for several reasons. While the concomitant use of a POP with another hormonal method of birth control or with an intrauterine device (IUD) is unnecessary, and would represent unnecessary expense, it is not unsafe. There would be no medical consequences of taking Opill® while using another contraceptive method since its concomitant use would not interfere with the efficacy of the other method or with the efficacy of Opill®, and adding a relatively small dose of progestin to another method would be unlikely to alter the pattern of side effects of either method. Because failure to heed this message would not result in a safety concern or a reduction in efficacy, this endpoint is designated as secondary.

B	Actual Use: Proportion of user population who report using a barrier method of contraception (or abstaining from intercourse) for the first 48 hours after starting to use the study medication	Directions ● Use a condom (or another barrier method) every time you have sex during the first 2 days of use (48 hours) after you start your first pack of this product, because it takes 2 days for this product to start working

Rationale: This endpoint measures how well subjects follow the instruction to use a condom or another barrier method every time they have sex during the first two days of use of the study product. The rationale for the instruction is that it takes 48 hours of product use for the establishment of full contraceptive efficacy. Use of a barrier method during the first 48 hours of POP use is recommended to reduce the risk of pregnancy during that time period.

While it is not possible to quantify the relative increase in the risk of contraceptive failure if a woman were to fail to heed this instruction, the risk of pregnancy with a single act of intercourse even when no contraceptive method is used is low. Therefore, this endpoint is designated as secondary.

C	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 (and cite that as the reason for not selecting), who select but do not use (and cite that as the reason for not using), or who report contacting a healthcare provider or pharmacist	Ask a doctor or pharmacist before use if ● you are taking a prescription drug to: ● prevent seizures (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine) ● treat tuberculosis (rifampin, rifabutin) ● treat HIV/AIDS ● treat pulmonary hypertension (bosentan) ● you are taking a supplement containing St. John's Wort (an herbal ingredient) ● you have used an emergency contraceptive containing ulipristal acetate in the past 5 days

Rationale: This secondary endpoint measures how well subjects follow the instruction to ask a doctor or pharmacist when taking one of the listed drugs of interaction. The interaction with POPs of some medications, such as certain anticonvulsants, antiretroviral therapies (e.g. efavirenz) and drugs for the treatment of tuberculosis (TB) (e.g. rifampicin) may reduce the effectiveness of the contraceptive [USMEC 2016]. While use of these medications may reduce the effectiveness of POPs, it does not present a safety risk to users. Failing to obey these instructions may result in an increased risk of pregnancy,

although this increased risk of pregnancy has not been quantified. Pregnancy is relatively contraindicated in women with these conditions taking these drugs, so use of any contraceptive method, even with reduced efficacy, is beneficial. This endpoint is designated as secondary also because the number of subjects expected to fall into this population is small and the study is not powered to provide for a narrow confidence interval around the estimate of these behaviors, due to this small denominator.

Please note that the denominator for this endpoint is the self-selection population, to account for subjects who may decide not to select the product based on this warning (which would be a correct behavior), but subjects taking these medications will be allowed to select the study product and use it, with adherence to the warning evaluated based on whether or not they report discussing with a doctor or pharmacist.

D	Self-Selection/Actual Use: Proportion of self-selection population who report having liver problems who either do not select (and cite that as the reason for not selecting), who select but do not use (and cite that as the reason for not using), or who report contacting a healthcare provider about use of the product	Ask a doctor before use if you have ● liver problems

Rationale: This endpoint measures how well subjects who report liver problems follow the instruction to consult a healthcare provider about use of the product. This is designated as a secondary endpoint because the types of liver problems potentially adversely affected by POP use, hepatocellular adenoma and carcinoma, are rare and the potential clinical consequences of those with such liver problems taking a POP are theoretical and also rare (White et al, 2012). Women with these specific conditions are likely to be under the care of a physician with regular follow up, which is likely to include discussion about any medication being used. If this instruction is ignored by a consumer in this very small population, the consequence is theoretical worsening of the prognosis of their hepatocellular adenoma and carcinoma. While the DFL directs all women with “liver problems” to “Ask a doctor before use” out of an abundance of caution, for women with "liver problems" other than hepatocellular adenoma and carcinoma, harmful effects are unlikely. This endpoint is designated as secondary also because the number of subjects expected to fall into this population is very small and the study is not powered to provide for a narrow confidence interval around the estimate, due to this small denominator.

Please note that the denominator for this endpoint is the self-selection population, to account for subjects who may decide not to select based on this warning (which would be a correct behavior), but subjects reporting liver problems will be allowed to select the product and use it, with adherence to the warning evaluated based on whether or not they report discussing with a doctor and following the doctor's advice.

E	Actual Use: Proportion of user population who experience one of the “Talk to a doctor” conditions listed within the “When using this product” or “Stop use and ask a doctor” sections who report talking with a healthcare provider and/or stop use as directed by the label	When using this product ● You are likely to experience changes in your menstrual periods ● Talk to a doctor AND continue taking this product every day if you have these unexpected bleeding symptoms: ●unexplained vaginal bleeding between your periods before you started using this product ● repeated vaginal bleeding brought on by sex

	● periods that lasts more than 8 days or are unusually heavy ● have not had any periods for 2 months or you think you may be pregnant – do a pregnancy test or talk to a doctor ● Talk to a doctor if you ● have sudden or severe pain in your lower belly – see a doctor immediately (you could have an ectopic pregnancy) ● start having migraines with aura (headaches that start with changes in vision) or your migraine headaches get worse ● Stop use and ask a doctor if you ● become pregnant ● develop yellowing of your skin or whites of your eyes (especially with fever, tiredness, loss of appetite or dark colored urine)

Rationale: This endpoint measures how well subjects follow the instruction to consult a healthcare provider and/or stop use of the product in the face of certain label-defined conditions. This is a composite endpoint measuring subjects' adherence to related instructions, namely asking a healthcare provider and/or stopping use of the product in response to a variety of possible conditions, none of which are likely to be independently seen in this study in significant numbers. While the frequency of each condition and the appropriate behavioral response will be reported independently as part of this endpoint, the calculated endpoint measure will be the composite. It is designated as a secondary endpoint for a number of reasons. Only one of the conditions that consumers are directed to talk to a doctor about, or stop use and ask a doctor about, are potentially caused by, or exacerbated by, use of the study product (i.e, cholestasis). The others are included in the labeling as they might be a sign of an underlying condition that should be evaluated by a healthcare provider. Additionally, for most of these conditions (apart from pregnancy and jaundice which develops during treatment) there is no contraindication to continued use. In the case of pregnancy, while there is obviously no contraceptive benefit to use of the study product while pregnant, neither would there be expected to be any risk incurred by such use. In the case of jaundice that develops during treatment, such cases are expected to be exceptionally rare. As with the other elements of the endpoint, if any such cases occur, they will be identified and reported independently. However, the expected frequency of these conditions argues for their inclusion as part of this composite measure.

F Actual Use: Number of pregnancies reported during the course of the study

Rationale: This endpoint is intended to characterize the pregnancies that may occur during the course of the study. While it does not directly measure behavior related to messages on the DFL, it is of interest. Please note that as efficacy of the product has already been established, this study is not powered as an efficacy study. Therefore, conclusions related to efficacy cannot be drawn.

Other Measures

A	Actual Use: Character and frequency of adverse events as reported by the user population	

Rationale: This endpoint is intended to characterize the type and frequency of adverse events among subjects in the use phase of this study. There is no reason to expect that rates or character of adverse events will differ from those expected in the prescription environment. This endpoint is designated an “other measure” as it is not a direct measure of participants' compliance with label directions.

B	Actual Use: Patterns of use (e.g., starting and stopping, discontinuation rates and reasons for discontinuation)	

Rationale: This endpoint is intended to characterize more general patterns of use, such as how and when subjects start to use the study product, how often subjects discontinue use and why, as well as to identify any unexpected uses (attempted use as an emergency contraceptive, if there is any such use, for example). Importantly, discontinuation, as contrasted to non-compliance, is not contrary to labeling; a woman is free to discontinue the product at any time, for whatever reason. This is designated as an “other measure.”

C	Actual Use: Proportion of user population who experience severe vomiting or diarrhea within 4 hours of taking their daily pill who report using a barrier method of contraception every time they have sex (or abstain from intercourse) for the next 48 hours	Directions ● If you vomit for any reason or have severe diarrhea within 4 hours of taking your daily tablet, use a condom (or another barrier method) every time you have sex for the next 2 days (48 hours), because the medicine may not have been fully absorbed

Rationale: This endpoint is intended to measure how well subjects follow the instructions to use a condom (or another barrier method) every time they have sex for the next 48 hours if they have vomited or had severe diarrhea within 4 hours of taking the product. This is designated as an "other measure," as the study product is not expected to cause vomiting or diarrhea. This message is intended for any woman for whom vomiting or severe diarrhea happen to occur within four hours of taking a pill (conditions expected to be quite uncommon and unrelated to product use), as vomiting or severe diarrhea may interfere with absorption of that dose. The risk for unintended pregnancy among a woman who fails to heed this message is expected to be very low.

D	Actual Use: Characterize healthcare seeking behavior among subjects	

Rationale: This endpoint is intended to characterize how subjects in this study typically interact with healthcare providers and how they do so under study conditions. This is designated as another measure, as it is of general interest but unrelated to any DFL message.

3 STUDY DESIGN

This is an observational, open-label, multi-center, 16-week study designed to create as much as possible an OTC-like environment in which participants will make an initial self-selection and purchase decision about Opill® based only on their reading of the outside of the package including the DFL. Qualified participants who choose to do so will then

purchase the study medication, leave the study site and use the product on their own, guided by the OTC labeling. 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 none of the information gathered at screening, enrollment, or during the 16-week study period will be discussed 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 exclusionary criteria imposed on participants, making this trial nearly an all-comers study to mimic the likely OTC population.
- The study will be conducted in retail pharmacies, representing typical locations where consumers now commonly purchase OTC medicines (adult and adolescent subjects) and women's health and adolescent clinics (adolescent subjects).
- The proposed OTC packaging and labeling is the only product information provided to participants during the study. Participants will only review the outer packaging including DFL at the initial visit. Study staff will not provide any additional information or encouragement regarding product selection at that visit. Staff will not answer participant questions about the study medication and will instead refer subjects to the labeling. However, any questions related to the “Ask a doctor or pharmacist before use” section of the DFL that are asked of study staff in their capacity as healthcare provider or pharmacist will be recorded.
- After purchasing the study product, participants will take the package with them when they leave the site. The package will include the outer packaging, (Appendix 18.1) and, inside the package, the consumer information leaflet (CIL, Appendix 18.2), a reminder card (which highlights key messages about directions for use from the DFL, Appendix 18.3) and study medication.

3.2 Study Sites

Approximately 36 retail pharmacy study sites will be chosen for this study as such sites provide an environment that is considered typical of those from which consumers may expect to find this product following approval. Additionally, approximately 10 women's health clinics or adolescent clinics will be chosen to serve as recruitment and enrollment sites for some adolescent subjects. Study sites will be selected to provide geographic and demographic diversity and to be representative of literacy in the general population. Sites will be selected from approximately 10 geographic regions in the US. Each site has a private office or a suitable semi-private area where the enrollment visit 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 (EDC) system.

3.2.1 Site Training and Procedural Integrity

PEGUS Research will select sites and train the site staff after approval by the Sponsor. 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 population of likely consumers is able to apply the information in nonprescription drug labeling to guide their own behavior. Participants should therefore represent a wide range of demographic characteristics.

In order to mimic the OTC marketplace as much as possible, initial participant selection will be self-driven by consumer response to advertising for the indication (e.g. “Are you looking for a birth control pill without a prescription? You may qualify to participate in a confidential research study on a prescription strength over-the-counter birth control pill.”). In this way, the study sample is generated in the same way that the potential users of an OTC oral contraceptive would self-identify and purchase. This generates a sample that is most likely to be representative of the eventual user population. Given that adolescents are an important subgroup in the study, adult (18+) participants will be constrained to no more than 725 purchasers, allowing for an adolescent sample (age 12-17) of 175. Among adolescents, the enrollment goal for those ages 12-15 will be 50. If passive recruitment of adolescents to study pharmacies is not robust enough to meet sample size goals, as is anticipated, staff within the women's health or adolescent clinic sites will be allowed to invite adolescents to participate in the study if the adolescent patient identifies a need for contraception in the context of a clinical visit and expresses a preference for an oral contraceptive. In those cases, clinicians will not instruct subjects about how to use the study product, they will simply inform potential subjects (adolescents seeking an OC in the clinic setting) about the study and extend the invitation to participate.

While it is unusual in an AUT to allow for active recruitment on the part of clinicians, the targets requested by the Food and Drug Administration (FDA) for adolescent enrollment are challenging and may well make this supplemental recruitment measure necessary. In order to minimize the potential for bias, clinicians will be trained to not counsel potential subjects about the use of oral contraceptives in general, and to not provide specific counseling about the study product. This supplemental mechanism of recruitment is unlikely to have any impact on the primary endpoints of the study. The usual concern about active clinician recruitment in an AUT is that it may bias self-selection. In this particular case, 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 subjects recruited in this manner.

Please note, subjects must personally enroll in this study, and certify that they are seeking the study product for their own use. Representative buyers (such as family members and/or male partners, etc.) will not be allowed.

3.3.1 Self-Selection Phase / Initial Enrollment Visit Inclusion Criteria

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

1. Able to read, speak and understand English
2. 12 years of age or older
3. Can see well enough to read information on the label
4. Another member of the respondent's household has not participated in this study
5. 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 healthcare 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)
6. Has not participated in any research studies about health-related products in the past 12 months
7. Has not participated in a clinical trial in the past 12 months
8. Has never participated in a study about over-the-counter birth control medicines

3.3.2 Use Phase Exclusion Criteria

All subjects who agree to participate in the study and attend the initial enrollment visit at the site will be asked to make a self-selection and purchase (or use) 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 though their self-selection decision and desire to purchase will be recorded):

1. Unwilling to purchase study medication (pharmacy sites)
2. Unwilling to be dispensed study product for use (clinic sites)
3. Unwilling to provide informed consent
4. Unwilling or unable to provide contact information
5. Unwilling to state that the product is for their own use and no one else's
6. Premenarchal females
7. Pregnant
8. Male
9. Known allergy to norgestrel or inactive ingredients.
10. History of any cancer

Additionally, subjects must meet all of the following study 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 guardian) has been informed of all pertinent aspects of the study.
- Willing and able to comply with the initial enrollment visit, planned phone calls and other study procedures, and the end of study visit.

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

3.3.3 Recruitment Methods

The recruitment methods discussed above and described below in more detail are designed to recruit a study population that will represent the likely OTC consumer population. The characteristics of the eventual OTC oral contraceptive user population are not known. In order to best simulate conditions of real OTC medicine use, every effort will be made to recruit subjects passively. In contrast to intercept recruitment and other direct contact methods (e.g., recruiting from databases), passive advertising requires consumers who are interested enough on their own to respond to advertising. The characteristics of the study sample will then be the best estimate of those characteristics among the eventual user population.

The content of the recruitment materials will be directed towards those who are interested in using an OTC birth control medicine. Recruitment methods will include some or all of the following: newspaper advertisements, direct mail postcards, in-store signs, posters, internet and other digital media, and handouts/flyers. Specific efforts will be made to make advertisements accessible to adolescents.

As described above, due to the importance of including a sufficient number of adolescents in the study, and the challenging targets set at FDA's request, active recruitment methods in clinic study sites will be implemented if passive recruitment of adolescents to study pharmacies is not robust enough to meet sample size goals.

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 four follow-up interviews). The interviews will be administered by a trained interviewer using an internet-based 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. 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 participants, nor will participants

be able to see them on the screen. Where close-ended questions are used (e.g., yes/no, or ok/not ok), participants 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 Opill® outer package including DFL will remain in front of the participant and the participant will be informed they can refer to the outer package at any time. However, the participant will neither be encouraged nor discouraged from referring to the package in response to any specific question.

Subjects who enter the use phase of the study will be asked to use an online diary to record their use of the study product daily. Of note, a device will be provided for subjects who do not have easy access to a device with internet access.

3.6 Test Materials

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

The product dispensed and taken home for use will include the exact same outer package, but will also have the study medication. A reminder card (Appendix 18.3) and a CIL (Appendix 18.2) will also be in the package, and will be available to the subject when she purchases the product and opens the box in order to mimic the experience of an OTC consumer.

Subjects who enter the use phase will be provided with a study information card (to include subject number and the central telephone number for any inquiries), the online medication use diary, as well the self-administered pregnancy test to use at the end of the study.

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 qualified to enroll in the use phase of this open-label study will be given the opportunity to purchase (or be dispensed, in the case of adolescent subjects enrolled at clinic sites) and use Opill® (norgestrel 0.075 mg). Those that are dispensed study product will be included in the use phase of the study.

4.2 Breaking the Blind

Not applicable

4.3 Drug Supplies

4.3.1 Formulation and Packaging

Opill® tablets for oral administration contain 0.075 mg norgestrel and the following inactive ingredients: cellulose, Food Drug and Cosmetics (US Federal Act) (FD&C) yellow No. 5, lactose, magnesium stearate, and polacrilin potassium.

Opill® is packaged in a box containing a blister card with 28 tablets, constituting a four-week supply.

4.3.2 Preparation and Dispensing

All subjects who are dispensed study medication will receive norgestrel 0.075 mg tablets. Subjects are to use the investigational product (IP) based on their understanding of the directions available on the outer packaging (on the DFL) and inside the product packaging (in the CIL and on the reminder card).

Subjects will be allowed to resupply with the study product at the study site during the study enrollment visit and if they choose to return to the site at any point. Subjects will not be allowed to receive more than 8 packages during the entire 16-week study period. This limit will not be disclosed to subjects unless they try to obtain more than a total of 8 packages over the course of the study. Any such requests that exceed the limit and the reason for that request will be recorded.

Please note that 8 packages constitute twice the product that would be needed for once daily use during the study period. It is typical in an AUT to allow subjects to obtain product in excess of the amount they would need, because without that allowance, no judgement can be made about whether subjects would take more than the instructed doses. Additionally, many women are accustomed (and advised) to obtaining several months of oral contraceptive supply at a time.

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]).

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 the range of 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.

At the end of the trial, subjects will be asked to return, any unused study medication, empty packaging, and e-diary device (if applicable) to the study site. If the study site or PEGUS Research has not received the unused medication or empty packaging within 10 days after the subject exits the study, follow-up telephone calls will be placed requesting that the subject return all study materials to the site. Subjects may also be provided with a pre-paid, pre-addressed United States Postal Service (USPS) envelope to send any materials directly to PEGUS Research.

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 Opill® 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 IP 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 online diary and four follow-up telephone interviews.

4.5 Concomitant Medication(s)

The IP packaging will contain information about the use of certain other medications when taking Opill® (the DFL includes the direction to ask a doctor or pharmacist before use if you are taking or have recently taken certain medications). Subjects will be queried at enrollment about medications that they are currently taking. During the four study telephone interviews, subjects will be queried about any changes to their enrollment medications and any new medications that they have begun taking since the start of the study.

4.6 Rescue/Escape/Salvage Therapy

Not applicable.

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 PEGUS Research matches the total number of IPs delivered to all sites. Any discrepancy must be explained.

5 STUDY PROCEDURES

5.1 Telephone Screening of Passively Recruited Potential Subjects

Potential subjects who respond to passive advertising will call a toll-free phone number or visit a study website. Telephone calls will be answered at a centralized unit and initial study inclusion and exclusion questions will be asked by screening interviewers trained on study-specific screening. The website will similarly check study inclusion/exclusion, and allow those qualified to make an appointment for the in-person enrollment visit. Subjects who meet the study inclusion criteria and remain interested will be assigned an appointment date and time for a face-to-face interview at the pharmacy site closest to their location (residence or place of work). The potential subjects will be provided the name and location of the pharmacy site.

5.2 Active Recruitment of Potential Subjects

As discussed above, potential adolescent subjects presenting to clinic sites seeking oral contraception will be informed of the study and invited to participate. If they choose to participate, they will be routed to study staff who will perform the initial screening in person, and conduct the remainder of the enrollment process as described below.

5.3 Study Period

5.3.1 Enrollment Visit, Self-Selection/Purchase Decision

At the enrollment visit, which takes place at the retail pharmacy or health clinic study site and is conducted by trained site staff, initial study inclusion criteria will be reviewed and potential subjects will be shown the Opill® outer package. Subjects will be given as much time as needed to review the information on the outer package. After reviewing the outer package, they will be asked if the product is right for them to use and for those that say the product is right for them, whether they want to purchase/obtain the product for their own use. Reasons for selection/non-selection and purchase/non-purchase will be collected.

5.3.2 Mock Purchase

In many AUTs, subjects are asked to “purchase” the study product, typically for a nominal fee. This purchase transaction is intended to make the study process more OTC-like, and helps minimize the likelihood of subjects enrolling who are not truly interested in the study medication. Subjects do not know at the time of the purchase decision or for the remainder of their study participation that any money that they pay for study product will be reimbursed to them at the end of the study.

In some AUTs, however, the “purchase” is not feasible for one reason or another. In this study, targets for adolescent participation are challenging, requiring the addition of active recruitment in a clinical environment for adolescent subjects only. Barriers to

participation are already quite high for adolescents. Because adolescents seeking care in the clinical environment are typically able to receive their care and medications without any cost to them, subjects enrolled in the clinical environment will not be asked a purchase question. Rather, they will be asked whether they want to receive study product for their own use. There will be no mock purchase transaction. This will eliminate that potential barrier to participation.

Adolescent subjects who respond to study advertising in the traditional way will all be enrolled at pharmacy sites, as will all adult subjects. The mock purchase procedures will be in place for all subjects who enroll at pharmacy sites.

Throughout this document, “purchase” and “purchasers” refers to any subject who either agrees to purchase and conducts a purchase transaction (as will be the case for all adults and any adolescents who enroll at pharmacy sites) or who agrees to be dispensed the study product for their own use (in the case of adolescent subjects enrolled at clinic sites).

5.3.3 After Purchase Decision and Before Study Entry

The purpose of this study is to see how the subject complies with the labeled directions; therefore, the date of the first use of study medication is determined by the subject. Study Day 1 will be defined as the day the product is dispensed to the participant.

On Study Day 1, at the site, subjects will complete the enrollment interview, providing information on any associated medications, associated medical conditions and selected demographic information. Subjects will then be asked to complete the REALM[1] or REALM-Teen[2] test to establish reading ability.

Next, use phase exclusion criteria will be assessed, and qualified subjects who decide to purchase/obtain the product will provide informed consent. Please note that in this study, as is typical in actual use trials, a waiver of consent will be sought for the prior elements of the enrollment interview, so as to avoid the potential bias to self-selection that the details necessary for informed consent may introduce. The informed consent document will be presented electronically, and signatures will be collected electronically. However, all consent procedures will be conducted face-to-face. There will be no consent administered remotely to subjects (or with parents or legal guardians, if applicable).

Subjects that provide consent will be provided with a self-administered pregnancy test and asked to use it there at the site. Results will be recorded, and any subjects who are found to be pregnant will be excluded from use, and the event documented. Adolescent subjects recruited from the clinical environment whose pregnancy test is positive because of a recent abortion will not be excluded. Subjects who are found to be pregnant based on their initial positive pregnancy test will be asked the self-selection question again to determine if they make a correct non-selection decision once they have the confirmation that they are likely pregnant.

Qualified subjects will be required to provide contact information (for the purposes of conducting telephone follow-up interviews and providing compensation). Subjects who

chose to will then purchase the IP and site study staff will complete the IP accountability form in the EDC system. Subjects will be told they are allowed to return to the study site at any time to purchase/obtain additional study medication. Subjects will subsequently be reimbursed for all purchases, but are not informed of this until the study is completed. Subjects will not be allowed to purchase/obtain more than 8 four-week supply packages during the study period, although this limit will not be communicated to the subjects unless they attempt to purchase/obtain more than that. Any requests for purchase/dispensing of more than the limit will be recorded, as will the reason for such requests.

Subjects will also be informed that interim and end-of-study phone interviews will be conducted at weeks 4, 8, 12, and 16 (with an allowable window of +/- 4 days for interviews at weeks 4 and 8, and +/-5 days for interviews at weeks 12 and 16). Subjects are not required or directed to continue taking the medication for this period. Subjects who have decided to proceed to the use phase of the study will be dispensed the product to use how and when they see fit based only on guidance from labeling.

Subjects will be introduced to and trained to use the online medication use diary. Subjects will also be provided with a subject information card and a self-administered pregnancy test and given instructions to use the test at the end of the study period. Subjects will record the results of the home pregnancy test in the online medication use diary.

5.4 Use Phase

Subjects who enter the use phase of the study take home the IP to use how and when they see fit based only on guidance from the labeling. Contact with subjects during the use phase is limited and targeted toward collecting data necessary to evaluate study endpoints.

5.4.1 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, answered, or directions given about the use of the IP by the study staff (except for questions that are explicitly directed to study staff in their capacity as a pharmacist as described above in Section 3.1 above).
2. Appropriately documenting the IP dispensed.
3. Assisting any subject presenting self-reported AEs by immediately having the subject contact PEGUS Research or by collecting the relevant details and reporting that to PEGUS Research staff.

5.4.2 Online Medication Use Diary

Subjects will be asked to record their use of the IP in an online, web browser-based medication use diary. If a subject does not have easy access to a device with internet connectivity, a device will be provided to them. The diary will record use of the product,

including time of day. Additionally, subjects will be asked to record each instance of heterosexual vaginal intercourse, along with any contraceptive method used.

5.4.3 Telephone Interviews

The four scheduled phone interviews at weeks 4, 8, 12 and 16 will be conducted by PEGUS Research clinical staff (trained nurse interviewers) to collect information such as specific subject behaviors, AEs and concomitant medications.

5.4.3.1 Week 4/8/12/16 Telephone Interview

Trained nurse interviewers will conduct the interim and end of study (EOS) interviews. Interim interviews will be conducted at week 4 (day 28 +/- 4), week 8 (day 56 +/- 4), week 12 (day 84 +/- 5), and week 16 (day 112 +/- 5). The intent of the monthly telephone interview is to collect information about use of the product, AEs and concomitant medications. Each interview will assess whether the subject has started taking the IP, and if so, collect information about how they have taken it. Questions will be designed to collect information about behaviors related to the use of the IP in a non-biasing and 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?”).

5.4.3.2 End-of-Study Interview / Early Termination Interview

In most cases, the EOS interview will take place during the week 16 telephone contact, after the week 16 interim interview is complete. 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 16-week telephone call. The EOS interview will collect information from the subject regarding the use of other forms of contraception, and the timing of such use. This interview allows for direct questions about the rationale behind any behaviors that are not consistent with the DFL and CIL instructions, without concern about biasing the subject's subsequent behavior. Additional questions will be asked to include subject's experience with the study product, future contraceptive plans, and history and plans for interactions with a healthcare provider. Subjects will also be asked about possible pregnancy and will be asked to take the EOS self-administered pregnancy test, conducted at home, and record the results in their online medication use diary. Electronic reminders to complete and record the results of the self-administered home pregnancy test as well as schedule the EOS visit (described in Section 5.4.4 below) will be delivered every other day beginning at the day following completion of the use phase. Any subjects who do not report the results of their self-administered pregnancy test and also have not completed the end of study visit by 5 days after completion of the use phase will be contacted via telephone and asked to take the provided home pregnancy test and report those results by telephone, and to schedule an EOS visit.

5.4.4 End of Study Visit

After completion of the EOS interview, subjects will be asked to return to the study site to return any study materials. At that visit, subjects will again conduct a self-administered

pregnancy test, with pregnancy test results confirmed and recorded by site staff. Any subjects that fail to return for an EOS visit will be contacted via telephone and asked to schedule an EOS visit. For subjects who complete the EOS visit (and its associated pregnancy test) but have not reported the at-home pregnancy test will not require additional follow up. While the intent is for the EOS visit to be conducted within 10 days of the subject's completion of the use phase, if a subject presents for the EOS visit outside of that window, EOS visit procedures will still be conducted until the study has ended.

5.5 Subject Withdrawal (Early Termination)

If a subject notifies study staff of their intention to withdraw from the study early, the clinical interviewer will attempt to complete the next scheduled interim interview (unless the subject withdraws consent for disclosure of future information). An EOS interview will also be conducted with any subject who discontinues or withdraws consent prior to Week 16. This interview will attempt to collect the EOS information and the reasons for the subject's early termination. These subjects will also be asked to perform and report the results of the EOS self-administered pregnancy test, and to return materials to the site where an additional self-administered pregnancy test will be performed.

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

- Significant protocol violation
- AEs, including serious adverse events (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), e-diary devices where applicable, and will be precluded from purchasing additional study medication. Data collected up to the point of withdrawal will be retained and used as appropriate in the data analysis. Ongoing data collection will be allowed if applicable (such as for AE follow-up), 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 effort made to contact the subject will be documented. In any circumstance, every effort will be made to determine and document subject outcome, if possible. The investigator will inquire about the reason for withdrawal, request the subject to return all unused IP and empty packaging, request

the subject to participate in a final telephone interview, if applicable, and follow up with the subject regarding any unresolved AEs.

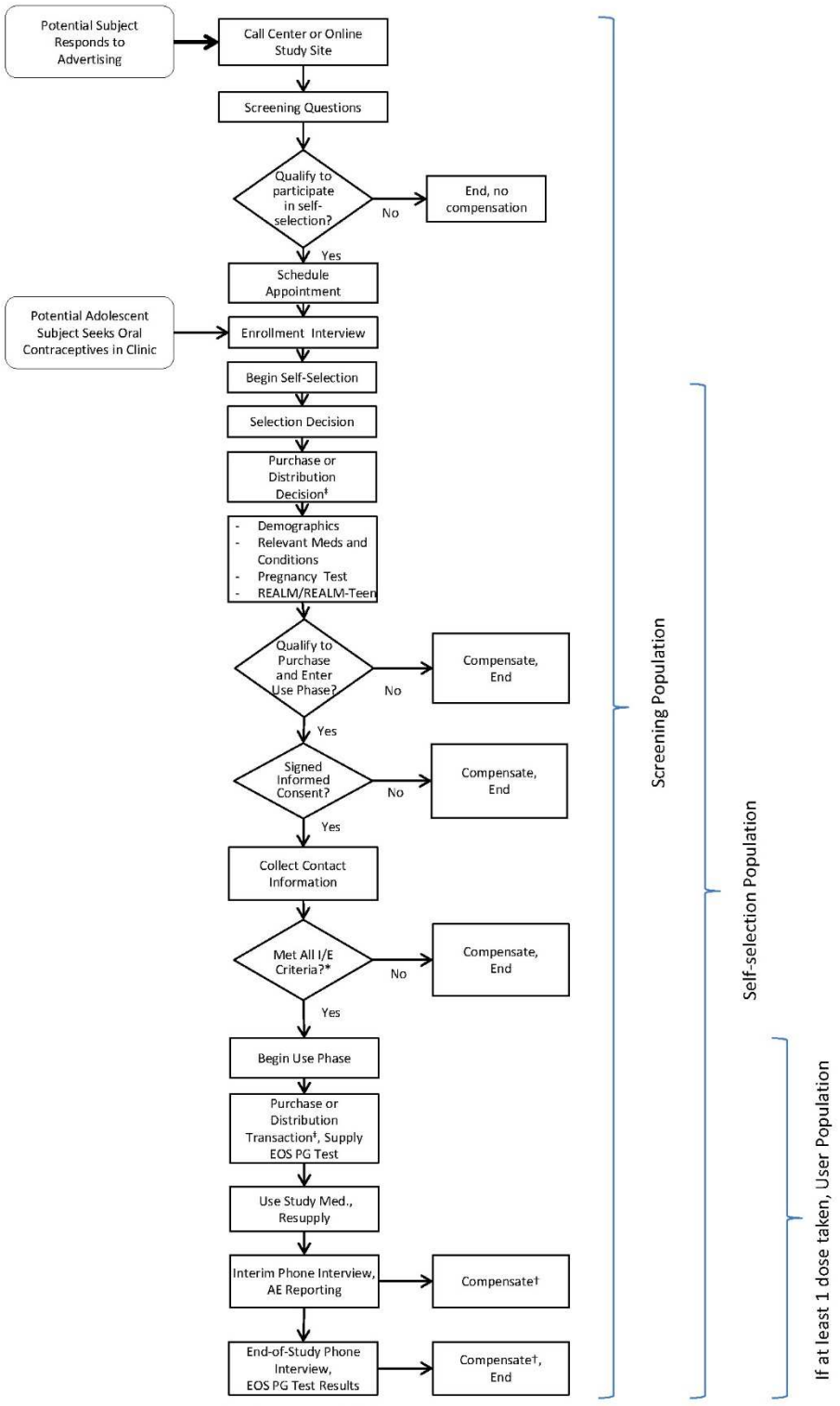
A subject may be declared lost to follow-up if, during the study, the available contact information is determined to be incorrect and no other information is available. Every attempt will be made to contact lost to follow-up subjects, including three phone call attempts and a letter sent via USPS. Subjects 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 study database.

If a subject wishes to stop participation in the study, the Investigator/interviewer will document the reason for withdrawal, ask the end of treatment questions where possible and follow up with the subject regarding any new or unresolved AEs, request that the subject conduct the at home EOS pregnancy test and instruct the subject to return all unused IP and any empty packaging. Data collected up to the point of withdrawal will be retained and used as appropriate in the data analysis.

5.6 Study Flow

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

Figure 1 Study Procedures Flowchart



*Evaluated programmatically in EDC System.
‡Subjects at all-ages sites include mock purchase, subjects at adolescent-only sites do not
†Subjects in use phase compensated as they complete each milestone

6 ASSESSMENTS

Every effort will be made to ensure that the protocol-required 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 procedure. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required procedure 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 EDC Data Collection Instrument (DCI).

6.1 Screening Assessment

Subjects will be screened both over the telephone and 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 Opill® outer package and allowed to make a decision about whether the product is appropriate for them to use and whether to purchase/obtain Opill® for their own use. Subsequent questions will be asked to gather limited medical and medication history as it pertains to use of the IP, as well as subject demographics.

6.3 Reading Level Assessment

The REALM[1] (for adults) or the REALM-Teen[2] (for adolescents age 12 to 17) 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 five 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 participants.

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 a cutoff for 10th grade-equivalent reading level.

The REALM-Teen will be used to demonstrate (along with demographics) that adolescent participants 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 goal 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 participants to comprise the overall low literacy subgroup for analysis.

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 AUT, 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 participants typically ranges from 12-18%. Every effort will be made to make the advertising accessible to those with lower literacy; however, in an AUT literacy cannot be controlled for without biasing the representativeness of the sample. It is not realistic or possible to control for who responds to the advertising or self-selects to use the product.

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 AUT is to enroll a sample that is representative of the likely OTC user population. In this setting, controlling for literacy would compromise the representativeness of the sample in a manner that is inappropriate. The number of responders that would need to be excluded in order to supplement the low literacy proportion of the sample would likely be as large as the target sample. With that degree of exclusion, the risk of introducing bias would be significant, and would run counter to the principal of enrolling a sample as representative of the likely OTC population as possible.

While it is inappropriate to control for literacy to force a specified proportion of low literacy participants 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 was selected to ensure that the absolute size of the subgroup of low literacy participants will be large enough to evaluate the endpoints in that subgroup. If 15% of 900 subjects are classified as low literacy by the REALM or REALM-Teen, the cohort of low literacy subjects will be approximately 135

subjects, representing a subgroup of sufficient size. As an illustration, the 95% confidence interval (calculated using the Exact method) around a point estimate of 85% for 135 subjects is +/-7.2%.

6.4 Pregnancy Testing

During the enrollment interview, after answering the self-selection question, all subjects will be asked if they are currently pregnant, and after informed consent is obtained, subjects will perform a self-administered pregnancy test at the site. Subjects with a positive result will be asked the selection question again, and then excluded from participating in the use phase of the study. Additionally, at the end of the enrollment interview, subjects who are proceeding into the use phase will be provided with a home pregnancy test with the instructions to use it at home at the end of the study and record the results in the online diary. Nurse interviewers will inquire about the results of the home pregnancy test during the EOS interview. After completion of the EOS interview, subjects will be asked to return to the study site to return all unused study medication and packaging. During that visit, an additional pregnancy test will be administered and results entered by site staff. If subjects have not completed the home pregnancy test at the EOS interview, and if they have not returned to the study site for the site-recorded pregnancy test, an additional call will be placed at 5 (+3) days following the EOS interview to collect home pregnancy test results. This will allow for shipping time if the subject requires an additional at home pregnancy test to be sent to them. In addition, at the time a subject withdraws or is withdrawn from the study early, nurse interviewers will inquire if the subject would be willing to take the pregnancy test and report the results in their electronic diary and return to the site for the EOS visit.

6.5 Medication Use Diary

Subjects will be asked to report their use of the study product daily using a web-based electronic diary. Date and time of each dose taken will be recorded, as well as instances of heterosexual vaginal intercourse and any additional contraceptive methods used in each instance. Subjects will also record the results of the EOS home pregnancy test in the electronic diary. An internet-connected device will be provided to subjects who do not have easy access to the internet.

6.6 Interim Follow-up Telephone Interviews

During the course of the study, all participants will be contacted four times via telephone by a trained nurse interviewer who will ask a series of scripted questions related to the use of the IP, as well as collect information related to concomitant medications and adverse events.

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 4 phone interviews, at weeks 4, 8, 12, and 16 during which the nurses will limit the dialogue with the subjects to the interview script.

6.7 End-of-Study/Early Termination Telephone Interview

At the end of the study (typically this will be in conjunction with the 16-week call), or upon early termination from the study, all participants 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 and the at-home, self-administered end of study pregnancy test results, as well as collect information related to concomitant medications and AEs.

As participation for that subject will then be complete, and therefore the risk of biasing future behavior irrelevant, this EOS 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 16-week telephone call immediately following the 16-week interim follow-up interview. However, in cases where subjects may withdraw or be withdrawn earlier for any reason, the EOS interview will be conducted by telephone at that time.

6.8 End-of-Study Visit

After the end-of-study interview is completed, subjects will be asked to return to the local study site within 10 days to return any unused medication and packaging, as well as any other study materials. Additionally, subjects will be asked to conduct an additional self-administered pregnancy test, with results confirmed and recorded by site staff. While the intent is for the EOS visit to be conducted within 10 days of the subject's completion of the use phase, if a subject presents for the EOS visit outside of that window, EOS visit procedures will still be conducted until the study has ended.

7 ADVERSE EVENT REPORTING

7.1 Adverse Events

All observed or volunteered AEs regardless of suspected causal relationship to the IP 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. 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 an 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

SAEs will be recorded on the specific case report form (CRF). 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, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, 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 the IP are to be reported to the Sponsor.

Non-serious AEs will be collected and recorded in the study database 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.

Medical and scientific judgment 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 7.12).

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. These 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. The Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the IP 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 the IP 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 investigational products 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 investigational product;
- A male has been exposed (e.g., due to treatment or environmental exposure) to the investigational product 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 a SAE and

EDP report, 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 EDP 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 EDP report. In the case of a live birth, the health 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 the 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 or Investigator 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 PV 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 EDP cases.

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 for a non-serious AE. 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 in the AE portion of the study database. It should be noted that the form for collection of SAE information is not the same as the form for collection of other AEs. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same event 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 participant 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 Code of Federal Regulations (CFR) Part 11 requirements.

8.2 Electronic Diary System

A web-based electronic diary will be provided to all subjects with a reliable internet connection. The e-diary will be programmed and hosted by a qualified vendor (eClinicalHealth Ltd, Stirling, United Kingdom), and will be compliant with 21 Code of Federal Regulations Part-11 requirements. Subjects will be instructed to record information regarding their use of the study product every day. Subjects will also be asked to enter additional data regarding sexual behaviors (heterosexual vaginal intercourse) and additional contraception methods to fully evaluate adherence to label directions. The electronic diary will also serve as the primary means of reporting the results of the EOS at-home self-administered pregnancy test. Diary data will be imported into the EDC system to be included in the study database.

8.3 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.

8.4 Conceptual Approach to Self-Selection

While this is not a dedicated self-selection study, one of the primary endpoints in this study is the proportion of the self-selection population that make a correct selection decision.

Conceptually, the self-selection decision can be characterized as a 2x2 table (Table 4 below) where the participant's decision to select or not select the study product for use is crossed with whether or not it is appropriate for participant to use, based on participant's self-reported health status and clinical characteristics.

Table 4 Self-Selection Decision Outcomes

Participant'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: Participants 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: Participants 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: Participants 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: Participants 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.

8.5 Classification Activities

To evaluate participants for the self-selection endpoint, each participant 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). Participants will be classified on these two variables as described in Sections 8.5.1 and 8.5.2 below.

8.5.1 Selection Decision

The selection phase of the interview consists of the self-selection question and the purchase (or equivalent) question, with accompanying neutral follow-up questions. All subjects who go on to purchase/obtain the study product will be categorized as selectors. Subjects who do not eventually complete the purchase/dispensing of the product will be classified as a selector or a non-selector primarily based on their responses to the initial self-selection and purchase questions. However, all information recorded during the selection phase of the interview will be considered in the classification of participants as selectors or non-selectors. Participants who offer modifying information in open-ended responses to neutral probing will be re-categorized accordingly.

A participant who initially indicates that the product is OK for their use, but who independently and unprompted changes their decision during the selection phase of the interview would be categorized as a non-selector. However, any information offered once the interview proceeds beyond the selection phase of the interview will not be considered during selection classification. Financial and cost-related reasons for saying no to the purchase question will not be used as rationale for re-classifying participants who would otherwise be selectors.

One exception to this will be for the subset of subjects that select the product, report not being pregnant, sign consent, and then receive a positive result from the subsequent enrollment pregnancy test. These subjects will be re-asked the selection question and their classification as a selector or non-selector will take into account this second selection decision made in light of new health status information.

The selection decision for each participant 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 participant is a selector or a non-selector. Discrepancies will be resolved by a third coder (as described in Section 8.5.4).

8.5.2 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 participants 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 participant who otherwise meets the labeled criteria for use does not select the product and cites the fact that they have unexplained vaginal bleeding between their menstrual periods 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 participant will be re-classified from Cell C to Cell D. A physician will review the casebook for each participant who falls into Cell C to determine if any participants meet that criterion.

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

> **Yes:** either meets the strict DFL 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**).

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

1) Correct Selectors. Participant meets the strict criteria of the DFL, including:

   a) No absolute contraindications (not male, no history of cancer, not pregnant, does not have a known allergy to one of the ingredients)

   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.

2) Acceptable Selectors. Participant does not meet the strict criteria of the DFL, but selection is classified as appropriate because they are judged clinically (see Section 8.5.3) to be an appropriate selector. This group is expected to be quite small and might include for example: a woman who has a history of breast cancer, but who reports that she knows that her cancer is not hormone sensitive or has been told by a healthcare provider she can use hormonal contraception.

3) Incorrect Selectors. This group includes selectors who are not correct or acceptable, including having any of the following:

   a) An absolute contraindication to the product (has a history of any cancer, is pregnant and intends to use while pregnant, and/or has a known allergy to an ingredient)

   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.

Please note that the criteria upon which initial selection is judged include the absolute contraindications, as translated from the prescription labeling contraindications section to the proposed DFL. In addition, in the selection classification, the second self-selection decision made by those subjects with a positive pregnancy test result during the enrollment visit will trump the initial decision those women made, although data regarding the initial decision will also be presented.

Two conditional contraindications from the prescription labeling are presented in other sections of the DFL (i.e., not in the “do not use” section) to reflect their conditional nature, namely, unexplained intermenstrual bleeding and liver problems. The fact that these two warnings are conditional rather than absolute (i.e. they are “ask a doctor before use” warnings rather than “do not use” warnings) means that consumer behavior relative to these warnings cannot be evaluated as part of the initial self-selection decision, because correct behavior depends on subsequent actions (asking a doctor), and initial selection is not necessarily inappropriate if the subject does select to use and then indeed follows those instructions to talk to a doctor about using the medicine.. Evaluation of the instructions regarding those two messages will be evaluated individually based on the complete subject behavior in discrete endpoints.

8.5.3 Physician Mitigation

Participants occasionally decide to select a product for use that according to the strict DFL-defined algorithm appears to be an incorrect decision, but when evaluated from a clinical perspective is acceptable. Examples might include a woman who has a history of breast cancer (which makes her algorithmically incorrect) but who clarifies that she knows that her cancer is not hormone sensitive, or that she has been told by a healthcare provider that she can use hormonal contraception. Note, however, that in this example she would still be excluded from the use phase of the study. 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 8.5.2) for evidence that the participant made a clinically justifiable selection decision. Their assessments are then compared, and any discrepancies resolved by a majority rule. In cases where a physician reviewer reclassifies a subject in this way, their justification for the reclassification will be recorded.

8.5.4 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. After completion of the study, 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. 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 participants.

9 DATA ANALYSIS/STATISTICAL METHODS

This is a naturalistic, observational trial to assess selection and 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.

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.

9.1 Sample Size Determination

For the purposes of this AUT, sample size has been set at approximately 900 purchasers (use phase participants). Given that subjects are responding to recruitment aimed at those interested in an OTC birth control medicine, most subjects who choose to purchase the study product are expected to actually use the product during the study.

Assuming approximately 900 purchasers, if 80% of those purchasers use the product within the study period, that would yield an actual user population of approximately 720. Allowing for a further 20% loss to follow-up would yield a measurable user population of approximately 576.

Because AUTs are not hypothesis-testing comparative trials, study sample size is designed to allow for adequate evaluation of key endpoints across all participants and among several subgroups. As the analysis of AUTs typically focuses on estimating the proportion (and associated 95% confidence intervals) of individual endpoints, sample size is most often based on the number of participants needed to constrain the confidence interval (CI) to a limited range. As an illustration, for this study, assuming an 85% correct behavior to any single endpoint (of course, the CI depends on the actual point estimate and will be calculated based on the data), a sample of 720 participants would constrain the CI to ±2.8%. Table 5 provides the 2-sided 95% CI 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=900[a]	N=720[b]	N=576[c]	N=135[d]
95% CI around a point estimate of 85%	+/-2.5%	+/-2.8%	+/-3.2%	+/-7.2%

[a] Purchasers
[b] User population (allowing for 20% non-users)
[c] User population (allowing for 20% loss-to-follow up)
[d] Low literacy subjects

9.2 Analysis Populations

The populations of interest are defined as follows:

- Screening Population: All those who respond to study advertisements and complete initial screening questions.
- Self-Selection Population: Participants who accept the invitation to participate and meet study inclusion criteria, participate in a face-to-face interview at the study site, make a self-selection decision, and provide responses to all relevant medical history questions.
- Purchasers: Responders who meet study enrollment criteria and purchase/obtain the study medication.
- User Population: Subjects who take at least one dose of study medication during the study.

9.3 Endpoint Analysis

A summary of the disposition of subjects (including those who respond to advertisements, the screening and self-selection populations, 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 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, without using assumptions or approximations based on distributions. 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 participants dichotomized on the corresponding variables, which include (but are not necessarily limited to) literacy, gender, age (adolescent vs. adult women), and history of previous hormonal birth control use.

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.

9.3.1 Primary Endpoint Analysis

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

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

The first primary 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.

9.3.1.1.1 Populating the Self-Selection Table

Each participant will be classified on two key variables: (1) whether they are a selector and (2) whether their use of the product would be appropriate, in order to populate the typical 2x2 self-selection table.

Selection Decision: The selection phase of the interview consists of the self-selection question and purchase (or equivalent) question, with accompanying neutral follow-up questions. All subjects who go on to purchase/obtain the study product will be categorized as selectors. Subjects who do not eventually complete the purchase/dispensing 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 (the second selection decision will be included for those with a positive enrollment pregnancy test). However, all information recorded during the selection phase of the interview, including verbatim responses to open-ended follow-up questions, will be considered in the classification of participants as selectors or non-selectors. Participants who offer

modifying information in open-ended responses to neutral probing will be re-categorized accordingly. For the subset of subjects that select the product, report not being pregnant, sign consent, and then receive a positive result from the subsequent enrollment pregnancy test, a second selection question will be asked. Their classification as a selector or non-selector will take into account this second selection decision made in light of new health status information.

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 participants 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 participant who otherwise meets the labeled criteria for use does not select the product and cites the fact that they have unexplained vaginal bleeding between their menstrual periods 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 participant will be re-classified from Cell C to Cell D. A physician will review the casebook for each participant who falls into Cell C to determine if any participants 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**).

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

> 1) Correct Selectors. Participant meets the strict criteria of the DFL, including:
>
> a) No absolute contraindications (not male, no history of any cancer, not pregnant, does not have a known allergy to one of the ingredients)
>
> 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.
>
> 2) Acceptable Selectors. Participant does not meet the strict criteria of the DFL, but selection is classified as appropriate because they are judged clinically (see Section 8.5.3) to be an appropriate selector. This group is

expected to be quite small and might include for example: a woman who has a history of breast cancer, but who reports that she has been told by a healthcare provider that her cancer is not hormone sensitive and she can use oral contraceptives.

3) Incorrect Selectors. This group includes selectors who are not correct or acceptable, including having any of the following:

   a) An absolute contraindication to the product (has a history of any cancer, is pregnant and intends to use while pregnant, and/or has a known allergy to one of the ingredients)

   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.

Please note that the criteria upon which initial selection is judged include the absolute contraindications. Two conditional contraindications from the prescription labeling are presented in other sections of the DFL to reflect their conditional nature, namely, unexplained intermenstrual bleeding and liver problems. The fact that these two warnings are conditional rather than absolute (i.e. they are “ask a doctor before use” warnings rather than “do not use” warnings) means that consumer behavior relative to these warnings cannot be evaluated as part of the initial self-selection decision, because correct behavior depends on subsequent actions (asking a doctor), and initial selection is not necessarily inappropriate if the subject does select to use the product but indeed follows those instructions to talk to a doctor about use of the medicine. Evaluation of the instructions regarding those two messages will be done individually based on the complete subject behavior in discrete endpoints.

9.3.1.1.2 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 participants 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 participants who, based on their health status, should not use the study medication (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 who should not use the medicine 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)/(all subjects)].

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 D)] (excluding cell C)

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.

9.3.1.2 Actual Use: Use of the study medication every day

This is adherence to the instruction to take one tablet every day, and is measured as the proportion of active dosing days among the user population (all subjects who take at least one dose of the IP) where a dose was taken (excluding days after a subject discontinues use of the IP—defined as the point at which no additional doses are taken). Specifically, to be included in the numerator (representing appropriate adherent use), a dosing day must meet one or more of the following criteria:

1. A tablet must be taken at some time during the dosing day.
2. Subject reports using a condom (or another barrier method) for any act of intercourse or abstaining from intercourse.

Regarding #2 above, the DFL provides explicit instructions for consumers when they miss pills which mitigate any risk of pregnancy related to that missed pill. So, while overall adherence to the daily dosing schedule will be presented as well (without accounting for secondary barrier method use for acts of intercourse or for abstinence), the overall measure of adherence will allow for those label-directed or appropriate consumer behaviors. Please note that for the purposes of this endpoint, diary data will serve as the primary source of data, with interview data collected by telephone used to supplement only in cases where diary data may be missing.

9.3.1.3 Actual Use: Use of the study medication at the same time of day

This endpoint is the proportion of active dosing days among the user population (all subjects who take at least one dose of the IP) which demonstrate adherence to the labeled directions for use related to the time of day the study medication is taken (excluding days after a subject discontinues use of the IP). Specifically, to be included in the numerator (representing appropriate adherent use), a dosing day must meet one or more of the following criteria:

1. For all dosing days where a tablet was taken the preceding day, the tablet is taken no later than 27 hours after the previous tablet (representing 24 hours from last dose plus three hours, consistent with the DFL instructions).
2. Subject reports using a condom (or another barrier method) for any act of intercourse or abstaining from intercourse.

Again, regarding #2 above, the DFL provides explicit instructions for consumers when they are late taking their pill which mitigates any risk of pregnancy related to that late dose. So, while overall adherence to taking the product at the same time every day will be presented as well (without accounting for secondary barrier method use for acts of intercourse or for abstinence), the overall measure of adherence to dose timing will allow for those label-directed or appropriate consumer behaviors. Please note that for the

purposes of this endpoint, diary data will serve as the primary source of data, with interview data collected by telephone used to supplement in cases where diary data may be missing.

9.3.1.4 Actual Use: Use of the study medication without an extended break or any break between packs

While another endpoint measures all instances of any missed pills, this endpoint is intended to capture the special cases in which any subjects take an extended break from daily pill taking for any reason at any time, including. subjects who miss any pills between packs. For example, there may be subjects who do not appreciate the difference between a COC (where a medication break during menstruation is common) and the IP instructions which call for use daily without any breaks. This concept is measured as the proportion of the user population who do not take an extended break or a break between packs (where a single pack is defined as 28 tablets). A "break" is distinguished from discontinuation (defined above), which is a consumer choice not proscribed by the label.

The numerator will comprise the total user population minus those subjects who miss taking the IP for seven consecutive days on at least one occasion OR for four consecutive days or more on at least two occasions during active use of the product OR who take any break between packs (including missing one pill between packs), as recorded in their medication use diary. Subjects with a qualifying use pattern will be asked directly about that use during the next scheduled follow-up telephone interview. Please note that missed pills that are not included this endpoint are accounted for in another primary endpoint. Also note that for the purposes of this endpoint, diary data will serve as the primary source of data, with interview data collected by telephone used only to supplement in cases where diary data may be missing.

9.3.2 Target Thresholds

Objective target thresholds will be set for all the primary endpoints. 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. Target thresholds and a summary of the associated rationale follow.

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

HRA proposes to test this message as a primary endpoint because it is the self-selection phase of the study that will determine appropriate use of the product based on the DFL. This endpoint measures several relevant messages in the label:

Use:
For daily use by women to prevent pregnancy
Allergy alert: Do not use if you are allergic to this product or any of its ingredients.
Do not use:
● if you are male

- if you have ever had any cancer
- if you are already pregnant or think you may be pregnant

This endpoint addresses both correct selection to use in order to prevent unintended pregnancy but also measures appropriate de-selection among individuals who should not use this product.

Do not use if you are male. This contraceptive pill is not intended for use by men. Use by a man would represent a fundamental misunderstanding of the product and its indication. Use by men is very unlikely: National Health and Nutrition Examination Survey (NHANES; 2011-2012) data showed no evidence of men of any age taking oral contraceptive pills[3]. However, if a man were to take a POP, it is unlikely to have serious clinical consequences. A variety of different progestogens, in a variety of doses and routes of administration, have been tested as hormonal contraceptives for men. Testosterone alone is effective but adding progestin results in an increased rate and extent of suppression[4]. High doses of progestins suppress endogenous production of gonadotrophins and testosterone thereby inhibiting spermatogenesis. Common side effects include acne and changes in mood and libido which are rarely severe enough to lead to discontinuation. Suppression of spermatogenesis is reversed when the treatment is stopped[5].

In theory, use of the POP could suppress spermatogenesis rendering a man less fertile. However, it is unlikely that 0.075 mg/day would have much of an effect on spermatogenesis and would be unlikely to render a man infertile unless he already had a very low sperm count. In any case, the effect is reversed when the treatment is stopped.

Other potential consequences would include the theoretical exacerbation of any pre-existing medical condition which is adversely affected by a progestin in the same way, and to the same extent as it would for a woman. Such conditions would include the United States Medical Eligibility Criteria (USMEC) Category 3 conditions[6], i.e. ischemic heart disease, stroke, Systemic Lupus Erythematosus (SLE) with anti-phospholipid antibodies, breast cancer with no evidence of current disease for five years, hepatocellular adenoma and malignant hepatoma and just one USMEC Category 4 condition, current breast cancer. The likely effect of progestin on these pre-existing conditions is discussed with respect to their occurrence in women later in this document.

In summary, use of the POP by a man would be inappropriate, but is not likely to expose the male user to significant or lasting harm.

Do not use if you have ever had any cancer. The warning against use of the product by women with a history of cancer arises from a concern that reproductive hormones may increase the likelihood of, or accelerate, recurrence of certain cancers, most prominently breast cancer. While the DFL warning is intended to protect women with any history of progestin-sensitive cancers, consumers may not know whether their specific cancer is

progestin-sensitive. Other non-breast cancers which are progestin-sensitive are exceedingly rare in this target population.

In the USMEC, breast cancer is a `category 4 condition' for all hormonal contraceptives including the POP. Note, however, that history of breast cancer is a `category 3 condition' for all hormonal contraceptives including the POP, when five disease-free years have passed. The USMEC recommendations are based on expert opinion relating to a theoretical risk based on the knowledge that some breast cancers have progesterone receptors[7]. In fact, there is no specific data on the risk of use of a POP in a woman with breast cancer that would allow this risk to be quantified.

There are no direct data on the effect of hormonal contraceptives on the progress or outcome of breast cancer if a POP is taken since use of hormonal contraceptives in those with breast cancer is generally avoided. While there are no data on hormonal contraceptives in those with breast cancer, there are limited data from trials of hormone replacement therapy (HRT) use among menopausal women with breast cancer and this is the closest to relevant evidence. Unlike POPs, HRT contains estrogen in combination with progestins. In the 1990s, two randomized clinical trials started in Scandinavia addressing whether HRT is safe for women with previous breast cancer. The HABITS (hormonal replacement therapy after breast cancer—is it safe?) study, an open randomized controlled trial (RCT) with allocation to either HRT or `best treatment without hormones' randomized 434 women[8]. After a median follow-up of 2.1 years, 26 women in the HRT group and seven in the non-HRT group had a new breast-cancer event and the trial was terminated. The Stockholm trial was started in 1997 and designed to minimize the dose of progestogen in the HRT arm. Disease-free women with a history of breast cancer were randomized to HRT (n=188) or no HRT (n=190). The trial was stopped in 2003 when the HABITS trial reported increased recurrence of breast cancer. However, the Stockholm data showed no excess risk after 4 years of follow-up[9]. A long-term follow-up published in 2013 after 10.8 years of follow-up reported no difference in new breast cancer events: 60 in the HRT group versus 48 among controls (hazard ratio (HR)=1.3; 95% confidence interval (CI) = 0.9-1.9). No differences in mortality or new primary malignancies were found[9].

So, should a woman with a history of breast cancer take norgestrel 0.075 mg tablets for a prolonged period of time, it is possible that her prognosis would be worse. It should be remembered that the limited data on HRT involves the use of estrogen in combination with progestins and that the dose of progestin in the POP is low. In the study by Trinh et al[10], there was no increased risk of breast cancer recurrence associated with use of the levonorgestrel-releasing intrauterine system (LNG-IUS). However, in a subgroup analysis of women who developed breast cancer while using an LNG-IUS and who continued to use the LNG IUS, there was a higher risk of recurrence of borderline statistical significance[10]. Thus, use of any hormonal contraceptive should be avoided in women with breast cancer unless otherwise directed by a doctor.

With respect to a comparison of risks, it should be noted that pregnancy itself (which Opill® use is aimed to prevent) worsens the prognosis for women with breast cancer[11].

It is, however, unlikely that women with a history of breast cancer would use norgestrel 0.075 mg tablets. The DFL clearly directs women with a history of breast cancer not to use the product and women with breast cancers are very likely to be well informed about the need to avoid `hormones'. They are also highly likely to be under the care of a physician who, since pregnancy is a major risk during breast cancer, is likely to encourage and monitor their use of contraception. Further, breast cancer is relatively rare among women of reproductive age. According to the 2011-2012 NHANES, among women 15-44 years of age, only 0.21% reported having ever been diagnosed with breast cancer. Among these women in the NHANES sample who had been diagnosed with breast cancer at some point in their lifetime, none reported currently taking birth control pills[3]. Several other studies also found that the prevalence of breast cancer was less than 1% among women seeking reproductive health services[12-14].

In summary, although the concern about the use of hormonal contraceptives among women with breast cancer arose primarily from COCs containing estrogen, there is also some concern about women with breast cancer being exposed to progesterone. Breast cancer is very rare in women of reproductive age, and women with breast cancer are very aware of their condition and unlikely to ignore a clear warning on the DFL, making the likelihood of such exposure due to use of a POP very low.

Do not use if you are already pregnant or think you may be pregnant. The OTC label warns against use of norgestrel 0.075 mg tablets in pregnancy, because a pregnant woman clearly has no need for contraception. The inadvertent use of hormonal birth control (HBC) in pregnancy is bound to occur occasionally, whether in the prescription or OTC setting, because some women may start HBC not knowing they are already pregnant or become pregnant while using HBC. There are no reports of adverse consequences of use of HBC in pregnancy.

There are two possible scenarios under which a pregnant woman might be exposed to a POP, whether in the prescription or OTC setting. Firstly, a woman might start taking norgestrel 0.075 mg tablets without realizing that she is already pregnant in which case the fetus would be exposed to norgestrel 0.075 mg/day from the day she started taking the pill until she stopped taking it. Second, a woman might become pregnant while taking norgestrel 0.075 mg tablets and not realize it immediately and continue taking the tablets for a period during that pregnancy in which case the fetus would be exposed to the product from the moment of conception until the woman stopped taking the pill. There are two possible consequences of a pregnant woman taking a POP for some period:

A. Teratogenesis. Taking norgestrel 0.075 mg tablets during pregnancy appears to pose little risk, although it is not recommended, and confers no benefit. The 2016 USMEC states that `there is no known harm to the woman, the course of her pregnancy, or the fetus if progestin only contraceptives (POC) are inadvertently used during pregnancy'[6]. In an American Society for Reproductive Medicine (ASRM) educational bulletin recommending luteal phase supplementation with progesterone in IVF cycles (which of course exposes the embryo and fetus to high doses of

progesterone), the authors state `there is no evidence to indicate that maternal exposure to progesterone or 17-hydroxyprogesterone during pregnancy increases risk for birth defects'[15]. The concern regarding exposure to synthetic progestins relates to a possible risk of virilization of female fetuses and hypospadias in male offspring. The same ASRM educational bulletin, however, concludes that analysis of the published literature relating to maternal progestogen exposure during pregnancy and virilization of the genitalia in female infants indicates that most reported cases involved high doses of progestins derived from androgens, particularly ethisterone and norethindrone[15]. Most reported cases of masculinized female infants are associated with maternal exposure to methyltestosterone, methandriol and danazol[16]. In a report of an investigation into the association between progestin intake and hypospadias using national US databases, the authors reviewed the literature[16]. They concluded that most of the studies did not report a significant increase in genital defects and that much of the data came from studies involving exposure to higher dose androgenic progestins no longer used in contraceptives. Moreover, these studies had many methodologic limitations, e.g. analysis of all exposures as a single entity regardless of indication; type of progestin, timing, or duration of exposure; small sample sizes; potentially differential ascertainment of outcomes between cases and controls; and inability to examine potential covariates. The Carmichael study included infants exposed to progestin contraceptives and examined bivariate risks associated with any intake during the month before pregnancy or the first three months of pregnancy, intake during each month separately, and intake by medication content[16]. They reported that progestin intake for the purpose of contraception was not associated with increased risk of hypospadias. In a recently published prospective observational cohort study on oral contraceptive use and birth defects, data were collected among 880,694 live births from Danish registries between 1997 and 2011[17]. The study did not distinguish between POPs and COCs. The main outcome measure was the number of major birth defects throughout one year of follow-up. No increase in prevalence of major birth defects was seen with oral contraceptive exposure among women with recent use before pregnancy.

In summary, taking norgestrel 0.075 mg tablets during pregnancy appears to pose little risk, although it is not recommended, and confers no benefit.

B. Delay in the diagnosis of pregnancy. In either scenario described above in which a pregnant woman takes norgestrel 0.075 mg tablets during pregnancy, there may be a delay in the diagnosis of pregnancy, thus delaying the provision of antenatal care if pregnancy is continued or limiting the woman's options for choosing pregnancy termination if desired. Most women experience a number of symptoms during early pregnancy (such as nausea) which alert them to the possibility they are pregnant. Moreover, the DFL advises women using the OTC POP to consult a health professional if they have not had a period for 8 weeks. It seems unlikely that the diagnosis of pregnancy would be delayed by more than 8 weeks, a delay which should not interfere critically with delivery of antenatal care.

In summary, inadvertent use of norgestrel 0.075 mg tablets in pregnancy is expected to be rare and the available data on the intake of low dose progestins for a limited period in pregnancy suggest that there are no significant clinical consequences.

Please note that the criteria upon which initial selection is judged include the absolute contraindications, as translated from the prescription labeling contraindications section to the proposed DFL. Two conditional contraindications from the prescription labeling are presented in the "ask a doctor before use" instead of the "do not use" section of the DFL to reflect their conditional nature, namely, unexplained intermenstrual bleeding and liver problems. Evaluation of the instructions regarding those two messages will not be included in this self-selection measure, but will instead be evaluated based on subsequent subject behavior in discrete endpoints.

Based on the rationale given above, HRA has designated a target threshold of 85% for overall self-selection, reflecting the relative safety of this product and the likely modest clinical consequences for failure to select appropriately.

9.3.2.2 Actual Use: Use of the study medication every day

This is designated a primary endpoint, due to the relevance of the instruction to efficacy.

The relevant message in the DFL:

Directions:
- Take 1 tablet … every day
  - This product will work best to prevent pregnancy when taken exactly as directed

- if you are more than 3 hours late taking your tablet or miss taking your tablet on 1 or more days:
  - take 1 tablet immediately, as soon as you remember that you missed it
  - then go back to taking your daily tablet at your usual time
  - use a condom (or another barrier method) every time you have sex during the next 2 days (48 hours), because it takes 2 days for Opill® to start working again

POPs contain a relatively low dose of progestogen. Distribution and elimination of progestogen are fairly rapid such that by 24 hours after administration, serum steroid concentrations are near baseline[18]. Thus, it is important for a POP user to take a pill every day in order to maintain the contraceptive effect of the progestin on the genital tract. The main mechanism of action of the POP is to thicken cervical-vaginal mucus, rendering it less permeable to sperm transport[18]. There are also effects on tubal motility, on the endometrium, and on ovulation - which contribute to contraceptive efficacy. Since ovulation is inhibited or impaired in around 50% of cycles among women taking the POP[18], strict adherence to daily pill taking may be more crucial to efficacy than it is with the COC, which inhibits ovulation in 99% of the cycles. Thus, failure to take a pill every day will reduce the contraceptive efficacy of the POP. While no contraceptive method is

100% effective, there are significant differences between POP failure rates during perfect use (when a pill is taken every day) and typical use when mistakes are made, primarily missing pills. The perfect-use failure rate of the POP is around 1%. During typical use, when POPs have been prescribed by a health professional, the failure rate is 9%[20], demonstrating the effect on effectiveness of diminished compliance.

In setting a threshold for this primary endpoint, it is important to look into the observed daily compliance with contraceptive pill taking in the Rx environment. It is known that compliance with all types of daily medication is far from perfect and that many women find it hard to comply with daily contraceptive pill taking. A number of published studies are available that provide insight into women's use of oral contraceptive pills, including the extent to which women adhere to the requirement to take the medication every day. A wide variety of methods, ranging from retrospective self-report surveys to electronic monitoring have been used to measure contraceptive pill use. Two studies whose methods most closely align to the proposed methods for measuring compliance in the actual use study (i.e., data collected via subject diaries and outcome expressed as average number of missed pills) suggest that women report missing between 1.0 -1.2 pills per cycle[21, 22]. Both of these studies utilized instrumented pill dispensers which allowed for electronic monitoring of pill use in addition to subject diary reports; results based on electronic monitoring indicated that women actually missed on average between 2.6[21] to 4.7[22] active pills per cycle. While these studies were conducted among women using a combined oral contraceptive (COC) pill, there is no reason to think that behavior may be different among women using a POP. These data were collected in a formal study in which women were highly likely to perform better than average (since they had received uniform instructions and knew that they were being monitored). Based on these data, typical use of oral contraceptive pills is likely to be characterized by women missing on average between 1 to 4.7 pills per month[21, 22]. As compliance is imperfect in the prescription environment, one should expect similarly limited compliance in an OTC setting. HRA may seek to identify or collect additional data to characterize compliance with oral contraceptives in the prescription environment, to provide perspective for evaluating compliance in this actual use study.

The potential outcome if women fail to follow the label instruction to take a POP pill every day is a risk of pregnancy, assuming they are sexually active. There are no data which directly quantify the risk of pregnancy after missed POPs. In contrast to COCs, there are also no data on the effect on the hypothalamo-pituitary-ovarian axis (HPO axis) of missing POPs (i.e., there is no indirect measure of the likelihood of conception after missed pills). In the recently updated US Selected Practice Recommendations for Contraceptive Use (US SPR)[23], `no evidence was found on the effects of missed POPs available in the United States of America (US/USA) on measures of contraceptive effectiveness including pregnancy, follicular development, hormone levels or cervical mucus quality.' Therefore, the likelihood of the occurrence of pregnancy if a woman does not adhere to the instruction to take a POP every day can only be hypothesized. It is not known how many POP pills need to be missed before contraceptive efficacy returns to zero.

The risk of pregnancy also depends crucially on when contraceptive pills are missed and when sexual intercourse occurs relative to the menstrual cycle. The risk of conception will be low among women who, for example, have intercourse less often than once a week or whose failure to take the pill in a timely way occurs eight days before ovulation. Thus, individual episodes of missed pills will not typically result in pregnancy. Despite the relatively poor pattern of pill-taking during typical (vs. perfect) use, over the course of one year, the failure rate of the POP in the Rx environment is <10%[24]. In contrast, a sexually active woman who uses no method of contraception has a risk of pregnancy of at least 80% over the course of one year[24]. It follows then that failure to take a pill every day in a manner which is typical of average contraceptive pill taking behavior as described above probably does not incur a very high risk of pregnancy.

As intermittent non-compliance with daily pill-taking is common even in the prescription environment, and has modest effects on pregnancy risk, as guided by FDA, HRA will evaluate this endpoint at a target threshold of 85%.

9.3.2.3 Actual Use: Use of the study medication at the same time of day.

HRA proposes to test this label message as the third primary endpoint as this message pertains to an important difference between POPs and COCs.

The relevant message in the DFL:

Directions:
- Take 1 tablet at the same time …
  - this product will work best to prevent pregnancy when taken exactly as directed

- if you are more than 3 hours late taking your tablet
or miss taking your tablet on 1 or more days:
  - take 1 tablet immediately, as soon as you remember that you missed it
  - then go back to taking your daily tablet at your usual time
  - use a condom (or another barrier method) every time you have sex during the next 2 days (48 hours), because it takes 2 days for Opill® to start working again

According to prescribing information, POPs are meant to be taken at the same time each day, within a 3-hour window. The OTC norgestrel 0.075 mg tablets DFL instructs users to take the pill at the same time every day, because doing so is important to product effectiveness. While there are no data specific to norgestrel, data from other POPs suggest that peak serum concentrations are reached around 2 hours after administration[18]. Distribution and elimination are fairly rapid such that by 24 hours after administration serum steroid concentrations are near baseline[18]. Thus, it is important to take a pill every day, and close to the same time each day, in order to maintain the contraceptive effect of the progestin on the reproductive tract. Instructions for use of POPs direct women to take the pill at the same time every day and regard failure to take

the pill during the three-hour period after this time as an indication for using back-up contraception if the woman has sex during the relevant time period. However, White et al[25] note that the recommendation that back-up contraception be used if a POP is taken more than three hours later than the scheduled time is not based on firm evidence. Moreover, no clinical data are available that correlate pregnancy rates with timeliness in taking POPs[26].

In the prescription environment, data suggest many people are poor at complying with daily pill taking, as discussed above. The Rx labeling for both COCs and POPs include directions that the pill be taken at the same time each day. There are data on the timing of oral contraceptive ingestion, collected via retrospective survey. One retrospective study of 1,311 women making initial family planning visits to metropolitan health department clinics found that only 20% of users said they took a pill every day, within two hours of the same time every day[23]. One study was identified that provides quantitative information on timing of pill use in the context of a randomized study evaluating the impact of an adherence aid among users of a particular COC (ethinylestradiol 20 µg/drospirenone 3 mg) over the course of one year[24]. All medication for this study was provided by a digital pill dispenser that had various capabilities for reminding women to take the pill at the appropriate time. The time at which the dispenser reminded the woman to take a pill each day (reference time) was set by the first pill release but could be changed. It is important to note that for the purposes of this study, pills that were dispensed early were considered to be dispensed at the reference time. Among women whose pill dispensers issued an audible alarm, the mean (SD) daily delay in pill release was 88 minutes (SD=126 minutes). It was 178 minutes (SD=140 minutes) among women whose dispenser only gave a visual prompt. These values indicate that a large proportion of women took the pill more than 2 hours late, despite being actively prompted. Failing to take a POP within the three-hour time window is likely to be quite common in both the Rx and OTC environments. Among women prescribed a POP in the Rx environment, the typical use failure rate is 3% to 10%, and this likely includes the contribution of women who take their pills late. One would not expect late pill taking to be any less common in the OTC situation.

Failure to follow the instruction to take a pill at the same time every day (failure to take the daily pill within the three-hour window) may diminish contraceptive efficacy. Although serum steroid concentrations will have returned to almost baseline 24 hours after POP administration, any effect on the HPO axis is likely to be sustained beyond 24 hours. This means the POP's action on cervical-vaginal mucus, tubal motility, endometrium, and ovulation – are still in effect, so taking a pill later than 27 hours after the previous pill is unlikely to be nearly as risky as having intercourse without any contraception. That is, some efficacy is likely to be retained even if the pill were taken late. Moreover, the chance of pregnancy in the event of late pill taking will depend on the time in the menstrual cycle when pills are taken late and on the occurrence of intercourse during the narrow window of vulnerability to conception.

HRA believes achieving good compliance is important, and accordingly has proposed this be a primary endpoint. However, it is apparent that a delay in taking the daily pill will have less potential consequence than taking a break for a number of consecutive days or missing a pill entirely (the other compliance-related primary endpoints assessing optimal use for efficacy). Considering the limited effect of delaying the daily pill, and the data that suggest that compliance is low in the prescription environment, and the fact that that low compliance is already accounted for by the known failure rate in typical Rx use of POPs, with guidance from FDA, HRA will evaluate this primary endpoint at a target threshold of 80%.

9.3.2.4 Actual Use: Use of the study medication without an extended break or any break between packs

This is designated a primary endpoint, due to the relevance of the instruction to efficacy.

The relevant message in the DFL are:

Directions:
● Take 1 tablet at the same time every day
● Never skip your daily tablet
● to prevent pregnancy, take this product every day, even when you bleed or have spotting
● When you finish this pack, start the next one the following day without a break

POPs including norgestrel 0.075 mg tablets are to be taken every day without any breaks at all, and it is particularly important that POP users do not take breaks of several consecutive days. In contrast to POPs, COC was developed to include a 7-day pill-free interval which induced a regular monthly `withdrawal' bleed, with some brands recommending shorter breaks. COCs are the more commonly used "birth control pill." This raises the potential that women who have taken a COC in the past, or who are familiar with COC dosing, may think that the same regimen is required for a POP and so may deliberately take a break from pill taking for some days at the end of their pill packet.

There are no data to suggest whether and how frequently this type of misunderstanding occurs in the prescription environment. The consequences of deliberately taking an extended (4-7 day) break from taking OTC norgestrel 0.075 mg tablets at the end of a pack or packs due to misunderstanding the OTC directions for use would be a potential risk of pregnancy. Missing a POP for a number of consecutive days impairs contraceptive efficacy and if this is repeated monthly and the norgestrel 0.075 mg tablets user is having sex, the risk of pregnancy is increased.

There are data to show that contraceptive efficacy is achieved after just two consecutive days of taking a POP[18], which mitigates the risk due to occasionally missing single pills intermittently. It follows, in contrast, that missing pills on consecutive days is riskier than

missing just one pill, and that the more pills that are missed consecutively, the more likely contraceptive failure becomes. In a randomized controlled trial (RCT) comparing two POPs, one containing 30 mcg LNG/day, the other 75 mcg desogestrel/day[19], two of the three in-treatment pregnancies that occurred during use of the desogestrel POP were attributed to gross non-compliance (missing 12 tablets; stopping the POP for `some weeks'). In the LNG-POP group, one of four pregnancies that occurred was attributed to missing 12 pills. So, missing one pill on three consecutive days is riskier than missing one pill three times over the course of a packet of pills but on non-consecutive days. Compliance with daily pill-taking (which is also assessed as a separate primary endpoint) is known to be challenging whether the pills are obtained by prescription or OTC, making assessment of this behavior an important endpoint.

Given the potential clinical significance of missing pills over several consecutive days, whether due to misunderstanding proper dosing of a POP or for any other reason, and based on FDA's feedback, HRA will evaluate this endpoint at a target threshold of 90%.

9.3.3 **Secondary Endpoint Analysis**

9.3.3.1 Actual Use: Proportion of user population who do not use together with another form of hormone-containing birth control

This secondary endpoint is the proportion in which the denominator is all users (the user population) and the numerator is all women who appropriately do not use the product together with another form of hormone-containing birth control.

9.3.3.2 Actual Use: Proportion of user population who report using a condom or other barrier method (or abstaining from intercourse) for the first 48 hours after starting to use the study medication

This secondary endpoint is defined as the proportion in which the denominator is all users of the product and the numerator is all subjects who either report using a condom (or another barrier method of birth control) if they had intercourse or who abstained from intercourse for the first 48 hours after starting the study medication.

9.3.3.3 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 (and cite that as the reason for not selecting), who select but do not use (and cite that as the reason for not using), 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, phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine, rifampin, rifabutin, bosentan, a prescription drug to treat HIV/AIDS, a supplement containing St. John's Wort, or use of an emergency contraceptive containing ulipristal acetate in the past 5 days) and the

numerator is all such subjects who either do not select or use (and cite this warning as the reason for not selecting or using), or who report talking with a doctor or pharmacist about use during the course of the study.

9.3.3.4 Self-Selection/Actual Use: Proportion of self-selection population who report having liver problems who either do not select (and cite that as the reason for not selecting), who select but do not use (and cite that as the reason for not using), or who report contacting a healthcare provider about use of the product

This secondary endpoint is the proportion defined by the denominator including all subjects who participate in the self-selection interview who report having liver problems and the numerator is all such subjects who either do not select or use (and cite this warning as the reason for not selecting or using), or who report talking with a healthcare provider about use during the course of the study.

9.3.3.5 Actual Use: Proportion of user population who experience one of the “Talk to a doctor” conditions listed within the “When using this product” or “Stop use and ask a doctor” sections who report contacting a healthcare provider and/or stop use as directed by the label

This secondary endpoint is the proportion defined by the denominator including all users who report experiencing one of the “Talk to a doctor” conditions within the “When using this product” section (including unexplained vaginal bleeding between periods before starting Opill®, vaginal bleeding that is repeatedly brought on by sex, menstrual periods lasting more than 8 days or unusually heavy, no periods for two months, sudden or severe pain in lower belly, migraines with aura/worsening migraines, pregnancy, or symptoms of jaundice) and the numerator is all such subjects who report talking with a doctor about use during the course of the study or stopping use.

Please note that this endpoint comprises measurement of behaviors related to a number of conditions that are expected to occur with relatively low frequency. The proportions related to each individual message/behavior will be presented individually, as well as being aggregated in the formal endpoint analysis.

9.3.3.6 Actual Use: Number of pregnancies reported during the course of the study

This endpoint is intended to characterize the pregnancies that may occur during the course of the study. While it does not directly measure behavior related to messages on the DFL, it is of interest. For the purposes of this endpoint, pregnancies will be defined as any reported pregnancy during the use phase of the study, or any confirmed positive pregnancy test (at home or at EOS visit) that is conducted within 12 days of the end of the subject's use phase.

9.3.4 Other Measures Analysis

The other measures are as follows:

A. Actual Use: Character and frequency of adverse events as reported by the user population.
B. Actual Use: Patterns of use in the user population, including discontinuation rates and reasons for discontinuation.
C. Actual Use: Proportion of user population who experience severe vomiting or diarrhea within 4 hours of taking their daily pill who report using a condom or other barrier method of contraception every time they have sex (or abstain from intercourse) for the next 48 hours.
D. Actual Use: Characterize healthcare seeking behavior among subjects.

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 8.5.4 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.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they 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.

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 participant 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 an internet connection is not available at the time of enrollment, subjects will be rescheduled for another time. If internet connection is interrupted during the course of an enrollment interview, the remainder of the interview will be completed when the internet connection is restored. Due to the complexity of the branching logic in the data collection instruments, use of electronic informed consent, and the requirement of creating a subject account for use in consenting and the electronic diary application, data will not be gathered on any paper copies of electronic case report forms in this study. In the event the interview is interrupted due to loss of internet connectivity, the interview must be continued within a 3-day period to ensure data consistency and quality.

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 participant's anonymity is maintained. On documents submitted to the Sponsor, participants will not be identified by name or

other personally identifiable information, but by numerical identification code generated by the EDC system.

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 Research is responsible for selecting sites and training study personnel. Training will consist of an overview of the protocol as well as detailed instructions on the methods, including participant recruitment, proper administration of the questionnaire, use of the EDC application and guidelines for correctly capturing and entering responses. Study-specific interview completion guidelines will be developed to serve as the basis for training. All training will be documented.

Regulatory authorities, the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), 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 Health-related Research Involving Humans (Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) 2016), International Council on Harmonization (ICH) Tripartite Guidelines for Good Clinical Practice (E6 (R1) Current Step 4 version dated 10 June

1996), and the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (World Medical Association, 2013).

In addition, the study will be conducted in accordance with the protocol, the 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 participants will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Participant names will be collected for compensation 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 personal identifiable information will be captured in the study database. In accordance with the Federal Privacy Standard, a Notice of Information Practices, which describes how participants' 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 personally identifiable information (PII) will be retained following the study for subjects that either did not pass the screening phase or who 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 informed consent from each subject before dispensing of study medication. Informed consent documents will be presented electronically, and signatures gathered digitally, however, all consent procedures (including obtaining informed consent from a parent or legal guardian, if necessary) will be conducted in person. An archived copy of the signed informed consent document will be made available to subjects digitally.

All subjects who are classified as children according to local laws and regulations will be required to have parental consent for participation in the study as is dictated in 21 CFR 50 subpart D. However, please note the definition of a child, according to 21 CFR 50.3(o) is as follows: "*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."* In many states, adolescents seeking contraception do not need parental consent for

treatment, and therefore do not meet the definition of “children” in § 50.3(o). These adolescents are not subject to the requirements of 21 CFR 50 subpart D and may consent for research related to that treatment. Please note that states define the age or conditions upon which an adolescent can consent to contraceptive services differently, and local laws and regulations will be adhered to based on the state of each research site.

In addition to being explicitly allowed for by regulation, there are compelling scientific reasons for not imposing a higher bar for entry into this study for adolescents who are not defined as children according to local laws. Adolescents are of special public health concern when it comes to access to contraception because of the implications of unintended pregnancy among that age group. Barriers to access to contraception are often higher for adolescents. Numerous professional organizations (AAFP, ACOG, AMA, APHA, ACCP) have called for the availability of oral contraceptive over-the-counter, to include access for all ages. Indeed, FDA has specifically requested a challenging quota of adolescent participants for this study, and has expressed specific concern about the bias that may be introduced by only including adolescents who have the degree of parental involvement required for parental consent.

No additional waiver of the need for parental consent will be sought (above and beyond the appropriate classification of those adolescents who have attained the legal age for consent to contraceptive services as not children, and therefore not needing parental consent). Where state and local laws define an adolescent as a child for the purposes of consenting to contraceptive services, parental consent and adolescent subject assent will be required for participation in this study and will be documented.

In the case of all subjects (but perhaps most notably for adolescents), the investigator must ensure that the subject understands the research procedures and is able to give truly informed consent. If a subject meets the regulatory requirements for signing informed consent, but in the judgement of the investigator is either inadequately informed or incapable of providing consent, that subject will not be allowed to proceed.

All records identifying participants will be kept confidential, and to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Participant names will be collected for scheduling and compensation only. No 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 participants' health information will be used and disclosed and how they can obtain access to this information, will be made available, if applicable.

Participants' 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.

Participant names, contact information, and other identifiable data will be maintained entirely separate from the study database. All parties will ensure protection of participant personal data and will not include participant 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 participant. In case of data transfer, PEGUS will maintain high standards of confidentiality and protection of participant personal data.

12.4 Opt in for Future Research Contact

During the informed consent process, subjects will be given the opportunity to opt in to allow the use of their contact information for the purpose of inviting them to participate in potential future research in topics related to their participation in this study. Subjects will be informed that their decision about whether or not to opt in for any potential future contact will in no way impact their participation in the current study.

While the purpose and procedures for any such hypothetical future study are unknown, and therefore cannot be described here or in the informed consent document associated with this study, any materials used to contact or invite those subjects who opt in to future studies would be submitted for IRB review, as would the associated protocol and data collection tools, in order to ensure subject safety.

Please note that under no circumstances will subjects' contact information collected as part of this study be disclosed to any other parties, including the study sponsor or other commercial or research entities.

12.5 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.

12.6 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 investigational product, 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.

12.7 Mandatory Reporting

There will not be questions in the interview addressing personal sexual experience and it is not expected that participants 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 participants. Participants 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 Opill® 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 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 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 8 months (from first subject enrolled in the study until last subject last visit), with subject recruitment proposed to start Q4 2017 and end in Q2 2018. The actual overall study duration or subject recruitment period may vary.

17 REFERENCES

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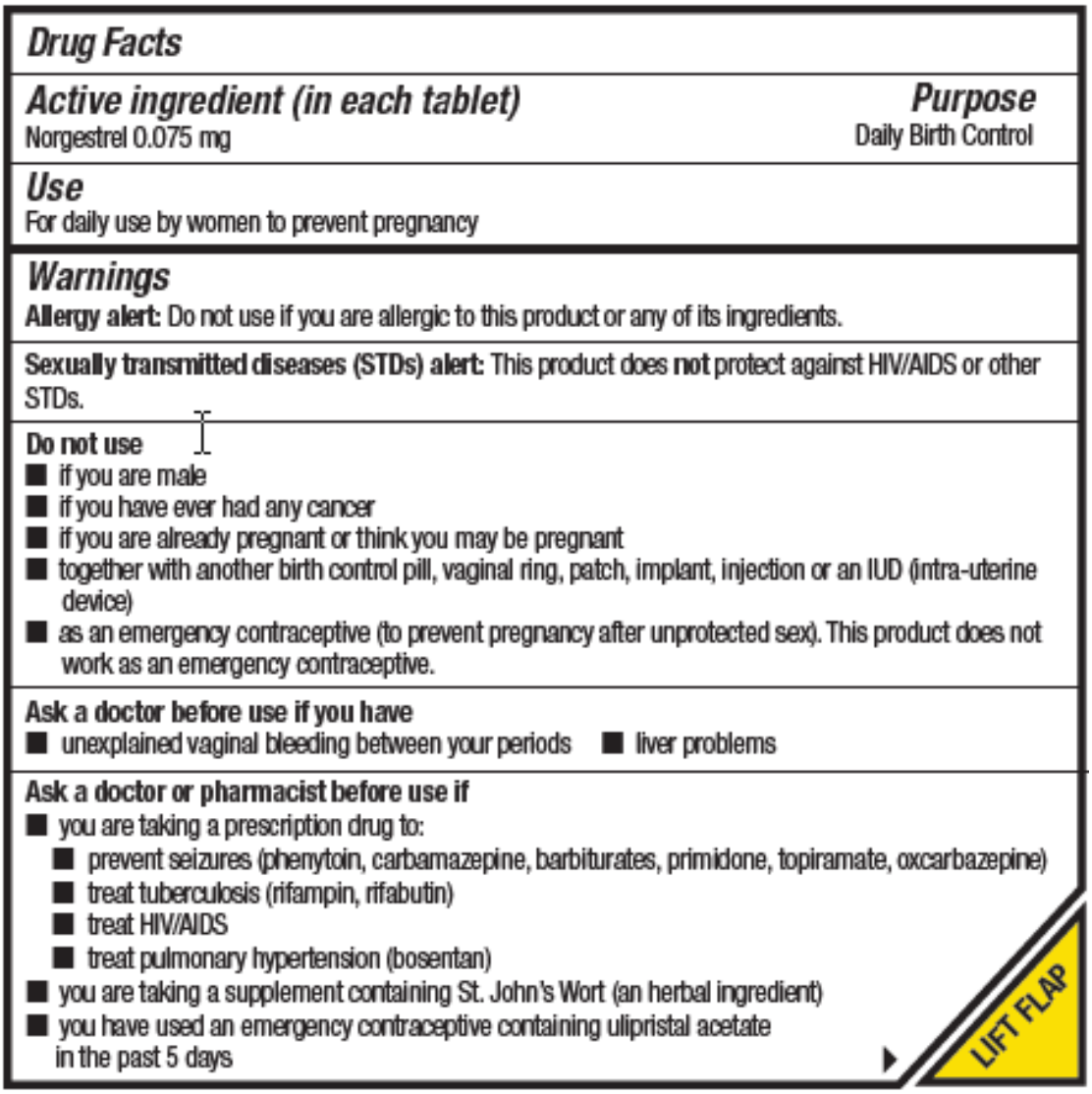
18 APPENDICES

18.1 Mock Package and Drug Facts Label

DFL Panel 1



DFL Panel 2

Drug Facts (continued)

When using this product

- **you are likely to experience changes in your menstrual periods**
- **continue taking this product every day** even if you start to have these changes
  - irregular periods or you stop having periods
  - spotting or bleeding when you are not having your period
- **talk to a doctor AND continue taking every day** if you have these unexpected bleeding symptoms
  - unexplained vaginal bleeding between your periods before you started using this product
  - repeated vaginal bleeding brought on by sex
  - periods that last more than 8 days or are unusually heavy
- **do a pregnancy test or talk to a doctor** if
  - your period is late after missing any pills in the last month
  - you have not had a period for 2 months or think you may be pregnant
- you may experience headaches, dizziness, nausea, increased appetite, abdominal pain, cramps or bloating
- **talk to a doctor** if you
  - have sudden or severe pain in your lower belly – see a doctor immediately (you could have an ectopic pregnancy)
  - start having migraines with aura (headaches that start with changes in vision) or your migraine headaches get worse

Stop use and ask a doctor if you

- become pregnant
- develop yellowing of your skin or whites of your eyes (especially with fever, tiredness, loss of appetite or dark colored urine)

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away. ▶

DFL Panel 3

Drug Facts (continued)

Directions

- **take 1 tablet** ***at the same time every day***
  - this product will work best to prevent pregnancy when taken exactly as directed
  - you can start on any day of the month
  - use a condom (or another barrier method) every time you have sex during the first 2 days of use (48 hours) after you start your first pack of this product, because it takes 2 days for this product to start working
- **never skip your daily tablet**
  - to prevent pregnancy, take this product every day, even when you bleed or have spotting
  - when you finish this pack, start the next one the following day without a break
- **if you are more than 3 hours late taking your tablet or miss taking your tablet** on 1 or more days:
  - take 1 tablet immediately, as soon as you remember that you missed it
  - then go back to taking your daily tablet at your usual time
  - use a condom (or another barrier method) every time you have sex during the next 2 days (48 hours), because it takes 2 days for Opill® to start working again
- **if you vomit** for any reason **or have severe diarrhea within 4 hours** of taking your daily tablet, use a condom (or another barrier method) every time you have sex for the next 2 days (48 hours), because the medicine may not have been fully absorbed

Drug Facts (continued)

Other information

- as with any birth control method, this product does not prevent pregnancy all the time.
- this product will work best if you take it exactly as directed.
- **read the instructions, warnings and enclosed product leaflet before use**
- contains FD&C yellow No.5 (tartrazine) as a color additive
- store between 20°-25°C (68°-77°F) .

Inactive ingredients

cellulose, FD&C Yellow No. 5, lactose, magnesium stearate, and polacrilin potassium.

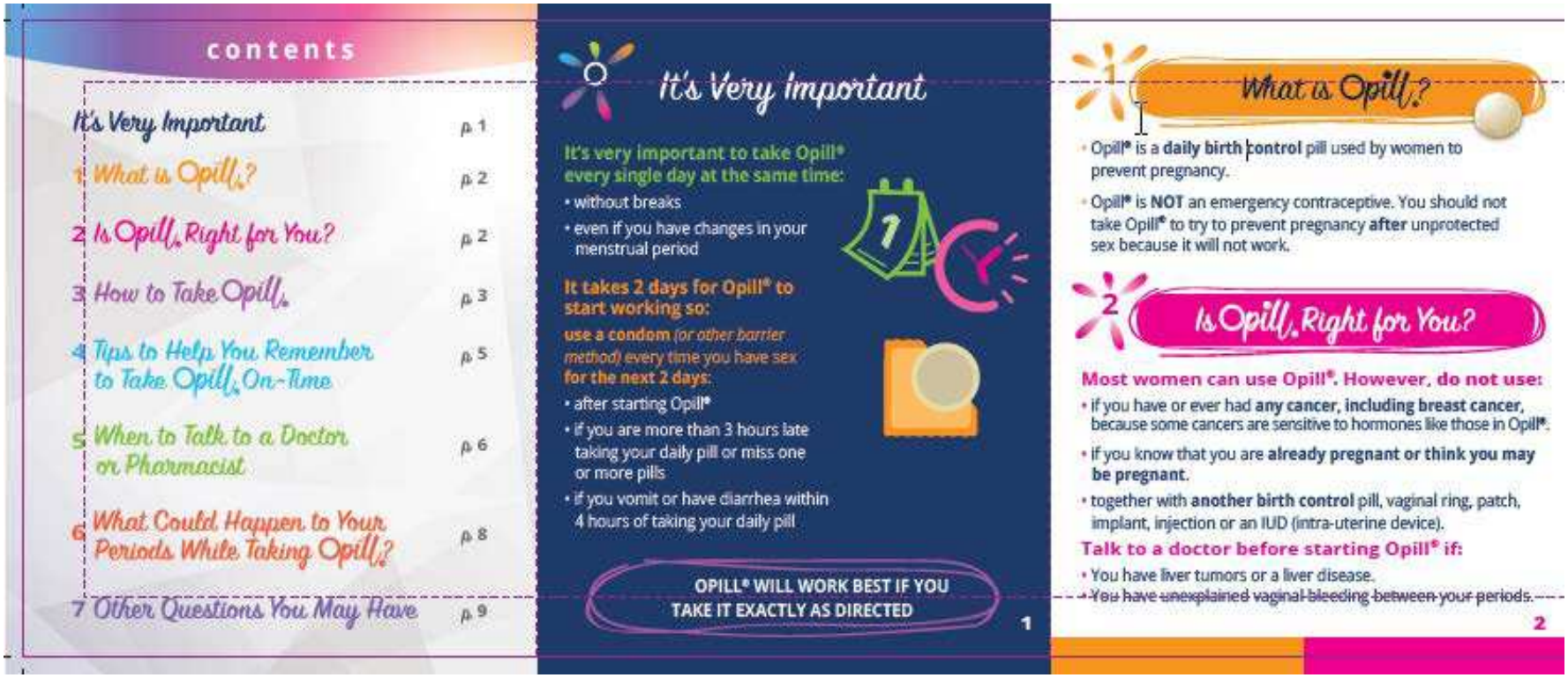
☎ *Questions?*

call 1-800-XXX-XXXX or visit www.xxxx.com

Carton including DFL

18.2 Consumer Information Leaflet

CIL Table of Contents – Page 2



contents

It's Very Important

It's very important to take Opill® every single day at the same time:

- without breaks
- even if you have changes in your menstrual period

It takes 2 days for Opill® to start working so:

use a condom *(or other barrier method)* every time you have sex **for the next 2 days:**

- after starting Opill®
- if you are more than 3 hours late taking your daily pill or miss one or more pills
- if you vomit or have diarrhea within 4 hours of taking your daily pill

OPILL® WILL WORK BEST IF YOU TAKE IT EXACTLY AS DIRECTED

1

What is Opill®?

- Opill® is a **daily birth control** pill used by women to prevent pregnancy.
- Opill® is **NOT** an emergency contraceptive. You should not take Opill® to try to prevent pregnancy **after** unprotected sex because it will not work.

Is Opill® Right for You?

Most women can use Opill®. However, do not use:

- if you have or ever had **any cancer, including breast cancer,** because some cancers are sensitive to hormones like those in Opill®.
- if you know that you are **already pregnant or think you may be pregnant.**
- together with **another birth control** pill, vaginal ring, patch, implant, injection or an IUD (intra-uterine device).

Talk to a doctor before starting Opill® if:

- You have liver tumors or a liver disease.
- You have unexplained vaginal bleeding between your periods.

2

CIL Pages 3-5

3

How to Take Opill®

Take 1 tablet at the same time every single day *(and no later than 3 hours from the time you took your pill the day before).*

Never skip your daily pill.

- Never take a break between packs. When you finish one pack *(all 28 pills)*, you should start the next pack the following day.
- Take Opill® every single day, even when you have your period, or if you have spotting or bleeding between periods.
- Do not skip pills even if you do not have sex very often.

To start using Opill®:

- You can start your first pack on any day.
- If you are switching from another birth control pill, vaginal ring, or patch, start taking Opill® the day after you stop the other method.
- You must take your daily pill at the same time of day every single day.
- You must use a condom *(or another barrier method)* every time you have sex during the first 2 days *(48 hours)*.

3

What if I am late taking my pill?

Less than 3 hours late:

- Don't worry. Take 1 pill immediately and go back to taking your pill at your usual time the following day.

More than 3 hours late OR you missed one or more pills:

- Take 1 pill immediately, as soon as you remember.
- Then, go back to taking your pill at your usual time. This means you may take 2 pills in 1 day.
  - For example, if you usually take your pill at night, but forget and remember in the morning, take 1 pill when you remember and take 1 pill again at the usual time that night.
- You must use a condom *(or another barrier method)* every time you have sex during the 2 days *(48 hours)* after you restart Opill®, because it takes 2 days to start working again.
- **Take a pregnancy test or talk to a doctor** if your period is late after missing any pills in the last month.

What if I vomit or have severe diarrhea within 4 hours of taking my pill?

- Use a condom *(or another barrier method)* every time you have sex for the next 2 days *(48 hours)* because the medicine may not have been fully absorbed.
- ~~The next day, take your daily pill at your usual time.~~

4

4

Tips to Help You Remember to Take Opill® On Time

- **Choose a convenient time of day.** It is best to link this to something you already do at **the same time every day**. For example, when you wake up or when you brush your teeth.
- **Set an alarm.** Consider using your smartphone to set a daily alarm, and using the reminder stickers included in your pack.
- **Buy a new pack of Opill®** a few days before finishing the pack, so you can start the next pack on time.

5

CIL Pages 6-8

5

When to Talk to a Doctor or Pharmacist

What if I am taking other medicines or herbal products?

Talk to a doctor or pharmacist if you are taking or start to take any of the following, as these may make Opill® less effective:

- Certain drugs to treat:
  - Seizures *(barbiturates, carbamazepine, oxcarbazepine, phenytoin, topiramate, primidone)*
  - Tuberculosis *(rifampicin, rifabutin)*
  - Pulmonary hypertension *(bosentan)*
  - HIV / AIDS
- St. John's Wort *(or any herbal products containing hypericum perforatum)*

What if I have taken an emergency contraceptive before starting Opill®?

- **Talk to a doctor or pharmacist** if you have taken an emergency contraceptive in the past 5 days.
- Opill® should not be used for 5 days after using the emergency contraceptive ella® *(which contains ulipristal acetate)*. This might reduce the ability of both Opill® and ella® to prevent pregnancy. Also, **use a condom** *(or another barrier method)* every time you have sex until your next period.

6

What if I have sudden or severe abdominal pain in my lower belly?

Contact a doctor immediately.
You may have an ectopic pregnancy *(a fertilized egg implanted in the wrong place)*.

What if I become pregnant while taking Opill®?

- **Stop taking this product and talk to a doctor** if you get pregnant while taking Opill®.
- Signs that you may be pregnant might include: missed periods, tender breasts, feeling nauseous, fatigue, and/or needing to urinate urgently or more frequently.
- **Take a pregnancy test or talk to a doctor** if your period is late after missing any pills in the last month, if you have not had a period for 2 months, or if you think you may be pregnant.

What if I get migraines while using Opill®?

- If you start having migraines with aura *(headaches that start with changes in vision)* or your migraine headaches get worse, **talk to a doctor,** as some women with migraine may be at increased risk of stroke.

What if I develop yellowing of skin or eyes while using Opill®?

- **Stop use and ask a doctor** if you develop the following rare symptoms - yellowing of the whites of your eyes or skin *(especially with fever, tiredness, loss of appetite or dark colored urine)*.

7

6

What Could Happen to Your Periods While Taking Opill®?

What changes in my menstrual period are normal while using Opill®?

Most changes to periods are to be expected.
Continue taking Opill® exactly as directed, even if you have the following changes in your periods:

- Your periods may be less or more frequent, shorter or longer, lighter or heavier than before you started Opill®. You may also have some spotting or bleeding between periods.
- Some women stop having periods while taking Opill®.
- **Take a pregnancy test or talk to a doctor** if your period is late after missing any pills in the last month, if you have not had a period for 2 months, or if you think you may be pregnant.

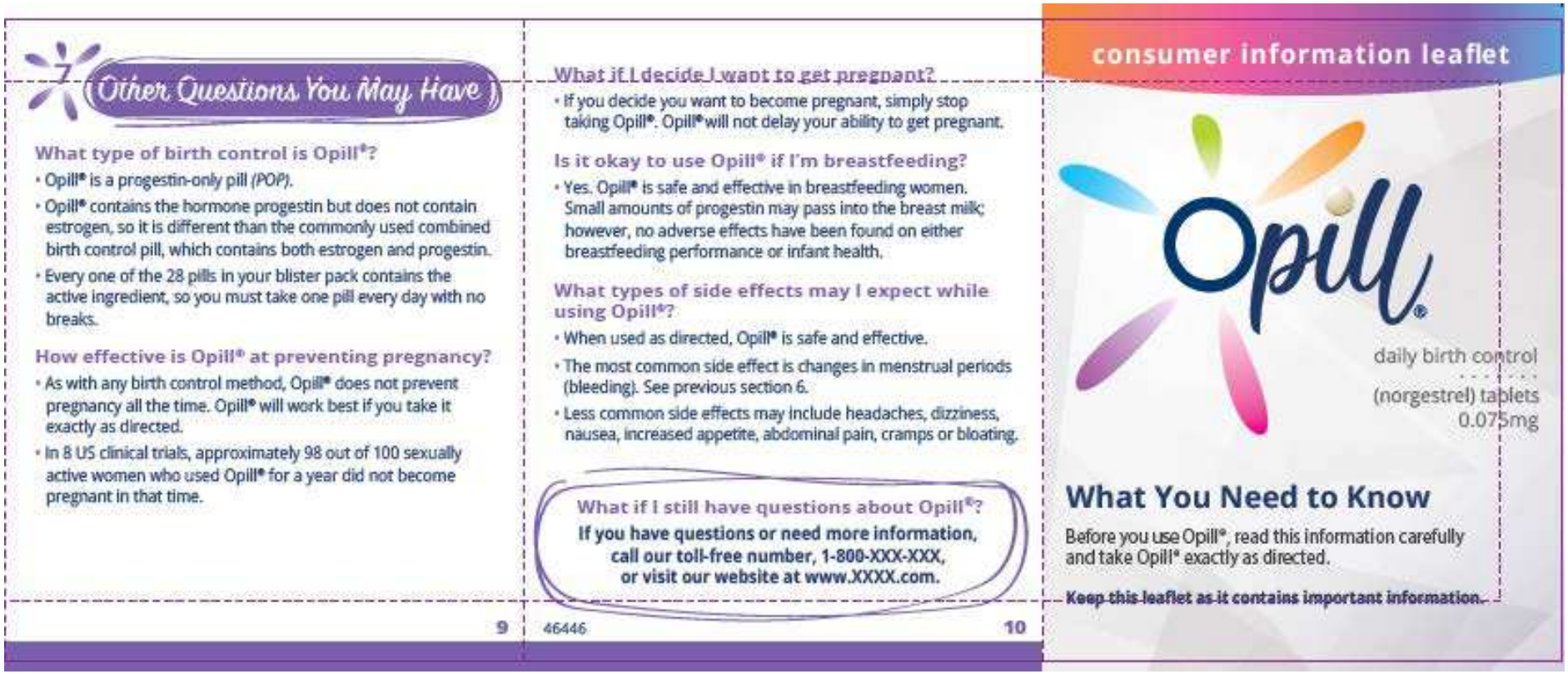
What changes to my period are NOT expected when using Opill®?

Talk to a doctor while continuing to take this product every day even if you experience any of the following:

- You had unexplained vaginal bleeding between your periods before you started this product.
- You repeatedly have bleeding that is brought on by sex.
- Your menstrual period lasts more than 8 days or is unusually heavy.

8

CIL Pages 9-10 and Cover Page



7 Other Questions You May Have

What type of birth control is Opill®?

- Opill® is a progestin-only pill *(POP)*.
- Opill® contains the hormone progestin but does not contain estrogen, so it is different than the commonly used combined birth control pill, which contains both estrogen and progestin.
- Every one of the 28 pills in your blister pack contains the active ingredient, so you must take one pill every day with no breaks.

How effective is Opill® at preventing pregnancy?

- As with any birth control method, Opill® does not prevent pregnancy all the time. Opill® will work best if you take it exactly as directed.
- In 8 US clinical trials, approximately 98 out of 100 sexually active women who used Opill® for a year did not become pregnant in that time.

What if I decide I want to get pregnant?

- If you decide you want to become pregnant, simply stop taking Opill®. Opill® will not delay your ability to get pregnant.

Is it okay to use Opill® if I'm breastfeeding?

- Yes. Opill® is safe and effective in breastfeeding women. Small amounts of progestin may pass into the breast milk; however, no adverse effects have been found on either breastfeeding performance or infant health.

What types of side effects may I expect while using Opill®?

- When used as directed, Opill® is safe and effective.
- The most common side effect is changes in menstrual periods (bleeding). See previous section 6.
- Less common side effects may include headaches, dizziness, nausea, increased appetite, abdominal pain, cramps or bloating.

What if I still have questions about Opill®?

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

consumer information leaflet

Opill®

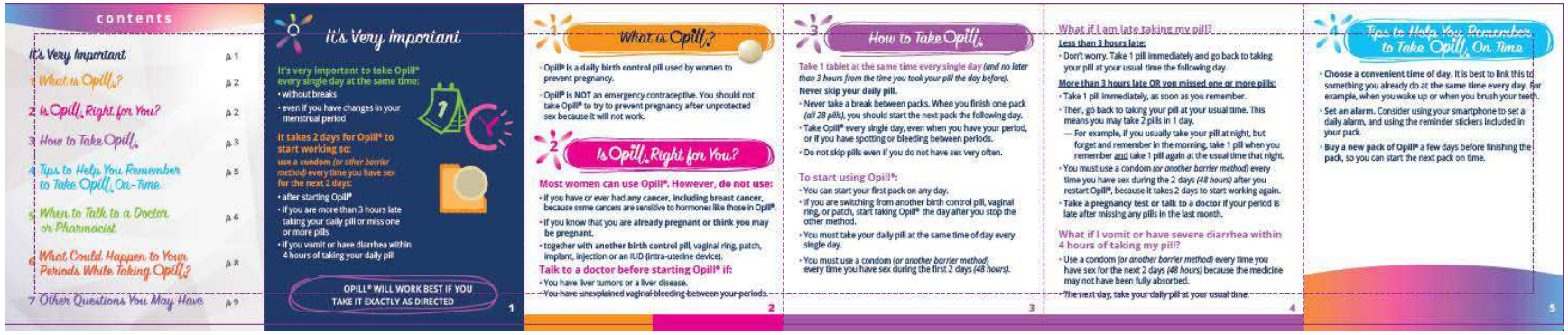
daily birth control
(norgestrel) tablets
0.075mg

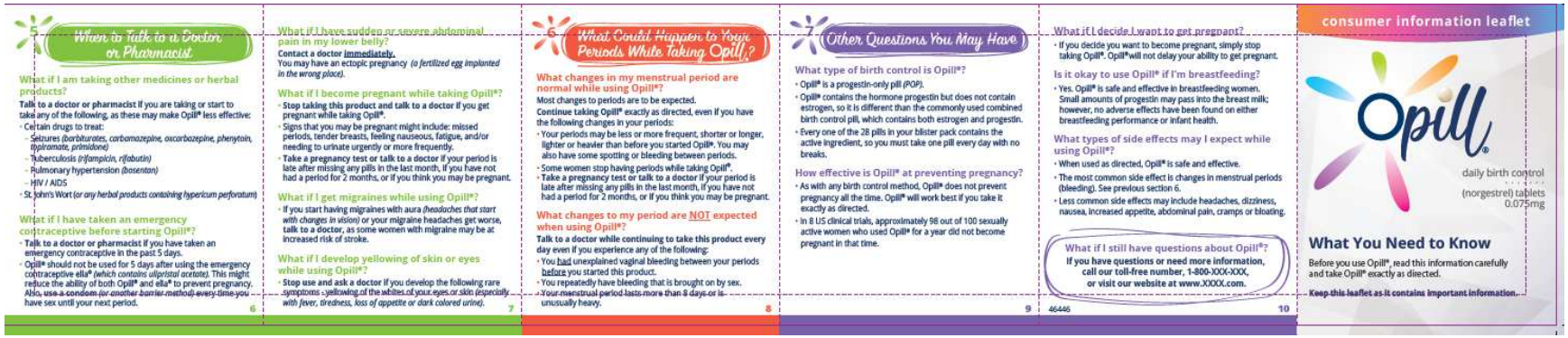
What You Need to Know

Before you use Opill®, read this information carefully and take Opill® exactly as directed.

Keep this leaflet as it contains important information.

CIL (Five Panel, Foldable)





18.3 Reminder Card

Front

Back